Guidelines for the diagnosis, prevention and management of Implantable Cardiac Electronic Device Infection.

Report of a joint working party project on behalf of the British Society for Antimicrobial Chemotherapy (BSAC, host organization), Heart Rhythm UK, British Cardiovascular Society (BCS), British Heart Valve Society (BHVS) and British Society for Echocardiography (BSE).

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A Summary.

C. Methods
- Guidelines were developed using AGREE II methodology and evidence rated according to Grade recommendations by a working party comprising consultant cardiologists, microbiologists, infectious diseases physician, an antimicrobial pharmacist and representatives of NHS management.

D. Epidemiology

D1. What is the incidence of ICED infection (in the UK)?
- The current incidence of ICED infection in the UK is unknown.
- More complex devices and procedures increase infection rates.
- ICED infections are increasing in incidence in the USA and are likely to increase in the UK.
- The risk of infection following the primary procedure is lower than that of subsequent procedures.

D2. Should incidence of ICED infection be measured and reported?
- Recommendation D1: Standardised definitions for ICED infection should be applied throughout the UK and data collected prospectively on infection rates per procedure.
- Recommendation D2: Infection rates should be collated separately for primary and subsequent procedures.
- Recommendation D3: The UK dataset of ICED infections should include risk factors for infection and pathogens.

What are the risk factors for ICED infection?
- The number of prior procedures, the complexity of the procedure and a lack of antibiotic prophylaxis are the most consistently identified risk factors for ICED infection.

D4. What is the mortality associated with ICED infection?
- All cause mortality ranges between 0-35%.

D5. What are the risk factors for mortality in ICED infections
- Mortality is high in the first year following ICED infection, but many deaths are not infection related.
- Abnormal renal function is the most consistently identified risk factor for mortality.
- Failure to remove an infected device is associated with relapse and mortality.
- ICED associated endocarditis has a higher mortality than localised generator pocket infection.

D6. What are the most common microbial causes of ICED infection?
- Staphylococci (and Gram-positive bacteria in general) cause the majority (68-93%) of infections.
- Gram-negative bacteria cause fewer than 18% of infections.
- Approximately 15% of ICED infections are culture negative.

D7. Which antimicrobial agents are they usually susceptible to?
- UK data on the antimicrobial susceptibility of ICED infection pathogens are not available.
- 67% of coagulase negative staphylococci and 42% of Staphylococcus aureus UK bloodstream isolates were methicillin resistant (surveillance data up to 2006).

D8. Does the microbiological cause with time of presentation?
- There are no clinically useful differences in the pathogens causing ICED infection in relation to time after implantation.
- Recommendation D4: The one year cut-off commonly used to define healthcare associated infection in device implantation should not be applied to ICED infections.

E. Pathogenesis
- Microbial contamination of a device can occur: i) during manufacture or packaging; ii) prior to implantation; iii) during implantation; iv) secondary to surgical site infection; v) via haematogenous seeding from a distant site, or; vi) via contamination after erosion through the skin.
- Asymptomatic colonization of ICEDs can occur with normal skin commensals and infection may develop at a later stage.

F. Clinical diagnosis

F1. What are the clinical features of ICED infection?
- Generator pocket infection is characterised by localised cellulitis, swelling, discharge, dehiscence or pain.
• Wound inflammation can be an early presentation of generator pocket infection.
• Generator pocket infection and ICED-IE or ICED-LI frequently coexist.
• Non-specific symptoms of systemic infection (including fevers, chills, night sweats, malaise and anorexia) may be the only clinical features of ICED-IE or ICED-LI.
• Fewer than 10% of patients present with septic shock.
• Clinical diagnosis of ICED-IE or ICED-LI can be challenging and is often delayed.
• ICED-IE or ICED-LI may present with secondary foci, such as spinal or pulmonary infection.
• The Duke criteria can be used to assist a diagnosis of ICED-IE or ICED-LI.

F2. What is the risk of ICED infection in patients with bloodstream infection?
• 30-45% of patients with a sustained staphylococcal bacteraemia and an ICED in situ, have ICED infection.
• Recommendation F1: Patients with an ICED and S. aureus in blood cultures or other microorganisms in multiple blood cultures should be actively investigated for ICED infection.

G. Echocardiography and other imaging modalities in ICED infection?

G1. What is the role of chest radiography?
• Recommendation G1: A chest x-ray should be carried out in all patients with suspected ICED infection. [C]
• Recommendation G2: CT scanning or CT pulmonary angiography should be considered when ICED infection is suspected and echocardiography is non-diagnostic. [C]

G2. What is the diagnostic accuracy of echocardiography?
• Transoesophageal echocardiography has higher sensitivity in establishing ICED-LI or ICED-IE than transthoracic echocardiography.
• In patients with ICED-IE the aortic and mitral valves can be involved in addition to lead and tricuspid valve infection.
• Echocardiographic findings consistent with a lead vegetation are defined as attachment of an oscillating or sessile mass to a lead, but findings should be interpreted in the clinical context, because masses can be present on non-infected leads.

G3. When should echocardiography be performed?
• Recommendation G3. Echocardiography should be carried out as soon as possible (within 24 hours) after a diagnosis of ICED infection is considered. [C]
• Recommendation G4. Echocardiography should be undertaken in all patients presenting with generator pocket infection and symptoms or signs of systemic infection/positive blood cultures to diagnose concurrent ICED-LI or ICED-IE. [B]
• Recommendation G5. Echocardiography should be performed in all patients in whom ICED-LI or ICED-IE infection is suspected clinically (according to Section F.1). [B]
• Recommendation G6. Echocardiography should be undertaken in patients with an ICED and S. aureus in one or more blood cultures or other microorganisms in multiple blood cultures. [B]
• Recommendation G7. Repeat echocardiographic imaging is recommended after ICED removal to identify persisting valve or mural vegetations. [C]

G4. What is the role of PET scanning?
• Recommendation G8: Routine use of PET scanning outside research studies is not currently recommended. [C]

H. Microbiological Sampling and Processing

H1. Which samples should be collected to establish the cause of ICED infection?
• Appropriate microbiological samples include: culture of blood, lead fragments (ideally distal and proximal), lead vegetation, generator pocket tissue and pus from a discharging generator pocket wound.

H2. When should blood cultures be taken?
• Recommendation H1. Blood cultures should be taken prior to starting antimicrobial therapy. [B]
• Recommendation H2: On clinical suspicion of ICED infection in patients with a chronic or subacute presentation, three sets of optimally filled blood cultures should be taken from peripheral sites with ≥6 h between them. [C]
• Recommendation H3: To avoid undue delay in patients with suspected ICED infection and severe sepsis or septic shock at the time of presentation, two sets of optimally filled blood cultures should ideally be taken at different times within 1 hour and prior to commencement of empirical antimicrobial therapy. [C]
• Recommendation H4: Blood cultures should be taken 48-72 hours after removal of an infected ICED [C]
Recommendation H5: Apply meticulous aseptic technique when taking blood cultures to reduce the risk of contamination with skin commensals. [B]

H3. How should the generator pocket be sampled at the time of removal?
• Recommendation H6: In patients with clinical evidence of infection, tissue (approximately 2 cm²) should be excised from the pocket-site and sent for culture. [B]

H.4. What laboratory methods should be used during processing?
See full guideline for discussion

I Definitions

I.1 Uncomplicated generator pocket wound 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. A localized area (<1cm) of erythema and or purulence associated with a suture is included in this group (“stitch abscess”).

I.2 Uncomplicated generator pocket infection
a. Spreading cellulitis affecting the generator site OR;
b. Incision site purulent exudate (excluding simple stitch abscess), OR;
c. Wound dehiscence, OR;
d. Erosion through skin with exposure of the generator or leads, OR;
e. Fluctuance (abscess) or fistula formation;
AND
No systemic symptoms or signs of infection AND negative blood cultures.

I.3 Complicated generator pocket infection.
As for uncomplicated criteria but evidence of lead or endocardial involvement, systemic signs or symptoms of infection or positive blood cultures.

I.4 ICED isolated lead infection (ICED-LI).
Definite ICED-LI:
1. Symptoms/signs of systemic infection (see Section F.1)
NO signs of generator pocket infection (see Section I.1)
AND
Echocardiography consistent with vegetation(s) attached to lead(s)
AND
Presence of major Duke microbiological criteria.¹

2. Symptoms/signs of systemic infection (see Section F.1)
NO signs of generator pocket infection (see Section I.1 a-d)
AND
Culture, histology or molecular evidence of infection on explanted lead.

Possible ICED-LI:
1. Symptoms/signs of systemic infection (see Section F.1)
AND
Echocardiography consistent with vegetation(s) attached to lead(s)
BUT
No major Duke microbiological criteria present.¹

2. Symptoms/signs of systemic infection (see Section F.1)
AND
major Duke microbiological criteria present¹
BUT
No echocardiographic evidence of lead vegetations.

I.5 ICED associated native or prosthetic valve endocarditis (ICED-IE)
• Duke criteria for definite endocarditis satisfied, with echocardiographic evidence of valve involvement in a patient with an ICED in situ.

J Management of ICED infection

J.1 How should the device be managed?
J.1.1 In uncomplicated generator pocket wound inflammation?

- Recommendation J1: In uncomplicated generator pocket wound inflammation, the ICED can initially be left in situ. [B]

J.1.2 In generator pocket infection, ICED-LI and ICED-IE?

- Recommendation J2: Complete and early (during the index admission) removal of an infected ICED system (generator and all leads) combined with appropriate antimicrobial therapy is the most effective, safe and efficient treatment option. [B]

J.1.3 What is the preferred means of device removal?

- Recommendation J3: Percutaneous methods of lead removal are preferred for infected leads, combined with complete removal of the generator. [B]
- Recommendation J4: Open surgical removal should be considered for large lead-associated vegetations (>20mm) and when valve surgery is indicated for other reasons. [C]

J.1.4 What proportion of patients are too unwell or refuse complete ICED removal?

- 3-15% patients decline, or are unsuitable for ICED removal.

J.1.5 How should an infected ICED be managed if removal is not an option?

- Recommendation J5: In a patient with ICED-associated IE, it is reasonable to attempt salvage of the device with a course of appropriate antimicrobial therapy when the risks of removing the infected ICED are considered too high, or a patient declines system removal. [C]
- Recommendation J6: In a patient with an infected ICED that involves generator pocket infection, in whom the risks of removing the entire device are considered too high (or a patient declines entire system removal) the generator should be removed, leaving the leads in situ, and a course of appropriate antimicrobial therapy given. [C]

J.1.6 Where should removal of infected ICEDs be undertaken?

- Recommendation J7: Removal of infected ICEDs should only be undertaken in recognised centres with expertise in the procedure and with appropriate surgical facilities immediately available. [C]

J.1.7 How should the device be managed in skin erosion?

- Recommendation J8: Erosion of skin to expose either leads or generator to the air requires removal of the entire system. [C]

J.1.8 If required, when should device re-implantation take place?

- Recommendation J9: The need for and timing of a replacement ICED after removal of an infected device will depend on the indications for its use. Wherever possible, implantation of a new ICED should not take place until symptoms and signs of systemic and local infection have resolved (after 7-10 days). [B]
- Recommendation J10: The venous access sheath used for percutaneous removal of an infected system should not be used for re-implantation of a new system. [C]

J.2 Principles of antimicrobial therapy.

- Recommendation J11: Antimicrobial treatment strategies should be discussed by the multidisciplinary team and determined by plans to remove or attempt to salvage an infected ICED, the presence of ICED-IE and any extra-cardiac foci of infection. [C]

J.2.1 Biofilm and ICED infection

- The biofilm nature of ICED infection makes eradication of infection very unlikely without removal of the device.

J.2.2 Which antimicrobials are recommended for uncomplicated generator pocket wound inflammation?

- Recommendation J12: The decision to commence antimicrobials for uncomplicated generator pocket wound inflammation should be determined on a case-by-case basis, using an oral antimicrobial appropriate for soft tissue infection (Figure 1). [C]

J.2.3 Which antimicrobials are recommended for uncomplicated generator pocket infections?

- Recommendation J13: When there is clinical evidence of generator pocket infection empirical antimicrobial therapy should be commenced (Table 6, Figure 2). [C]
- Recommendation J14: Directed (targeted) antimicrobial regimens for treatment of generator pocket infection when the microbial cause is known are shown in Table 7. [C]
- Recommendation J15: Local antimicrobial instillation into an infected generator pocket is not recommended. [C]
J.2.4 Which antimicrobial agents are recommended for complicated generator pocket infections?
- Recommendation J16: Treat complicated generator pocket infection as for ICED-LI or ICED-IE depending on final diagnosis. [C]

J.2.5 Which antimicrobial agents are recommended for ICED-LI or ICED-IE?
- Recommendation J17: Empirical regimens for ICED-LI or ICED-IE are shown in Table 6. [C]
- Recommendation J18: The need for empirical antimicrobial treatment for ICED-LI or ICED-IE (prior to the availability of microbiological data) is a clinical decision based on the severity of infection. [C]
- Recommendation J19: The antimicrobial regimen for empirical treatment or culture-negative ICED infection needs to have activity against both Gram-positive (including methicillin-resistant staphylococci) and Gram-negative bacilli. [B]
- Recommendation J20: Vancomycin, teicoplanin and daptomycin are suitable anti-Gram-positive agents for empirical treatment or for culture-negative ICED infection. [B]
- Recommendation J21: Local resistance patterns should be considered in choosing anti-Gram-negative agents for empirical treatment of suspected ICED infection. Gentamicin and meropenem are both usually appropriate. [C]
- Recommendation J22: Modify treatment regimens once the microbial cause is identified. [C]

J.2.6 What regimens are recommended for attempted ICED salvage?
- Recommendation J23: Regimens for attempted salvage of ICED infection are summarized in Table 8. [D]
- Recommendation J24: Careful clinical observation is required to determine success after a course of antimicrobial therapy for attempted ICED salvage. [D]

J.2.7 What is the optimal route of administration of antimicrobial therapy for ICED infection?
- Recommendation J25: The type of vascular access device used to deliver antimicrobial therapy should be chosen according to a particular patient’s needs. Risks of healthcare associated infection, jeopardy to future potential ICED sites and convenience should be considered. [C]
- Recommendation J26: Peripheral cannulae carry the lowest infection risk and reduce the risk of damaging future sites for ICED implantation. [B/C]
- Recommendation J27: A peripherally inserted central catheter (PICC) or “midline” are preferred for long-term IV access and should be inserted and maintained according to national guidelines. [C]
- Recommendation J28: A switch to oral antimicrobials is appropriate for generator pocket infections after device removal but intravenous therapy is recommended for ICED-associated IE and attempted ICED salvage. [C]

J.2.8 What is the optimal duration of therapy for ICED infection?
- Recommendation J29: Duration of therapy should be determined by the type of ICED infection, proposed device management, involvement of other cardiac structures and the presence of extra-cardiac foci of infection (Table 5). [C]

J.2.9 What therapy is recommended if ICED salvage fails?
- Recommendation J30: If infection cannot be eradicated from an infected ICED in a patient who is unsuitable for system removal, long-term oral suppressive antimicrobial therapy can be attempted following discussion with an infection specialist. [C]

K. Prevention of ICED infection

K.1 Where should ICED insertion take place?
- Recommendation K1: ICED insertion should take in place in an appropriately ventilated, equipped and cleaned room. [C]

K.2 Does operator experience affect infection rates?
- Recommendation K2: Procedures, including generator change, should be performed or supervised by experienced operators as per Heart Rhythm UK guidelines. [B]

K.3 Should temporary pacing be avoided to reduce infection?
- Recommendation K3: Wherever possible, temporary transvenous pacing should be avoided prior to implanting a permanent ICED. [B]

K.4 Should ICED procedures be carried out in patients with signs of infection?
- Recommendation K4: Elective ICED implantation/replacement/revision should be delayed if there are any signs of systemic infection. [C]

K.5 Should patients having ICED insertion or manipulation be screened for MRSA?
There are no studies specifically relating to screening for MRSA or MSSA prior to ICED implantation.

