Clinical Guideline No: CG304

Diabetic Foot Infections: Antibiotic Management Clinical Guideline

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Government of South Australia

SA Health

Disclaimer

This statewide guideline has been prepared to promote and facilitate standardisation and consistency of practice, using a multidisciplinary approach. The guideline is based on a review of published evidence and expert opinion, with consideration to antibiotic resistance epidemiology in South Australia. In facilities where the prevalence of multi-resistant organisms may differ, local hospital guidelines may take precedence. Health practitioners in the South Australian public health sector are expected to review specific details of each patient and professionally assess the applicability of the relevant guideline to that clinical situation. If for good clinical reasons, a decision is made to depart from the guideline, the responsible clinician must document in the patient's medical record, the decision made, by whom and detailed reasons for the departure from the guideline.

This statewide guideline does not address all the elements of clinical practice and assumes that the individual clinicians are responsible for:

- Discussing care with consumers in an environment that is culturally appropriate and which enables respectful confidential discussion. This includes the use of interpreter services where necessary,
- Advising consumers of their choice and ensure informed consent is obtained.
- Providing care within scope of practice, meeting all legislative requirements and maintaining standards of professional conduct and
- Documenting all care in accordance with mandatory and local requirements.

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Contents

1. Introduction

Diabetic foot infections are associated with substantial morbidity, with an increased risk of amputation or mortality [1]. Foot ulceration in a diabetic patient is serious and needs to be managed immediately.

The aim of this guideline is to assist prescribers in the choice of appropriate empiric antibiotic therapy based on the assessment of the severity of foot infections and the likely pathogens involved. The duration of antibiotic therapy and the need for surgical intervention is dependent upon the extent of tissue or bone involvement and the response to treatment.

Key stewardship points

- Avoid using piperacillin / tazobactam in all diabetic foot infections. Reserve for patients with risk factors for *Pseudomonas aeruginosa*, or severe infection where IV amoxicillin / clavulanic acid is not available. Indiscriminate use of piperacillin / tazobactam may result in the development of resistant *Pseudomonas*.
- In mild to moderate infection with no recent antibiotic treatment, target Gram-positive cocci, especially *Staphylococci*. Add metronidazole if anaerobes suspected clinically (unless using clindamycin).
- Ceftriaxone is **not** a drug of choice for diabetic foot infections. Ceftriaxone does not adequately cover *Staphylococci*. Inappropriate use of third- generation cephalosporins increases the risk of multi-drug resistant organisms.
- If unsure of antibiotic choice, seek ID/micro advice

2. Background and aetiology

In 2014-2015, an estimated 1.2 million (6%) of Australian adults aged 18 years and over were known to have diabetes (type 1 and type 2 diabetes) [2]. Approximately 15% of people with diabetes will have a foot ulcer during their life with an annual incidence of 1% to 4% [3, 4]. Foot ulceration is the leading cause of hospitalisation for people with diabetes, and diabetes is the most common cause of non-traumatic lower-limb amputation [4]. In 2012-2013 in Australia, there were 3570 lower limb amputations performed in hospital to patients with a diagnosis of diabetes [5]. Five-year survival for patients with diabetes who have had limb amputation is poor, with mortality rates ranging from 39 to 80%[6].

Poor glycaemic control, peripheral vascular disease and neuropathy are risk factors for diabetic foot infections [7] . Patients with sensory neuropathy have reduced awareness of pain and temperature associated with foot injury or infection. Healing of ulcers and infections is impaired in peripheral vascular disease due to impaired blood flow to the tissues. Hyperglycaemia impairs neutrophil function and immune response to infection.

The likely pathogens vary depending on the extent of the foot wound. See under Choice of antibiotic therapy for further discussion on the likely microorganisms.

