Joint Trust Guideline for the Antibiotic Management of Diabetes Related Foot Infections in Adults

A clinical guideline recommended

For use in:	Clinical areas treating patients with diabetes related foot infections
By:	Staff who prescribe for patients with diabetes related foot infections
For:	Adult patients with diabetes related foot infections
Division responsible for document:	Medical Division (Including Emergency Medicine)
Key words:	Diabetes, Diabetes related foot infections, Antibiotics, Infection
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Assessed and approved by the:	Antimicrobial Sub-Committee If approved by committee Chair's Action; tick here ☐ Clinical Guidelines and Assessment Panel (CGAP) If approved by committee Chair's Action; tick here ☐
Date of approval:	10/10/2019 Extension Granted 10/08/2022
Ratified by or reported as approved to:	Clinical Safety and Effectiveness Sub-board
To be reviewed before:	10/10/2022 Extension Until 30/04/2023
To be reviewed by:	Catherine Gooday, Ketan Dhatariya, Caroline Hallam, Reham Soliman, Darren Morrow
Trust Docs ID No:	1289
Version No:	5.1
Description of changes:	Osteomyelitis Inpatient Treatment section updated
Compliance links:	NICE Guidance NG19 (Aug 2015): Diabetic foot problems: prevention and management
If Yes - does the strategy/policy deviate from the recommendations of NICE? If so why?	No

This guideline has been approved by the Trust's Clinical Guidelines Assessment Panel as an aid to the diagnosis and management of relevant patients and clinical circumstances. Not every patient or situation fits neatly into a standard guideline scenario and the guideline must be interpreted and applied in practice in the light of prevailing clinical circumstances, the diagnostic and treatment options available and the professional judgement, knowledge and expertise of relevant clinicians. It is advised that the rationale for any departure from relevant guidance should be documented in the patient's case notes.

The Trust's guidelines are made publicly available as part of the collective endeavour to continuously improve the quality of healthcare through sharing medical experience and knowledge. The Trust accepts no responsibility for any misunderstanding or misapplication of this document.

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Quick reference guidelines (See pages 4 to 7)

Objective/s

The aim of this guideline is to offer antibiotic guidance on the empirical treatment of diabetes related foot infections.

Rationale

Many patients with diabetes present with foot infections which require empirical antibiotic treatment to prevent serious complications. There are no trials that offer definitive advice on appropriate antibiotic treatment for the treatment of foot infections in people with diabetes. This guideline incorporates guidance given in the IDSA guidelines 'Diagnosis and Treatment of Diabetic Foot Infections' published in 2012. See reference below. Local resistance patterns have also been taken into account as has the risk/benefit ratio of prescribing antibiotics that may cause a high likelihood of *Clostridioides difficile* (*C.diff)* infection.

This guideline is for use as *empirical 1st line therapy* and the choice of antimicrobial agents may need to change when microbiological sensitivity data becomes available.

Broad recommendations

Antibiotic therapy needs to cover gram positive organisms, mainly aerobic gram-positive cocci. In some cases cover for anaerobic pathogens and *Pseudomonas* needs to be commenced. Antibiotic therapy should be used for the minimum time possible and regularly reviewed to help prevent C.*diff* infection developing. Patients who are prescribed ciprofloxacin, clindamycin or a cephalosporin should be counselled what to do if diarrhoea develops.

Clinical audit standards

100% of patients should receive appropriate antibiotics as stated in table 2 according to their stage of infection and whether the wound is partial or full thickness or extending to underlying soft tissue/bone.

Summary of development and consultation process undertaken before registration and dissemination

The authors listed above originally drafted this guideline on behalf of the antimicrobial subcommitee who has agreed the final content. During its development it has been circulated for comment to Professor Turner and Dr Wallace, the podiatrists and the Foot MDT, Mr Morrow, Mr Loveday, Mr Brightwell and Mr Smith
Comments were addressed and incorporated if appropriate.

In 2019 the guideline was reviewed and only the Osteomyelitis Inpatient Treatment section needed updating. This version has been endorsed by the Clinical Guidelines Assessment Panel.