Recommendation K5: Current national guidelines should be followed on screening for MRSA colonisation prior to elective ICED procedures. [C]

K.6 Should patients undergoing ICED procedures undergo “decolonization”?  
Recommendation K6: Pre-procedural topical antimicrobial agents aimed at eliminating *S. aureus* are not required in patients who are not colonized with MRSA. [C]

Recommendation K7: Bathing or showering with detergent is recommended prior to ICED insertion. [C]

K.7 How should anticoagulation be managed during ICED insertion or manipulation?  
Recommendation K8: Uninterrupted warfarin (with careful INR monitoring) is preferable to bridging with heparin in those patients in whom interruption of anticoagulation is contra-indicated. [B]

Recommendation K9: Where feasible, antiplatelet and/or anticoagulants should be discontinued prior to the procedure to allow a normal thrombotic/coagulation profile. [B]

K.8 Which infection control measures should be in place before ICED implantation?  
Recommendation K10: ICED insertion should be carried out using an aseptic technique, in an environment observing operating theatre discipline including appropriate clothing. [C]

Recommendation K11: Patients should be given specific theatre wear (including a hat) that provides easy access to the operative site and intravenous canulae, and considers the patient’s comfort and dignity. [C]

Recommendation K12: All staff should wear theatre specific clothing in all areas where ICED procedures are undertaken. Scrub suits, hats, masks and theatre footwear are essential parts of theatre discipline. [C]

Recommendation K13: The operating team should wear sterile gowns in the operating theatre during ICED procedures. Consider wearing two pairs of sterile gloves when there is a high risk of glove perforation. [C]

Recommendation K14: Staff number and movements should be kept to a minimum in the operating theatre. [C]

Recommendation K15: The operating team should remove hand/wrist jewelry, artificial nails and nail polish before procedures. [C]

Recommendation K16: The operating team should wash their hands prior to the first operation on the list using an aqueous antiseptic surgical solution, with a single-use brush or pick for the nails, and ensure that hands and nails are visibly clean. [C]

Recommendation K17: Before subsequent operations on a list, hands should be washed using either an alcoholic hand rub or an antiseptic surgical solution. If hands are soiled then they should be washed again with an antiseptic surgical solution. [B]

Recommendation K18: Any equipment brought into the operating field should be covered to reduce the risk of contamination. [C]

Recommendation K19: Devices and surgical equipment should be left uncovered for the minimum possible time. [C]

K.9 How should skin be prepared before ICED insertion/manipulation?  
Recommendation K20: If hair has to be removed, use electric clippers (with a single-use head) on the day of the procedure. Do not use razors for hair removal, because they increase the risk of surgical site infection. [A]

Recommendation K21: The skin over the operative site should be prepared using an alcoholic chlorhexidine preparation containing a minimum of 2% chlorhexidine. The skin prep should be left on for a minimum contact time of thirty seconds and should not be allowed to pool. [C]

Recommendation K22: A pragmatic approach to draping is recommended i.e. one large fenestrated drape can be used to cover the patient including the head. Do not use non-iodophor impregnated incise drapes routinely for ICED insertion as they may increase the risk of surgical site infection. [C]

K.10 Antibiotic Prophylaxis

K.10.1 Should systemic antimicrobial prophylaxis be used for ICED insertion?  
Recommendation K23: Systemic antibiotic prophylaxis should be used prior to ICED implantation. [A]

K.10.2 When should prophylaxis be administered?  
Recommendation K24: Intravenous antibiotics should be administered within the hour prior to skin incision. [A]

Recommendation K25: Repeat dosing of antimicrobials is not recommended after skin closure. [A]

K.10.3 Which agent(s) should be given?  
Recommendation K26: The choice of prophylactic agent should cover the most likely pathogens in ICED infection. [C]
• Recommendation K27: A glycopeptide (e.g. intravenous teicoplanin, according to local dosing protocols) is the current preferred agent (with or without gentamicin depending on local Gram-negative infection rates). [C]

K.10.4 Should antimicrobials be instilled into the generator pocket after implantation?
• Recommendation K28: Local instillation of antimicrobials or antiseptics should be avoided until evidence of benefit has been demonstrated. [C]

K.11 What represents ideal post-operative wound closure and care?
• Recommendation K29: National guidelines on postoperative wound closure and care should be followed. [C]

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Areas for future research

M. List of Abbreviations

N. Appendix 1 - Outline of structure and materials used in ICEDs

M. Appendix 2. Methods of Implantation and removal of ICED.
B  Introduction.

Implantable cardiac electronic devices (ICED) were introduced into routine clinical use in the 1960s. Since then their use has increased worldwide and now includes implantable cardiac defibrillators (ICD) and cardiac resynchronisation therapy (CRT) devices in addition to pacemakers (PPM). Infection is an uncommon but serious complication, which can manifest as infection of the generator ("box") pocket, the leads and can also involve endocardial structures; ICED infections now comprise approximately 10% of all endocarditis cases. Approximately 40 000 ICEDs were implanted in the UK in 2010, and the number of ICD and CRT implantations increased by 12.5% and 15.8%, respectively. The incidence of ICED infection per implanted device is usually less than 2% but infection rates per 1000 device days may be a more useful measure; a rate of 4.82/1000 device days was reported after first device implantation in a large Danish series. Mortality continues to be a concern. Analyses of the mortality following generator pocket infection compared to lead associated endocarditis has yielded conflicting results. The incidence of infections involving ICEDs is increasing in the US. Although equivalent data for the UK are unavailable, an increase in incidence is likely in the UK because the prevalence of patients with these devices is increasing.

Like endocarditis, ICED infections can be difficult to diagnose. In fact, diagnostic difficulties may be even greater than in IE because echocardiography is less accurate, blood culture is less sensitive and the diagnosis is often not considered. ICED infections are also complex to manage because there are intra-cardiac and extra-cardiac components, both of which may become infected and removal of the device can be a major undertaking, with a risk of mortality and significant complications. Long hospital stays and multiple inpatient episodes are common and attempts to salvage infected systems often result in unnecessarily prolonged courses of treatment. Prevention is therefore of vital importance.

Anecdotal and survey data suggest that clinical management and strategies for prevention of ICED infections are highly variable in the UK and frequently not based on currently available evidence. The British Society for Antimicrobial Chemotherapy (BSAC), Heart Rhythm UK and British Cardiovascular Society (BCS) all felt that there was a general lack of knowledge concerning ICED infections and their optimal management and a working party was established to synthesise currently available evidence and expert opinion into a clinical guideline.

The working party aimed to provide a pragmatic set of guidelines relating to the diagnosis, treatment and prevention of ICED infection in the UK, to promote a standardised approach to this important clinical problem, whilst accepting that the evidence-base for many recommendations was likely to be limited. This document should be read in conjunction with the Heart Rhythm UK Standards for implantation and follow-up of cardiac rhythm management devices in adults.

C  Methods.

The guideline was developed in accordance with AGREE II.

C.1  Scope and purpose.

The scope and purpose of the guideline were drafted by the Chair and approved by the Councils of the British Society for Antimicrobial Chemotherapy (BSAC), the British Cardiovascular Society (BCS), Heart Rhythm UK and the British Society of Echocardiography. The objectives can be summarized as:

1. To improve the quality of care provided to patients with ICEDs;
2. To provide an educational resource for all relevant healthcare professionals;
3. To encourage a multidisciplinary approach to ICED infection management;
4. To promote a standardized approach to the diagnosis, management and prevention of ICED infection through pragmatic evidence-rated recommendations;
5. To advise on future research projects/audit.
The guideline is intended to assist in the clinical care of patients with suspected or confirmed ICED infection in the UK. It is intended to inform local infection prevention and treatment policies and guidelines and to be used in the development of educational and training material by the relevant professional societies.

The questions covered by the guideline are presented at the beginning of each section.

C.2 Stakeholder involvement
The BSAC was the host organization in collaboration with the BCS and Heart Rhythm UK. The working party comprised members of all three organisations. The membership included a patient’s representative, Consultants in cardiology, medical microbiology, infectious diseases, clinical pharmacy, and NHS management.

C.3 Literature review
An initial PubMed keyword search using the terms “infection” and either “pacemaker”, “defibrillator” or “cardiac resynchronization therapy” was undertaken in October 2012 and found 869, 259 and 5 references, respectively. After deduplication 991 references remained. Additional references were added following review of manuscripts derived from the original search.

The working party agreed key questions and then used the results of the literature search when answering specific questions. Endnote X5 was used to store and access references. The level of evidence available to support each recommendation was categorised as: A, high-quality randomized controlled trials and meta-analysis of randomized controlled trials; B, observational data and non-randomized trials; and C, expert opinion or Working Party consensus.

Estimates of incidence were confined to studies of over 1000 patients. Descriptions of risk factors were confined to studies using multivariate statistical analysis. Summary descriptions of microbiological cause and outcomes were confined to studies of over 100 patients. Restricting the review to larger studies has a risk of bias against pure lead infections, hence case reports were included to illustrate specific points.

C.4 Consensus process and guideline development.
A lack of high quality evidence was anticipated because of the low incidence of ICED infection. The literature pertaining to each section of the guideline was initially reviewed by small subgroups of the working party and draft recommendations written. Each section was compiled into a draft guideline, which was circulated electronically within the working party for comment. Consensus was reached by an iterative process. Feedback was sent by each member to the Chair and the draft was revised until consensus was reached. Any issues where consensus could not be reached were discussed in a face-to-face meeting and it was agreed that either no consensus could be reached or a final decision was made.

D Epidemiology.

D.1 What is the incidence of ICED infection (in the UK)?
Summary:
- The current incidence of ICED infection in the UK is unknown.
- More complex devices and procedures increase infection rates.
- ICED infections are increasing in incidence in the USA and are likely to increase in the UK.
- The risk of infection following the primary procedure is lower than that of subsequent procedures.

In order to quantify the problem, plan healthcare provision and benchmark between centres, it is necessary to know the incidence of ICED infection. Twenty-two studies identified that included at least 1000 patients. Studies were heterogeneous and included patients from North America, various European
countries and Australia. The overall incidence of ICED infections ranged from 0.5-2.2% of patients in eighteen studies with follow-up or study periods between six weeks and 11 years. Incidence was measured in different ways in different studies: an incidence of 1.82 per 1000 pacemaker years following primary pacemaker implantation was described in Denmark, 9 1.9 per 1000 device years (85% PPM) in Minnesota, USA, 22 3.1 per 1000 patient years in a global study of ICDs, 29 and, 10.0 per 1000 patient years for cardiac resynchronisation therapy with defibrillator (CRT-D) in Italy. 26 The Minnesota study showed a significantly higher incidence in patients with ICDs compared to PPM (8.9 versus 1.0 per 1000 device years), 27 similar to the incidence found in the large CRT-D study from Italy (N = 3253). 26 However, in the Minnesota study only 15% of 1524 patients had an ICD. Two other large studies, that included a variety of devices, compared the proportion of patients developing infection in different device types over 6 and 11 year study periods. 33, 34 There was no difference in the rate of lead associated endocarditis (ICED-IE) in PPM vs ICD 35 and minimal differences in PPM vs ICD and CRT. 34 Four non-comparative studies that included only ICD patients showed that 0.2-1.8% developed infection over follow-up periods of 10.5-35 months. 29-31, 35 In a study that included data from four randomised-controlled trials (n = 1903), 1% of patients receiving a CRT device developed infection over 6 months of follow-up. 33 A summary of incidence studies is provided in Table 1.

The incidence of infection associated with primary implantation is approximately two to five times lower than for revision procedures (primary 0.5-0.8%, revision 1-4%) over follow-up periods of between 1 year and 3 years. 20, 24, 36 Using different measures, infection rates for primary and revision procedures were 1.82 and 5.32 per 1000 pacemaker years, respectively 9 and for CRT-D infection, 9.0 and 18 per 1000 patient years, respectively. 26 The REPLACE study only included patients undergoing a revision or upgrade of a pacemaker or defibrillator and found that 1.4% (no leads added) and 1.1% (one or more leads added) of patients suffered an infection over six months follow-up. 7

A large study from the USA recently showed a year on year increase (from 4.1% in 2004 to 5.8% in 2006) in the proportion of patients developing an ICED infection relative to the number of implantations each year. 15 The authors suggested a number of potential reasons for this including a significant year on year increase in the proportion of patients with organ system failure or diabetes receiving an ICED and an increase in the proportion of patients receiving a device who were not Caucasian. 15 In a study of 4.2 million patients, a 1.6% increase in infections was found between 1993 and 2008 with a significant increase from 1.53% to 2.41% between 2004 and 2008. 7 This coincided with a marked increase in the proportion of patients with renal failure, respiratory failure, heart failure or diabetes mellitus, with a significantly increased risk of mortality in those with renal, respiratory or heart failure. 7

Historically, the incidence of infection associated with devices sited in the wall of the abdomen or implanted at thoracotomy was higher than devices implanted at the pectoral site or transvenously; for example, 3.2% vs. 0.5% for primary abdominal versus pectoral implantation and 5.8% vs. 0.8% for thoracotomy versus non-thoracotomy route of insertion. 33, 37 Based on studies that reported the time of presentation, the majority of patients with infection present within 12 months of implantation (63-77% in 3 studies with prolonged follow-up), 21-31% within 1 month and 23-37% after 1 year. 20, 34, 37 In an eleven year study that included only patients with lead associated endocarditis, however, two-thirds of patients presented after one year. 33

D.2 Should incidence of ICED infection be measured and reported?

Summary:
- Recommendation D1: Standardised definitions for ICED infection should be applied throughout the UK and data collected prospectively on infection rates per procedure. [C]
- Recommendation D2: Infection rates should be collated separately for primary and subsequent procedures. [C]
- Recommendation D3: The UK dataset of ICED infections should include risk factors for infection and pathogens. [C]

There are no currently agreed UK (or international) definitions of ICED infection. We therefore propose standardised definitions in Section I. Infections of ICEDs are potentially preventable. Infection rates therefore need to be monitored and actions taken if infection rates rise or exceed expected levels. A period of surveillance using standardized definitions will be necessary to determine baseline infection rates in the UK.
D.3 What are the risk factors for ICED infection?

Summary:
- The number of prior procedures, the complexity of the procedure and a lack of antibiotic prophylaxis are the most consistently identified risk factors for ICED infection.

Establishing the risk factors for ICED infection is important to designing preventative strategies. Twelve studies were identified that employed multivariate statistical techniques. A variety of patient characteristics and procedural issues have been associated with ICED infections. Male sex, younger age, anticoagulation, chronic obstructive pulmonary disease (COPD), renal impairment, lack of administration of antibiotic prophylaxis, the type of device, the need for re-intervention prior to discharge and a higher number of prior procedures have all been identified as risk factors for ICED infection in at least two studies; the number of prior procedures and lack of antibiotic prophylaxis have been the most consistently identified risk factors. A shorter time from implantation (within 1 year), an earlier year of implantation (before 1985), fever in the 24 hours prior to implantation, use of a temporary pacemaker prior to implantation, congestive heart failure, azotemia, chronic corticosteroid therapy, haemodialysis, procedure time and post-operative haematoma were all associated with infection in one of several studies of various design and size.

Risk factors for early infection (within 6 months of implantation) in patients with ICD appear to be different to risk factors for later infection. The presence of epicardial leads or post-operative “wound complications” were associated with early infection and the length of hospitalisation (more than 1 day) and the presence of COPD with later infection. However, the post-operative wound complications included wound discharge and dehiscence, suggesting infection may already have been present. In a cohort of 416 patients with ICED infection (93 with lead-associated endocarditis), non-steroid immunosuppressive therapy, chronic corticosteroid therapy, haemodialysis, a remote site of infection, elevated white cell count, fever, malaise and the absence of pocket symptoms or signs were associated with ICED-IE.

