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Guidelines for the diagnosis, management and prevention of implantable cardiac electronic device infection

James L Harrison¹, Bernard D Prendergast², Jonathan A T Sandoe³

1 Electrophysiology Fellow and Specialist Registrar in Cardiology, Imperial College Healthcare NHS Trust, London, UK

2 Consultant Cardiologist, Oxford University Hospital NHS Trust, Oxford, UK

3 Associate Clinical Professor and Consultant Microbiologist, University of Leeds and Leeds Teaching Hospital NHS Trust, Leeds, UK

Introduction

Implantable cardiac electronic devices (ICED) comprise permanent pacemakers (PPM), implantable cardioverter defibrillators (ICD) and cardiac resynchronisation therapy (CRT). Implantation rates in the UK are increasing¹ and are set to rise further in the wake of recent guidelines that significantly widen eligibility criteria.² However, an unfortunate consequence is the associated increase in ICED infections with attendant morbidity and mortality. The incidence of ICED infections is increasing in the US³ and a similar increase in the UK seems inevitable.

ICED infections can be extremely challenging to diagnose and manage, and can involve any combination of the generator pocket, device leads and endocardial structures; the latter associated with particularly high mortality. Device extraction has a significant risk of serious complications and mortality.⁴ Multiple and long hospital attendances are common and attempts to salvage infected devices are frequently unsuccessful.⁵

Strategies for preventing and managing ICED infections vary widely and the evidence to guide practice is limited. Until now, the only published guidelines in this difficult area were from the American Heart Association (AHA) in 2010.⁶ Recent joint guidelines from the British Society for Antimicrobial Chemotherapy (BSAC), British Heart Rhythm Society (BHRS), British Cardiovascular Society (BCS), British Heart Valve Society (BHVS) and British

Society of Echocardiography (BSE) promote a standardised approach to this important and increasing clinical problem.⁷ In this article we summarise their key messages.

Epidemiology

The UK incidence of ICED infection is unknown and extrapolating international estimates may be inappropriate due to varying case definitions and measures of incidence. Acknowledging variable follow up periods, the international literature suggests an overall incidence of infection of 0.5-2.2% of implants, with higher incidence for ICD/CRT compared with PPM and redo procedures compared with primary implants. An increasing number of patients receiving ICED have renal impairment, heart failure and diabetes mellitus, which increase the risk of subsequent infection.

The new guidelines⁷ recognise the paucity of UK data and recommend prospective collection of infection rates at 6 months, 1 and 2 years (as well as per 1000 device-years) to define the baseline UK incidence of ICED infection against which future data could be compared. Accurate mortality data are needed – current assessments vary widely due to varying definitions, device types and co-morbidities.

Diagnosis

The guidelines categorise ICED infections as early post implantation inflammation, uncomplicated and complicated generator pocket infections, ICED-infective endocarditis (ICED-IE) and ICED lead infections (ICED-LI) (Table 1). Pocket infections are characterised by localised cellulitis, swelling, discharge, dehiscence or pain. Wound inflammation occurring soon after implantation (“superficial cellulitis”) can be an early sign of pocket infection, but can also be caused by non-infective conditions. The device should be considered infected once the skin is breached due to erosion. Pocket infections frequently co-exist with ICED-IE/LI and often present insidiously with fevers, rigors, night sweats, malaise and anorexia – the presence of an ICED is all too often disregarded. Patients with ICED-IE/LI may also present with secondary spinal or pulmonary infection - fewer than 10% present with

septic shock. Whilst the modified Duke criteria for IE are unproven in this setting, the guidelines recommend their use as an objective tool.

Echocardiography

Echocardiography should be performed as soon as possible (< 24 hours) once a diagnosis of ICED infection has been considered and in all patients with generator pocket infections and signs/symptoms of systemic infection or positive blood cultures. Echocardiography should also be repeated after ICED removal to identify persisting vegetations.

Transthoracic (TTE) and transoesophageal echocardiography (TOE) are complementary techniques, although TOE has higher diagnostic sensitivity in ICED-IE/LI. An oscillating or sessile mass attached to a lead suggests vegetation although masses can be seen on non-infected leads and false negatives are common.

Microbiological sampling

Culture samples should include blood, distal and proximal lead fragments, lead vegetations, generator pocket tissue and pus from the pocket wound, as appropriate. Meticulous technique is needed to prevent contamination – coagulase-negative staphylococci are a common contaminant as well as a frequent cause of ICED infection. Lead fragments can be easily contaminated if there is pocket infection.

