Chronic Osteomyelitis of Upper and Lower Limbs in Adults - Microbiology Full Clinical Guideline

Reference number: CG-ANTI/2019/065

Introduction

- Bacterial invasion of bone initiates host inflammatory responses.
- In the early stages, bacteria are planktonic and infective-inflammatory sequelae include lysis, ischaemia, and/or bone necrosis.
- In the later stages, bacteria transition to a sessile state and form biofilms. Infection and inflammation can, again, cause lysis, ischaemia, and/or bone necrosis; infective-inflammatory sequelae can also include formation of sequestra, involucrum, and cloacae.
- The commonest cause of chronic osteomyelitis is *Staphylococcus aureus*.
- *Streptococcus* species, *Enterobacterales* (e.g. *Escherichia coli*), *Pseudomonas aeruginosa*, and *Enterococcus* species are other relatively common bacterial causes.
- The majority of chronic osteomyelitis is contiguous, iatrogenic, or traumatic in origin; inoculation is via local dissemination, surgery, or injury, respectively.
- Symptoms and signs of chronic osteomyelitis include pain, local heat, swelling, a sinus tract, and functional impairment.
- Temperatures > 38 ° C or < 36 ° C, a respiratory rate > 20 breaths/minute, a heart rate > 90 beats/minute, and hypotension can denote progression of localised infectious disease into sepsis and septic shock.

Investigation

Radiology

- First line:
    - X-ray (XR).
- Second line, if the XR is negative and if clinical suspicions remain high:
    - Magnetic resonance imaging (MRI).

Microbiology

- Diagnoses of chronic osteomyelitis can be established by the culture of a microorganism consistent with bone infection from ≥ 2 sterile site samples; e.g. (i) biopsy × 2; e.g. (ii) biopsy and blood culture.
- Biopsy:
    - With the range of bacterial pathogens, variations in bacterial resistance and susceptibility profiles, variable antimicrobial bone penetration, contraindications, side-effects, and with prolonged durations of 6-8 weeks of antimicrobial chemotherapy, biopsy is integral to best practice:
        - Tissue(s):
            - Into a universal container, with Ballotini beads, for microscopy, culture, and susceptibilities (MC&S); ±
            - If the differential diagnosis includes fungal chronic osteomyelitis (e.g. penetrating traumatic injury, with soil contact/potential inoculation of the bone), ≥ 1 extra

tissue in a universal container, without Ballotini beads, for MC&S.

- Wound swab for culture and susceptibilities.
- Methicillin resistant *Staphylococcus aureus* (MRSA) screen.
- ± Blood cultures × 2:
    - E.g. if episode(s) of fever; or
    - E.g. if the differential diagnosis includes bloodstream infection, sepsis, or septic shock; or
    - E.g. if for initiation of treatment with intravenous antibiotics.

Blood sciences

- Full blood count (FBC), erythrocyte sedimentation rate (ESR), C reactive protein (CRP), urea and electrolytes (U&Es), and liver function tests (LFTs).

Treatment

Surgical intervention

- The pathology of chronic osteomyelitis is complex:
    - Bacteria transition from planktonic to sessile states:
        - Active bacterial metabolism is integral to the mechanism of action for antibiotics; slow growing bacteria are less susceptible to antimicrobial chemotherapy.
    - Biofilm forms:
        - The matrix secreted by the microbial pathogen restricts antibiotic diffusion, impeding antimicrobial chemotherapy delivery.
    - Bacterial-coated sequestra form:
        - Detachment from the body of the bone detaches the bony fragment from the vasculature, further impeding antibiotic delivery.

  Therefore, microbiologists commonly advocate surgical intervention to remove infective foci, biofilm, and restore perfusion.

- The clinical decision for surgical intervention is also complex, involving patient background and prognosis. Ultimately, the clinical decision for surgery remains the responsibility of the surgeon, in collaboration with the anaesthetist.
- With the benefits and risks of operating, a surgical consultant opinion on intervention is recommended.