3. Abbreviations / Acronyms

ABI	Ankle-brachial index
AMH	Australian Medicines Handbook©
BD	Twice daily
CLI	Critical limb ischaemia
CNA	Charcot's neuroarthropathy
CrCl	Creatinine clearance
CRP	C-reactive protein
DFI	Diabetic foot infection
DKD	Diabetes-related kidney disease
DRESS	Drug reaction with eosinophilia and systemic symptoms
eGFR	Estimated glomerular filtration rate
ESR	Erythrocyte sedimentation rate
HbA1c	Glycosylated haemoglobin
IBW	Ideal body weight
ID	Infectious Disease
IDSA	Infectious Diseases Society of America
LFTs	Liver function tests
MC&S	Microscopy, culture and sensitivities
MSSA	Methicillin-sensitive *Staphylococcus aureus*
MRSA	Methicillin-resistant Staphylococcus aureus
PAD	Peripheral artery disease
PEDIS	Perfusion, Extent, Depth, Infection and Sensation
PBT	Probe-to-bone test
QID	Four times a day
SeCr	Serum creatinine
SIRS	Systemic inflammatory response signs
SJS	Stevens Johnson Syndrome
TEN	Toxic EpidermalNecrolysis
TDS	Three times daily
TMA	Transmetatarsal amputation
TP	Toe pressure
$TcPO_2$	Transcutaneous oxygen tension
WIFI	Wound ischaemia and foot infection

4. Examination, investigations and assessment of severity

Determining the severity of a foot infection includes evaluation of the depth and extent of the tissues involved, determining the adequacy of arterial perfusion and possible need for revascularisation, and assessing for systemic toxicity [1, 8]. The PEDIS classification system developed by the Infectious Diseases Society of America (IDSA) and the International Working Group on the Diabetic Foot (IWGDF) for defining the presence and severity of an infection of the foot in a person with diabetes is provided in table 1 in the appendix of this document [9].

In patients with mild infection, wound culture is usually not required. In moderate to severe infection, wound cultures can be helpful, especially if there is a high risk of multi-drug resistant organisms. Ideally wound cultures should be obtained prior to initiating antibiotics however if systemic symptoms are present empirical antibiotics should not be delayed for wound culture. The preferred specimens for culture include aspirate from an abscess or curettage from the ulcer base following debridement of necrotic tissue [10]. Wound culture of infected ulcers is useful in detecting multi-resistant organisms, especially if there is a poor response to empiric therapy [1].

Although soft-tissue infection may be clinically obvious, the diagnosis of osteitis / osteomyelitis underlying a diabetic foot ulcer may be challenging. The risk of osteitis / osteomyelitis in foot wounds in diabetic patients is increased if bone is visible or able to be probed, if the ulcer is greater than $2cm^2$, the duration of ulceration is longer than 1-2 weeks or if the ESR >70mm/h [11]. Conventional X-ray can detect destructive bone changes, however the sensitivity of X-ray for diagnosis of osteomyelitis is variable [11]. Nuclear medicine scans can detect increased blood flow and inflammatory activity in the bone, with a reported sensitivity for osteomyelitis of 80-90%, however specificity is less than 50% because they cannot distinguish for other conditions such as arthritis, fracture or recent trauma or surgery [12]. MRI is the most sensitive imaging modality for osteomyelitis and is indicated if the diagnosis remains uncertain after conventional X-ray [1].

5. Choice of antibiotic therapy

The choice of empiric antibiotic therapy should be based on the severity of infection and the likely pathogens involved. Most diabetic foot infections are polymicrobial and the likely organisms vary depending upon the extent of the foot wound. Acute infection in a previously untreated patient is usually caused by aerobic Gram-positive cocci, but deeper or chronic wounds are commonly polymicrobial including aerobic Gram-negative and obligate anaerobic bacteria [1].

Antibiotics should not be used for *uninfected* skin wounds as there is no published evidence that antibiotics hasten healing of the wound, and unnecessary use of antibiotics increases the risk of antibiotic resistance [13].

There are limited published data comparing outcomes of various antibiotic treatment regimens, however empiric therapy should be decided on the basis of the assessment of wound severity and the likely organisms involved, with modification to a narrower spectrum of cover according to culture and sensitivity results [14].

Empiric treatment of an infected ulcer must cover Gram-positive cocci, however patients who have recently been treated with antibiotics should have broader spectrum treatment to cover Gram-negative bacilli [1]. The choice of empiric antibiotic treatment must take into consideration any previous history of β-lactam allergy (see Appendix for treatment algorithm). In patients at higher risk for MRSA, such as those with a history of previous MRSA infection or known colonisation within the past year, intravenous vancomycin should be added while awaiting definitive cultures and sensitivity results. Recent hospitalisation or residence in a long-term care facility may also increase the risk of MRSA.