D.4 What is the mortality associated with ICED infection?

Summary:
- All cause mortality ranges between 0-35%.

Mortality data are important for benchmarking between units and to help clinicians and patients quantify the risks associated with different therapeutic approaches. All-cause mortality following ICED infection is considerable, ranging from 0-35% in 19 studies that included 100 patients or more and reported this outcome over follow-up of periods of up to 5.5 years. Two-thirds of studies reported that the vast majority (>90%) of patients had undergone explantation; three studies (15%) did not report the explantation rate. Differences in mortality between studies are likely to be explained by variation in, for example, the proportion of patients included with different comorbidities, device types, and definitions of infection. Mortality increased with the length of follow-up; 2-15% in eight studies reporting in-hospital or 30 day mortality, 4-29% at six months, 9-35% at 1 year, and 6% to 35% at 2 years or longer.

D.5 What are the risk factors for mortality in ICED infections?

Summary:
- Mortality is high in the first year following ICED infection, but many deaths are not infection related.
- Abnormal renal function is the most consistently identified risk factor for mortality.
- Failure to remove an infected device is associated with relapse and mortality.
- ICED associated endocarditis has a higher mortality than localised generator pocket infection.

Despite the heterogeneous nature of the studies, some themes were identified. Studies that included only patients with ICED-IE all reported high mortality; 24.5-29%, with follow-up periods of up to a year and
explantation rates of 80-100%. In contrast, in the single study with at least 100 patients that included only pacemaker associated infections, mortality was 6% over a follow-up period of 24 months (explantation rate 92%). A small study of 52 patients, found a significantly higher mortality in ICED-IE or bloodstream infection (29%) compared to only generator pocket infection (5%) ; a larger study also found a significantly lower mortality in those who did not have ICED-IE. Likewise, Deharo et al. found higher (albeit not statistically significant) mortality (15.5% versus 12.5%), in patients with endocarditis compared to pocket infection. Greenspon et al. did not find a difference in mortality between early and late presenters (6% and 7% in hospital mortality, respectively; 25% and 29% at 6 months).

A high proportion of all deaths were reported to be due to cardiac or other non-infection causes with infection related mortality being considerably lower than all cause mortality in the same studies; between 0-15% in 12 studies including 100 patients or more reporting this outcome . The largest study (n = 5817 infections) found a higher adjusted mortality in patients with infection (26.5-35.1% depending on device versus 17.8-20.1% in patients without infection) over the admission period and the subsequent four quarters. Mortality was also higher in the Deharo et al study; 14.3% in infection patients versus 11% in controls, but this was not statistically significant. Long-term mortality was significantly higher in pacemaker infection (36.3%) compared to either ICD (24.4%) or CRT-D (30%) infection, in contrast to a smaller study , which did not find a difference between pacemaker and defibrillator patients.

Six studies looked for associations between various risk factors and mortality in ICED infections using multivariate analyses. The most consistently reported risk factors for mortality were abnormal renal function, endocarditis or features likely to be associated with endocarditis (systemic embolisation or moderate/severe tricuspid regurgitation) and older age. Although the number of patients reported to have been treated medically was relatively small, mortality appeared to be higher when explantation was not undertaken. Using multivariate analysis, significantly higher survival was seen in those who underwent explantation, and medical therapy was identified as a risk factor for death.

In a small study (n = 52), significantly higher mortality was also found in those patients in whom explantation occurred after three or more days in hospital.

D.6 What are the most common microbial causes of ICED infection?

Summary:
- Staphylococci (and Gram-positive bacteria in general) cause the majority (68-93%) of infections.
- Gram-negative bacteria cause fewer than 18% of infections.
- Approximately 15% of ICED infections are culture negative.

The microbiology of ICED infections is relevant to the pathogenesis of infection and the selection of both antimicrobial prophylaxis and empirical treatment regimens. Eighteen studies that included at least 100 patients were reviewed. The microbial epidemiology of ICED infections was found to be remarkably consistent. Gram-positives were by far the most commonly isolated bacteria (from 67.5% of patients to 92.5% of isolates across nine studies reporting the proportion of Gram-positives with coagulase-negative staphylococci (CoNS) the most consistently isolated bacteria followed closely by Staphylococcus aureus. Gram-negative bacilli were isolated in 1-17% of patient episodes (6% to 10.6% of isolates in studies using the total number of isolates as the denominator). Fungal infection is uncommon, occurring in no more than 2% of patients. The proportion of patients with polymicrobial infection was reported in seven studies and ranged from 2-24.5%. Thirteen studies reported the proportion of patients with clinical infection but negative cultures, which ranged from 12-49% of patients. Table 3 summarises the reported microbial epidemiology of ICED infections.

D.7 Which antimicrobial agents are they usually susceptible to?

Summary:
- UK data on the antimicrobial susceptibility of ICED infection pathogens are not available.
• 67% of coagulase-negative staphylococci and 42% S. aureus UK bloodstream isolates were methicillin resistant (surveillance data up to 2006).

Antimicrobial susceptibility of the predominant pathogens is relevant to selection of empirical treatment and prophylaxis regimens. Considering only the studies with at least 100 patient episodes, the proportion of CoNS isolates found to be methicillin resistant ranged from 33% (Italy) to almost 50% (USA). In four studies that included fewer than 100 patients, but reported methicillin resistance in CoNS, 12.5% (Australia) to 29% (France) of isolates were resistant. In S. aureus (reported studies were from USA, Europe and one from 28 countries), 2.6% (Germany) to 55% (USA) of isolates were methicillin resistant. In over 1000 isolates, UK antimicrobial resistance surveillance data for the period 2001-2006 found that 67% (range 54-80%) of CoNS and 42% of S. aureus bloodstream isolates were methicillin resistant.

D.8 Does the microbiological cause with time of presentation?

Summary:
• There are no clinically useful differences in the pathogens causing ICED infection in relation to time after implantation.
• Recommendation D4: The one year cut-off commonly used to define healthcare associated infection in device implantation should not be applied to ICED infections. [B]

Establishing clear relationships between the pathogen and time of onset or type of infection can help with interpretation of study data, assessment of study design and planning of preventative measures. Although a significantly higher proportion of ICED infection patients with endocarditis were found to be infected with S. aureus (43 versus 27.5%) and Gram-negative bacilli (12 versus 6%) than those without, this is not a consistent finding. In each of three other studies that only included patients with ICED associated endocarditis, S. aureus was the most common pathogen (35-59% of patients) followed by CoNS (14-32%). Gram-negatives were only reported in two studies (1% and 4.5%).

Two studies were identified that had compared the microbiology of “early” (within six months of implantation) and “later” infections; although the reasoning behind a six month cut-off is not described. S. aureus was the cause of 35-48% of early infections compared to 41-45% of later infections in the two studies, respectively. Likewise, CoNS caused a similar proportion of infections in early (16%, 23%) and late (24.5%, 27%) presenters. Detailed analysis of cases where both the pathogen and onset of infection were described, found no difference in the microbial causes of infection within and beyond one year of implantation, indicating that the one year cut-off often applied to procedure-related acquisition in device implantation surgery may not be applicable to ICED infections.

E Pathogenesis

Summary:
• Microbial contamination of a device can occur: i) during manufacture or packaging; ii) prior to implantation; iii) during implantation; iv) secondary to surgical site infection; v) via haematogenous seeding from a distant site, or; vi) via contamination after erosion through the skin.
• Asymptomatic colonization of ICEDs can occur with normal skin commensals and infection may develop at a later stage.

A concise discussion of pathogenesis is included because it is relevant to diagnostic, therapeutic and preventative strategies. In theory, microbial contamination of a device can occur: i) during manufacture and packaging; ii) prior to implantation; iii) during implantation; iv) secondary to surgical site infection or infected haematoma, for example; v) via haematogenous seeding from a distant site or; vi) via contamination after erosion through the skin.

The first of these is rare, but should be considered if clusters of infection or unusual environmental microorganisms are identified. Contamination prior to implantation may occur via the hands of anyone
handling the device or from operating theatre air. Since ICEDs are not usually implanted in laminar flow operating theatres, CoNS, shed on skin squames from anyone present in the operating theatre (both patient and staff), are likely to be present in significant numbers. This was illustrated in a study of diagnostic methods in which 14 unused sterile “control” leads were placed on the operating table during an ICED insertion procedure and subsequently cultured; one lead (7%) was culture positive for Staphylococcus epidermidis. During implantation, there is a risk of device contamination with the patient's own skin flora, introduced into the wound at the time of skin incision. Surgical site infection can progress to involve the device.

The theories above are supported by the identification of asymptomatic colonisation of ICEDs with normal skin commensals: Five studies (including 36-122 patients) have described this phenomenon, in patients undergoing removal for reasons other than infection. Between 21-47% of patients had microbes isolated from various specimen types with CoNS and Propionibacterium species being the most commonly and consistently isolated bacteria. In a study of asymptomatic patients with positive lead or generator pocket cultures, 7.5% subsequently developed ICED infection, but no significant difference in ICED infection rates was seen between patients with positive or negative. Another study found an infection related mortality of 2% (1 patient; not endocarditis) in 51 patients over a median follow-up period of 25 months.

The role of biofilm in infection and treatment is outlined in Section 26. The reason why ICD and CRT-Ds are more prone to infection (see Section 12) than PPMs is currently unexplained but may relate to the complexity and duration of the procedure often in older patients with higher anticoagulant use and higher prevalence of co-morbidity. The preventative measures in Section K reflect the fact that the predominant microbial causes of ICED infection are skin commensals (staphylococci), Enterococci and coliforms can be transiently present on skin but should be dealt with by washing and appropriate skin decontamination.

F Clinical diagnosis

F.1 What are the clinical features of ICED infection?

Summary:
- Generator pocket infection is characterised by localised cellulitis, swelling, discharge, dehiscence or pain.
- Wound inflammation can be an early presentation of generator pocket infection.
- Generator pocket infection and ICED-IE or ICED-LI frequently coexist.
- Non-specific signs and symptoms of systemic infection (including fevers, chills, night sweats, malaise and anorexia) may be the only clinical features of ICED-IE/ICED-LI.
- Fewer than 10% of patients present with septic shock.
- Clinical diagnosis of ICED-IE/ICED-LI can be challenging and is often delayed.
- ICED-IE/ICED-LI may present with secondary foci, such as spinal or pulmonary infection.
- The Duke criteria can be used to assist the diagnosis of ICED-IE/ICED-LI.

Generator pocket infection is characterised by localised erythema, localised cellulitis, swelling or pain over the pocket. The severity of symptoms can vary considerably. This may progress to wound dehiscence, purulent discharge, skin erosion or sinus formation. Symptoms and signs may fluctuate and can be insidious in onset. Pus may discharge intermittently from a chronic skin sinus and in this situation there may be minimal local signs of inflammation. The diagnosis of generator pocket infection may be simple, with obvious and easily identified local inflammatory changes, but early post implantation inflammatory changes brought about by a variety of processes, such as skin reactions to disinfection products, can be difficult to distinguish from infection (Figure 5 and Figure 6). “Superficial cellulitis” may be an early presentation of generator pocket infection. Once the generator or proximal leads have eroded through the skin, a device should be considered infected, whatever the mechanism for erosion. Skin changes resulting from tension on, or elevated pressure within, the pocket due to too small a pocket being made (“undersizing”), or other anatomical restriction, should therefore be resolved before the skin is breached. Generator pocket infection may be accompanied by systemic signs of infection. Conversely, lead infection is common in patients with symptoms and signs localized to the generator site. Where reported, concurrent
generator pocket infection in patients with ICED-IE and ICED-LI varies between 6-58% of cases,\textsuperscript{16, 17, 20, 43, 69, 70} this variation being partly explained by differences in case definition and study methodology.

It can be challenging to establish the diagnosis of ICED-LI or ICED-IE, especially in the absence of generator pocket infection and many months may elapse between symptom onset and diagnosis.\textsuperscript{60} Systemic symptoms of infection such as fevers, chills, night sweats, malaise and anorexia are common in ICED-LI and ICED-IE (78-86%) and the CRP is often elevated (96%).\textsuperscript{13, 60, 67, 68, 71} An elevated CRP will not help distinguish between generator pocket infection and ICED-LI or ICED-IE. Septic shock has been reported in 9% of episodes.\textsuperscript{69} Vascular and embolic phenomena occurred in fewer than 5% of cases of ICED-IE or ICED-LI\textsuperscript{69} but clinical (e.g. dyspnoea, pleuritic chest pain) or radiological evidence of pulmonary involvement has occurred in 38-44% of cases.\textsuperscript{60} Working Party members have observed patients with ICED-LI and ICED-IE treated for “recurrent chest infections” prior to diagnosis. Secondary foci of infection, such as vertebral osteomyelitis and discitis may also be the presenting feature.\textsuperscript{60, 72}

The role of the modified Duke criteria\textsuperscript{1, 73} in establishing ICED-IE or ICED-LI is unproven, but they remain an objective tool for assessing clinical evidence. The sensitivity of the modified Duke criteria may be enhanced by including evidence of pocket infection or echocardiographic evidence of lead vegetations as major criteria\textsuperscript{67} and the latter is often used in practice. Laboratory analysis of samples taken at device removal can also support the diagnosis (see Section H). Working Party members have observed that junior doctors frequently disregard the presence of an ICED when assessing a patient presenting with symptoms and signs of systemic infection, highlighting the need for improved education.

F.2 What is the risk of ICED infection in patients with bloodstream infection?

Summary:

- **30-45%** of patients with a sustained staphylococcal bacteraemia and an ICED in situ, have ICED infection.
- **Recommendation F1:** Patients with an ICED and *S. aureus* in blood cultures or any microorganism in multiple blood cultures should be actively investigated for ICED infection. [B]

In patients with ICEDs in situ whose blood cultures grow a *Staphylococcus* spp. at least 35% will ultimately have ICED infection confirmed.\textsuperscript{74, 75} Regardless as to whether the ICED is the primary focus of bloodstream infection, a number of studies have shown the high probability of ICED infection in patients with bacteraemia due to *S. aureus* (35-45%)\textsuperscript{75, 76} and other Gram-positive cocci (30%)\textsuperscript{77} with a much lower risk in Gram-negative bacteraemia (6%).\textsuperscript{78} Multiple positive blood cultures with the same microorganism rarely result from contamination and patients presenting with an ICED in situ and persistently positive blood culture should be investigated for ICED-IE and ICED-LI, even if symptoms and signs of infection are mild.

G Echocardiography and other imaging modalities in ICED infection.

G.1 What is the role of chest radiography?

Summary:

- **Recommendation G1:** A chest x-ray should be carried out in all patients with suspected ICED infection. [C]
- **Recommendation G2:** CT scanning or CT pulmonary angiography should be considered when ICED infection is suspected and echocardiography is non-diagnostic. [C]

No studies have specifically addressed this issue. Evidence of multifocal consolidation on chest x-ray suggestive of embolic foci of infection may support a diagnosis of ICED infection in difficult cases\textsuperscript{79} and pulmonary involvement occurs in 10-45% of patients with ICED infection.\textsuperscript{13, 60, 69} A plain chest x-ray (CXR) may demonstrate features of pulmonary involvement, including consolidation, loss of vascular markings or pleural effusion. The CXR will also provide additional information regarding the presence and position of the pacemaker generator, number of leads present and their macroscopic position, particularly in the acute setting when full case notes may not be available. Comparison with previous x-rays may show generator migration, which can be a feature of chronic generator pocket infection. Pulmonary imaging with CT
scanning or CT pulmonary angiography may confirm the presence of pulmonary involvement and also assist diagnosis, but the latter will only reliably image large central intraluminal emboli. Septic pulmonary emboli are a minor Duke criterion.