Empiric, intravenous antibiotics

- If there are no clinical concerns regarding sepsis:
    - With the rationale of enabling *Staphylococcus aureus* and *Streptococcus* groups A/C/G activity:
        - After the biopsy:

	No history of MRSA	History of MRSA
First line	Flucloxacillin 2 g 6 hourly	Vancomycin or teicoplanin, dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 20-40 mg/l
Second line	If non-immediate without systemic	Daptomycin 6 mg/kg 24

	involvement penicillin allergy, cefuroxime 1.5 g 8 hourly	hourly
Third line	If immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy, vancomycin or teicoplanin, dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 20-40 mg/l	Linezolid 600 mg 12 hourly (or per oral [absorption 100%])

- If there are clinical concerns regarding sepsis (life threatening organ dysfunction caused by a dysregulated host immune response to infection) secondary to osteomyelitis:
    - With the rationale of enabling *Staphylococcus aureus*, *Streptococcus* groups A/C/G, *Enterobacterales* (e.g. *Escherichia coli*), *Pseudomonas aeruginosa*, and *Enterococcus* species activity:
        - After blood cultures × 2:

First line	Piperacillin tazobactam 4.5 g 6 hourly **±** If there are clinical concerns regarding the risk of MRSA, vancomycin or teicoplanin, dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 20-40 mg/l
Second line, if non-immediate without systemic involvement penicillin allergy	Ceftazidime 2 g 8 hourly **and** Vancomycin or teicoplanin, dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 20-40 mg/l
Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy	Ciprofloxacin 400 mg 8 hourly **and** Vancomycin or teicoplanin, dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 20-40 mg/l

Directed, intravenous antibiotics (with susceptibilities)

- Methicillin susceptible *Staphylococcus aureus* (MSSA), according to susceptibilities:
    - First line:
        - Flucloxacillin 2 g 6 hourly.
    - Second line, if non-immediate without systemic involvement penicillin allergy:
        - Cefuroxime 1.5 g 8 hourly.
    - Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy:
        - Vancomycin or teicoplanin, dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 20-40 mg/l.
- Methicillin resistant *Staphylococcus aureus* (MRSA), according to susceptibilities:
    - First line:
        - Vancomycin or teicoplanin, dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 20-40 mg/l.
    - Second line:
        - Daptomycin 6 mg/kg 24 hourly.

    - Third line:
        - Linezolid 600 mg 12 hourly (or per oral [absorption 100%]).
- *Streptococcus* species, according to susceptibilities:
    - First line:
        - Benzylpenicillin 2.4 g 6 hourly.
    - Second line, if non-immediate without systemic involvement penicillin allergy:
        - Ceftriaxone 2 g 24 hourly.
    - Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy:
        - Vancomycin or teicoplanin, dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 20-40 mg/l.
- *Enterobacterales* (e.g. *Escherichia coli*) according to susceptibilities:
    - First line:
        - Penicillin; narrowest spectrum of amoxicillin or co-amoxiclav or piperacillin tazobactam standard dosage.
    - Second line, if non-immediate without systemic involvement penicillin allergy:
        - Cephalosporin; narrowest spectrum of cefuroxime or ceftriaxone standard dosage.
    - Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy:
        - Ciprofloxacin 400 mg 12 hourly (consider 500 mg per oral 12 hourly [absorption 60-80%]).
- *Pseudomonas aeruginosa*, according to susceptibilities:
    - First line:
        - Piperacillin tazobactam 4.5 g 6 hourly.
    - Second line, if non-immediate without systemic involvement penicillin allergy:
        - Ceftazidime 2 g 8 hourly.
    - Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy:
        - Ciprofloxacin 400 mg 8 hourly (consider 750 mg per oral 12 hourly [absorption 60-80%]).
- *Enterococcus* species, according to susceptibilities:
    - First line:
        - Amoxicillin 1 g 6 hourly.
    - Second line:
        - Glycopeptide (vancomycin or teicoplanin), dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 20-40 mg/l.
    - Third line:
        - Daptomycin 6 mg/kg 24 hourly.

Multi-disciplinary meeting, intravenous to per oral step down, and outpatient parenteral antimicrobial therapy

- After 7-14 days of intravenous antimicrobial chemotherapy, if the patient is afebrile, observations stable, and inflammatory markers downward trending, collaborate with the physician/surgeon regarding their preference for:
    - Referral to the University Hospitals of Derby and Burton (UHDB) orthopaedic multi-disciplinary meeting (1200-1300 Fridays); or
    - Per oral step down; or
    - Outpatient parenteral antimicrobial therapy (OPAT).