Empiric IV antibiotics are required for all patients with severe or systemic infections and for some moderate infections [1]. The dose and dosing interval needs to consider the severity of the infection and extent of vascular insufficiency to ensure sufficient drug levels at the site of infection [15]. Empiric treatment of severe infection involving deep tissues should be broad spectrum, covering streptococci, *S. aureus*, aerobic Gram-negative bacilli and anaerobes.

Failure to respond to empiric antibiotic therapy may be due to inadequate source control, antibiotic resistance (e.g. MRSA), reduced antibiotic concentration at the site of infection due to ischaemia or inadequate antimicrobial cover. *Pseudomonas aeruginosa* is an uncommon cause of diabetic foot infection and empiric cover of *P.aeruginosa* is usually not required [16]. However the risk of *Pseudomonas aeruginosa* involvement is increased in macerated ulcers, foot soaking and other exposure to water or moist environments. In addition, diabetic foot infections with *Pseudomonas spp.* have higher mortality rates [16, 17]. In patients with no history of penicillin allergy who fail to respond to non-pseudomonal antimicrobial therapy, or have a higher risk of *Pseudomonas* involvement, IV amoxicillin/clavulanic acid should be replaced with IV piperacillin/tazobactam. (Note: For patients at moderate or high risk of penicillin allergy, the recommended antibiotics for treatment of severe infection are anti-pseudomonal therefore no change to empiric therapy isrequired).

For diabetic patients with severe foot infection who also have a history suggestive of high risk beta-lactam allergy (e.g. anaphylaxis), the therapeutic options are limited. QT prolongation is a known risk with the use of fluoroquinolones, however a number of large population-based and cohort studies suggests that the risk of QT prolongation with ciprofloxacin is lower than with other fluoroquinolones [18, 19]. In patients with a history of QT prolongation, or concomitant use of other drugs associated with a risk of QT prolongation, ciprofloxacin should be used with caution.

The duration of intravenous treatment is dependent upon response (see *Duration of antibiotic therapy*). A switch from intravenous to oral therapy is appropriate once the patient's clinical condition has stabilised and the infection is responding to treatment.

6. Duration of antibiotic therapy

The duration of antibiotic therapy is dependent upon the clinical severity of infection, vascular supply and the response to treatment.

Although there is no high level evidence to inform the optimal duration of antibiotic therapy, for patients with mild infection 5-7 days of antibiotic therapy in conjunction with wound care, is usually adequate to resolve infection [1].

For patients requiring surgical debridement, IV antibiotics should be administered peri-operatively, and 2-4 weeks of antibiotic treatment post-operatively, switching from IV to oral when possible (see IV to oral switch clinical guideline)[1].

The duration of antibiotic treatment in osteitis / osteomyelitis depends on the extent of residual affected tissue after surgery, or if management is non-surgical. Following amputation, if all infected and necrotic bone and soft tissue has been resected with good surgical margins, a short course (2 to 5 days) may be sufficient [1]. Where there is residual infected bone following debridement of necrotic bone, four to six weeks of antibiotic treatment is appropriate. If residual necrotic bone remains, several months of antibiotic therapy may be required for clinical cure[1].

7. Other considerations regarding antibiotic therapy

Renal impairment

Renal impairment is common in diabetic patients, and increases with age. It is estimated that approximately a quarter of Australian adults with diabetes have diabetes-related kidney disease (DKD), defined as eGFR <60mL/min/1.73m^2 and/or persistent albuminuria or proteinuria [20]. Estimate the patient's creatinine clearance (CrCl) using the Cockroft-Gault equation (see appendix).

For dose adjustments in renal impairment or for patients on dialysis, consult the *Therapeutic Guidelines: Antibiotic*®. For vancomycin dosing in renal impairment, refer to Vancomycin dosing and monitoring clinical practice guideline.