G.2 What is the diagnostic accuracy of echocardiography?

Summary:
- Transoesophageal echocardiography (TOE) has higher sensitivity in establishing ICED-LI or ICED-IE than transthoracic echocardiography (TTE).
- In patients with ICED-IE the aortic and mitral valves can be involved in addition to lead and tricuspid valve infection.
- Echocardiographic findings consistent with a lead vegetation are defined as attachment of an oscillating or sessile mass to a lead, but findings should be interpreted in the clinical context because masses can be present on non-infected leads.

The role of echocardiography in ICED infection is to establish the presence of endocardial or pacing lead involvement and the complications of lead or valvular infection. Echocardiographic diagnostic parameters should include valve and lead vegetations in addition to new valve regurgitation and abscess formation. Valve involvement is often not limited to the tricuspid valve. Aortic or mitral valve vegetations are present 10%-15% of patients with ICED endocarditis and valvular involvement in ICED infection is associated with higher in-hospital mortality (see section D.5). TTE has a lower sensitivity than TOE in ICED-LI and ICED-IE; several observational studies have demonstrated TTE identification of lead involvement in 22-43% of cases compared to 90-96% with TOE. However, the techniques are complementary. TTE usually provides more accurate information regarding left ventricular function, right heart size and pulmonary artery pressure estimation. TOE can more accurately visualise the intra and extra cardiac portions of the leads and has higher sensitivity in detecting aortic and mitral valve endocarditis as well as the number, size and mobility of vegetations. Because of artifact and shielding from the electrodes and any prosthetic heart valve it may be difficult even on TOE to reliably differentiate attachment of a vegetation to the tricuspid valve rather than the electrode. Furthermore TOE cannot reliably differentiate masses caused by thrombus, fibrosis and infection. In a study that included patients undergoing TOE for reasons other than investigation of possible ICED-IE or ICED-LI, masses were seen in 10% of cases, highlighting the possibility of false positive results. Echocardiographic images must therefore be interpreted in conjunction with the clinical features and on an individual case basis.

G.3 When should echocardiography be performed?

Summary:
- Recommendation G3. Echocardiography should be carried out as soon as possible (within 24 hours) after a diagnosis of ICED infection is considered. [C]
- Recommendation G4. Echocardiography should be undertaken in all patients presenting with generator pocket infection and symptoms or signs of systemic infection/positive blood cultures to diagnose concurrent ICED-LI or ICED-IE. [B]
- Recommendation G5. Echocardiography should be performed in all patients in whom ICED-LI or ICED-IE infection is suspected clinically (according to Section F.1). [B]
- Recommendation G6. Echocardiography should be undertaken in patients with an ICED and S. aureus in one or more blood cultures or other microorganisms in multiple blood cultures. [B]
- Recommendation G7. Repeat echocardiographic imaging is recommended after after ICED removal to identify persisting valve or mural vegetations. [C]

See Sections F.1, F.2 and G.2. No studies have specifically examined the timing of echocardiography on outcome but early removal (within 3 days of admission) of ICEDs has been associated with better survival and the need therefore for a timely diagnosis is self evident. Patients presenting with generator pocket infection may have concurrent lead or valve involvement, necessitating echocardiography in all such patients with systemic symptoms or signs of infection or positive blood cultures (Section F.1). Serial echocardiograms may be required to confirm or exclude ICED-LI or ICED-IE. Persistently positive blood cultures are an important pointer to ICED infection and S. aureus bacteraemia has been repeatedly associated
with ICED infection. Recent UK data support the need for echocardiography for all patients with an ICED in situ and *S. aureus* bacteraemia. The size of the vegetation may influence the method of device removal, with larger vegetations necessitating surgical/open device explantation; therefore vegetation size needs to be reported (see Section J.1.3). Intracardiac echocardiography (ICE) may provide enhanced diagnostic accuracy compared to TOE but its availability is limited and remains unable to distinguish between infected and non-infected masses such as thrombus, Lamb’s excresences or fibrin strands. There is no evidence to support ultrasound evaluation of a potentially infected device pocket, above clinical examination.

G.4 What is the role of PET scanning?

**Summary:**
- **Recommendation G8:** Routine use of PET scanning outside research studies is not currently recommended. [C]

In case reports and pilot series, fluorodeoxyglucose positron emission tomography imaging (FDG PET) has been used to assist the diagnosis of ICED infection. At the present time there is insufficient evidence to know what PET adds to a clinical diagnosis and this should be considered a research tool.

H Microbiological Sampling and Processing

Identification of the causative organism(s) in ICED infection is necessary to inform appropriate antimicrobial therapy; this is particularly important given the range of potential pathogens and antimicrobial resistance profiles (see Sections D.6 and D.7). Negative blood cultures appear to be more common in ICED infection than native valve endocarditis (see section D.6) and do not exclude a diagnosis of infection.

H.1 Which samples should be collected to establish the cause of ICED infection?

**Summary:**
- Appropriate microbiological samples include: culture of blood, lead fragments (ideally distal and proximal), lead vegetation, generator pocket tissue and pus from a generator pocket wound.

The current means of establishing a microbiological diagnosis include: culture of blood, lead tips and generator pocket samples. See more detailed discussions in each section. The results of all of these analyses should be considered together with all relevant clinical information before attributing the infection to a particular microorganism(s). Meticulous attention to sampling technique is necessary because of ease with which samples may become contaminated and the fact that CoNS are among the most common causes of ICED infection and common sample contaminants.

H.2 When should blood cultures be taken?

**Summary:**
- **Recommendation H1:** Blood cultures should be taken prior to starting antimicrobial therapy. [B]
- **Recommendation H2:** On clinical suspicion of ICED infection in patients with a chronic or subacute presentation, three sets of optimally filled blood cultures should be taken from peripheral sites with ≥6 h between them. [C]
- **Recommendation H3:** To avoid undue delay in patients with suspected ICED and severe sepsis or septic shock at the time of presentation, two sets of optimally filled blood cultures should ideally be taken at different times within 1 hour and prior to commencement of empirical antimicrobial therapy. [C]
- **Recommendation H4:** Blood cultures should be taken 48-72 hours after removal of an infected ICED [C]
- **Recommendation H5:** Apply meticulous aseptic technique when taking blood cultures to reduce the risk of contamination with skin commensals. [B]

In patients presenting with ICED infection, blood cultures are positive in 20-67% of cases. Consistently positive blood cultures with the same organism are highly specific for an intravascular source
of infection but lack sensitivity. Taking multiple blood cultures with time between them helps to distinguish between transient and persistent bacteraemia and increases sensitivity. Although poor concordance (35%) between the results of blood culture and lead tip cultures was found in 359 patients, blood cultures are usually taken early in the clinical course and lead cultures are often collected after administration of antimicrobials (either for treatment or prophylaxis). Whilst there is no good evidence to guide the timing or usefulness of blood cultures following ICED removal, a positive blood culture in this setting may indicate a persistent uncontrolled infection - reimplantation of a new ICED would be unwise in this situation. It should be noted that blood cultures lack sensitivity, particularly in patients already on antimicrobial therapy, and reliance on a negative blood culture alone in this situation would be equally unwise. Results of blood cultures taken following ICED removal should therefore be interpreted carefully and in their clinical context.

H.3 How should the generator pocket be sampled at the time of removal?

Summary:
- **Recommendation H6:** In patients with clinical evidence of infection, tissue (approximately 2 cm²) should be excised from the pocket-site and sent for culture. [B]

Culture of tissue has been shown to have a statistically greater sensitivity than swab culture for recovery of pathogens implicated in ICED. In the Microbiology laboratory, tissue should be subjected to Gram stain and culture. It is recommended that pocket site tissue be taken only from patients who show clinical evidence of ICED infection, as detection of colonisation (or contamination, see Section E) in the absence of signs of infection is of little clinical value and may lead to unnecessary antimicrobial therapy or even surgery.

H.4 What laboratory methods should be used during processing?

Pus samples or fluid (for example, collected via a needle and syringe or even just a syringe from a discharging wound) are generally more reliable than swabs for Gram staining and culture. These samples should be plated onto a range of media (solid and liquid) to recover the most likely pathogens (see Table 3). Suitable culture media and incubation conditions are as follows: Chocolate agar (35-37°C in 5% CO₂ for 48 hours), CLED or MacConkey agar (35-37°C in air for 24 hours), blood agar (35-37°C in an anaerobic cabinet for 48 hours) and Sabouraud agar (30°C in air for 5 days). An enrichment broth (e.g. Robertson’s cooked meat broth) should also be inoculated and incubated at 37°C for at least 48 hours before subculture onto the same media. These media should recover the vast majority of bacteria and fungi that have been implicated in ICED infection.

Lead tips should also be cultured using the media listed above though it is important to note that lead tips may become contaminated during the process of extraction if the generator pocket is infected, giving rise to false positive results. ICED infection may occasionally be caused by fastidious or slow growing bacteria such as *Mycobacterium* spp., *Nocardia* spp. and auxotrophic staphylococci. If culture of pocket-site tissue is negative despite convincing evidence of infection, Microbiologists may wish to consider prolonged incubation of media, or preferably, referral of tissue for amplification and sequencing of bacterial 16S ribosomal RNA genes to detect atypical causes which are not detected by routine culture. The use of sonication for the recovery of bacteria from the surface of implantable IECD devices or lead tips may have a useful role to play in patients with clinical signs of infection and this merits further study.

I Definitions

There are no universally agreed definitions of ICED infection so these definitions have been synthesised from current available evidence, those used previously and by Working Party consensus. It may take some days to undertake clinical assessment, investigations and, in some cases, device removal before the final diagnosis can be established. These different clinical entities are relevant because they require different management pathways.
I.1 Uncomplicated generator pocket wound 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. A small localized area (<1cm) of erythema and or purulence associated with a suture (“stitch abscess”) is included in this group. There should be clinical resolution with treatment or removal of the cause (if allergic reaction to local dressing/preparation) within two weeks. (Figure 5 and Figure 6)

I.2 Uncomplicated generator pocket infection.

a. Spreading cellulitis affecting the generator site, OR;
   b. Incision site purulent exudate (excluding simple stitch abscess), OR;
   c. Wound dehiscence, OR;
   d. Erosion through skin with exposure of the generator or leads, OR;
   e. Fluctuance (abscess) or fistula formation;

No systemic symptoms or signs of infection AND negative blood cultures.

Notes: Although we have used the term “generator pocket”, essentially the device and local soft tissues are involved. A 30-day cut off is recommended since most superficial infections present within this is the time frame. A microbiological cause may be identified from pus samples.

I.3 Complicated generator pocket infection.

As for uncomplicated generator pocket infection but WITH evidence of lead or endocardial involvement, systemic signs or symptoms of infection or positive blood cultures.

I.4 ICED isolated lead infection (ICED-LI).

Definite ICED-LI:

1. Symptoms/signs of systemic infection (see Section F.1)
2. NO signs of generator pocket infection (see Section I.2)
3. AND
4. Echocardiography consistent with vegetation(s) attached to lead(s)
5. AND
6. Presence of major Duke microbiological criteria.¹

Possible ICED-LI:

1. Symptoms/signs of systemic infection (see Section F.1)
2. AND
3. Echocardiography consistent with vegetation(s) attached to lead(s)
4. BUT
5. No major Duke microbiological criteria present.¹

Note: ICED-LI can occur with or without evidence of generator pocket infection. Possible ICED-LI is a common problem; the diagnosis of ICED lead infection may be strengthened by evidence of pulmonary
emboli (see Section F.1). Diagnosis of isolated ICED-LI, i.e. exclusion of ICED associated endocarditis (ICED-IE) can be difficult but is possible if the tricuspid valve is structurally normal and remains structurally normal after system removal with no remaining vegetation seen on echocardiography following device extraction. The presence of right atrial lesions on echocardiography following ICED removal (fibrin sheaths, sometimes referred to as “ghosts”) can cause confusion and can sometimes represent a persistent source of infection requiring treatment as ICED-IE. If there is uncertainty, manage as for ICED-IE.

I.5 ICED associated native or prosthetic valve endocarditis (ICED-IE).

Duke criteria for definite endocarditis satisfied, with echocardiographic evidence of valve involvement in a patient with an ICED in situ.

J Management of ICED infection.

The aim of managing ICED infection is to cure the patient of infection, as efficiently as possible, while minimising the risk of harm. Efficiency in this context would include: i) reducing time in hospital, ii) readmission rates, iii) number of procedures, and iv) exposure to unnecessary antimicrobials. Harms would include: i) the risks associated with device removal and replacement, ii) adverse reactions to antimicrobials, iii) complications of long term vascular access, iv) further healthcare associated infections and v) colonisation and infection with antimicrobial resistant organisms. Management of ICED infection should be individualised to each patient but there are clear principles, supported by varying degrees of evidence, to guide management plans. Figure 1-3 summarise the management pathways for uncomplicated generator pocket wound inflammation, generator pocket infection and suspected ICED-LI/ICED lead infection, respectively. This section contains principles of device management and antimicrobial therapy and scenario-based management recommendations.

J.1 How should the device be managed?

The options for ICED management when infection is diagnosed or suspected are summarised in Table 5. An infected ICED may be left in situ, partially removed, or removed entirely. Partial removal may be planned and this usually involves removal of the infected generator, cutting the leads and burying the extravascular portion in the soft tissues, leaving the leads in the heart. Unplanned partial removal may occur if a lead breaks during attempted removal, leaving a remnant of lead in the heart.

J.1.1 In uncomplicated generator pocket wound inflammation?

Summary:
- Recommendation J1: In uncomplicated generator pocket wound inflammation, the ICED can initially be left in situ. [B]

Although uncomplicated generator pocket wound inflammation may precede generator pocket infection this entity does not constitute confirmed ICED infection and can initially be managed without device removal (Figure 1).

J.1.2 In generator pocket infection, ICED-LI and ICED-IE?

Summary:
- Recommendation J2: Complete and early (during the index admission) removal of an infected ICED system (generator and all leads) combined with appropriate antimicrobial therapy is the most effective, safe and efficient treatment option. [B]

The biofilm nature of ICED infections (Section J.2) means that device removal is usually required to enable cure. The majority (usually over 90%) of large, single centre, reports of ICED infections managed with device removal and appropriate antimicrobial therapy demonstrate cure with this approach, although relapse of infection was reported in 0-7% of episodes. Relapse is more common when devices are not removed; for example, over half of patients who did not have complete removal
Case series describe success in 82-98% of attempted system removals for ICED infection. Furthermore, removal techniques have evolved with improved success rates and lower interventional thresholds, shedding doubt on the current relevance of older studies. The likelihood of failure of percutaneous removal increases with the duration of time the device has been in situ. Indeed, a linear relationship was demonstrated in one study with a 5% risk of failure with a device 0-3 years old increasing to a 20% risk of failure with a device 9-12 years old. The risk of mortality associated with device extraction is multifactorial and appears to vary with the indication for removal. Nevertheless, the presence of current infection increases the risk of death. A 2.7% in-hospital mortality from severe sepsis was reported following device removal in one series. In a prospective cohort study of patients from the International Collaboration on Endocarditis, device removal during the initial hospitalisation was associated with a significantly lower 1 year mortality than if the device was left in situ. A similar analysis comparing outcomes of immediate removal with initial conservative management (device left in situ and antimicrobial therapy) found 1-year mortality was three fold higher in patients managed conservatively. A single centre analysis has demonstrated similar results. In summary, early ICED removal is usually successful, is associated with a small but clear risk of mortality (which is lower than for delayed removal) and results in high cure rates. The Heart Rhythm Society (US) cites infection as the strongest indication for complete system removal.