NB If for orthopaedic multi-disciplinary meeting discussion, please liaise with the clinical audit team of the orthopaedic department, of the Royal Derby Hospital, regarding the pro forma and the Microsoft Teams meeting hyperlink.

- After 7-14 days of intravenous antimicrobial chemotherapy, if the patient is febrile, observations unstable, and/or inflammatory markers upward trending, collaborate with the surgeons regarding surgical intervention or return to theatre, update the microbiologist, and continue intravenous therapy.

Directed, per oral antibiotics (with susceptibilities)

- *Staphylococcus aureus* (MSSA and MRSA), according to susceptibilities:
    - First line:
        - Ciprofloxacin 500-750* mg 12 hourly **and**
        - Rifampicin 300-450* mg 12 hourly or fusidic acid 500 mg 8 hourly.
    - Second line:
        - Clindamycin 300-450* mg 6 hourly **and**
        - Rifampicin 300-450* mg 12 hourly or fusidic acid 500 mg 8 hourly.
    - Third line:
        - Doxycycline 100 mg 12 hourly **and**
        - Rifampicin 300-450* mg 12 hourly or fusidic acid 500 mg 8 hourly.
- *Streptococcus* species, according to susceptibilities:
    - First line:
        - Amoxicillin 500 mg-1* g 8 hourly.
    - Second line:
        - Clindamycin 300-450* mg 6 hourly.
    - Third line:
        - Doxycycline 100 mg 12 hourly.
- *Enterobacterales* (e.g. *Escherichia coli*), according to susceptibilities:
    - First line:
        - Ciprofloxacin 500 mg 12 hourly.
    - Second line:
        - Co-trimoxazole 960 mg 12 hourly.
    - Third line:
        - Penicillin; narrowest spectrum of:
            - Amoxicillin 1 g 8 hourly **or**
            - Co-amoxiclav 625 mg 8 hourly plus amoxicillin 500 mg 8 hourly.
- *Pseudomonas aeruginosa*, according to susceptibilities:
    - First line:
        - Ciprofloxacin 750 mg 12 hourly.
- *Enterococcus* species, according to susceptibilities:
    - First line:
        - Amoxicillin 1 g 8 hourly.
    - Second line:
        - Linezolid 600 mg 12 hourly**.
    - Third line:
        - Co-trimoxazole 960 mg 12 hourly.
- * Final dosage to be tailored to specific parameters of the patient (e.g. weight) and the pathogen (e.g. minimum inhibitory concentration) in collaboration with the microbiology consultant responsible for sterile site investigation or within the orthopaedic multi-disciplinary meeting.

- ** In general, maximum duration of treatment 28 days.

Directed, outpatient parenteral antimicrobial therapy

- Collaborate with the OPAT consultant.