8. Safety, quality and risk management

This guideline is in accordance with National Standard 3.15 and 3.16, implementing systems for safe and appropriate prescribing of antimicrobials as part of antimicrobial stewardship.

National Standard 1 Clinical Governance	National Standard 2 Partnering with Consumers	National Standard 3 Preventing & Controlling Healthcare Associated Infections	National Standard 4 Medication Safety	National Standard 5 Comprehensive Care	National Standard 6 Communicating for Safety	National Standard 7 Blood Management	National Standard 8 Recognising & Responding to Acute Deterioration
☐	☐	☒	☒	☐	☐	☐	☒

9. Appendices

Diabetic Foot Infection Antibiotic Management

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11. Document Ownership & History

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20/03/19	V1.0	Safety and Quality Strategic Governance Committee	Original Policy Document

Perform initial local and systemic clinical examination

Localexamination

- Ulcer – depth, size, necrotic tissue, callus, sinus, abscess
  - > Probe-to-bone with sterile blunt metal probe. Debridement of ischaemic wounds with necrosis should not be performed (refer for vascular surgery opinion)
  - > Although osteitis / osteomyelitis is highly likely if an ulcer can be probed to the bone, it may be present in the absence of such findings
- Signs of infection – localised swelling / induration, local warmth, erythema, local tenderness / pain, purulent discharge

Examination oflimb

- Arterial pulses, femoral bruits, capillary refill time, temperature of limb, signs of venous insufficiency
- Neuropathy – pressure (10g nylon monofilament), vibration (128Hz tuning fork), discrimination (pin prick), reflexes (ankle jerk)
- Structural changes / deformities – Charcot arthropathy, claw, hammer toes, biomechanical problems, pressure areas
- Gangrene of toes or proximal foot

Systemic examination

- Pulse rate, blood pressure, respiratory rate
  - > Fever, chills, hypotension, tachycardia indicates increased severity of infection

Social andpsychological

- For example, ability to self-care

Perform further investigations as appropriate

- Complete blood counts, HbA1c, LFTs, SeCr
- CRP, ESR
- Blood cultures (in moderate / severe infections)
- Diagnostic imaging:
  - > X-ray (for patients with suspected non-superficial DFI, particularly if ulcer present > 2 weeks)
  - > MRI (if abscess, osteitis/ osteomyelitis or Charcot's suspected, esp. if ulcer deep, chronic or overlying bony prominence)
  - > Bone scan or radio-labelled white cell scan (if MRI not possible)
- Toe Pressure, $TcPO_2$ (TP > 30mmHg & $TcPO_2$ > 25mmHg increases pre-test probability of healing by at least25%)
- Ankle-brachial index (N 0.9 – 1.3). If ABI > 1.3, exclude arterial calcification especially in the presence of peripheral neuropathy
- Colour Doppler or Digital subtraction angiogram (DSA) or CT angiogram (CTA) or MR angiogram (MRA) – consider when an ulcer doesn't heal in 6 weeks
- Deep tissue histology and MC&S – punch biopsy or curettage (soft tissue from base of debrided ulcer, or bone) after cleaning and debridement of wound (avoid superficial swabs of inadequately debrided wounds or sinus tracts) or aspirate any purulent secretions using sterile needle & syringe

Do not obtain repeat cultures unless evaluating non-response or for infection control surveillance

Determine severity of infection & commence empiric antibiotics

Determine severity of infection

The choice of empiric antibiotic therapy is guided by the PEDIS grade of infection severity:

Table 1: IDSA/PEDIS Classification of Infection Severity[9]

Classification manifestation of infection	PEDIS grade	Infection severity
No local signs of infection	1	Uninfected
Infection present, as defined by presence of at least 2 of the following: • Local swelling or induration • Erythema between 0.5-2cm around the ulcer • Local tenderness or pain • Local warmth or purulent discharge (thick, opaque to white sanguineous secretion)	2	Mild
Local infection with erythema > 2cm around the ulcer, or involving structures deeper than skin and subcutaneous tissues (e.g. bone, joint, tendon, muscle) **and NO** systemic signs or symptoms (see below)	3	Moderate
Local infection with 2 or more of the following systemic signs or symptoms: • Temperature >38°C or <36°C • Heart rate > 90 beats / min • Respiratory rate > 20 breaths / min or $PaCO_2$<32mmHg • White cell count < 4 x 10^9/L or > 12 x10^9/L	4	Severe

