Fracture Associated Metalwork Infection in Adults - Microbiology Full Clinical Guideline

Reference number: CG-ANTI/2023/063

Introduction

- Fixation of fractures with metalwork introduces foreign material into sterile sites.
- The host response includes a macromolecule-coating of the implant; microbial adherence to this protein-coat facilitates invasion. Biofilm formation enables persistence.
- The commonest causes of fracture associated metalwork infection (FAMI) are *Staphylococcus* species:
    - Methicillin susceptible or resistant *Staphylococcus aureus* (MSSA or MRSA); and
    - Coagulase negative staphylococci (e.g. *Staphylococcus epidermidis*).
- *Enterobacterales* (e.g. *Escherichia coli*) are other relatively common bacterial causes.
- Less common causes include *Streptococcus*, *Enterococcus*, and *Pseudomonas* species.
- The pathogens of FAMI can be inoculated through various mechanisms of transmission:
    - Haematogenous: another focus of infection culminates in bacteraemia; the microorganism disseminates via the blood and inoculates the metalwork.
    - Iatrogenic: direct inoculation via the surgical operation.
    - Traumatic: direct inoculation via the injury.
    - Contiguous: another focus of colonisation/infection (e.g. skin) disseminates locally and invades the implant.
- Symptoms and signs of FAMI include pain, fever, skin erythema, local heat, swelling, and wound discharge.
- 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.

Suggestive and diagnostic criteria

An international expert group (Metsemakers, WJ, et al.) has provided both surgeons and pathologists with clinical and pathological means to suspect and diagnose FAMI.

Suggestive criteria

- “Clinical signs − any one of:
    - Pain (without weight bearing, increasing over time, new-onset)
    - Local redness
    - Local swelling
    - Increased local temperature
    - Fever (single oral temperature measurement of ≥38.3°C (101°F))
- Radiological signs − any one of:
    - Bone lysis (at the fracture site, around the implant)
    - Implant loosening
    - Sequestration (occurring over time)
    - Failure of progression of bone healing (i.e. non-union)

    - Presence of periosteal bone formation (e.g. at localizations other than the fracture site or in case of a consolidated fracture)
- A pathogenic organism identified by culture from a single deep tissue/implant (including sonication-fluid) specimen taken during an operative intervention. In case of tissue, multiple specimens (≥3) should be taken, each with clean instruments (not superficial or sinus tract swabs). In cases of joint effusion arising in a joint adjacent to a fractured bone, a fluid sample obtained by sterile puncture is permitted.
- Elevated serum inflammatory markers: in musculoskeletal trauma, these should be interpreted with caution. They are included as suggestive signs in case of a secondary rise (after an initial decrease) or a consistent elevation over a period in time, and after exclusion of other infectious foci or inflammatory processes:
    - Erythrocyte sedimentation rate (ESR)
    - White blood cell count (WBC)
    - C-reactive protein (CRP)
- Persistent, increasing or new-onset wound drainage, beyond the first few days postoperatively, without solid alternative explanation.
- New-onset of joint effusion in fracture patients. Surgeons should be aware that fracture-related infection can present as an adjacent septic arthritis in the following cases:
    - Implant material which penetrates the joint capsule (e.g. femoral nailing)
    - Intra-articular fractures".

Diagnostic criteria

- "Fistula, sinus or wound breakdown (with communication to the bone or the implant).
- Purulent drainage from the wound or presence of pus during surgery.
- Phenotypically indistinguishable pathogens identified by culture from at least two separate deep tissue/implant (including sonication-fluid) specimens taken during an operative intervention. In case of tissue, multiple specimens (≥3) should be taken, each with clean instruments (not superficial or sinus tract swabs). In cases of joint effusion, arising in a joint adjacent to a fractured bone, fluid samples obtained by sterile puncture may be included as a single sample.
- Presence of microorganisms in deep tissue taken during an operative intervention, as confirmed by histopathological examination using specific staining techniques for bacteria or fungi."