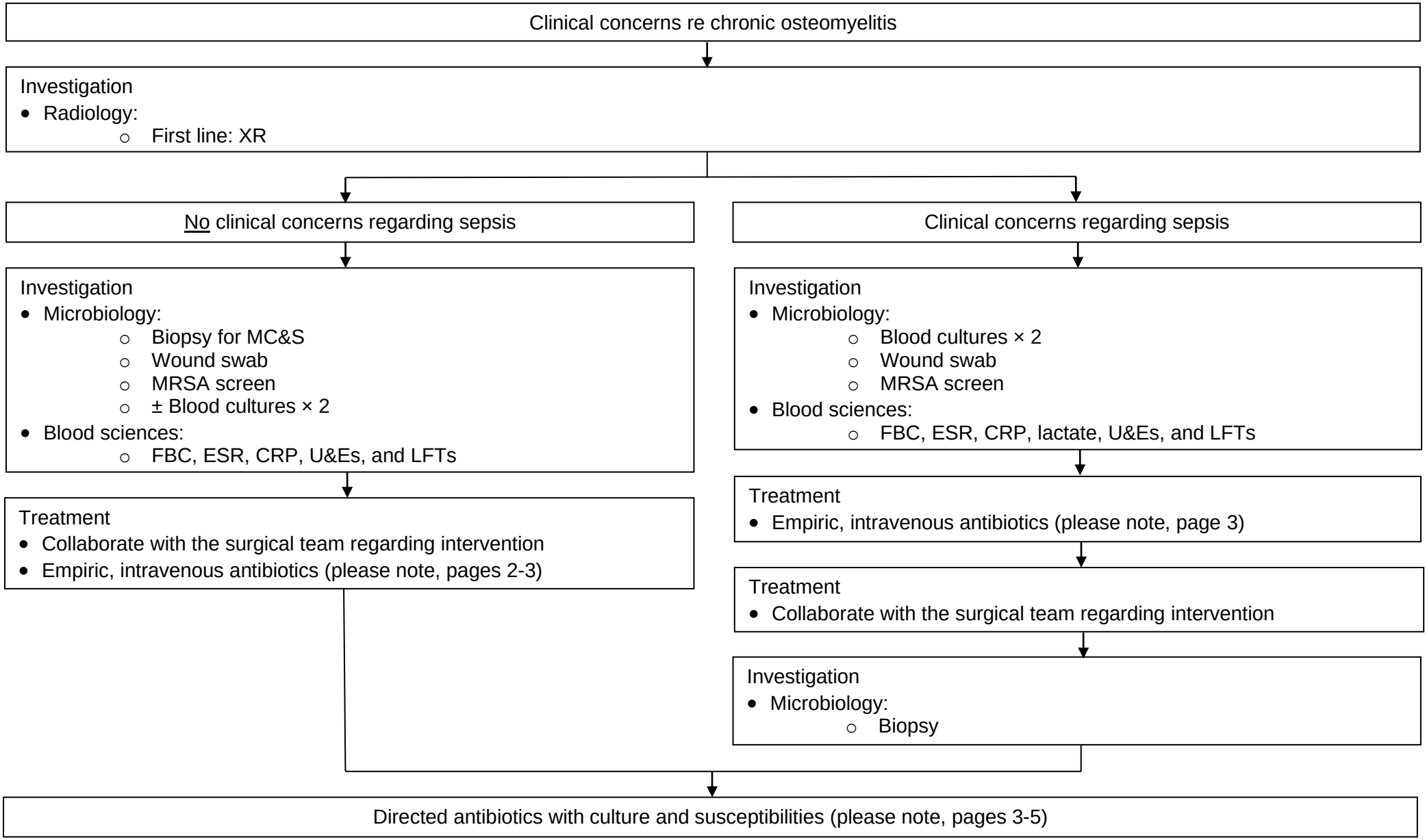
Empiric, per oral or outpatient parenteral antibiotic treatment

- If radiological features of chronic osteomyelitis, and if the microbiology is negative, collaborate with a microbiologist regarding empiric options.

Duration of antibiotics

- If for per oral step down or OPAT, monitor bloods (FBC, CRP, U&Es, and LFTs) weekly with OPAT or fortnightly with the general practitioner.
- 6-8 weeks of antibiotics (e.g. 2 weeks of intravenous therapy and 4 weeks of per oral treatment).
- Follow up with the medical/surgical team, on intravenous or per oral therapy.

Management


Clinical concerns re chronic osteomyelitis
Investigation
• Radiology:
○ First line: XR
No clinical concerns regarding sepsis
Clinical concerns regarding sepsis
Investigation
• Microbiology:
○ Biopsy for MC&S
○ Wound swab
○ MRSA screen
○ ± Blood cultures × 2
• Blood sciences:
○ FBC, ESR, CRP, U&Es, and LFTs
Treatment
• Collaborate with the surgical team regarding intervention
• Empiric, intravenous antibiotics (please note, pages 2-3)
Investigation
• Microbiology:
○ Blood cultures × 2
○ Wound swab
○ MRSA screen
• Blood sciences:
○ FBC, ESR, CRP, lactate, U&Es, and LFTs
Treatment
• Empiric, intravenous antibiotics (please note, page 3)
Treatment
• Collaborate with the surgical team regarding intervention
Investigation
• Microbiology:
○ Biopsy
Directed antibiotics with culture and susceptibilities (please note, pages 3-5)

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Document control

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