**J.1.3 What is the preferred means of device removal?**

**Summary:**
- **Recommendation J3:** Percutaneous methods of lead removal are preferred for infected leads, combined with complete removal of the generator. [B]
- **Recommendation J4:** Open surgical removal should be considered for large lead-associated vegetations (>20mm) and when valve surgery is indicated for other reasons. [C].

In patients listed for percutaneous lead extraction in a large UK series, the procedure was successful in over 98% of cases. Only the time a device had remained in situ was a risk factor for failed percutaneous removal in this series, but it is unclear whether vegetation size was included in the analysis. One case with a 15 mm vegetation vegetation required surgical lead removal. Size of vegetation was not associated with mortality in one single centre series, but data on vegetation size were unavailable in 80% of cases. Some clinicians have routinely listed patients with vegetations over 10mm for surgical lead extraction, while others use a 20mm cut-off while some are wary of “large vegetations” without specifying a cut-off dimension. Major complications are more common after open surgical lead removal than percutaneous techniques, but percutaneous removal can also be complicated: Five (55%) of nine patients with large vegetations (10-38mm) and percutaneous removal suffered pulmonary embolism, although this complication did not appear to affect mortality or inpatient stay. The presence of concurrent native or prosthetic valve IE is not a contraindication to percutaneous lead removal, even if vegetations are present on the tricuspid valve. Clinical practice among working party members in terms of the threshold for referral for surgical removal varied between 10mm and 40mm highlighting this as an area for further study. A variety of methods can be used to remove infected devices but analysis of the preferred method and a review of supporting evidence are beyond the scope of this guideline.

**J.1.4 What proportion of patients are too unwell or refuse complete ICED removal?**

**Summary:**
- 3-15% patients decline, or are unsuitable for ICED removal.

Although complete ICED removal represents the ideal management of an infected system, some patients are considered medically unfit for this procedure and others may decline system removal. Of the seven studies that reported on this outcome, 3-15% of patients were either unsuitable or refused ICED removal.

**J.1.5 How should an infected ICED be managed if removal is not an option?**
Summary:
- Recommendation J5: In a patient with ICED-associated IE, it is reasonable to attempt salvage of the device with a course of appropriate antimicrobial therapy when the risks of removing the infected ICED are considered too high, or a patient declines system removal. [C]
- Recommendation J6: In a patient with an infected ICED that involves generator pocket infection, in whom the risks of removing the entire device are considered too high (or a patient declines entire system removal) the generator should be removed, leaving the leads in situ, and a course of appropriate antimicrobial therapy given. [C]

Salvage of infected ICEDs with antimicrobial therapy alone has been reported as has success with partial system removal. Excluding “superficial infections,” seven studies reported cure rates ranging between 13-71% for patients managed with partial device removal. A recent series of ICED-associated IE reported a 100% failure rate with attempted salvage. In contrast, a series containing only one episode of ICED-IE found that 46% of cases managed without removal (or with partial removal) were medically cured. In a small Swedish series of 44 patients, 64% of the 28 patients managed with device removal had no signs of infection at follow-up, compared to just 9% of the 16 patients managed with the device in situ. Similarly, an Australian series of 39 ICED infections over a 10-year period reported complete system removal in 67% and a recurrence rate of 28% in patients who did not have complete removal of the system. Recurrence of infection is associated with failure to remove all prosthetic material. Generator removal with lead shortening resulted in a relapse of infection in 20% (1 of 5) patients with generator pocket infection treated without lead removal and vacuum assisted dressings.

In this situation, it is necessary to formulate a treatment plan based on antimicrobial therapy alone or in combination with generator removal (and leads left in situ). Removal of a generator is usually an uncomplicated procedure, compared with the risks of removing leads (which increases with the length of time that leads have been in situ). If percutaneous removal of an infected system is considered unsafe (e.g. very large vegetations), open surgical removal may be required.

J.1.6 Where should removal of infected ICEDs be undertaken?

Summary:
- Recommendation J7: Removal of infected ICEDs should only be undertaken in recognised centres with expertise in the procedure and with appropriate surgical facilities immediately available. [C]

This recommendation reinforces standards developed by Heart Rhythm UK. Myocardial and vascular tears and cardiac tamponade are recognised complications of lead extraction, which require the immediate availability of appropriate cardiac, vascular and/or thoracic surgical facilities. Lead removal (more than 3 months after implantation) should not be attempted outside such centres since damage to the lead may further complicate subsequent removal attempts. If percutaneous removal of an infected system is considered unsafe (e.g. very large vegetations), open surgical removal may be required.

J.1.7 How should the device be managed in skin erosion?

Summary:
- Recommendation J8: Erosion of skin to expose either leads or generator to the air requires removal of the entire system. [C]

Leads or generator can erode through the skin often as a result of superficial positioning of the device, for example in very thin patients. frank erosion through the skin may be preceded by “tethering”, where a superficial portion of lead becomes adherent to the overlying skin, often without accompanying signs of inflammation. “Pre-erosion” is a term often used to describe inflamed skin over a superficial portion of lead. Once the ICED device is exposed, microbial contamination is inevitable, meaning that erosion should be treated as infection. Pre-erosion may also be a manifestation of infection and if skin integrity is lost (for example, if granulation tissue is present over a superficial portion of lead) microbial contamination or infection are likely. Repositioning of the generator box into a subpectoral position for exposed leads resulted
in a 14% infection rate in a small series of seven patients. However, a 62.5% infection rate has been documented with erosion or pre-erosion association with skin inflammation or granulation of the scar.

Although procedures may be undertaken to reposition exposed leads, this should be considered a holding measure until system removal and re-implantation at a different site can be arranged. If there are no local or systemic signs of infection and blood cultures are negative, antimicrobial therapy is unlikely to be beneficial. However, prophylaxis is advised during removal of the old system and implantation of the new system.

J.1.8 If required, when should device re-implantation take place?

Summary:

- Recommendation J9: The need for and timing of a replacement ICED after removal of an infected device will depend on the indications for its use. Wherever possible, implantation of a new ICED should not take place until symptoms and signs of systemic and local infection have resolved (after 7-10 days). [B]
- Recommendation J10: The venous access sheath used for percutaneous removal of an infected or system should not be used for re-implantation of a new system. [C]

Robust evidence to support this recommendation is lacking but it is well recognised that sepsis is a contraindication to permanent device implantation. In case series, 70-77% of patients required a new device after removal of an infected ICED, indicating that this is a common dilemma. Re-implantation was usually undertaken when systemic symptoms had resolved. Fever at the time of device implantation is a well described risk factor for subsequent device infection, so ideally patients should be apyrexial, and without other symptoms or signs of systemic infection at the time of implantation. The optimal reported time to re-implantation after removal of the infected device is approximately 7-10 days. In patients who are pacemaker dependent, it seems sensible to use a temporary device until symptoms and signs of systemic infection (including fever) have resolved, before implanting a permanent device. However, temporary pacing has been associated with an increased risk of subsequent infection, although this may be a marker of the urgency of the procedure rather than a true causal relationship. Some cardiologists use temporary external pacemakers and internal jugular leads to bridge the gap between old and new permanent devices. In this instance, venous access for temporary pacing should take into consideration the need for a future ICED; the pectoral region contralateral to the infected site should therefore be avoided for temporary pacing access if possible. Clearly, if possible, the avoidance of re-implantation of any permanent device is preferable. If the patient is not pacemaker dependent, the need for any ICED should be reviewed and those who require re-implantation should be observed on the ward until the procedure is considered safe. It would be unusual to immediately implant a new ICED after removal of an infected system, but re-implantation should occur at a new site if this is necessary. At least seven days should be allowed before re-implantation if at all possible. This recommendation is a pragmatic attempt to reduce the risk of seeding the new device, which is likely to be highest when the patient is still bacteraemic.

J.2 Principles of antimicrobial therapy.

Summary:

- Recommendation J11: Antimicrobial treatment strategies should be discussed by the multidisciplinary team and determined by plans to remove or attempt to salvage an infected ICED, the presence of ICED-IE and any extra-cardiac foci of infection. [C]

The approach to antimicrobial therapy for ICED infection depends on a number of factors including: the severity of illness at presentation; plans for device management (see Table 5); the involvement of native cardiac structures or extra-cardiac foci of infection; and other patient factors such as a history of allergy, concurrent medication and renal function. This information is best collated, discussed and acted upon by the multidisciplinary team with expertise in ICED infection. A number of different antimicrobial regimens are advised in order to cover a number of different clinical scenarios.

J.2.1 Biofilm and ICED infection

Summary:
• The biofilm nature of ICED infection makes eradication of infection very unlikely without removal of the device.

Biofilm is now a well-established term to describe the growth of bacteria on solid surfaces and ICED infections are a typical example. In modern medicine biofilm-mediated infections have become more prominent as the use of implanted medical devices has become more common. Although S. aureus is a ubiquitous human pathogen and does not require prosthetic material to cause infection, it can form biofilm. The presence of prosthetic materials in the body, if contaminated, allow normally non-pathogenic microorganisms such as CoNS to adhere and establish a focus of infection. The biofilm mode of growth is important since it renders bacteria far more resistant to antimicrobial therapy than traditional in vitro susceptibility testing would suggest. Some bacteria are far more adept at sticking to non-biological materials than others, which explains, for example the predominance of staphylococci in ICED infection and the rarity of “coliform” lead infections (see Section D.6).  

Like other medical devices, ICEDs are susceptible to biofilm formation but unlike other devices (such as intravascular catheters, prosthetic heart valves or some orthopaedic implants), eradication of infection can rarely be achieved.\(^{33,116}\) We suggest that the formation of biofilm on or within these complex devices (such as polyurethane, silicone or fluoropolymer lead insulation or leads with a hollow lead lumen\(^{117}\) ) is inaccessible to antimicrobials, regardless of the mode of administration to the patient, explaining why eradication is so difficult. Even when infection appeared to be clinically confined to the generator pocket, the intravascular section of leads were culture positive in 72% of cases\(^{47}\) illustrating how bacteria can migrate along the leads from an infected generator pocket. Although there are diagnostic limitations and reporting bias, the pathogenesis of infection may explain the differences in reported rates of cure: a generator infection, involving the complex elements of the device may not be curable with antimicrobial therapy alone, but a haematogenously seeded insulated lead, with associated surface biofilm and vegetation, may on occasion, respond to antibiotic therapy.\(^{118}\)

Native valve endocarditis can occur in patients with ICEDs in situ, without lead involvement\(^{22}\) which may explain some apparent cures of ICED. Antimicrobial therapy is often effective against bacteria shed into the bloodstream or soft tissues from the primary source of infection, which explains why patients may show an initial clinical response to antimicrobial therapy but then relapse when antimicrobials are withdrawn.\(^{20,69}\) This initial response to therapy seems to be enough to encourage some clinicians to persist with antimicrobial therapy, resulting in a relapsing course and repeated visits to hospital. Patients with an ICED in situ may sometimes present acutely with severe sepsis or septic shock when a diagnosis of ICED infection may not be immediately apparent or considered. In this setting patients are likely to be treated according to local antimicrobial guidelines. These antimicrobial recommendations only apply once a diagnosis of ICED infection is considered.

J.2.2 Which antimicrobials are recommended for uncomplicated generator pocket wound inflammation?

Summary:
• Recommendation J12: The decision to commence antimicrobials for uncomplicated generator pocket wound inflammation should be determined on a case-by-case basis, using an oral antimicrobial appropriate for soft tissue infection (Figure 1). [C]

Inflammation of a generator pocket wound occurring early after implantation can be caused by several factors including early infection, reaction to dressings, suture-related infection and haematoma formation.\(^{47}\) Six studies describe superficial infections, with a wide variation in the proportion of infections falling in this category (5-86%).\(^{23,25,10,33,42,118}\) The lowest proportion of superficial infections was reported in retrospective studies and those where the method of identifying infected cases was unclear, raising the possibility of under reporting. Generator pocket infection may manifest as an apparently superficial infection\(^{27}\) and the Working Party therefore recommend careful follow up of these patients (Figure 1) with rigorous attention to wound hygiene and avoidance or removal of exposed or retained suture material. Whether the clinical course of early onset “superficial” infection (i.e. avoidance of generator pocket infection) can be altered by oral antimicrobial therapy is not known. Although numbers are small, the reported success rate for treatment of
superficial infection with short courses of antimicrobial therapy is high (80-100%). The Working Party was unable to reach a consensus concerning the need for antimicrobial therapy in this situation. Some members felt that oral antimicrobial therapy might prevent progression, whilst others were concerned that oral therapy might mask generator pocket infection and delay appropriate management. *S. aureus* is the most common organism to cause superficial infection and cefazolin for 10 days has been effective in this setting, but treatment regimens are often not reported. Flucloxacinil would therefore be the most appropriate choice in the UK in the absence of risk factors for MRSA or penicillin allergy and alternative regimens are provided in Table 6. See also section J.2.8 and Figure 1.

**J.2.3 Which antimicrobials are recommended for uncomplicated generator pocket infections?**

**Summary:**
- Recommendation J13: When there is clinical evidence of generator pocket infection empirical antimicrobial therapy should be commenced (Table 6, Figure 2). [C]
- Recommendation J14: Directed (or targeted) antimicrobial regimens for treatment of generator pocket infection when the microbial cause is known are shown in Table 7. [C]
- Recommendation J15: Local antimicrobial instillation into an infected generator pocket is not recommended. [C]

Please also see discussion below. There are no RCTs to guide therapy in this situation, so recommendations are based on anecdotal reports of success, spectrum of antimicrobial activity and consideration of potential adverse effects. The timing of antimicrobial administration in generator pocket infection has not been assessed. Since a small proportion of patients develop severe sepsis and may deteriorate rapidly, in the presence of overt evidence of generator pocket infection (even without systemic signs of infection) it seems reasonable to commence empirical therapy, after blood cultures have been obtained. Because of the high frequency of lead involvement and concurrent endocarditis, initial intravenous therapy is advised (Table 6). Vancomycin, teicoplanin, daptomycin and linezolid have similar broad spectrum activity against Gram-positive bacteria, but linezolid is generally not favoured for treatment of endocarditis and is therefore not recommended until echocardiography has been undertaken. Treatment for Gram-negative infections will depend on susceptibility testing.

Once the device has been removed, residual infection involves only soft tissues and antimicrobial regimens can be kept short (see Section 31).

Local delivery of antimicrobials into or around the generator has been investigated. This approach has no role in the management of an infected ICED and we recommend complete removal of infected devices and positioning of any new system in a different anatomical location.

**J.2.4 Which antimicrobial agents are recommended for complicated generator pocket infections?**

**Summary:**
- Recommendation J16: Treat complicated generator pocket infection as for ICED-LI or ICED-IE depending on final diagnosis. [C]

See Section J.2.5.

