Use of antibiotics in people with diabetic foot disease: A consensus statement

Article points

- Narrow spectrum

 antibiotics should be used
 where possible to reduce
 the risk of meticillin
 resistant Staphylococcus
 aureus and Clostridium
 difficile infection.
- 2. The choice of antibiotic agent, and route of delivery used, in the treatment of the infected diabetic foot should reflect the severity of the infection.
- Initial treatment of infection of the diabetic foot is frequently based on targeting the pathogen presumed involved.
- 4. This guidance assists healthcare professionals treating the infected diabetic foot until microbiological investigations and clinical response shed further light on the nature of the infection.

Key words:

- Antibiotic guidance
- Consensus statement
- Diabetic foot disease
- Infection

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The authors, on behalf of the Scottish Diabetes Group and the Scottish Infectious Diseases Society, provide broad, practical guidance on the use of antibiotics in people with diabetic foot disease complicated by infection. Recommendations on the most appropriate investigative techniques, antibiotics and likely infecting organisms are provided. This guidance is dependent on local microbiological epidemiology and susceptibility patterns, and prescribing guidelines, and the authors encourage all those managing infection in the diabetic foot to seek local specialist infection advice, where necessary, on the use of antibiotics.

he following guidance aims to help healthcare professionals make decisions about antibiotic agents for the treatment of the infected diabetic foot in order to improve patient outcomes.

This is a consensus document based on limited available clinical trial evidence, review of international guidelines and expert opinion. There may be circumstances where alternative courses of action are appropriate. Guidance about antibiotic choice is dependent on local microbiological epidemiology and susceptibility patterns. However, the consensus group felt that the pathogens causing various diabetic foot infections in Scotland are unlikely to vary substantially within Scotland. Therefore, merit was seen in providing broad, practical guidance on antibiotic choice, subject to local adaptation when necessary.

General approach to diabetic foot ulcer management

The multidisciplinary team

Diabetic foot ulcers should be treated by a multidisciplinary footcare team as this managment strategy has been shown to reduce amputation rates. In addition, attention to aggressive treatment of macrovascular risk factors in people with diabetic foot ulcers has been shown to prolong survival.

Re-ulceration

Previous ulceration is the strongest predictor for recurrent ulceration and preventative measures need to be addressed following healing. Re-ulceration rates of up to 70% at 5 years have been reported.

Specimens for culture

There is some debate over when a culture is necessary. Clinically uninfected ulcers rarely need to be cultured. An acutely infected wound of mild or moderate severity in a person who has not recently been treated with antibiotics does not need to be cultured. Other wounds should almost always be cultured. If a specimen is not taken at presentation of clinical signs, then cultures should be taken if there is clinical failure of empirical antibiotics.

Aspiration of purulent secretions, curettage of the post-debridement wound base, punch biopsy and extruded or biopsied bone are the best specimens for culture.

Diagnosing bone infection

Inability to touch bone when probing a wound with a sterile metal probe makes osteomyelitis unlikely, with a negative predictive value of approximately 90% (Jeffcoate and Lipsky, 2004). The positive predictive value of a positive probe-to-bone test is around 50%, meaning that half of all ulcers that probe to bone do not have osteomyelitis (Jeffcoate and Lipsky, 2004).

If there is clinical suspicion of osteomyelitis plain X-ray is the usual initial investigation of 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. If there is

- If you suspect
 osteomyelitis, plain
 X-ray is the usual initial
 investigation of choice.
- The presence and severity of infection should be classified according to one of the recognised systems.
- Antibiotic choice is dependent on local microbiological susceptibility and epidemiology.
- 4. Initial antibiotic treatment is frequently empirical, based on the presumed pathogen.
- 5. In light of international concerns over *Clostridium difficile* and meticillinresistant *Staphylococcus aureus*, narrow-spectrum antibiotic therapy should be used wherever possible.

ongoing concern of osteomyelitis and it cannot be diagnosed using X-ray, secondary investigations of choice are (in order of preference):

- Magnetic resonance imaging (MRI).
- Isotope white cell scan.
- Triple phase bone scan (highly sensitive at diagnosing osteomyelitis, but is not specific, and can remain positive for >1 year).

Imaging options may be dictated by the local availability of imaging equipment.