Three sets of blood cultures should be taken from peripheral sites at least six hours apart prior to starting antibiotics unless there is severe sepsis and suspected ICED infection when two sets at different times within an hour will suffice. Blood cultures should be repeated 48-72 hours after ICED removal.

In a patient with an ICED, a single positive blood culture for *Staphylococcus aureus* or multiple positive cultures for another organism necessitate active exclusion of ICED infection.

Treatment

The aims of treatment are to provide a cure whilst minimising harm to the patient, reduce the number and duration of hospital admissions, reduce the

number of procedures and reduce exposure to unnecessary antibiotics. Potential risks include device removal and replacement, adverse antibiotic reactions, complications of long-term vascular access, healthcare-associated infection and involvement of antimicrobial-resistant microorganisms.

ICED removal

An infected ICED may be left in situ, or removed partially (either intentionally, or unintentionally during an attempted complete removal) or entirely. The guidelines recommend that the ICED can be initially left in situ if there is early post implantation inflammation whilst the patient is observed. However, complete removal of the ICED system (generator and all leads) should be undertaken as early as possible (< 2 weeks from diagnosis), in combination with appropriate antibiotic therapy, for pocket infections and ICED-IE/LI. Early ICED removal increases the chance of successful removal and is associated with high cure rates, albeit with a small risk of mortality.⁸ Consistent with this, a large international prospective cohort study demonstrated significantly lower one year mortality if the ICED was removed during the initial hospitalisation.⁴ Percutaneous procedures for ICED removal are preferred and should only take place in expert centres where surgical facilities are immediately available owing to the risk of life-threatening complications. Open surgical removal should be reserved for large (>20 mm) lead-associated vegetations or when surgery is indicated for other reasons.

Re-implantation and temporary pacing

The need for ICED re-implantation (and its timing) after removal of an infected system depends on the indications for the original implant. Where possible, reimplantation should be delayed until symptoms and signs of local and systemic infection have resolved. An externalised tunneled system is preferable to a temporary pacing wire via central venous access if interim pacing is needed.

Antibiotic therapy

The antimicrobial strategy should involve a multidisciplinary approach and depends on clinical status, plans for device reimplantation, endocardial involvement and extra-cardiac foci of infection. Allergies, concurrent medication and renal function need to be considered in the choice of agent.

The use of antibiotics for early post implantation inflammation is controversial – a short course of treatment may prevent progression, but may also mask a pocket infection, delay appropriate treatment or expose the patient to unnecessary treatment if infection is absent. Empirical antibiotics are always indicated for generator pocket infections. The presentation of ICED-IE/LI is often indolent and it is preferable to await culture and sensitivity testing where feasible.

Suggested empirical regimens are detailed in Table 1 – definitive treatment should be determined by culture results. Whilst administration via peripheral cannulae (changed every 72 hours) confers lowest risk, peripherally inserted central catheters are recommended for long-term antibiotic administration. Central venous access increases the risk of venous thrombosis and infection, reduces access options for future ICED re-implantation and should be avoided.

The total duration of antibiotic therapy should be judged on an individual basis - a blanket approach would result in inappropriate antibiotic exposure. Generator pocket infections usually require 10-14 days of treatment, provided the ICED has been removed and local soft tissue infection has resolved. ICED-IE/LI requires a longer duration dependent upon the rapidity of ICED removal, presence or absence of a prosthetic valve or extra-cardiac infection and the initial clinical response to treatment. Six weeks of therapy is recommended if ICED salvage is attempted although the risk of relapse is high.

Prevention

Operating environment and personnel

The guidelines acknowledge that implanting ICEDs in an operating theatre environment with dedicated laminar airflow is aspirational. Nevertheless, procedures should take place in an appropriately ventilated (at least 15, but ideally 25 air changes/hr), equipped and cleaned room. Implantations should be performed or supervised by experienced operators⁹ and particular reference is made to generator changes, which are associated with a higher incidence of ICED infection than primary implants and are often performed by inexperienced trainees without supervision.

Pre-procedure

Temporary transvenous pacing should be avoided where possible and the guidelines endorse the trend towards use of permanent ICED implantation in the acute setting, while acknowledging that the timing of re-implantation requires research.

Elective procedures should be delayed if there are signs of systemic infection. Patients colonised by methicillin-resistant *Staphylococcus aureus* should receive topical decontamination prior to ICED implantation.

Post-operative haematoma formation is a risk factor for ICED infection and anticoagulants and antiplatelet agents should be stopped five days before the procedure where possible. Uninterrupted warfarin (with careful INR monitoring) rather than heparin bridging is recommended in situations where anticoagulation cannot be stopped.