**J.2.5 Which antimicrobial agents are recommended for ICED-LI or ICED-IE?**

- Recommendation J17: Empirical regimens for ICED-LI or ICED-IE are shown in Table 6. [C]
- Recommendation J18: The need for empirical antimicrobial treatment for ICED-LI or ICED-IE (prior to the availability of microbiological data) is a clinical decision based on the severity of infection. [C]
• **Recommendation J19:** The antimicrobial regimen for empirical treatment or culture-negative ICED infection needs to have activity against both Gram-positive (including methicillin-resistant staphylococci) and Gram-negative bacilli. [B]

• **Recommendation J20:** Vancomycin, teicoplanin and daptomycin are suitable anti-Gram-positive agents for empirical treatment or for culture-negative ICED infection. [B]

• **Recommendation J21:** Local resistance patterns should be considered in choosing anti-Gram-negative agents for empirical treatment of suspected ICED infection. Gentamicin and meropenem are both usually appropriate. [C]

• **Recommendation J22:** Modify treatment regimens, once the microbial cause is identified. [C]

Gram-positive bacteria (usually staphylococci) account for more than 80% of ICED infections while Gram-negative bacteria, cause a significant minority (<20%, Table 3). Yeasts are a rare cause and routine empirical antifungal therapy is not recommended. Empirical treatment (that started prior to knowledge of the pathogen) must therefore be broad-spectrum, requiring increasingly complex and potentially toxic antimicrobial regimens. The emergence of endocarditis caused by staphylococci that are resistant to glycopeptides (e.g. vancomycin and teicoplanin), highlights this problem. In general, empirical treatment regimens are often less clinically effective than “directed” (or “targeted”) antimicrobial regimens. For example, flucloxacillin is more effective for *S. aureus* endocarditis than vancomycin. If patients have severe sepsis and/or septic shock, then empirical therapy should be started urgently, after obtaining blood for culture. However, many patients with ICED-LI or ICED-IE have an indolent presentation and it is preferable, whenever possible, to await the results of cultures and susceptibility testing. This is because it is not possible to predict the pathogen causing ICED infection based on clinical characteristics alone. When a prosthetic valve is *in situ*, in addition to an infected ICED, it can be difficult to determine if the prosthetic valve is involved. When there is doubt, it should be assumed that the valve is involved and an appropriate course of treatment for prosthetic valve IE completed, even if the ICED is removed. For this indication see BSAC endocarditis guidelines. The indications for surgery on an infected prosthetic valve are as described in BSAC endocarditis guidelines.

Microbiological details have often been omitted in multivariate analyses of risk factors for mortality (Section D.5). However, positive blood cultures with *S. aureus* or methicillin-resistant *S. epidermidis* are associated with increased six months mortality.

There are no RCTs of therapy for ICED-LI or ICED-IE and many of the large case series do not present details of antimicrobial therapy (including doses, route of administration, duration and microbial cause). In some the types of antimicrobial regimen are described but not the outcomes. The regimens included in Table 6 are chosen on the basis of anecdotal reports of success, spectra of antimicrobial activity and side effect profiles. No empirical regimen can be expected to cover all possible pathogens underpinning the recommendation to undertake appropriate microbiological investigation and await microbiological results wherever possible.

Until the results of microbiological investigations are available, and decisions about system removal have been made, it seems prudent to keep antimicrobial regimens simple (i.e. avoiding the complex “biofilm-active” regimens in Table 8).

Antimicrobial regimens that have been used successfully in the treatment of ICED-IE infection after removal of the system include vancomycin and aminoglycosides, vancomycin monotherapy, cloxacillin plus gentamicin, ceftaroline, ceftazidime and aminoglycoside, methicillin, methicillin combined with an aminoglycoside, daptomycin monotherapy, daptomycin combined with gentamicin and daptomycin combined with rifampicin. “Beta lactams” and vancomycin were the predominant agents used in one study but success rates were not reported. Meropenem maintains a very broad spectrum of activity against Gram-negative organisms, but there is little experience of its use in ICED infection. Carbapenemase-producing Gram-negatives are more prevalent in some locations and may preclude the empirical use of carbapenems.

**J.2.6 What regimens are recommended for attempted ICED salvage?**
Summary:
- **Recommendation J23**: Regimens for attempted salvage of ICED infection are summarized in Table 8. [D]
- **Recommendation J24**: Careful clinical observation is required to determine success after a course of antimicrobial therapy for attempted ICED salvage. [D]

There are no trials to guide recommendations for device salvage and limited clinical experience. The biofilm nature of ICED infections and their role in treatment failure has been outlined above. Use of antimicrobial combinations including rifampicin and gentamicin are recommended for treatment of prosthetic valve endocarditis because of the enhanced activity of such regimens against biofilms and concerns about resistance developing during therapy. For example, daptomycin and vancomycin had superior activity *in vitro* against biofilm-associated methicillin-resistant *S. aureus* (MRSA) when compared to linezolid, tigecycline and clindamycin. In a different model, daptomycin, tigecycline and minocycline demonstrated superior activity against MRSA biofilms when compared to vancomycin, linezolid and rifampicin (monotherapy). However, addition of rifampicin to the other five antimicrobials resulted in eradication of the biofilm. Combination therapy has therefore been used in a number of reports. Anecdotal success in curing ICED infection with the device *in situ* has been reported with vancomycin and aminoglycosides and *Candida ICED* infection, daptomycin and ciprofloxacin plus flucloxacillin. Recommended regimens are summarized in Table 8.

After a period of treatment to attempt salvage of infected ICED leads, the only way to determine successful eradication of infection is to stop antimicrobial therapy, observe the patient and repeat blood cultures. Relapse is an indication to review the decision not to remove the ICED and consider long-term oral suppressive therapy (Sections J.2.8 and J.2.9).

**J.2.7 What is the optimal route of administration of antimicrobial therapy for ICED infection?**

Summary:
- **Recommendation J25**: The type of vascular access device used to deliver antimicrobial therapy should be chosen according to a particular patient’s needs. Risks of healthcare associated infection, jeopardy to future potential ICED sites and convenience should be considered. [C]
- **Recommendation J26**: Peripheral cannulae carry the lowest infection risk and reduce the risk of damaging future sites for ICED implantation. [B/C]
- **Recommendation J27**: A peripherally inserted central catheter (PICC) or “midline” are preferred for long-term IV access and should be inserted and maintained according to national guidelines. [C]
- **Recommendation J28**: A switch to oral antimicrobials is appropriate for generator pocket infections after device removal but intravenous therapy is recommended for ICED-associated IE and attempted ICED salvage. [C]

The risk of intravascular catheter-related bloodstream infection (CRBSI) is less with peripheral cannulae than cuffed tunnelled (e.g. Hickman) central venous cannulae (CVCs). CRBSI acquired during treatment of IE is associated with increased mortality and is influenced by the type of vascular access device. Patients can be managed with peripheral cannulae (that are changed every 72 hours) for long periods. Cuffed, tunnelled central venous catheters may not be the most appropriate device for delivering antimicrobials to patients with IE. Peripherally inserted central catheters (PICCs) or “mid lines” may be a safer alternative to cuffed, tunnelled CVCs when peripheral access becomes difficult, but have not been evaluated in this context. Central venous catheters run the risk of venous thrombosis and reducing access options for future ICED placement. The risks of infection in any vascular access device increase with the duration of time they remain *in situ*, so the choice between rotating peripheral cannulae and PICC/midlines should be made according to individual patient needs. If patients are managed with rotating peripheral cannulae, plans for alternative access should be made as soon sited cannulae becomes problematic.

An early series of pacemaker infections describes treatment of a generator pocket wound infection with oral antibiotics, subsequent relapse of infection and death of the patient. This sequence of events is still
observed in current practice. Oral antimicrobial therapy will not eradicate infection in established generator infection, but may be appropriate treatment for the associated soft tissue infection, once the device has been completely removed. Oral therapy would also be appropriate for long term suppressive therapy if required, following discussion with an infection specialist. To ensure adequate doses and compliance, the Working Party recommend that intravenous therapy should be the standard of care for most ICED-associated IE cases and attempted ICED salvage.

J.2.8 What is the optimal duration of therapy for ICED infection?

Summary:
- **Recommendation J29**: Duration of therapy should be determined by the type of ICED infection, proposed device management, involvement of other cardiac structures and the presence of extra-cardiac foci of infection (Table 5). [C]

There are no trials comparing different durations of antimicrobial therapy and this information is absent in many case series. Several series amalgamate generator pocket infections, ICED-IE and ICED -LI together when describing duration of therapy and are therefore unhelpful in deciding on the optimum duration of antimicrobials (all cases receiving six weeks; 4-6 weeks; 28.5 days; 26 days; median 25.7 days; 2-4 weeks; or two weeks intravenous therapy followed by four weeks oral antimicrobials). ICED-IE (and ICED-LI) has been treated for: six weeks; 5.4 weeks; or 14-28 days of therapy. In cases of ICED-IE, the Working Party recommend that the duration of therapy after system removal should depend on: the involvement of native or prosthetic heart valves, the initial clinical response to antimicrobials and the presence of extra-cardiac foci of infection (such as haematogenous vertebral osteomyelitis). Where there has been a good initial clinical response and no evidence of extracardiac infection, a total of four weeks therapy is usually sufficient for native valve IE, regardless of the timing of system removal. If symptoms and signs of infection persist until the time of ICED removal, then a further four weeks therapy after system removal is appropriate. Six weeks therapy is advised for prosthetic valve endocarditis, for patients with extra-cardiac foci of infection, and for attempted salvage of ICEDs in the setting of associated IE or lead infection. Prolonged antimicrobial therapy after device removal may not be required for isolated lead infection.

Where reported, the duration of therapy used for generator pocket infections is reasonably consistent: 10 days to 2 weeks. In a patient with a generator pocket infection, the remaining infection, once the system has been removed and any pus has been drained, is a skin and soft tissue infection that should be treated until resolution of local symptoms and signs of infection (usually 10-14 days).

J.2.9 What therapy is recommended if ICED salvage fails?

Summary:
- **Recommendation J30**: If infection cannot be eradicated from an infected ICED in a patient who is unsuitable for system removal, long-term oral suppressive antimicrobial therapy can be attempted following discussion with an infection specialist. [C]

There are no available data to answer this question. In a patient who has responded clinically to attempted salvage of an ICED, the only reliable way to confirm eradication of infection is to stop therapy and observe for relapse of symptoms or bacteraemia. If this were to occur, suppression of symptoms with long term oral antimicrobials may be necessary; this should be considered a last resort and involvement of an infection specialist is advised.

K Prevention of ICED infection

K.1 Where should ICED insertion take place?

Summary:
Recommendation K1: ICED insertion should take in place in an appropriately ventilated, equipped and cleaned room. [C]

The design recommendations for a catheter laboratory or operating theatre vary from country to country. The procedure should be carried out in a room that meets local standards. All apparatus that comes into contact with the patient must be appropriately decontaminated before contact. All equipment in the room should be cleanable and regularly decontaminated. Heart Rhythm UK has published guidelines for suitable room and equipment standards for ICED implantation and Health Technology Memorandum 03-01 specifies ventilation and air change requirements for cardiac catheterisation laboratories.

K.2 Does operator experience affect infection rates?

Summary:
• Recommendation K2: Procedures, including generator change, should be performed or supervised by experienced operators as per Heart Rhythm UK guidelines. [B]

Operator experience did not appear as a risk factor for ICED infection in the review of multivariate studies in Section D.3 because it was not included in the statistical models used in these papers. However, increased operator experience and centres with a higher volume of implants have been associated with fewer complications in studies that focussed on this issue. Comparing 30 and 60 day ICD infection incidence, physicians who implanted 1-10 devices per year had a higher complication rate than those who implanted more than 29 devices (30 days 0.9% vs. 0.4%; 90 days 1.3% vs. 0.6%; P=0.01). This observation was to be supported by a later finding by the same group that showed decreased complication rates as the device implant rate increased over time. Devices implanted by thoracic surgeons had a higher 90 day infection rate than those that were implanted percutaneously (2.1% vs. 5.1%), although the total number of surgical implants was very low (311 vs. 8062). This finding could be explained by a lower implant rate, or a higher risk group requiring a surgical approach. Similar findings were reported from the US national cardiovascular data registry (2006-2008): The overall complication rate was 3.82% in centres performing less than 24 implants per year versus 3.08% in those implanting more than 110 devices a year (P<0.0001). A smaller more recent registry of 1744 patients with ICED implants, and followed up prospectively for six months, detected higher complication rates in lower volume centres (<250 procedures per year). From these studies, it is difficult to determine whether cardiologists in training contribute to a higher complication rate. One study did not show any difference in complication rate when trainees were supervised by an experienced operator. Nevertheless, since operator volume appears to be associated with the overall complication rate, it seems sensible to ensure that junior trainees (who have usually undertaken fewer procedures) are carefully supervised by a senior operator during ICED implantation.

The risk of ICED infection is much greater after generator change or device revision (see Section D.3). It has been suggested that this is related to bacterial contamination of the avascular pocket that forms around the generator, which may be impede penetration of systemic antimicrobials and inflammatory cells during generator replacement. Recrudescence of bacteria inoculated during an earlier implant when exposed to blood and tissue during re-operation might also occur, but is unproven. Temporary wire backup for pacing-dependent patients might be an added route for contamination. The common assumption that generator changes are a “straightforward” procedure could potentially result in the procedure being performed by trainees with limited experience and without supervision. We endorse the pragmatic recommendations made by Heart Rhythm UK on this issue.

K.3 Should temporary pacing be avoided to reduce infection?

Summary:
• Recommendation K3: Wherever possible, temporary transvenous pacing should be avoided prior to implanting a permanent ICED. [B]

A review of cases published in the literature before 2007 showed that the risk of sepsis following insertion of a temporary wire ranged from 2-18%. In light of this data, it is probable that the introduction of these external leads is associated with a higher rate of infection following permanent system implantation because
of bacteraemia and occult sepsis. In a prospective multicentre survey of 6319 patients to determine complications occurring within one year of PPM or ICD implantation, the odds ratio of infection was 2.46 (95% CI 1.09-5.13) when a temporary wire was in situ.\textsuperscript{36} In addition, in a single centre retrospective study over 12 years, the presence of a temporary wire was also associated with an increased risk; however this was after AV node ablation in a non-emergency setting.\textsuperscript{39} It is increasingly commonplace to implant PPMs in the acute setting, in order to avoid the risks of temporary pacing. The Working Party endorse this approach from an infection prevention perspective.

K.4 Should ICED procedures be carried out in patients with signs of infection?

Summary:

- Recommendation K4: Elective ICED implantation/replacement/revision should be delayed if there are any signs of systemic infection. [C]

Clinical studies to definitively support this are difficult to conduct, as most operators would not proceed with implantation when there are any signs of systemic infection. Some data suggest that the presence of fever increases the risk of infection, see Section D.3. The role of systemic markers of infection, e.g. CRP or white cell count, has not been studied. In the acute setting, it is preferable to delay permanent ICED implantation until sepsis has resolved.

K.5 Should patients having ICED insertion or manipulation be screened for MRSA?

Summary:

- There are no studies specifically relating to screening for MRSA or MSSA prior to ICED implantation.
- Recommendation K5: Current national guidelines should be followed on screening for MRSA colonisation prior to elective ICED procedures. [C]

There are no studies on the benefits of pre procedural screening of ICED patients for carriage of MRSA or MSSA. Screening methods for MRSA and target patient groups vary from country to country. The Working Party recommends adherence to national guidelines. A risk assessment for the likelihood of MRSA should be undertaken in all patients, and prophylaxis tailored to screening results.\textsuperscript{50, 136} If a patient is found to be colonized with MRSA before a proposed procedure, prior to the operation an assessment should be made on a case by case basis as to whether an attempt should be made to clear carriage pre operation or whether topical agents should be used to suppress carriage pre and post procedure. The decision on timing will depend not only on the urgency of the procedure but also on the likelihood of success of decolonisation therapy. For example, throat carriage, colonised chronic skin lesions or colonised indwelling devices may make decolonisation therapy unlikely to succeed and perioperative suppression may be preferable in these circumstances. MRSA eradication therapy should ideally consist of nasal mupirocin and topical chlorhexidine washes.\textsuperscript{137} Where high-level mupirocin resistance exists, other alternative regimens to which the organism is sensitive should be used e.g. nasal neomycin/chlorhexidine (naseptin© or prontoderm©).

K.6 Should patients undergoing ICED procedures undergo “decolonization”?

