Cardiac Implantable Electronic Device Pocket Infection - Microbiology Full Clinical Guideline

Reference number: CG-ANTI/2019/062

Introduction

- Established cardiac implantable electronic devices (CIED) include permanent pacemakers (PPM), implantable cardioverter-defibrillators (ICD), and cardiac resynchronisation therapy pacemakers (CRT-P).
- In general, PPM, ICD, and CRT-P cardiac devices have:
    - Generators sited in the left anterior chest; and
    - Leads – introduced through the venous vasculature – residing in the atrial or ventricular myocardium.

  The electrical stimulus from the generator pocket is transmitted, via the transvenous leads, to the heart.
- CIEDs are emerging – for example, leadless pacemakers and subcutaneous implantable cardioverter-defibrillators – without transvenous leads.
- Established PPM, ICD, and CRT-P cardiac devices – with generators and leads – are the focus of this microbiology clinical guideline.

- The commonest causes of CIED infections are the Gram positive *Staphylococcus* species:
    - Methicillin susceptible or resistant coagulase negative staphylococci, e.g. *Staphylococcus epidermidis*; or
    - Methicillin susceptible or resistant *Staphylococcus aureus*.
- Less commonly isolated pathogens include:
    - Further Gram positive bacteria: *Corynebacterium*, *Cutibacterium*, *Enterococcus*, and *Streptococcus* species.
    - ± Gram negative bacteria.
    - ± Fungi.

- In general, the pathogens of CIED infection are inoculated via:
    - An iatrogenic mechanism of transmission:
        - Contamination of the generator/lead – with host/healthcare professional flora – on implantation/manipulation.
    - Or, a haematogenous mechanism of transmission:
        - Another focus of infection culminates in bloodstream infection; the microorganism disseminates via the blood to inoculate the cardiac device.

- Microbial invasion of the generator pocket – manifesting with pain, erythema, warmth, tenderness, swelling, purulent discharge, and/or erosion – is termed CIED pocket infection.

- Please note, specific hospital guidelines exist for CIED lead infection.

Differential diagnosis

- Whilst microbial invasion of the generator pocket can manifest with soft tissue symptoms and signs; equally, stigmata can be limited to fever only.
- Therefore, if the past medical history includes CIED, and if there are clinical concerns regarding pyrexia of unknown origin, consideration of pocket and lead infection in the differential diagnosis is recommended.

- NB The symptoms and signs of CIED pocket infection can also be mimicked by other infective (e.g. superficial incisional site infection) and non-infectious pathologies (e.g. postimplantation inflammation).

Criteria for diagnosis of CIED pocket infection

- The European Heart Rhythm Association (EHRA) outlined, in 2019, International CIED Infection Criteria:
    - "'Definite' CIED clinical pocket/generator infection =
        - Generator pocket shows swelling, erythema, warmth, pain, and purulent discharge/sinus formation OR
        - Deformation of pocket adherence and threatened erosion OR
        - Exposed generator or proximal leads".

Investigation

- The provision of clinical details is the duty of the requesting physician and is integral to best practice.
- The microbiology department processes thousands of blood cultures annually. The provision of clinical details enable:
    - The biomedical scientists and medical laboratory assistants to process the blood cultures appropriately. For example, with regard to culture, extending the period of incubation – from the standard 5 days – to 10 days.
    - The consultant microbiologists to interpret the blood cultures appropriately. For example, communicating coagulase negative staphylococci bacteraemia to physicians re patients with past medical histories of CIEDs.
- The echocardiographers perform thousands of echocardiograms annually. The provision of clinical details enable:
    - The echocardiographers to vet and prioritise requests appropriately.
    - The echocardiographers and cardiologists to interpret the images appropriately.