Investigation

± Radiology

- Symptoms and signs of FAMI may prompt radiological investigation:
    - ± X-ray (XR); and/or
    - ± Ultrasound (US); and/or
    - ± Computed tomography (CT).
- Radiological investigation may reveal criteria suggestive of FAMI; however, no imaging modality reveals criteria diagnostic of FAMI, presently.

Microbiology

- Biopsy/Aspirates:
    - 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 weeks of antimicrobial chemotherapy, 6 surgical samples obtained with 6 sets of instrumentation are 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 FAMI (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.
- Fluid:
  - ≥ 1 ml of fluid in a universal container for MC&S; and
  - ≥ 1 ml of fluid in a blood culture aerobic bottle and ≥ 1 ml of fluid in a blood culture anaerobic bottle.

- 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.

Histology

- Biopsy:
  - ≥ 2 Tissues for histopathology.

Blood sciences

- Full blood count (FBC), ESR, CRP, urea and electrolytes (U&Es), and liver function tests (LFTs).

Treatment

Surgical intervention

- Collaborate with the orthopaedic consultant regarding:
  - Removal versus retention of the metalwork.

Empiric, intravenous antibiotics

First line	Piperacillin tazobactam 4.5 g 6 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
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 antibiotics (with susceptibilities)

- Methicillin susceptible *Staphylococcus* species, according to susceptibilities:
    - First line:
        - Flucloxacillin 2 g 6 hourly **±**
        - If metalwork retained, rifampicin 300-450* mg per oral 12 hourly.
    - Second line, if non-immediate without systemic involvement penicillin allergy:
        - Cefuroxime 1.5 g 8 hourly **±**
        - If metalwork retained, rifampicin 300-450* mg per oral 12 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 **±**
        - If metalwork retained, rifampicin 300-450* mg per oral 12 hourly.
- Methicillin resistant *Staphylococcus* species, 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 **±**
        - If metalwork retained, rifampicin 300-450* mg per oral 12 hourly.
    - Second line:
        - Daptomycin 6 mg/kg 24 hourly **±**
        - If metalwork retained, rifampicin 300-450* mg per oral 12 hourly.
- *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 per oral [absorption 60-80%]).
- *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.
- *Enterococcus* species, according to susceptibilities:
    - First line:
        - Amoxicillin 1 g 6 hourly.

    - Second 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.
    - Third line:
        - Daptomycin 6 mg/kg 24 hourly.
- *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.
- * 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 investigations or within the orthopaedic multi-disciplinary meeting.

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 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* species (methicillin susceptible and resistant), 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.
- *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.
- *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.
- *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.
- *Pseudomonas aeruginosa*, according to susceptibilities:
    - First line:
        - Ciprofloxacin 750 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 investigations 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 antimicrobial therapy