Loose bone

Loose bone extruded from an ulcer, or any bone debrided, should be sent for bone culture and microbiological assessment. The extrusion of a bone fragment (sequestrum) is highly suggestive of underlying osteomyelitis, although the infection may have arrested coincident to the passage of the sequestrum.

"Sausage" digit

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).

Differential diagnosis

Differentiating between osteomyelitis and Charcot foot can be difficult. Diagnosis is based on a good history and physical examination, and is assisted by obtaining supplementary investigations such as X-ray, MRI, and possibly isotope white cell and triple phase bone scans. It is important to note that osteomyelitis and Charcot foot frequently occur simultaneously. Osteomyelitis most often affects the forefoot and heel, while Charcot neuroarthropathy usually affects the forefoot or ankle.

Prophylactic antibiotic use

Antibiotics should be used only in those who have clinical signs of infection (i.e. "mild", "moderate" or "severe" in the Infectious Disease Society of America [IDSA] infection grading system; see *Table 1*).

Foot ulcer classification

Various ulcer classification schemes are used. The primary ones are the Wagner score (Wagner, 1981), the University of Texas system (Lavery et al, 1996), the SINBAD (Site, Ischaemia,

Neuropathy, Bacterial Infection, and Depth) score (Ince et al, 2008), the PEDIS (Perfusion, Extent/size, Depth/tissue loss, Infection, Sensation) score (Schaper, 2004). The Scottish Care Information – Diabetes Collaboration electronic ulcer management programme is based on the Texas classification system.

Classification of infection

It is recommended that the presence and severity of infection be classified according to the IDSA system (*Table 1*) or the PEDIS system developed by the International Working Group for the Diabetic Foot.

General principles of antibiotic use

Antibiotic choice is primarily dependent on causative pathogens and epidemiology. However, treatment with antibiotics often needs to be commenced before culture and sensitivity results are available. Thus initial therapy is usually empirical, and based on the local epidemiological information and local susceptibility data. As the pathogens in diabetic foot infections do not vary significantly in different parts of Scotland, the authors offer practical guidance on antibiotic use. These recommendations are, however, subject to circumstances related to local epidemiology and prescribing policy. Direct contact with local specialists may be necessary for advice on specialised use of these, or other, antibiotics.

Initial antibiotic treatment is frequently empirical, based on the presumed pathogen (Table 2). This guidance is of value until microbiological investigations and clinical response shed further light on the nature of the infection, where available. In light of international concern over Clostridium difficile infection associated with certain antibiotics (especially clindamycin, co-amoxiclay, cephalosporins and quinolones) and the risk of meticillinresistant Staphylococcus aureus (MRSA) infection (associated with co-amoxiclay, cephalosporins, quinolones and macrolides), narrow-spectrum antibiotic therapy should be used wherever possible. C. difficile is a particular risk for people aged >65 years and for inpatients. Adjustment of therapy based on microbiology results, when available and clinical response to

- 1. This guidance is categorised by the severity of infection, and by whether the person is, or is not, antibiotic-naïve.
- Mild infections of the diabetic foot in an antibiotic-naïve person are likely to be caused by *Staphylococcus aureus* or beta-haemolytic streptococci.
- 3. A microbiological culture should be taken if the presence of an unusual organism is suspected, or if initial treatment fails, in a mild infection.

empirical therapy is important in the management of these risks.

The choice of antibiotic and the route of delivery should reflect the severity of infection (*Table 1*). Duration of antibiotic treatment should be adjusted according to the severity of infection and should be guided by monitoring clinical improvement. In general, the duration of antibiotic therapy should be kept to a minimum. Antibiotic therapy is used only to treat evidence of infection, not to heal a wound, which typically takes much longer.

Allergies to antibiotics include skin rashes and anaphylaxis, but do not include minor side-effects such as nausea.

Enterococci, Pseudomonas and anaerobes are frequently isolated from diabetic foot wounds, but often represent colonising, rather than infecting, organisms. If, however, there is a chronic, persisting infection, or they are the predominant organisms, they may represent pathogens and need targeted treatment.

Table 1. Grading the severity of diabetic foot infection (based on the Infectious Disease Society of America classification system; Lipsky et al, 2004)

GRADE 1 NO INFECTION

No purulence or signs of infection.