Empiric antibiotic therapy

SEVERITY OF INFECTION*	NO PENICILLIN / CEPHALOSPORIN ALLERGY	MODERATE RISK PENICILLIN ALLERGY (Delayed rash which is not urticarial or DRESS/SJS/TEN)	HIGH RISK PENICILLIN / CEPHALOSPORIN ALLERGY (History suggestive of high risk, e.g. anaphylaxis, urticaria, angioedema, bronchospasm, DRESS/SJS/TEN)
Ulceration (no infection)	*Antibiotics **not recommended***		
Mild infection (PEDIS grade 2)	**Flucloxacillin±* 1g orally QID**	**Cefalexin* 1g orally QID**	**Clindamycin 450mg orally TDS**
Moderate infection (PEDIS grade 3)	**Flucloxacillin* 2g IV 6-hourly PLUS Metronidazole 400mg orally BD** *Then step down to oral therapy:* **Flucloxacillin* 1g orally QID PLUS Metronidazole 400mg orally BD** *(Starting with oral therapy is acceptable)*	**Cefazolin* 2g IV 8-hourly PLUS Metronidazole 400mg orally BD** *Then step down to oral therapy based on response:* **Cefalexin* 1g orally QID PLUS Metronidazole 400mg orally BD**	**Clindamycin 450mg orally TDS**
Severe infection (PEDIS grade 4)	**Amoxicillin / Clavulanic acid*1.2g IV 6-hourly** *Or if IV amoxicillin / clavulanic acid unavailable,* use: **Piperacillin / tazobactam* 4.5g IV 8-hourly** *Once systemically improved, step down to oral therapy based on response & sensitivity results (Seek advice from ID)*	**Cefepime* 2g IV 8-hourly PLUS Metronidazole 400mg orally BD** *Once systemically improved, step down to oral therapy based on response & sensitivity results (Seek advice from ID)*	**Clindamycin 900mg IV 8-hourly (slow infusion) PLUS** **Ciprofloxacin*# 400mg IV 12-hourly *OR*** **Ciprofloxacin*# 750mg orally BD** *Once systemically improved, step down to oral therapy based on response & sensitivity results (Seek advice from ID)*

High risk for MRSA – i.e. history of previous MRSA infection or colonisation within the past year or the infection is sufficiently severe that failing to empirically cover MRSA while awaiting **definitive** cultures would pose an unacceptable risk of treatment failure:

→ **Add vancomycin and seek ID advice (ID approval required)**

Refer to *Vancomycin dosing and monitoring clinical practice guideline* for instructions on dose adjustment in renal impairment.

High risk of infection with Pseudomonas spp. – i.e. presence of ulcers with prolonged water exposure in patients who have failed therapy with non-pseudomonal agents:

→ **Replace IV amoxicillin / clavulanic acid with piperacillin/tazobactam 4.5g IV 6-hourly (ID approval required if > 72 hours) Note: Antibiotics recommended for severe infection in patients with beta-lactam allergies cover *Pseudomonas* therefore no change to empiric therapy required**

***Renal impairment**

For IV amoxicillin / clavulanate, CrCl 10-30mL/min: Use 1.2g 8 to 12 hourly; CrCl<10mL/min: Use 1.2g 12 hourly

For all other antibiotics, refer to *Therapeutic Guidelines: Antibiotic* for dosing adjustment in renal impairment.

Ciprofloxacin should be used with caution in patients with a history of QT prolongation, or if taking other medication known to increase the risk of QT prolongation. In patients with *severe* infection **and** high risk penicillin allergy **and** higher risk for QT prolongation, seek advice from ID/micro

Key stewardship points

- Avoid using piperacillin / tazobactam in all diabetic foot infections. Reserve for patients with risk factors for *Pseudomonas aeruginosa, or* severe infection where IV amoxicillin / clavulanic acid is not available. Indiscriminate use of piperacillin / tazobactam may result in the development of resistant *Pseudomonas*.
- Mild to moderate infection with no recent antibiotic treatment → target Gram-positive cocci, especially *Staphylococci.* Add metronidazole if anaerobes suspected clinically (unless using clindamycin).
- Ceftriaxone is **not** a drug of choice for diabetic foot infections. Ceftriaxone does not adequately cover *Staphylococci*. Inappropriate use of third-generation cephalosporins increases the risk of multi-drug resistant organisms.
- If unsure of antibiotic choice, seek ID/micro advice.