Blood sciences

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

Microbiology

- Before starting antibiotics:
    - If the patient is clinically stable:
        - Blood cultures × 3; drawn approximately 12 hours apart; from 3 locations/venepunctures.
    - If the patient is clinically unstable (haemodynamic instability, sepsis, or septic shock):
        - Blood cultures × 3; drawn approximately 1-15 minutes apart; from 3 locations/venepunctures.
    - Please provide relevant clinical details:
        - For example: "Fever. Cardiac device. ?Pocket/Lead infection."
    - NB In CIED infections limited to the pocket only, blood cultures are – in general – negative.
- If purulent discharge:
    - Fluid for microscopy, culture, and susceptibilities (MC&S).
- If medicine/surgery intervenes:
    - If returned to the cath lab or taken to theatre:

        - Pocket swab for MC&S; and
        - Tissue sample for MC&S; and
        - Lead tip for MC&S.

Radiology

- Chest x-ray (CXR).

Echocardiogram, provided by cardiology and clinical measurements

- Clinical suspicions of CIED infection – emanating from physicians and/or pathologists – warrant echocardiogram investigation:
    - First line: transthoracic echocardiogram (TTE).
- Please provide relevant clinical details:
    - Symptoms and/or signs.
    - Past medical history of CIED.
    - If positive, microbiology investigative history of:
        - *Staphylococcus aureus* or *Candida* species bloodstream infection.
        - Persistent bloodstream infection with a microorganism typical (or atypical) for CIED infection.
    - For example: “Fever. CIED. Bacteraemic with *Staphylococcus* species. ?CIED infection.”
- Requests are triaged and can be rejected, e.g. a request received without symptoms or signs or differential diagnosis of CIED infection.
- Clinical suspicions of CIED infection and initial TTE findings may warrant further echocardiogram investigation:
    - Second line: transoesophageal echocardiogram (TOE).
        - Indications can include: past medical history of CIED; negative TTE and clinical suspicions remaining high; equivocal TTE and clinical suspicions persisting; positive TTE and clinical suspicions regarding complications.

  With regard to TOE, this specialist procedure requires collaboration with cardiology. Specifically, via switchboard, the physicians contact the cardiology registrar on call. The specialty trainee reviews the patient, and then contacts the cardiology consultant performing the next TOE list, regarding ± proceeding with the TOE.
- NB1 TTE and TOE can periodically require repeating:
    - If the initial TTE and TOE are negative, and clinical suspicions remain high.
    - If the initial echocardiograms are positive, and clinical suspicions arise regarding cardiovascular complications.
- NB2 In CIED infection limited to the pocket only, echocardiogram is negative; within the limits of the investigation, TTEs ± TOEs are utilised to rule out lead and/or valve vegetations.

Radiology and nuclear medicine

- If the differential diagnosis includes both infective and non-infective pathologies and/or:
    - If there is no ’definite’ CIED clinical pocket/generator infection:
        - Healthcare professionals may consider:
            - Cardiac computed tomography (CT); or
            - Fluorine-18 fluorodeoxyglucose (^{18}F-FDG) positron emission tomography (PET) CT; or

- Technetium metastable-99 hexamethylpropylene amine oxime (^{99m}Tc HMPAO) labelled white cell single photon emission computed tomography (SPECT) CT

In collaboration with one of the consultant radiologists with a specialist interest in cardiac imaging for cardiac CT and nuclear medicine for PET CT or SPECT CT.

- With regard to nuclear medicine:
  - First line, in Nottingham, if the patient can be transferred:
    - ^{18}F-FDG PET CT.
    - Turnaround time approximately 7 days.
  - Second line, in Derby, if the patient cannot be transferred:
    - ^{99m}Tc SPECT CT.
    - Turnaround time approximately 10-14 days.
  - Third line, in Derby, if the patient cannot be transferred:
    - Gallium-67 SPECT CT.
    - Turnaround time approximately ≥ 14 days.
  - NB Ward doctor to liaise with one of the three radiologists supporting nuclear medicine regarding:
    - The request; and
    - The logistics of the procedure (for example, Atkin's diet for ≥ 72 hours before ^{18}F-FDG PET CT).