GRADE 2 MILD INFECTION

No systemic illness and evidence of either: (a) pus (purulent secretions) or (b) two or more signs or symptoms of inflammation (i.e. erythema, warmth, pain, tenderness, induration). Any cellulitis <2 cm around the wound. Infection is confined to the skin or subcutaneous tissue. No evidence of systemic infection.

GRADE 3 MODERATE INFECTION

Either: (a) lymphatic streaking, deep tissue infection (involving subcutaneous tissue, fascia, tendon, bone) or abscess, or (b) cellulitis >2 cm. No evidence of systemic infection.

GRADE 4 SEVERE INFECTION

Any infection accompanied by systemic toxicity (fever, chills, shock, vomiting, confusion, metabolic instability). The presence of critical ischaemia of the involved limb may make the infection severe.

Specific antibiotic guidance

Specific clinical symptoms identified during careful examination shed light on the likely microbiology of a diabetic foot ulcer. From the likely pathology, initial antibiotic therapy can be decided on with some degree of confidence – although there will on occasion be circumstances suggesting different selections. We emphasise the importance of getting good quality specimens (see page 64 for a guidance on specimens for culture) for microbiological investigation, and close liaison with local infection specialists.

This guidance is categorised by the severity of infection, and by whether the person is, or is not, antibiotic-naïve. The primary choice of antibiotic, and alternatives, for use in people with diabetic foot infections are provided and discussed. A summary of the guidance is provided in *Table 3*.

Mild infection (IDSA) or PEDIS 2 in an antibiotic-naïve person

Likely pathogens

- *S. aureus* (and sometimes coagulase-negative staphylococci) or beta-haemolytic streptococci.
- If the person has recently been treated with antibiotics, enterococci and gram-negative rods are more likely to be present.

Note

▶ Take a microbiological culture if the presence of an unusual organism is suspected, or if initial treatment fails.

Antibiotics

Primary

- Oral flucloxacillin 1 g four times a day (qds).
 - Assuming that the first course of flucloxacillin was given in high dose and for a full 5–7 days, a second course is rarely effective if the first was unsuccessful.
 - There is an increased prevalence of resistant organisms after the first exposure to flucloxacillin.

Oral alternatives

- Doxycyline 100 mg twice a day (bd), or
- Clindamycin 300–450 mg qds, if the person is allergic to, or intolerant of, flucloxacillin.

- 1. A good quality microbiological culture is particularly helpful.
- 2. People with chronic infections, especially if they have received antibiotics previously, often have polymicrobial infections, including aerobic gram-negative bacilli among the flora.

Treatment duration

► Treat for 5–7 days. Adjust therapy in light of clinical response and microbiological culture and sensitivity results.

Moderate infection (IDSA) or PEDIS 3 in an antibiotic-naïve person

Likely pathogens

- S. aureus or beta-haemolytic streptococci.
- Obligate anaerobes are often associated with limb ischaemia, gangrene, necrosis or wound odour and must also be addressed.

Note

► A good quality microbiological culture can be particularly helpful in this circumstance. See page 63 for guidance on specimens for culture.

Antibiotics

Primary

- Oral flucloxacillin 1 g qds, or
- Intravenous (IV) flucloxacillin 1 g qds.

Oral alternatives

- Co-trimoxazole 960 mg bd, or
- Co-amoxiclav 625 mg three times a day (tds).

Allergic to penicillins

- Clindamycin (oral, 300–450 mg qds;IV, 450–600 mg qds), or
- Co-trimoxazole 960 mg bd.

Addition

• Add oral metronidazole 400 mg tds if anaerobes are suspected (unless using clindamycin, which has anaerobic cover).

Moderate infection (IDSA) or PEDIS 3 in a person who is not antibiotic-naïve

Likely pathogens

 People with chronic infections, especially if they have received antibiotics previously, often have polymicrobial infections, including aerobic gram-negative bacilli among the flora.

Table 2. Likely infecting organisims of the diabetic foot and the primary and alternative antibiotic therapies suggested for treatment.