Assess criteria for surgery

Bone / joint involvement should be suspected when:

1. Infection is severe
2. Toe is erythematous and swollen (dactyllitis)
3. Bone is exposed
4. Probe-to-bone test (PBT) is positive
5. Ulcer lies over bony prominence
6. Ulcer fails to heal or respond as expected despite off-loading

Classification for surgery:

- Emergency – severe infections / moderate infections with gas or pus in the deeper tissues / necrotising fasciitis / compartment syndrome
- Urgent – in cases of osteomyelitis with spreading soft tissue infection, destroyed soft tissue envelope, protruding bone through ulcer and progressive body destruction

Surgical options:

- Debridement / drainage of deep abscess / decompression of foot compartment to minimize necrosis
- Amputation of digits
- Amputation of foot or leg

Consider revascularisation for non-healing ulcer with ankle pressure < 50mmHg or ABI < 0.5 / critical limb ischaemia (CLI)

Duration of antibiotic therapy

The duration of antibiotic therapy should be adjusted according to response and extent of vascular insufficiency.

No bone involvement	
Mild	5 to 7 days
Moderate	2 weeks of oral antibiotics (or initial IV antibiotics). Can extend if slow to resolve.
Severe	2 to 4 weeks (IV initially, followed by oral antibiotics), dependent on response
Bone / Joint involvement	
No surgery; or Surgery with residual dead bone post-operatively	Initial IV therapy for 2 to 4 weeks followed by oral antibiotics (depending on extent of residual infection & vascular supply). Expected total duration: Approximately 6 weeks if satisfactory response. Needs review at 6 weeks – duration may be extended if unsatisfactory response
Surgery with residual infected but viable bone	2 to 4 weeks of IV therapy, followed by oral antibiotics. Will need at least 6 weeks of antibiotic therapy
Surgery with residual infected tissues but no infected bone	1 to 3 weeks of oral or IV antibiotics, depending on clinical response
Amputation with no residual infected tissue and good surgical margins	2 to 5 days of IV antibiotics – cease all antimicrobials if wound is healing well with no ongoing evidence of infection

Review antibiotics with culture results & change to narrow spectrum antibiotics when microbiology results available. Refer to IV to Oral Antibiotic Switch Guideline . Consider broadening cover if no response. Cease antibiotic when clinical signs of infection are resolved (not necessary to continue until wound has healed).

Renal impairment

For antibiotic dose adjustments in renal impairment, refer to the AMH or Therapeutic Guidelines: Antibiotic. For vancomycin dose adjustments in renal impairment, refer to the Vancomycin dosing and monitoring clinical practice guideline.

Estimate creatinine clearance (CrCl) using the Cockcroft-Gault equation:

Ideal body weight estimation table

Feet & inches	Cm	IBW (female)	IBW (male)
5'1	155	48	53
5'3	160	53	57
5'5	165	57	62
5'7	170	62	66
5'9	175	66	71
5'11	180	71	76
6'0	183	73	78
6'2	188	78	82
6'4	193	82	87

IBW (female) = 45.5kg + 0.9kg per cm over 152cm

IBW (male) = 50kg + 0.9kg per cm over 152cm

$$\text{CrCl (mL/min)} = \frac{\textbf{(140-age) x IBW (kg)}^{\wedge}}{\textbf{0.815 x SeCr (micromol/L)}} \times 0.85 \text{ (for female patients)}$$

^ Use Actual Body Weight (ABW) if this is LESS than IBW

If obese (ABW is ≥ 30% above IBW or BMI > 30kg/m2), consider using adjusted body weight (AdjBW) to calculate creatinine clearance[21]:

AdjBW = IBW + 0.4 x (ABW-IBW)