Treatment

The EHRA states:

- "Definitive treatment of CIED infection is early and complete removal of all parts of the system and antibiotic therapy is to be seen as a complement."

Medical or surgical intervention[1]: explantation of the CIED

- Collaborate with the cardiology consultant regarding potential removal versus possible retention of the CIED.
- Indications for explantation include:
  - Diagnosis of 'definite' CIED clinical pocket/generator infection.
- NB If the CIED has been in situ for > 12 months, the nature of the host responses to the cardiac device necessitates referral to a surgical team specialising in removal of chronic, connective tissue coated CIEDs.
- Consider retention of the CIED if:
  - An extensive past medical history, with co-morbidities contraindicating a return to the cath lab/theatre; or
  - A past medical history of a long-standing CIED.

Medical or surgical intervention[2]: temporary pacing

- If the past medical history dictates continuous pacing, the cardiologist may contemplate explantation of the device and then cardiac support with:
  - The insertion of a temporary pacing lead; introduced transcutaneously through the venous vasculature (in general, the right internal jugular vein) into the heart; and
  - The attachment of this pacing lead to an external generator; with the temporary generator sited on the neck or back, with an adherent skin dressing maintaining its location.

Medical or surgical intervention[3]: reimplantation of the CIED

- If returned to the cath lab or taken to theatre for removal of the CIED regarding pocket infection:
    - Perform blood cultures on the date of removal (NB after removal of the CIED):
        - If the blood cultures remain negative after ≥ 72 hours of culture, proceed with reimplantation*.

- * NB The new CIED is inserted contralateral to the old, removed cardiac device.

Empiric antibiotics

- If there are no clinical concerns regarding sepsis (life threatening organ dysfunction caused by a dysregulated host immune response to infection):
    - After blood cultures × 3:

First line	Vancomycin or teicoplanin intravenously, dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 30-40 mg/l, **and** Gentamicin 1 mg/kg intravenously 12 hourly, target pre dose trough < 1 mg/l and target post dose peak 3-5 mg/l, **and** Rifampicin 300-600* mg per oral 12 hourly
Second line	Daptomycin 8-10 mg/kg intravenously 24 hourly **and** Gentamicin 1 mg/kg intravenously 12 hourly, target pre dose trough < 1 mg/l and target post dose peak 3-5 mg/l, **and** Rifampicin 300-600* mg per oral 12 hourly
* Rifampicin 300 mg if creatinine clearance < 30 ml/min, 600 mg if creatinine clearance ≥ 30 ml/min	

- If there are clinical concerns regarding sepsis (life threatening organ dysfunction caused by a dysregulated host immune response to infection) secondary to pocket infection:
    - After blood cultures × 3:

First line	Piperacillin tazobactam 4.5 g intravenously 6 hourly **and** Vancomycin or teicoplanin intravenously, dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 30-40 mg/l
Second line, if non-immediate without systemic involvement penicillin allergy	Ceftazidime 2 g intravenously 8 hourly **and** Vancomycin or teicoplanin intravenously, dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 30-40 mg/l
Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy	Ciprofloxacin 400 mg intravenously 8 hourly **and** Vancomycin or teicoplanin intravenously, dose as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 30-40 mg/l

CIED in situ: directed antibiotics (with susceptibilities)

- Methicillin susceptible *Staphylococcus* species, according to susceptibilities:
    - First line:
        - Flucloxacillin 2 g intravenously 6 hourly **and**
        - Rifampicin 300 mg per oral 12 hourly.
    - Second line, if non-immediate without systemic involvement penicillin allergy:
        - Cefuroxime 1.5 g intravenously 8 hourly **and**
        - Rifampicin 300 mg per oral 12 hourly.

    - Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy:
        - Vancomycin or teicoplanin intravenously, deep-seated dosage as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 30-40 mg/l, **and**
        - Rifampicin 300 mg per oral 12 hourly.
- Methicillin resistant *Staphylococcus* species, according to susceptibilities:
    - First line:
        - Vancomycin or teicoplanin intravenously, deep-seated dosage as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 30-40 mg/l, **and**
        - Rifampicin 300 mg per oral 12 hourly.
    - Second line:
        - Daptomycin 6-8* mg/kg intravenously 24 hourly **and**
        - Rifampicin 300 mg per oral 12 hourly.
    - Third line:
        - Linezolid 600 mg intravenously 12 hourly (or per oral [absorption 100%]).
- *Streptococcus* species, according to susceptibilities:
    - First line:
        - Benzylpenicillin 1.2-2.4* g intravenously 6 hourly.
    - Second line, if non-immediate without systemic involvement penicillin allergy:
        - Ceftriaxone 2 g intravenously 24 hourly.
    - Third line, if immediate rapidly evolving or non-immediate with systemic involvement penicillin allergy:
        - Vancomycin or teicoplanin intravenously, deep-seated dosage as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 30-40 mg/l.
- *Enterococcus* species, according to susceptibilities:
    - First line:
        - Amoxicillin 1 g intravenously 6 hourly.
    - Second line:
        - Vancomycin or teicoplanin intravenously, deep-seated dosage as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 30-40 mg/l.
    - Third line:
        - Linezolid 600 mg intravenously 12 hourly (or per oral [absorption 100%]).
- *Corynebacterium* species, *Cutibacterium* species, Gram negative bacteria, and fungi:
    - Collaborate with the microbiology team.
- * Final dosage to be tailored to specific parameters of the pathogen (e.g. minimum inhibitory concentration) in collaboration with the microbiology consultant responsible for sterile site investigation or within a cardiology multi-disciplinary meeting.

CIED explanted: directed, intravenous antibiotics (with susceptibilities)

- Methicillin susceptible *Staphylococcus* species, 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, deep-seated dosage as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 30-40 mg/l.
- Methicillin resistant *Staphylococcus* species, according to susceptibilities:
    - First line:
        - Vancomycin or teicoplanin, deep-seated dosage as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 30-40 mg/l.
    - Second line:
        - Daptomycin 6-8* mg/kg 24 hourly.
    - Third line:
        - Linezolid 600 mg 12 hourly (or per oral [absorption 100%]).
- *Streptococcus* species, according to susceptibilities:
    - First line:
        - Benzylpenicillin 1.2-2.4 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, deep-seated dosage as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 30-40 mg/l.
- *Enterococcus* species, according to susceptibilities:
    - First line:
        - Amoxicillin 1 g 6 hourly.
    - Second line:
        - Vancomycin or teicoplanin, deep-seated dosage as per hospital guidelines, vancomycin target pre dose level 15-20 mg/l, teicoplanin target pre dose level 30-40 mg/l.
    - Third line:
        - Linezolid 600 mg 12 hourly (or per oral [absorption 100%]).
- *Corynebacterium* species, *Cutibacterium* species, Gram negative bacteria, and fungi:
    - Collaborate with the microbiology team.
- * Final dosage to be tailored to specific parameters of the pathogen (e.g. minimum inhibitory concentration) in collaboration with the microbiology consultant responsible for sterile site investigation or within a cardiology multi-disciplinary meeting.

Intravenous to per oral step down

- If returned to the cath lab or taken to theatre for removal of the CIED, and if the patient is afebrile, observations stable, and inflammatory markers downward trending, collaborate with the cardiology consultant regarding ± per oral step down.