LIKELY PATHOGEN	ANTIBIOT	IC THERAPY
	PRIMARY	ALTERNATIVES
Staphylococcus aureus	• Penicillinase-resistant penicillin (e.g. flucloxacillin)	Doxycycline, orClindamycin.
Meticillin-resistant Staphylococcus aureus	 Vancomycin, Teicoplanin, or Discuss other options with an infection specialist. 	 Rifampicin with either: Trimethoprim, Doxycycline, or Fusidic acid, Co-trimoxazole, or Linezolid.
Beta-haemolytic streptococcus	• Amoxicillin.	• Clindamycin.
Enterococcus	Amoxicillin, orCo-amoxiclav.	Vancomycin, orLinezolid.
Pseudomonas (gram-negative bacillus)	 Quinolones (e.g. high- dose ciprofloxacin). 	Piperacillin-tazobactam,orMeropenem.
Anaerobes	Metronidazole.	• Clindamycin.

Table 3. Summary of guidance on antibiotics for the treatment of infection in the diabetic foot.

MILD INFECTION

MODERATE INFECTION

- Pus or two or more of: erythema, warmth, pain, tenderness, induration,
- confined to skin or subcutaneous tissue, and Any cellulitis <2 cm around the wound

Symptoms

- No evidence of systemic infection.
- treatment should be reviewed and continued recommended for 5-7 days, after which Treatment with the following agents is or discontinued as appropriate.

Treatment duration

- infection involving subcutaneous tissue, tendon, fascia, bone or abscess, or Lymphatic streaking, deep tissue
 - Cellulitis > 2 cm, and
- No evidence of systemic infection.
- recommended for 5-7 days, after which treatment should be reviewed and continued or discontinued Treatment with the following agents is as appropriate.
- preparations after an appropriate interval. IV antibiotics may be switched to oral
 - least 4-6 weeks, after which treatment • If osteomyelitis is present, treat for at should be reviewed and continued or discontinued as appropriate.

Oral fluxcloxacillin 1 g qds (for MSSA or beta-haemolytic streptococci).†

Alternatives

Co-trimoxazole 960 mg bd,

Clindamycin 300–450 mg qds.

Antibiotic-naïve

• Doxycycline 100 mg bd, or

Alternatives

• Oral flucloxacillin 1 g qds.†

Primary

- Co-amoxiclay 625 mg tds, or Clindamycin 450 mg qds,
- Add metronidazole 400 mg tds if
 - anaerobes suspected.

SEVERE INFECTION

- presence of critical ischaemia of the involved Any infection accompanied by systemic confusion, metabolic instability). The toxicity (fever, chills, shock, vomiting, limb may make the infection severe.
- continued or discontinued as appropriate. which treatment should be reviewed and is recommended for 10-14 days, after Treatment with the following agents

IV antibiotics may be switched to oral

preparations after an appropriate interval. least 4-6 weeks, after which treatment • If osteomyelitis is present, treat for at should be reviewed and continued or discontinued as appropriate.

Primary

- IV co-amoxiclav 1.2 g tds,
- Add gentamicin 5-7 mg/kg once NOTE: Oral therapy inappropriate. daily if required.**

If allergic to penicillin, or concern about renal function

- IV ciprofloxacin 400 mg bd and metronidazole 500 mg tds,
- Add IV vancomycin if MRSA infection suspected.**

● Doxycycline 100 mg bd, or • Clindamycin 300–450 mg qds.	 Primary IV co-amoxiclav 1.2 g tds. Primary oral switch Co-amoxiclav 625 mg tds, or Co-trimoxazole 960 mg bd. Alternatives IV ciprofloxacin 400 mg tds and IV metronidazole 500 mg tds (add IV vancomycin† if MRSA infection suspected), or IV gentamicin†‡ and IV metronidazole 500 mg tds (add IV vancomycin†* if MRSA infection suspected). Alternative oral switch Ciprofloxacin 500-750 mg bd and metronidazole 400 mg tds, or Ciprofloxacin 500-750 mg bd and clindamycin 300-450 mg qds. 	 Primary IV piperacillin/tazobactam 4.5 g tds, Add IV vancomycin if MRSA infection suspected (aim for a trough vancomycin concentration of 15–20 mg/L).** If allergic to penicillin IV ciprofloxacin 400 mg bd and IV metronidazole 500 mg tds. Oral switch Ciprofloxacin 500–750 mg bd and metronidazole 400 mg tds, or Ciprofloxacin 500–750 mg bd and clindamycin 300–450 mg qds.
	Primary Home IV service IV vancomycin.** Oral switch† Rifampicin 300 mg bd (with either: trimethoprim 200 mg bd, doxycycline 100 mg bd, or fusidic acid 500 mg tds)*, or Linezolid 600 mg bd.* Osteomyelitis MRSA infection of bone, add either: Rifampicin 600 mg bd, or Sodium fusidate 500 mg tds.	Primary Primary Home IV service IV vancomycin.** Oral switch† Rifampicin 300 mg bd (with either: trimethoprim 200 mg bd, doxycycline 100 mg bd, or fusidic acid 500 mg tds)*, or Linezolid 600 mg bd.* Osteomyelitis MRSA infection of bone, add either: Rifampicin 600 mg bd, or Sodium fusidate 500 mg tds.