Summary:

- Recommendation K6: Pre-procedural topical antimicrobial agents aimed at eliminating \textit{S. aureus} are not required in patients who are not colonized with MRSA. [C]
- Recommendation K7: Bathing or showering with soap is recommended prior to ICED insertion. [C]

This question has not been specifically addressed in the context of ICED insertion. The NICE guidelines\textsuperscript{138} modelled three strategies in the use of nasal mupirocin to prevent surgical site infection (SSI): no treatment; screen for \textit{S. aureus} and treat identified carriers with mupirocin; or, treat all patients with mupirocin. Their model suggested screening for \textit{S. aureus} carriage was not as cost effective as treating all patients. However they concluded that mupirocin or chlorhexidine nasal decontamination does not reduce the overall rate of
SSI. Nevertheless, there was a non-statistically significant reduction in SSIs caused by *S. aureus* in *S. aureus* carriers when mupirocin was used. An economic model suggested considerable uncertainty concerning the cost-effectiveness of treating all patients with mupirocin nasal ointment to prevent SSI caused by *S. aureus*, and the NICE guideline development group consensus was that it should not be recommended, especially as the potential harm of increased antibiotic resistance had not been factored into the model. Washing with chlorhexidine is also of uncertain benefit and washing with soap, as advised by NICE, prior to implantation is therefore advised.138 Both these areas warrant prospective evaluation.

K.7 How should anticoagulation be managed during ICED insertion or manipulation?

Summary:

- **Recommendation K8**: Uninterrupted warfarin (with careful INR monitoring) is preferable to bridging with heparin in those patients in whom interruption of anticoagulation is contraindicated. [B] (see text under 7)
- **Recommendation K9**: Where feasible*, antiplatelet and/or anticoagulants should be discontinued prior to the procedure to allow a normal thrombotic/coagulation profile. [B]

Post-operative haematoma formation is a recognised risk factor for ICED infection.6 The use of dual antiplatelet agents such as clopidogrel in combination with aspirin have been shown to increase the risk of bleeding at least threefold.138, 140 In addition, when “bridging” patients with intravenous heparin, the incidence of bleeding was 14.3% vs 4.3% in patients where warfarin was stopped and no heparin given.139 Meticulous attention to detail and good surgical technique are important to ensure all haemostasis has been achieved prior to wound closure. In those patients where antithrombotic or anticoagulants can be stopped, they should be discontinued before the procedure (in practice approximately five days beforehand). *In instances where anticoagulation with warfarin cannot be discontinued (prosthetic heart valves, atrial fibrillation with high thromboembolic risk), it is preferable to undertake the procedure with an international normalised ratio (INR) of 2, rather than bridge with heparin. In patients on warfarin with an INR 2-2.5, there was no statistically increased risk of bleeding compared to patients with an INR less than 1.5, but an INR more than 2.5 significantly increased the risk of bleeding.138, 141 Another study showed no increased risk of bleeding when warfarin was continued with an INR less than or equal to 1.5.139 Patients taking dual anti-platelet therapy in the wake of coronary stent implantation present similar concerns – a tailored approach according to stent type and time elapsed since implantation should be discussed with an interventional cardiologist.141

K.8 Which infection control measures should be in place before ICED implantation?

- **Recommendation K10**: ICED insertion should be carried out using an aseptic technique, in an environment observing operating theatre discipline including appropriate clothing. [C]
- **Recommendation K11**: Patients should be given specific theatre wear (including a hat) that provides easy access to the operative site and intravenous cannulae, and considers the patient’s comfort and dignity. [C]
- **Recommendation K12**: All staff should wear theatre specific clothing in all areas where ICED procedures are undertaken. Scrub suits, hats, masks and theatre footwear are essential parts of theatre discipline. [C]
- **Recommendation K13**: The operating team should wear sterile gowns in the operating theatre during ICED procedures. Consider wearing two pairs of sterile gloves when there is a high risk of glove perforation. [C]
- **Recommendation K14**: Staff number and movements should be kept to a minimum in the operating theatre. [C]
- **Recommendation K15**: The operating team should remove hand/wrist jewellery, artificial nails and nail polish before procedures. [C]
- **Recommendation K16**: The operating team should wash their hands prior to the first operation on the list using an aqueous antiseptic surgical solution, with a single-use brush or pick for the nails, and ensure that hands and nails are visibly clean. [C]
• Recommendation K17: Before subsequent operations on a list, hands should be washed using either an alcoholic hand rub or an antiseptic surgical solution. If hands are soiled then they should be washed again with an antiseptic surgical solution.[B]
• Recommendation K18: Any equipment brought into the operating field should be covered to reduce the risk of contamination.[C]
• Recommendation K19: Devices and surgical equipment should be left uncovered for the minimum possible time.[C]

We have extracted or adapted these recommendations from NICE guidelines, which are considered to be the most evidence based parts of the theatre ritual. These measures are perhaps even more important in the context of device implantation where the numbers of bacteria needed to establish an infection are lower than in procedures not involving man-made materials. All staff in the operating theatre, and the patient themselves, can potentially shed skin squames harbouring staphylococci (and other skin micro-organisms) into the environment and operative field, this includes the hair and the recommendation for both staff and patients to wear a hat.

Because of the potential for contamination of devices in the operating room (see Section E), any equipment brought into the operating field must be covered. Devices and surgical equipment should be taken out of protective packaging as late as possible and left uncovered for the minimum time.

K.9 How should skin be prepared before ICED insertion/manipulation?

• Recommendation K20: If hair has to be removed, use electric clippers (with a single-use head) on the day of the procedure. Do not use razors for hair removal, because they increase the risk of surgical site infection. [A]
• Recommendation K21: The skin over the operative site should be prepared using an alcoholic chlorhexidine preparation containing a minimum of 2% chlorhexidine [B]. The skin prep should be left on for a minimum contact time of thirty seconds and should not be allowed to pool. [C]
• Recommendation K22: A pragmatic approach to draping is recommended i.e. one large fenestrated drape can be used to cover the patient including the head. [C] Do not use non-iodophor impregnated incise drapes routinely for ICED insertion as they may increase the risk of surgical site infection. [C]

Removing chest hair was considered by the Cardiologists on the Working Party to be routine practice to maintain a clear operative field and avoid hairs getting into the wound. There is strong evidence that the use of razors is associated with an increase in SSI.138

A meta-analysis of peri-operative prophylaxis and skin antisepsis concluded that there was evidence for the use of both.142 We also found one prospective, observational, multicentre, evaluation, that examined skin preparation prior to ICED insertion.6 This study found higher infection rates with povidone iodine compared to chlorhexidine.6 The NICE review of the evidence pertaining to skin preparation prior to various types of procedure concluded there is no difference between aqueous or alcoholic preparations of povidone iodine and chlorhexidine138 but a systematic review concluded chlorhexidine was superior.143 There has only been one good quality randomized controlled trial that demonstrated superiority of alcoholic chlorhexidine over povidone-iodine for surgical skin antisepsis.144 However, this trial did not include details of the length of application of the agents. We conclude that skin preparation with 2% chlorhexidine in alcohol should be the current preparation of choice and should be left until dried; this usually involves a minimum contact time of 30 seconds.145 Pooling of alcoholic solutions should be avoided as there is a fire risk from diathermy during the procedure.146 Painting on alcoholic preparations may reduce pooling and thus fire risk.

Use of multiple drapes was considered to be unnecessary by the Working Party. In theory, shaking out multiple drapes may disturb more dust particles and render larger numbers of bacteria airborne. The ritual of placing multiple drapes probably also wastes time. The Working Party felt that a single large drape was the most appropriate draping technique. Most of the group did not use incised drapes for ICED insertion. However, if an incised drape is used, NICE guidelines recommend use of an iodophor-impregnated drape unless the patient has an iodine allergy.138
K.10 Antibiotic Prophylaxis

K.10.1 Should systemic antimicrobial prophylaxis be used for ICED insertion?

Summary:
- **Recommendation K23**: Systemic antibiotic prophylaxis should be used prior to ICED implantation. [A]

Two meta-analyses of randomized controlled trials of antimicrobial prophylaxis prior to ICED insertion concluded that prophylaxis was potentially beneficial but the limitations of collating studies with different definitions, antimicrobial regimens and follow up periods have been highlighted. The best evidence of benefit of antibiotic prophylaxis comes from a trial using cefazolin as the active agent. This study included superficial infections as an outcome and only followed patients for six months. The metaanalysis included eight studies. A randomized placebo controlled trial of five days of flucloxacinil did not show any benefit of prophylaxis. A trial of flucloxacinil plus benzylpenicillin did show benefit, but this study excluded infections related to wound dehiscence or erosion making interpretation difficult. Cloxacillin prophylaxis significantly reduced infections while not affecting pocket culture results.

K.10.2 When should prophylaxis be administered?

Summary:
- **Recommendation K24**: Intravenous antibiotics should be administered within the hour prior to skin incision. [A]
- **Recommendation K25**: Repeat dosing of antimicrobials is not recommended after skin closure. [A]

A recent meta-analysis of prophylaxis for ICED implantation concluded that evidence supported administration of single dose prophylaxis in the hour prior to implantation. Antibiotic prophylaxis should be given at a time that ensures tissue and plasma concentrations exceed the minimum inhibitory concentration (MIC) for the microorganisms commonly associated with infection at the time of incision and throughout the procedure. This would normally be within one hour for intravenous drugs given as a bolus or short infusion, but some longer infusions that are given over 30 minutes or more may need to be started earlier to ensure that the infusion is completed at least 20 minutes before incision eg. vancomycin, fluoroquinolones. The oral route is an option for agents with good oral bioavailability. Repeat dosing of antimicrobials after the procedure does not appear to offer any benefit.

K.10.3 Which agent(s) should be given?

Summary:
- **Recommendation K26**: The choice of prophylactic agent should cover the most likely pathogens in ICED infection. [C]
- **Recommendation K27**: A glycopeptide (e.g. intravenous teicoplanin, according to local dosing protocols) is the current preferred agent (with or without gentamicin depending on local Gram-negative infection rates). [C]

A recent survey of ICED implantation prophylaxis in England showed a wide range of antibiotic agent(s) in use - flucloxacinil was the most common. The Working Party agreed that the agent used for prophylaxis should have activity against the most common causative organisms (Section D.6). In this respect, flucloxacinil is not currently ideal because of its lack of activity against many CoNS. In general, trials of prophylaxis in ICED have not taken into account the long incubation period of many ICED infections. There are theoretical grounds for suggesting that a glycopeptide is superior to cephalosporins or penicillins (such as flucloxacinil) since most infections are caused by staphylococci (coagulase negative, MSSA and MRSA) and cephalosporins are not recommended in many countries because of their association with Clostridium difficile infection. Moreover, high dose flucloxacinil has been associated with nephrotoxicity in orthopaedic surgery. If a glycopeptide antibiotic is to be used, teicoplanin has some practical advantages over vancomycin in terms of administration as it can be given as a bolus rather than a long infusion. Although
teicoplanin was inferior to cefazolin in preventing Gram-positive infections in cardiac surgical patients\textsuperscript{156} a combination of teicoplanin and gentamicin was as effective as a multidose cephalosporin-based regimen in a similar patient population.\textsuperscript{157} Further randomised trials may therefore be needed to determine the optimal agent(s) for prophylaxis. Use of a glycopeptide also avoids the problem of selecting alternative agents for patients reporting an allergy to penicillin.

With regard to Gram-negative cover, there was no consensus within the Working Party as to whether adding gentamicin to a glycopeptide was necessary. As for any antimicrobial, the risks and benefits need to be assessed and discussed with the patient. The rate of carriage of the mitochondrial gene defect associated with gentamicin induced deafness in the UK 1958 birth cohort study is of the order of 1 in 385 suggesting that the problem is not rare.\textsuperscript{158, 159} Therapeutic usage of gentamicin has been associated with a 24.4\% rate of acute kidney injury and 2.4\% risk of renal failure,\textsuperscript{138, 160} but an increase in nephrotoxicity was not seen with a 2mg/kg single dose prophylaxis regimen in cardiac surgical patients.\textsuperscript{157} Although it is argued that the risk of renal failure is lower with single dose prophylaxis there is a paucity of evidence on this subject. The benefits of adding gentamicin to a glycopeptide in ICED prophylaxis are unproven and it may be advisable to avoid gentamicin in patients with impaired renal function, particularly those where a deterioration in renal function may precipitate the need for long term renal replacement therapy. The Working Party recommends use of a glycopeptide as the first choice agent. Intravenous gentamicin may be beneficial but the drug should be used with caution in patients at risk of toxicity.

K.10.4 Should antimicrobials be instilled into the generator pocket after implantation?

Summary:

- **Recommendation K28:** Local instillation of antimicrobials or antiseptics should be avoided until evidence of benefit has been demonstrated. [C]

A recent meta-analysis\textsuperscript{142} pooled data from two studies to compare pre-operative systemic antimicrobial prophylaxis with locally instilled antibiotics (rifampicin\textsuperscript{161} in one and cloxacillin\textsuperscript{162} [equivalent to flucloxacillin] in the other). The meta-analysis found no difference in infection rate between the two but noted the studies to be underpowered. The meta-analysis also found no evidence that concomitant local antimicrobials offered any benefit\textsuperscript{142} and concluded that local instillation of antimicrobials did not reduce infection rates.

K.11 What represents ideal post-operative wound closure and care?

Summary:

- **Recommendation K29:** National guidelines on post-operative wound closure and care should be followed. [C]

There is no clear evidence base to make recommendations on wound closure and post operative care following insertion of ICED. Pending a very large randomized controlled trial, the Working Party recommends pragmatic interpretation of NICE clinical guideline 74.\textsuperscript{138} An example of a pragmatic interpretation is provided in the description of the bundle of care used in the randomised controlled trial on antibiotic prophylaxis.\textsuperscript{42} Attention to good surgical technique and attendance at appropriate training courses are advised.

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M Areas for future research

The following list summarises the currently important research questions defined by the Working Party:

- Establishing the incidence of ICED infection in the UK.
• Establishing whether complex devices have a genuinely higher incidence of infection than other devices and if so, why?
• Clarifying the importance of Gram-negative bacteria in ICED infection in the UK.
• Determining the antimicrobial susceptibility of CoNS in UK ICED infecting isolates.
• Identifying interventions that mitigate the increased risk of infection associated with revision procedures.
• Determining if sonication of explanted devices improves the sensitivity of culture.
• Determining the treatment regimens and outcomes for patients managed without device removal.
• Establishing the role of MSSA and MRSA screening and decolonization protocols.
• Determining the frequency of uncomplicated generator pocket wound inflammation and how often it progresses to generator pocket infection.
• Determining the benefit of local delivery of antimicrobials and/or antiseptics.
• Establishing the optimal choice of antimicrobial agent(s).
• Determining the role of pre-incisional polyacrylamide based sealants.
• Determining the role of laminar flow theatre environments compared to standard operating theatre and cardiac catheterisation laboratories.

N List of Abbreviations

CoNS               coagulase negative Staphylococcus
ICED               implantable cardiac electronic device
ICED-IE            implantable cardiac electronic device associated endocarditis (see definitions)
ICED-LI            implantable cardiac electronic device lead infection (see definitions)
INR                international normalized ratio
IV                  intravenous
MSSA               methicillin susceptible Staphylococcus aureus
MRSA               methicillin resistant Staphylococcus aureus
PO                  oral route

O Appendix 1-Outline of structure and materials used in ICEDs.

An ICED consists of a generator that is connected to leads, which attach to the heart. The generator contains the battery and electronics. The aim of this section is to describe the materials that are in direct contact with tissue (and therefore of relevance to treatment and prevention of infection), rather than a detailed description of the individual components.

O.1 The generator

The size of the generator is principally determined by the size of the battery and capacitors. Pacemaker generators are typically 50mm(h) x 50mm(l) x 6mm(t), weight 20 grams, volume 12cc and defibrillators are 80mm(h) x 50mm(l) x 14mm(t), weight 80 grams, volume 40cc.

The components are hermetically sealed in a titanium case by welding two halves with a laser or by tungsten inert gas welding. The seal is tested by filling the can with helium before closure in an ultra high vacuum with a helium leak tester. High grade titanium is used because it is strong, light, resistant to corrosion and has a very low risk of allergic response. The header is the portion of the generator where the leads are connected, is composed of clear polymethylmethacrylate resin or acrylic glass, and has small screws made from stainless steel that secure the leads.