CIED explanted: directed, per oral antibiotics (with susceptibilities)

- Methicillin susceptible *Staphylococcus* species, according to susceptibilities:
    - Please liaise with the microbiology consultant responsible for sterile site investigations, or collaborate and discuss within cardiology multi-

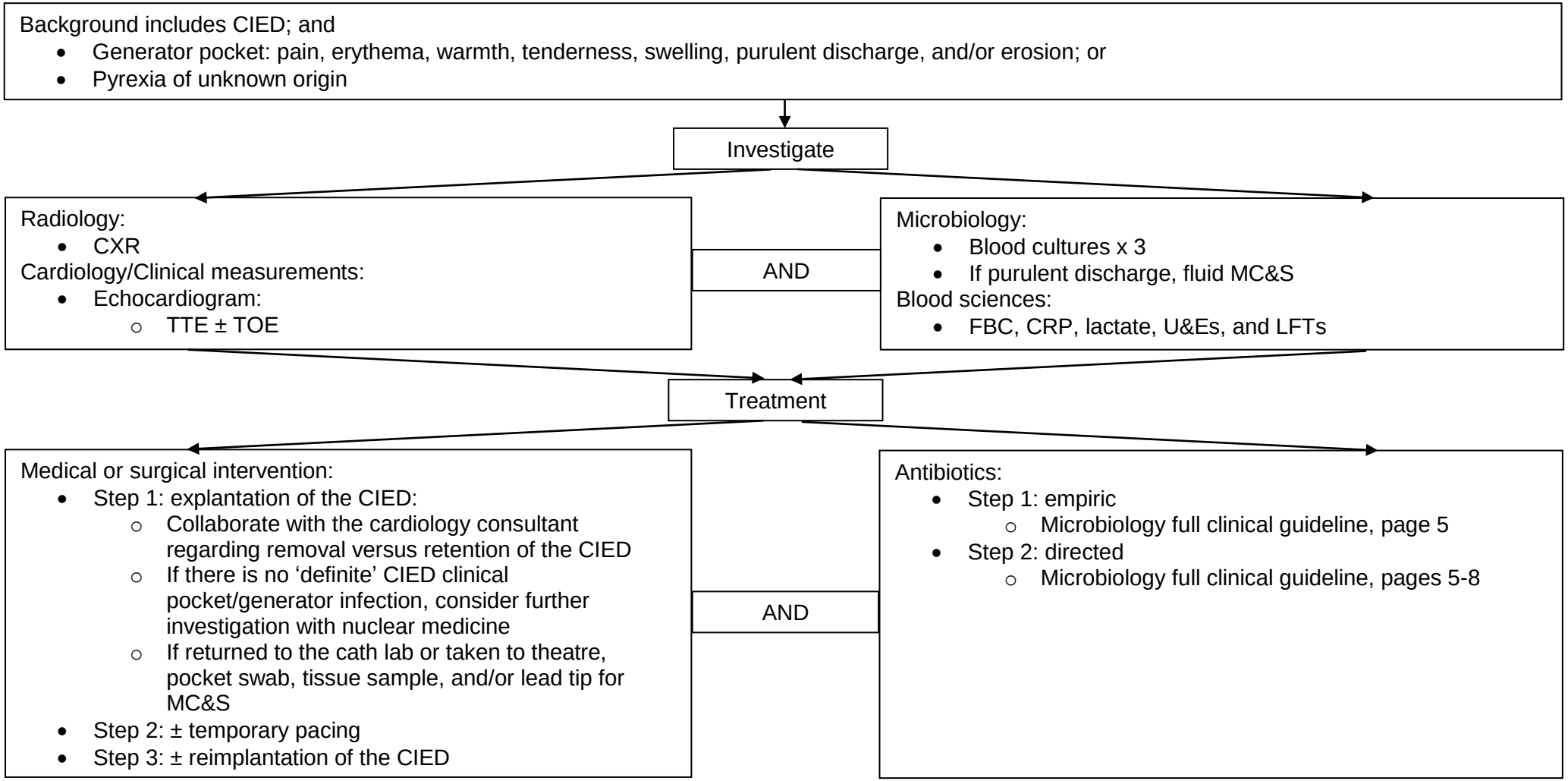
disciplinary meetings, regarding *Staphylococcus* species pocket infections.
    - Per oral options may include:
        - Flucloxacillin 1 g 6 hourly; or
        - Cefalexin 1 g 8 hourly; or
        - Doxycycline 100 mg 12 hourly; or
        - Clindamycin 300-450 mg* 6 hourly; or
        - Co-trimoxazole 960 mg 12 hourly.
- Methicillin resistant *Staphylococcus* species, according to susceptibilities:
    - Please liaise with the microbiology consultant responsible for sterile site investigations, or collaborate and discuss within cardiology multi-disciplinary meetings, regarding *Staphylococcus* species pocket infections.
    - Per oral options may include:
        - Doxycycline 100 mg 12 hourly; or
        - Clindamycin 300-450* mg 6 hourly; or
        - Co-trimoxazole 960 mg 12 hourly.
- *Streptococcus* species, according to susceptibilities:
    - First line:
        - Amoxicillin 500 mg 8 hourly.
    - Second line:
        - Doxycycline 100 mg 12 hourly.
    - Third line:
        - Clindamycin 300-450* mg 6 hourly.
- *Enterococcus* species, according to susceptibilities:
    - First line:
        - Amoxicillin 1 g 8 hourly.
    - Second line:
        - Linezolid 600 mg 12 hourly.
    - Third line:
        - Collaborate with the microbiologist.
- *Corynebacterium* species, *Cutibacterium* species, Gram negative bacteria, and fungi:
    - Collaborate with the microbiology team.
- * 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 a cardiology multi-disciplinary meeting.