Not antibiotic—naïve

Dosing frequencies: bd=twice a day; dds=four times a day; tds=three times a day.

IV=intravenous; MRSA=meticillin-resistant Staphylococcus aureus; MSSA=meticillin-sensitive Staphylococcus aureus.

*Requires monitoring for complications; *Monitor serum concentration; *Note concerns about linezolid toxicity with protracted therapy.

MRSA

- 1. As severe infection implies systemic toxicity, it is generally advised that people at this level of infection should be admitted to hospital for the initial phase of management.
- 2. A good quality microbiological culture should be taken from severe infections.
- 3. Severe infections in people who are antibiotic naïve are usually caused by Staphylococcus aureus or beta-haemolytic streptococci. Anaerobes, enterobacteriaceae and Pseudomonas aeruginosa (usually a coloniser rather than the infecting organism) may also need to be treated.
- 4. If infection with an extended-spectrum beta-lactamase-producing pathogen is proven, seek specialist infection advice.

Antibiotics

Primary

 IV co-amoxiclav 1.2 g tds (especially when anaerobes or coliforms are suspected).

Oral switch

- Co-amoxiclav 625 mg tds, or
- Co-trimoxazole 960 mg bd.

Allergic to penicillins

- IV ciprofloxacin 400 mg tds and IV metronidazole 500 mg tds, or
- IV gentamicin¹ (monitor serum concentration) and IV metronidazole 500 mg tds.
 - Add vancomycin (monitor serum concentration) to either of the above if MRSA infection is suspected.
- Choice will depend on the relative risks of *C. difficle* infection versus those of renal impairment.

Oral switch options if allergic to penicillins

- Oral ciprofloxacin 500–750 mg bd with either:
 - Oral metronidazole 400 mg tds, or
 - Clindamycin 300-450 mg qds.

Treatment duration

➤ Treat for 5–7 days. Adjust therapy in light of clinical response and microbiological culture and sensitivity results.

Severe infection (IDSA) or PEDIS 4 in an antibiotic-naïve person

Likely pathogens

- S. aureus or beta-haemolytic streptococci.
- Anaerobes, enterobacteriaceae and *Pseudomonas aeruginosa* may also need to be treated. *P. aeruginosa* is usually a coloniser rather than being the infecting organism.

Notes

- ► A good quality microbiological culture should virtually always be taken (see page 63 for guidance).
- ► *Caution:* As Severe or PEDIS 4 infection implies systemic toxicity, it is generally advised that people at this level of infection

be admitted to hospital for the initial phase of management.

Antibiotics

Primary

- IV co-amoxiclav 1.2 g tds.
 - If necessary, add gentamicin¹ 5–7 mg/kg once daily or as per local practice.

Allergic to penicillins or concern about renal function

- IV ciprofloxacin 400 mg bd and IV metronidazole 500 mg tds.
 - Add vancomycin (monitor serum concentration) if MRSA infection is suspected.

Treatment duration

► Treat for a minimum of 10–14 days. Adjust therapy in light of clinical response and microbiological culture and sensitivity results.

Severe infection (IDSA) or PEDIS 4

The following guidance is for the treatment of severe or PEDIS 4 diabetic foot infections in number of circumstances:

- People who have recently received antibiotic therapy (i.e. those who have received antibiotic treatment within the preceding 90 days).
- People with a proven drug-resistant infection.
- Those at risk of a drug-resistant infections (e.g. those who have previous had an MRSA colonisation).
- Those infected with an extended-spectrum beta-lactamase-producing (ESBL) *Escherichia coli* or *Klebsiella* spp. If infection with an ESBL pathogen is proven, seek specialist infection advice.