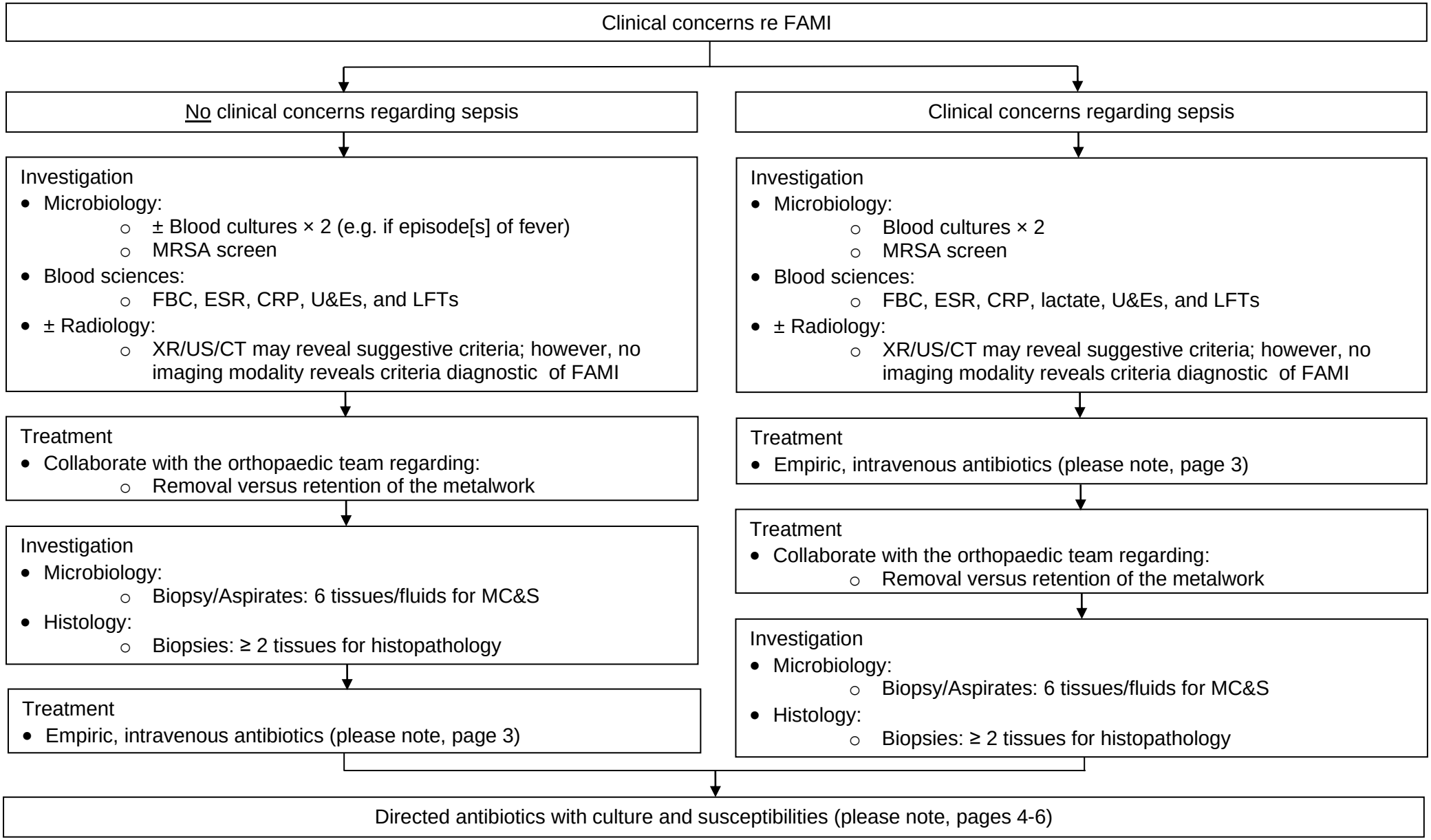
- If a clinical diagnosis of FAMI, and if the microbiology is negative, collaborate with a microbiologist regarding empiric options.

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.

- If removal of the metalwork:
    - 6 weeks.
- If retention of the metalwork:
    - ≥ 6 weeks:
        - Intravenous or per oral therapy to continue whilst metalwork in situ and until bone union.
- Follow up with the surgical team, on intravenous or per oral therapy.

Management


Clinical concerns re FAMI
No clinical concerns regarding sepsis
Clinical concerns regarding sepsis
Investigation
• Microbiology:
○ ± Blood cultures × 2 (e.g. if episode[s] of fever)
○ MRSA screen
• Blood sciences:
○ FBC, ESR, CRP, U&Es, and LFTs
• ± Radiology:
○ XR/US/CT may reveal suggestive criteria; however, no imaging modality reveals criteria diagnostic of FAMI
Treatment
• Collaborate with the orthopaedic team regarding:
○ Removal versus retention of the metalwork
Investigation
• Microbiology:
○ Biopsy/Aspirates: 6 tissues/fluids for MC&S
• Histology:
○ Biopsies: ≥ 2 tissues for histopathology
Treatment
• Empiric, intravenous antibiotics (please note, page 3)
Investigation
• Microbiology:
○ Blood cultures × 2
○ MRSA screen
• Blood sciences:
○ FBC, ESR, CRP, lactate, U&Es, and LFTs
• ± Radiology:
○ XR/US/CT may reveal suggestive criteria; however, no imaging modality reveals criteria diagnostic of FAMI
Treatment
• Empiric, intravenous antibiotics (please note, page 3)
Treatment
• Collaborate with the orthopaedic team regarding:
○ Removal versus retention of the metalwork
Investigation
• Microbiology:
○ Biopsy/Aspirates: 6 tissues/fluids for MC&S
• Histology:
○ Biopsies: ≥ 2 tissues for histopathology
Directed antibiotics with culture and susceptibilities (please note, pages 4-6)