Distribution list/ dissemination method

All Diabetologists and Diabetic Nurses (via Dr Dhatariya), All Podiatrists (via Catherine Gooday) and all Vascular Surgeons (via Darren Morrow) and Trust intranet

For QEH via Dr F Haddadin, Consultant Endocrinologist (QEH)

References/ source documents

Lipsky B, Berendt A et al, 2012. Infectious Diseases Society of America Clinical Practice Guideline for the diagnosis and treatment of diabetic foot infections CID. 54;12:e132-e173.
SIGN Guideline 116 (Sept 2013) http://www.sign.ac.uk/pdf/sign116.pdf

NICE Guidance NG19 (Aug 2015): Diabetic foot problems: prevention and management. http://www.nice.org.uk/guidance/ng19

Gooday C, Hallam C, Sieber C *et al.* An antibiotic formulary for a tertiary care foot clinic: admission avoidance using intramuscular antibiotics for borderline foot infections in people with diabetes. *Diabetic Med* 2013; **30**(5)**:**581-589

Lipsky B, Silverman M, Joseph W. A Proposed New Classification of Skin and Soft Tissue Infections Modeled on the Subset of Diabetic Foot Infections. Open Forum Infectious Diseases. 1-8

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Quick Reference Guideline

Table 1: Stages of Infection of Diabetes Related Foot Infection

Clinical Description	Degree of infection
No purulence or evidence of inflammation	**Uninfected**
Evidence of inflammation 2cm or less around the ulcer	**Mild**
Cellulitis >2cm around the ulcer	**Moderate**
Cellulitis >2cm around the ulcer associated with; • Lymphangitis • Foot failing to respond to oral antibiotics alone	**Severe – Borderline admission**
Cellulitis as well as evidence of systemic toxicity; • Fever • Hypotension • Leukocytosis or • Abscess formation • Infection tracking beneath fascia • Foot not responding to antibiotics • Wet gangrene	**Severe - Admission**
Visible bone in wound or where there is a positive 'probe to bone' test with an overlying wound, or if there are X-ray changes consistent with osteomyelitis	**Osteomyelitis**

Table 2:	First choice treatment	Second choice treatment or alternatives (e.g. if penicillin allergic patient)	At high risk of MRSA or MRSA positive	Duration	Comments
Mild	Flucloxacillin PO 500mg qds	1st line: Doxycycline PO 200mg STAT Day 1 then 100mg bd **OR** 2nd line: If Doxycycline resistant or allergy: Clarithromycin PO 500mg bd **OR** 3rd line: Cotrimoxazole PO 960 mg bd (contra-indicated if patient on methotrexate or has trimethoprim allergy)	**Prescribe according to sensitivities.** Doxycycline PO 200mg STAT Day 1 then 100mg bd **OR** combination of 2 of the following oral antibiotics trimethoprim po 200mg bd, rifampicin po 300mg-600mg bd, fusidic acid po 500mg tds. (Fusidic acid not to be used in combination with rifampicin). **OR** Cotrimoxazole PO 960 mg bd (contra-indicated if patient on methotrexate or has trimethoprim allergy)	Review at 1-2 weeks	**Cotrimoxazole**: unlicensed in diabetic foot. Monitoring: 2 weekly FBC and U's and E's See information sheet **Sodium fusidate monitoring**: See notes at bottom of table
Moderate	Co-amoxiclav PO 625mg tds	1st line: Clindamycin PO 300mg qds (consider adding in Ciprofloxacin 500mg PO bd if no improvement after 1-2 weeks) **OR** 2nd line: Cotrimoxazole PO 960 bd (contra-indicated if patient on methotrexate or has trimethoprim allergy)	Doxycycline PO 200mg STAT Day 1 then 100mg bd **AND** Clindamycin PO 300mg qds **OR** Cotrimoxazole PO 960mg bd (contra-indicated if patient on methotrexate or has trimethoprim allergy)	2-4 weeks	**Cotrimoxazole**: unlicensed in diabetic foot. Monitoring: 2 weekly FBC and U's and E's See information sheet
Severe Borderline Admission (this regimen will be reviewed regularly as to whether admission is necessary)	Ceftriaxone 1-2g od IM **AND** Ciprofloxacin PO 500mg bd **AND** Metronidazole PO 400mg tds	**Penicillin Allergy** (NOT anaphylaxis or urticarial response to penicillins) Ceftriaxone 1-2g od IM **AND** Ciprofloxacin PO 750mg bd **AND** Metronidazole PO 400mg tds **In Severe Penicillin Allergy (history of anaphylaxis or urticaria occurring immediately after penicillin therapy) or if MRSA positive use** Ciprofloxacin PO 500mg bd **AND** Metronidazole PO 400mg tds **AND** Teicoplanin IM 800mg loading dose in clinic (given in 2 sites) then if <70kg 400mg od OR if ≥70kg 6mg/kg od	Teicoplanin IM 800mg loading dose in clinic (given in 2 sites) then <70kg 400mg od ≥70kg 6mg/kg od **AND** Ciprofloxacin PO 500mg bd **AND** Metronidazole PO 400mg tds	Review in <1 week Usual max 2 weeks in this category	Consider using 750mg bd ciprofloxacin instead of 500mg bd if bone involvement