Notes

- ► A good quality microbiological culture should always be taken (see page 63 for guidance).
- ► Caution: As Severe or PEDIS 4 infection

¹Gentamicin should be given as a high dose, determined by local practice, once daily. Close monitoring of serum levels and renal function will be required. Treatment with gentamicin for >48 hours should only be undertaken with specific advice from an infection specialist.

implies systemic toxicity, it is generally advised that people at this level of infection be admitted to hospital for the initial phase of management.

Antibiotics

Primary

- IV piperacillin/tazobactam 4.5 g tds,
 - Add vancomycin if MRSA infection is suspected (consult pharmacy for dose, but aim for a trough vancomycin level of 15–20 mg/L).

Penicillin allergy

• IV ciprofloxacin 400 mg bd and IV metronidazole 500 mg tds.

Oral switch

- Be guided by microbiology where possible.
 - Otherwise try oral ciprofloxacin
 500–750 mg bd and metronidazole
 400 mg tds.

Treatment duration

➤ Treat for minimum of 10–14 days. Adjust therapy in light of clinical response and microbiological culture and sensitivity results.

MRSA

If continuing MRSA cover is required, and the person can safely be discharged from hospital, the authors suggest either:

- Outpatient or home parenteral antimicrobial therapy (OHPAT) if available (usually IV teicoplanin).
- Oral linezolid 600 mg bd. Note that treatment beyond 2 weeks' duration with this agent needs to be monitored closely as it can be associated with bone marrow toxicity (particularly thrombocytopenia or leucopenia) and lactic acidosis, which are usually reversible on discontinuation of the drug.
- Rifampicin 300 mg bd with either:
 - Oral doxycycline 100 mg bd,

Page point

1. Continuing meticillinresistant *Staphylococcus aureus* cover may be required, whether the person can safely be discharged from hospital will influence the choice of agent.

- Early, local surgery to excise infected bone can help accelerate healing and reduce the length of time antibiotics are required in cases of osteomyelitis.
- 2. The evidence base for antibiotic choice for osteomyelitis is poor.
- There is no evidence that intravenous antibiotic therapy is superior to oral therapy in the treatment of osteomyelitis.
- 4. Tolerability of oral antibiotics during osteomyelitis is a significant issue and therapy may need to be tailored accordingly.

- Fusidic acid 500 mg tds, or
- Trimethoprim 200 mg bd.

All these agents can be used to treat people allergic to penicillins.

Osteomyelitis

Early, local surgery to excise infected and necrotic bone may help accelerate healing and reduce the length of time that treatment with antibiotics are required in cases of osteomyelitis (Berendt et al, 2008). The exact role of local surgery in treating osteomyelitis remains controversial.

Published studies have shown that antibiotic therapy without surgery can lead to resolution of infection in up to 80% of cases of osteomyelitis (Game and Jeffcoate, 2008). The evidence base for antibiotic choice for these infections is poor. However, the group recommends that, in those people who show evidence of osteomyelitis, and in all cases where infected bone is not resected, the treatments outlined above should be continued for at least 4-6 weeks, or longer if the clinical response is poor.

There is no evidence that IV antibiotic therapy is superior to oral therapy in the treatment of osteomyelitis, although in certain infections, like those caused by MRSA, IV therapy delivered in the OHPAT setting enhances compliance and reduces the duration of hospitalisation. For MRSA-related osteomyelitis there is some evidence that adding rifampicin 600 mg bd or sodium fusidate 500 mg tds to the usual therapies can be beneficial. Rationalisation of therapy should be discussed with an infection specialist.

Tolerability of oral antibiotics during osteomyelitis is a significant issue and therapy may need to be tailored accordingly. Various antibiotics require monitoring of liver function tests, full blood counts and or serum levels. If considering linezolid for the treatment of osteomyelitis, the prescriber must be aware of its unlicensed status for osteomyelitis, and of the risk of bone marrow toxicity, peripheral or optic neuropathy and lactic acidosis. Measurement of serial

C-reactive protein and white blood cell counts may assist in determining the course of the osteomyelitis, but should not be taken more than once per week.

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