Supported by meta-analysis,¹⁰ the guidelines recommend that intravenous antibiotics should be given within one hour prior to ICED implantation. It is important that tissue and plasma antibiotic concentrations exceed the minimum inhibitory concentration throughout the procedure and likely infective pathogens are covered. The guidelines therefore recommend routine use of glycopeptides (teicoplanin may be given as a bolus and has practical advantages over vancomycin) and supplementary gentamicin may be considered depending on local epidemiology. There is no benefit from repeat dosing after the procedure and no evidence to support locally instilled antibiotics.

Procedure

Strict aseptic technique must be observed at all times, including operating theatre discipline and appropriate clothing. Razors increase the risk of infection and electric clippers should be used for hair removal. Skin should be decontaminated with 2% chlorhexidine and left until dry (minimum 30 seconds). Multiple drapes probably render bacteria airborne and a single large drape is recommended.

Conclusion

ICED infection is an increasing and challenging clinical problem. Current practice in diagnosis, treatment and prevention varies widely and is based on limited evidence. The recent UK multidisciplinary guidelines provide a standardised approach and highlight the importance of accurate data monitoring, rigorous implantation technique, standardised protocols and a more rapid and aggressive approach to complete ICED removal in all cases of pocket, lead or endocardial infection. Adherence to these guidelines should substantially reduce the significant morbidity and mortality associated with this dangerous condition.

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	Definition	Treatment	Empirical antibiotics*
Early post implantation inflammation	Erythema affecting the box implantation incision site, without purulent exudate, dehiscence, fluctuance or systemic signs of infection and occurring within 30 days of implantation. Includes a small, localised area (<1 cm) of erythema and/or purulence associated with a suture (“stitch abscess”).	Close observation. ICED can initially be left in situ. Role of antimicrobials unclear.	Consider 7-10 days of treatment with flucloxacillin 0.5-1g po qds (Penicillin allergy or MRSA colonisation – doxycycline 100mg po bd OR linezolid 600mg po bd OR clindamycin 450mg po qds)
Uncomplicated generator pocket infection	Any one of: <ol style="list-style-type: none"> 1. Spreading cellulitis affecting the generator site 2. Incision site purulent exudate (excluding simple stitch abscess) 3. Wound dehiscence 4. Erosion through skin with exposure of the generator or leads 5. Fluctuance (abscess) or fistula formation AND no systemic symptoms or signs of infection AND negative blood cultures	Complete removal of the ICED system (generator and all leads) as soon as possible (< 2 weeks from diagnosis) followed by antimicrobial treatment for skin and soft tissue infection (see guidelines for preferred agents).	Vancomycin 1g iv bd OR daptomycin 4mg/kg iv od OR teicoplanin 6mg/kg to a maximum of 1g given at 0, 12 and 24 hours and then 24 hourly
Complicated generator pocket infection	As for uncomplicated generator pocket infection but with any one of: <ol style="list-style-type: none"> 1. Evidence of lead or endocardial involvement 2. Systemic signs or symptoms of infection 3. Positive blood cultures 	Complete removal of the ICED system. Antimicrobial treatment options and duration of antimicrobial therapy depend on echo findings: if no native valve involvement treat as uncomplicated generator	Vancomycin 1g iv bd AND meropenem 1g iv tds OR Daptomycin 8-10mg/kg iv od AND meropenem 1g iv tds

		pocket infection.	
ICED lead infection (ICED-LI)	<p>Symptoms and signs of systemic infection without signs of generator pocket infection, but with:</p> <p>Definite ICED-LI – either:</p> <ol style="list-style-type: none"> 1. Echocardiography consistent with vegetation(s) attached to lead(s) and major modified Duke microbiological criteria 2. Culture, histology or molecular evidence of infection on explanted lead <p>Possible ICED-LI – either:</p> <ol style="list-style-type: none"> 1. Echocardiography consistent with vegetation(s) attached to lead(s) but no major modified Duke microbiological criteria 2. Major modified Duke microbiological criteria but no echocardiographic evidence of lead vegetation(s). 		<p>N.B. gentamicin or other anti Gram-negative agents may be appropriate depending on local epidemiology.</p> <p>Choice of vancomycin or daptomycin depends on risk of acute kidney injury.</p>
ICED associated infective endocarditis (ICED-IE)	<p>All of:</p> <ol style="list-style-type: none"> 1. ICED in situ 2. Modified Duke criteria for definite infective endocarditis 3. Echocardiographic evidence of valve involvement 		

*Doses should be checked/revised in patients with renal/hepatic impairment; drug interactions and allergies considered.

Table 1: ICED infection definitions, treatment and empirical antibiotic regimens.