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Table 2:cont.	First choice treatment	Second choice treatment Or alternatives (e.g. if penicillin allergic patient)	At high risk of MRSA or MRSA positive	Duration	Comments
Severe requiring admission	Piperacillin/Tazobactam IV 4.5g tds If polymicrobial infection suspected with MRSA add in IV vancomycin (dose as per Vancomycin policy)	**Penicillin Allergy:** Vancomycin IV (dose as per vancomycin policy) **AND** Metronidazole PO 400mg tds (only use IV if oral route not available) **AND** Ciprofloxacin PO 750mg bd	Vancomycin IV (dose as per vancomycin policy) **AND** Metronidazole PO 400mg tds (only use IV if oral route not available) **AND** Ciprofloxacin PO 750mg bd (only use IV if oral route not available)	Regular review on diabetic foot round. IVs usually for 5-7 days after which review whether to step down to oral. Initial treatment duration usually 2-4 weeks (IV and oral course together)	Oral treatment should be guided by microbiology results, if none available consider Co-amoxiclav PO 625mg **OR** In penicillin allergy Ciprofloxacin PO 750mg **AND** Clindamycin PO 450mg qds
Osteomyelitis Inpatient Treatment	Piperacillin/Tazobactam IV 4.5g tds	Vancomycin IV dosed as per Trust policy **AND** Ciprofloxacin PO 750mg bd **AND** Metronidazole PO 400mg tds (only use IV if oral route not available) If patient to be discharged to NNUH @ Home / OPAT switch Vancomycin to Teicoplanin prior to discharge. Teicoplanin IV 10mg/kg every 12 hours for 3 doses then 10mg/kg IV od (round dose to nearest 100mg) .	Piperacillin/Tazobactam IV 4.5g tds **AND** Vancomycin IV dosed as per Trust policy In penicillin allergy use treatment option in 2nd choice column If patient to be discharged to NNUH @ Home / OPAT switch Vancomycin to Teicoplanin prior to discharge. Teicoplanin IV 10mg/kg every 12 hours for 3 doses then 10mg/kg IV od (round dose to nearest 100mg)	Total therapy usually 4-6 weeks, minimum of 2 weeks of IV antibiotics usually required. Oral depending on progress, senior doctor to review.	**PLEASE CONSIDER OPAT** **Monitoring:** Weekly LFTs, serum Cr, CRP, ESR and WBC **Teicoplanin levels.** Target trough level at 3-5 days, then once a week during maintenance Therapeutic Range: 20mg/L-60mg/L

Table 2:cont.	First choice treatment	Second choice treatment Or alternatives (e.g. if penicillin allergic patient)	At high risk of MRSA or MRSA positive	Duration	Comments
Osteomyelitis outpatient	Co-amoxiclav PO 625mg tds If no evidence of healing after 2-4 weeks review culture and sensitivities and substitute with sodium fusidate + a second agent which organism known to be sensitive to.	Clindamycin PO 450mg qds Consider stopping Clindamycin and switching to Ciprofloxacin PO 750mg bd **AND** Metronidazole PO 400mg tds if a gram negative organism identified or no evidence of improvement after 4 weeks	**Prescribe according to sensitivities.** Doxycycline PO 200mg STAT then 100mg bd **OR** combination of 2 of the following oral antibiotics trimethoprim po 200mg bd, rifampicin po 600mg bd, fusidic acid po 500mg tds. (Fusidic acid not to be used in combination with rifampicin).	6 weeks – 3 months	Sodium fusidate may cause an elevation of liver function tests (LFTs). Perform LFTs at baseline and then every 2 weeks during treatment for the first month. After this time according to clinical judgement – minimum requirement is every 4 weeks throughout treatment
OPAT (link to trust guideline, OPAT bone and joint)	Teicoplanin IV 10mg/kg every 12 hours for 3 doses then 10mg/kg IV od (round dose to nearest 100mg) AND If gram negative suspected add ciprofloxacin PO 750 mg bd If anaerobe suspected add Metronidazole PO 400mg tds				**Monitoring:** Weekly LFTs, serum Creatinine, CRP, ESR and WBC **Teicoplanin levels**. Target trough level at 3-5 days, then once a week during maintenance Therapeutic Range: >20mg/L-60mg/L

Notes:

- IM antibiotics should only be given where there are appropriate facilities available to treat anaphylaxis. Ceftriaxone 2g IM should be given as two separate 1g injections in different sites.