References

Bennett, J. E., Dolin, R., and Blaser, M. J. 2015. Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 8th Edition. Elsevier.
emc. 2022. Available at: https://www.medicines.org.uk/emc/.
Grayson, M. L., Crowe, S. M., McCarthy, J. S., Mills, J., Mouton, J. W., Norrby, S. R., Paterson, D. L., and Pfaller, M. A. 2010. Kucers' The Use Of Antibiotics, 6th Edition. CRC Press.
Li, H. -K., Rombach, I., Zambellas, R., Walker, A. S., McNally, M. A., Atkins, B. L., Lipsky, B. A., Hughes, H. C., Bose, D., Kumin, M., Scarborough, C., Matthews, P. C., Brent, A. J., Lomas, J., Gundle, R., Rogers, M., Taylor, A., Angus, B., Byren, I., Berendt, A. R., Warren, S., Fitzgerald, F. E., Mack, D. J. F., Hopkins, S., Folb, J., Reynolds, H. E., Moore, E., Marshall, J., Jenkins, N., Moran, C. E., Woodhouse, A. F., Stafford, S., Seaton, R. A., Vallance, C., Hemsley, C. J., Bisnauthsing, K., Sandoe, J. A. T., Aggarwal, I., Ellis, S. C., Bunn, D. J., Sutherland, R. K., Barlow, G., Cooper, C., Geue, C., McMeekin, N., Briggs, A. H., Sendi, P., Khatamzas, E., Wangrangsimakul,T., Wong, T. H. N., Barrett, L. K., Alvand, A., Old, C. F., Bostock, J., Paul, J., Cooke, G., Thwaites, G. E., Bejon, P., and Scarborough, M. 2019. Oral versus Intravenous Antibiotics for Bone and Joint Infection. The New England Journal of Medicine.
Metsemakers, W. J., Morgenstern, M., McNally, M. A., Moriarty, T. F., McFadyen, I., Scarborough, M., Athanasou, N. A., Ochsner, P. E., Kuehl, R., Raschke, M., Borens, O., Xie, Z., Velkes, S., Hungerer, S., Kates, S. L., Zalavras, C., Giannoudis, P. V., Richards, R. G., and Verhofstad, M. H. J. 2018. Fracture-related infection: A consensus on definition from an international expert group. Injury.
Sanford Guide Antimicrobial Therapy. 2022. Available at: https://www.sanfordguide.com/products/digital-subscriptions/.
Zimmerli, W. 2021. Bone and Joint Infections, 2nd Edition. WILEY Blackwell.

Document control

Development of guidelines:	Kayleigh Lehal, Dr Peter Slovak
Consultation with:	Lead Antimicrobial Pharmacist, Microbiology Consultant
Version:	3
Approval date:	Antimicrobial Stewardship Group on 31/01/2023 and by Surgical division 24/01/2023
Changes from previous version:	Introduction: reworded (minor) and reformatted (minor). Suggestive and diagnostic criteria. Investigation: reworded (minor) and reformatted (major). Treatment: reworded (minor) and reformatted (minor). Management: reworded (minor) and reformatted (major). References: updated (minor).
Date uploaded:	01/03/2023
Next review date:	01/03/2026
Key contacts:	Dr Peter Slovak, Microbiology Consultant p.slovak@nhs.net Kayleigh Lehal, Lead Antimicrobial Pharmacist kayleigh.lehal@nhs.net