Duration of antibiotics

- 14 days, from removal of the CIED.

University Hospitals of Derby and Burton NHS Foundation Trust

Management of CIED pocket infection



Appendix 1: Gentamicin

Please note the bespoke gentamicin infective endocarditis prescription chart.

Treatment dose	Infective endocarditis: 1 mg/kg intravenously 12 hourly
Contraindications	BNF: "myasthenia gravis"
Interactions	Please review the BNF for up-to-date interactions
Common or very common side-effects (please review the BNF for uncommon and rare or very rare)	Skin reactions, tinnitus
Important side-effects of note	Vestibular toxicity, ototoxicity, nephrotoxicity
Renal impairment	BNF: "If there is impairment of renal function, the interval between doses must be increased; if the renal impairment is severe, the dose itself should be reduced as well. Excretion of aminoglycosides is principally via the kidney and accumulation occurs in renal impairment. Ototoxicity and nephrotoxicity occur commonly in patients with renal failure"
Therapeutic drug monitoring • Recommended • Sample 1 of 2, pre dose • Sample 2 of 2, post dose • Therapeutic level, trough • Therapeutic level, peak • Repeat	Yes, before and after the 3rd dose 1-2 ml serum, pre dose 1-2 ml serum, post dose (1 hour after the end of administration) < 1 mg/l 3-5 mg/l Daily, until pre/trough and post/peak levels are within range. Twice weekly, thereafter
Dose and frequency advice	Within the working day, discuss with the ward pharmacist or antimicrobial pharmacist Out-of-hours, discuss with the on call pharmacist

Regarding CIED pocket infection empiric antibiotics:

- Please inform the patient of gentamicin's known side-effects, especially vestibular toxicity, ototoxicity, and nephrotoxicity.
- Please refer the patient to the audiology department for baseline assessment of hearing, and re-refer if the patient or the physician notes side-effects, for example impaired balance, dizziness, and/or hearing impairment.
- Please monitor the patient's kidney function ≥ twice weekly.
- If side-effects of vestibular toxicity, ototoxicity, or kidney dysfunction-failure manifest, stopping/withholding gentamicin is recommended. Please notify the microbiology team if gentamicin is stopped/withheld.

References

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Document control

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