- Co-amoxiclav may cause cholestatic jaundice if use is prolonged, especially in patients over 65 years. If treatment continues over 2 weeks liver function tests (LFTs) should be carried out fortnightly for the first month and then monthly from then on for the duration of treatment.

- Cholestatic jaundice may occur up to 6 weeks after treatment is stopped.

- If macrolide resistant the organism is likely to be resistant to clindamycin unless sensitivities show otherwise.
- Sodium fusidate may cause an elevation of liver function tests (LFTs). Perform LFTs at baseline and then every 2 weeks during treatment for the first month. After this time according to clinical judgement – minimum requirement is every 4 weeks throughout treatment

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Co-trimoxazole Information Sheet: For use by prescribers in the Diabetic Foot Clinic

This sheet is to be used as a guide to prescribing co-trimoxazole and is not exhaustive. For further information consult the BNF.

Indications:
Co-trimoxazole PO 960mg bd as a 2nd line treatment in patients with mild to moderate diabetic foot infection according to policy.

Contra-indications
- Co-trimoxazole should not be given to patients with a history of hypersensitivity to sulphonamides, trimethoprim, co-trimoxazole or any excipients of Co-trimoxazole
- Patient on methotrexate
- Severe liver disease
- Reduce dose by 50% if eGFR 15mL/minute to 30mL/ minute, if eGFR <15 avoid or discuss with pharmacy
- Patients with acute porphyria

Cautions
- Patients with asthma or severe allergies
- Avoid in patients with blood disorders
- Elderly – increased risk of serious side effects
- G6PD deficiency (risk of haemolytic anaemia)
- Pts who can't maintain adequate fluid intake
- Pts with a predisposition to folate deficiency or hyperkalaemia

Special Monitoring Requirements
2 weekly FBC and U's and E's
Reduce dose if patients Creatinine Clearance is <30mL/min

Side effects
Commons/Very common: Diarrhoea, headache, hyperkalaemia, nausea, rash
Uncommon: Vomiting
Rare: Agranulocytosis, bone marrow depression, hypoglycaemia and several others – consult BNF for full list
Co-trimoxazole is associated with rare but serious side effects. Discontinue immediately if blood disorders (including leukopenia, thrombocytopenia, megaloblastic anaemia, eosinophilia) or rash (including Stevens- Johnson syndrome, toxic epidermal necrolysis, photosensitivity) develop.

Interactions: consult the BNF for full lists under Trimethoprim and Sulfamethoxazole
Zidovudine, Lamivudine, Dapsone, Ciclosporin, Rifampicin, Pyrimethamine, Warfarin (monitor INR carefully)
Phenytoin, Repaglinide, Digoxin or Amiodarone, Methotrexate, Azathioprine, Mercaptopurine
Caution should be exercised in patients taking any other drugs that can cause hyperkalaemia.e.g ACE inhibitors, Angiotensin 2 antagonists

Counselling Points
Take co-trimoxazole with food or drink. This will help prevent nausea and diarrhoea.
Although it's better to take with food you can take on an empty stomach.
Drink plenty of fluids when taking co-trimoxazole
Discontinue immediately if rash develops (including Stevens-Johnsons syndrome, toxic epidermal necrolysis, photosensitivity). This can develop initially as reddish target- like spots or circular patches often with central blisters on the trunk. Additional signs to look for include ulcers in the mouth, throat, nose, genitals and conjunctivitis (red and swollen eyes). The highest risk for occurrence of serious skin reactions is within the first weeks of treatment. If patient develops a rash or these skin symptoms, stop taking Co-Trimoxazole, seek urgent advice from a doctor and tell them that you are taking co-trimoxazole

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Guidance Notes

1. Prescribing in Penicillin allergy:

- Patients with a history of anaphylaxis or urticaria occurring immediately after penicillin therapy are at increased risk of immediate hypersensitivity to penicillins and should not receive treatment with a beta-lactam antibiotic (this includes cephalosporins) or carbapenem, unless they have previously received a beta-lactam and had no adverse effects.
- Patients with a history of rash occurring more than 72 hours after administration of penicillins are probably not allergic to penicillins, (SIGN, 2000) and many patients with a history of rash after penicillins will have received cephalosporins with no ill effect. For patients who do NOT report an anaphylactic or urticarial response to penicillin, a cephalosporin may be administered with caution.

Please note that penicillins include amoxicillin, co-amoxiclav (Augmentin®), flucloxacillin, Tazocin®.

2. Prescribing of Ciprofloxacin/Cephalosporins/Clindamycin

- Ciprofloxacin, cephalosporins and clindamycin are currently considered to be high risk of precipitating Clostridioides difficile infection and should only be used where specifically recommended below.
    - **Please counsel patients to stop antibiotics immediately and to contact their doctor if diarrhoea develops.**

3. MRSA Infection

If MRSA is suspected and it is thought that the infection is polymicrobial then see quick reference guide. Vancomycin should be prescribed with caution in renal impairment. See trust guidelines for the prescribing and monitoring of vancomycin available on the trust intranet under the microbiology section (Vancomycin and Teicoplanin in Adults Trustdocs id 1192

4. Duration of Treatment

The treatment lengths specified are a guide only. It may be necessary to continue the course longer than is specified. Clindamycin should normally be used for no longer than 4 weeks due to the risk of C.diff diarrhoea.

5. Treatment of Moderate Infection extending to underlying soft tissue/bone

Ciprofloxacin can be added in to either co-amoxiclav or clindamycin ONLY if the patient has one or more of the following.

- Ulcer that is macerated because of soaking
- Long duration non healing wounds with prolonged, broad spectrum antibiotic therapy or two or more previous courses of co-amoxiclav or clindamycin as a single agent
- 'Fetid foot': extensive necrosis or gangrene, malodorous

See notes above regarding C.difficile. Only use ciprofloxacin in combination with clindamycin with the utmost care and the patient should be counselled as in guidance point 2. Review regularly and stop antibiotics as soon as possible.

6. Osteomyelitis

Diagnosis

Spread of infection to bone (osteomyelitis) may be difficult to distinguish from non-infectious osteoarthropathy. Clinical examination (e.g. presence of visible bone and bone fragments) and imaging tests may suffice. The presence of a red, swollen 'sausage' shaped digit is suggestive of osteomyelitis, but can be the result of other foot problems (e.g. fracture). The probe to bone test can be used as a screening test although it is not entirely reliable. Do not exclude osteomyelitis based on a negative probe to bone test alone. Often therapy is initiated for suspected osteomyelitis on the basis of these tests while awaiting confirmation.

X –ray is the usual initial investigation on choice. However it can take 2 weeks before any changes of acute osteomyelitis are seen on plain radiograph and thus serial X-rays may be required to rule out osteomyelitis. Do not exclude osteomyelitis on the basis of X-rays alone. If you suspect osteomyelitis but the initial X-ray was not diagnostic, carry out magnetic resonance imaging (MRI) or white blood cell scanning if MRI is contraindicated. Do not delay starting therapy for suspected osteomyelitis pending MRI results.

Bone biopsy is sometimes used for defining the pathogenic organism(s) and for determining the antibiotic susceptibilities of such organisms.

If there is diagnostic uncertainty then it is advisable to refer to the Diabetic Foot Clinic or In Patient Foot Team.

Duration of treatment

Usually 4-6 weeks treatment if required for osteomyelitis but the final duration will depend on presence of infected bone. The course may be shorter if the entire infected bone is removed or longer if not. The length of treatment could be 10-12 weeks but this decision will be made by the Diabetic Foot Clinic.

MRSA

If MRSA is isolated treat as per sensitivities. Discuss with microbiology if guidance is needed.

Surgical Intervention

Refer for a surgical opinion if deteriorating despite antibiotics or if not healed after a 12 week course.

Following debridement/amputation, antibiotics could be stopped after 48 hours if the surgeon is satisfied that all infected tissue has been removed. If there is residual infection then this should be treated according to the protocol taking into account the results of any microbiology specimens sent from theatre.

7. Follow up

Careful observation of the patient's response to therapy is essential and should be performed daily for inpatients. Appropriate follow up should be arranged for outpatients, usually within a week either at the diabetic foot clinic or by a member of the primary care team. Review the culture and drug susceptibility results and inquire about any adverse effects related to the current antibiotic therapy. Choose a definitive antibiotic regimen on the basis of the results of cultures, imaging or other investigations and the initial clinical response. It is not always necessary to cover all microorganisms isolated from cultures. For further advice contact a medical microbiologist.