O.2 Pacing and defibrillator leads

The key structural components of the leads include:

- **Connector pins:** Composed of stainless steel and generally enclosed by the header. It is possible for tissue fluid/blood and fibrous tissue to fill the potential gap between the header conductor and pins.
• **Insulation:** The conductor is completely covered by insulation that is electrically inert. The materials used are biocompatible and bio-stable - silicone rubber, polyurethane or fluoropolymers (e.g Teflon). No conductor is exposed unless the insulation is breached.

• **Pacing Leads:** These are the interface between the generator and the heart and are comprised of coils and/or cables made of an alloy of platinum (90%) and iridium (10%). The electrodes may be embedded onto a porous titanium nitride microstructure and/or may be steroid-eluting. Leads are around 2mm thick and up to 64cm in length, although longer leads are available.

• **Defibrillator coils:** These breach the external insulation of the lead and are a coil of platinum iridium alloy attached to the conductor material inside the lead. In order to prevent tissue in-growth between the adjacent portions of coil, some manufacturers ensure the coil is very tight, use silicone to close potential gaps or cover the coils in Goretex or titanium nitride. There can be either one or two coils on the leads - the distal coil is usually in the right ventricle and the proximal coil stays in the superior vena cava. The average coil is up to 10cm in length.

• **Tines:** In leads that are passively fixed, small tines, composed of either silicone or polyurethane, that allow the lead to hook onto endocardial trabeculae are present just proximal to the distal electrode (cathode).

• **Active fixation lead:** A small screw (helix) can be deployed into the myocardium to allow the distal portion of the lead to attach to the endocardium in the absence of trabeculae. In some cases, the screw is able to conduct. Approximately 2-3mm of the helix is deployed into the endocardium and is usually composed of platinum/iridium alloy with a low polarization coating.

• **Steroid:** The lead tips/electrodes are almost always coated with a slowly-eluting steroid (e.g. approximately 1mg of dexamathasone acetate) to reduce the inflammatory response at the interface between the heart and the electrode which may result in poor electrical pacing parameters.

• **Central core:** Most leads are helical in construction and have a fine inner central lumen (~0.45mm) that accommodates a stylet or angioplasty wire to enable lead manipulation. Most leads used for simple pacing have a lumen that ends blindly at the distal end of the lead. In coronary sinus leads, this lumen is continuous and the wire can exit the other end. Some manufacturers cover the distal end of the lumen with a one way haemostatic valve. There is currently only one endocardial lead that does not have an inner lumen, which is placed into the heart with the aid of long sheaths. Epicardial leads do not need a central lumen as the distal end of the lead is directly attached to the heart by deploying an active helix or suturing the conductor onto the heart with non-resorbable stitches (e.g. prolene). Otherwise the composition of the leads are similar.

• **Subcutaneous leads:** These are designed for extravascular placement. The lead composition and design are similar to conventional ICD leads.

P Appendix 2. Methods of Implantation and removal of ICED.

For those who are less familiar with these procedures, this section provides an outline of how ICEDs are implanted and removed. The key aspects of de novo implantation are selection of site, creating the pocket, access to the heart, securing the leads and closing up. Generator revision can be complex as leads may need revision or the whole system may require upgrading. Almost all ICEDs in the UK are implanted by cardiologists in a catheter laboratory setting. Although the procedure is less invasive than surgical implantation, it is vital that meticulous attention is paid to maintenance of a sterile surgical field.

P.1 De novo ICED implantation.

P.1.1 Generator site selection

The right or left subclavicular pre-pectoral site is the most commonly used because of ease of access, proximity to central veins and patient comfort. The procedure can be performed under local anaesthesia with conscious sedation if required. The incision is made horizontally or obliquely approximately 1-2 centimetres below the clavicle between the deltopectoral groove and the junction between the middle and lateral third of the clavicle, or in line with the deltopectoral groove, one centimetre below the clavicle. The incision is between 4-5 centimetres long. The skin and subcutaneous tissues are dissected to expose the pectoral muscles sparing the overlying fascia. The pocket is then created by bluntly dissecting caudally and medially to fit the device. In some patients it is preferable to place the generator sub-muscularly - in this instance, the pectoral muscles are separated using blunt dissection to access the plane between the ribs and muscle, the
pocket is created in this space by blunt dissection.\textsuperscript{163} Diathermy can be used to aid dissection and haemostasis. Abdominal placement of generators is often used in children as the devices are large compared to the size of the patient. The first ICDs were routinely implanted in this position because of their size. The incision is made below the rib cage and the pocket created under the rectus sheath. This procedure is usually performed under general anaesthesia.\textsuperscript{164} Placement of ICDs in the supra-inguinal region may be indicated if the femoral vein is used for access. The incision is made between the inguinal ligament and groin crease, and the pocket is created underneath the deep fascia cranial to the incision;\textsuperscript{165} longer leads are required for this approach.

P.1.2 Access to the heart and lead placement
The transvenous route is the preferred method of lead placement. In the majority of patients, leads are placed into the right atrium and ventricle. Venous access is obtained by the Seldinger technique or by cut down under direct vision. The subclavian, axillary and cephalic veins are the most frequently used. Access to the latter is generally by dissection between the deltoid and pectoral muscles, visualising the vein, securing it with ties and making a small incision to allow leads to be inserted directly or by the Seldinger technique after insertion of a guide wire. The subclavian and axillary veins are punctured with a needle and a guidewire placed in the vein. Fluoroscopy or ultrasound may be used to allow localisation of the veins as they are rarely exposed and accessed directly. Less commonly used veins are the internal jugular and femoral. Rarely the trans-hepatic route can be considered. Once venous access has been obtained, peel away introducers are advanced into the vein over the guidewires and leads are placed into the central circulation. If more than one lead is being placed, multiple venous punctures can be performed or, placement of multiple guidewires into a sheath allows more than one lead to be placed using one puncture site. Occasionally, leads are placed directly into the epicardial aspect of the heart by a surgeon (“Epicardial systems”). This requires either a thoracotomy or median sternotomy, and the procedure is performed in the cardiothoracic theatre.

The transvenous approach allows access to the endocardial aspect of the right atrium, right ventricle, coronary sinus (epicardial left ventricle) and rarely endocardial left ventricle following a trans-septal puncture. Leads are manipulated percutaneously with the use of stylets, long sheaths and guidewires to position the tip of the lead in the required position. Some procedures can be technically challenging, for example placement of leads via the coronary sinus. These procedures often take longer (approximately 2 hours) compared to standard dual chamber pacemaker insertion (approximately 1 hour). Surgical lead placement can occur anywhere on the epicardial aspect of the atrium or ventricles and the leads are attached directly onto the surface. In infants for example, it is routine to place leads surgically.

In order to pace the heart it is paramount that the lead electrodes remain in direct stable contact with the heart. In order to facilitate this, endocardial leads have “tines” that attach to the endocardial trabeculae (passive fixation) or have a screw at the tip that is deployed directly into the endocardium (active fixation). Leads that are placed into the coronary sinus rely on either tines, their shape (spiral or curved) or expanding lobes (that lock the lead in the vein) to keep them in place. Surgical leads are either “screwed in” or stitched onto the epicardium. Lead repositioning may be required if pacing parameters or anatomical position is suboptimal.

Recently, a subcutaneous ICD has been introduced. Vascular access is not needed. The generator is placed submuscularly in the lateral thoracic wall, and the lead is tunnelled underneath the lateral sternal border and secured with non resorbable stitches.

P.1.3 Securing leads and closing the skin
Transvenous leads are secured to muscle (usually the pectoral) where they enter the vein. Plastic sleeves that cover the lead insulation are tied onto muscle with non absorbable sutures. The leads are then connected to the generator. If the venous access site is remote from the box or in the case of surgically implanted leads, subcutaneous or submuscular tunnelling is needed to connect the leads to the generator. Once secured, the generator is placed into the pocket, and the wound closed. Deep and superficial sutures are required to ensure that the pocket is tight (limits device movement and tamponades any potential bleeding sites). Furthermore, meticulous attention is paid to haemostasis. Absorbable sutures are used for this step, most commonly vicryl to close the wound and tie any bleeding points. The skin is closed with absorbable sutures, steristrips or glue,
and a clean dressing can be applied over the site. If non absorbable sutures e.g. prolene are used to stitch the skin, it is essential to ensure that arrangements are made to remove the sutures in due course.

P.1.4 Generator replacement or ICED revision

ICED generators have a finite battery life and need to be replaced before they run out of power. This is also a good opportunity for considering device upgrade or downgrade. Although generator replacement is usually straightforward if the current leads are functioning normally and do not need replacement, the risk of ICED infection is higher following subsequent interventions. ICED revision may be required prior to generator change because of lead or generator problems (e.g. lead displacement), upgrade (e.g. from a pacemaker to defibrillator) or potential pocket problems (e.g. threatened erosion or generator migration).

Patient preparation and technique is similar to de novo implantation. However because of the previous procedure there will be scarring and fibrosis which makes dissection more challenging. Furthermore, access can be difficult because of stenosed or occluded veins and a peripheral venogram is recommended to help plan a strategy which may include venous angioplasty, extraction of leads to provide access and placement of the leads at a new site with tunnelling to the generator. These are just a few examples, and it may be necessary to modify the technique depending on the circumstance. If an ICED is being upgraded, it is likely that there will be old leads that will no longer be needed. These can be capped and buried in the pocket; cut tied and buried or extracted. It is important to ensure that all hardware is securely stitched to the pocket. There is a group of patients who undergo a percutaneous procedure who will later on have a surgical lead implanted, this will necessitate the pocket being opened twice and lead tunnelling. This does have a potential bearing on ICED infection.

P.1.5 Non infective complications associated with ICED implantation

ICED implantation is now routine clinical practice and as experience has grown, the number of devices implanted has increased, and the complication rate has fallen. Complications that can occur at the time of implantation include vascular damage (e.g. acute venous thrombosis) and haematoma, pneumothorax (rarely haemothorax and chylothorax), cardiac perforation resulting in tamponade, and rhythm problems (e.g. ventricular tachycardia). Longer term complications include lead displacement, lead failure (damage to conductor or insulation), generator migration and functional problems including pacemaker mediated tachycardia, inappropriate therapy (e.g. defibrillator discharge for atrial fibrillation), pacemaker syndrome and heart failure as a result of right ventricular pacing.

P.1.6 Removal of ICEDs

Infection is probably the commonest indication for ICED removal. Extraction is a term applied if the leads have been in place for more than one year or specialised equipment is needed. Explantation is used to describe procedures requiring simple traction, and removal is the generic term. The procedure can be straightforward requiring only manual traction to remove the leads if the implant was performed very recently, or extremely complex requiring specialised tools and an associated morbidity and mortality. It is for this reason that guidelines recommend that these procedures are performed by cardiologists who perform at least 20 or more procedures a year in a cardiothoracic surgical centre. A multi-disciplinary approach is often needed to facilitate ICED extraction; in addition to the cardiologist, anaesthetic and cardiothoracic surgical teams may be required. Lead removal can be performed under conscious sedation, however, general anaesthesia may be preferable when explanting leads that have been in place for many years as the procedure can be very uncomfortable for the patient, it can take a long time and intensive monitoring may be required. Moreover, if emergency surgery is required the patient is already anesthetised.

Most ICEDs can be extracted percutaneously and the procedures are performed by a cardiologist. However, occasionally a surgeon is needed to assist with removal of intravascular / intracardiac lead fragments, extraction of systems that cannot be done percutaneously (e.g epicardial systems) or for management of complications such as cardiac or venous perforation.
It is beyond the scope of this document to cover ICED extraction in detail, but a basic outline of the procedure will be described.

**Patient preparation**
If the infection is localised and the patient not acutely unwell the procedure can be planned semi-urgently. However, in a patient with severe sepsis, the ICED should be explanted as soon as possible.

The ICED indication should be revisited and if the patient is pacemaker-dependent a temporary wire will need to be inserted. Consideration should be given to the implantation of an externalised pacemaker that uses standard pacing leads connected to an external generator. This facilitates patient mobilisation and allows for stable pacing during the period that the patient does not have a permanent device.

Procedures are carried out in the cardiac catheter laboratory or theatre. The implant site together with the groins are prepped and draped. The latter access may be required for temporary wire placement, femoral workstations and arterial access for invasive blood pressure monitoring. If surgical extraction is anticipated the thoracic/abdominal region can be prepared.

**Generator and Lead Removal**
Complete ICED removal comprises removal of the generator (usually straightforward) and lead removal (often far more challenging). Leads that have been *in situ* for many years may be enclosed by tough fibrous tissue and need to be freed with removal of all suture material. Diathermy is often useful to aid dissection. The next step is lead removal. Simple manual traction may be sufficient to remove recently implanted leads. However, if there is resistance then specialised equipment is required to help free adhesions that could form anywhere along the length of the lead. Counter-traction is the most commonly employed technique and aims to minimise strain on the lead and prevent fracture. Table 9 shows commonly employed tools in extraction and their indication. Following removal of all hardware, haemostasis is achieved, and the wound closed. A drain may be left in place. Surgical extraction is performed by cardiothoracic surgeons under direct vision. A thoracotomy or median sternotomy is required with cardiopulmonary bypass available if necessary.

**Complications of lead removal**
The major complication rate is 1.6% and the following factors appear to predict which patient group is at risk; implant duration of oldest lead, female gender, defibrillator lead removal and use of the laser. Complications associated with lead removal are well described and the procedure should be undertaken by an experienced team in a centre that can provide emergency cardiothoracic cover.
<table>
<thead>
<tr>
<th>Devices included</th>
<th>Number of studies (n = 22)</th>
<th>Range of incidences [Follow-up range]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IP only</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 reporting as %</td>
<td></td>
<td>0.8%, 1.8% [6 weeks-2 months]</td>
</tr>
<tr>
<td>1 reporting rate</td>
<td></td>
<td>1.82/1000 years (primary)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>5.32/1000 years (revision)</td>
</tr>
<tr>
<td><strong>ICD only</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 reporting as %</td>
<td></td>
<td>1.1%, 1.2%, 1.8% [12.2 months, not clear, 35 months]</td>
</tr>
<tr>
<td>1 reporting as rate</td>
<td></td>
<td>3.1/1000 patient years</td>
</tr>
<tr>
<td><strong>CRT only</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 reporting as %</td>
<td></td>
<td>1% [6 months]</td>
</tr>
<tr>
<td>1 reporting as rate</td>
<td></td>
<td>10/1000 years</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9/1000 primary</td>
</tr>
<tr>
<td></td>
<td></td>
<td>18/1000 revision</td>
</tr>
<tr>
<td><strong>Mixed devices</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>12 reporting as %</td>
<td></td>
<td>0.5% to 2.2% [6 weeks to 11 years]</td>
</tr>
<tr>
<td>1 reporting as rate</td>
<td></td>
<td>1.9/1000 years</td>
</tr>
</tbody>
</table>

CRT, cardiac resynchronisation therapy; ICD, implantable cardiac defibrillator;
<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Number of studies identifying risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedure related risk factors</strong></td>
<td></td>
</tr>
<tr>
<td>Lack of antibiotic prophylaxis</td>
<td>4</td>
</tr>
<tr>
<td>Type of device (CRT/dual chamber, CRT-D vs CRT-P, biventricular, and &gt;2 pacing leads)</td>
<td>4</td>
</tr>
<tr>
<td>Need for intervention prior to discharge</td>
<td>2</td>
</tr>
<tr>
<td>Epicardial or transvenous/epicardial lead placement (early infection)</td>
<td>1</td>
</tr>
<tr>
<td>Procedure time</td>
<td>1</td>
</tr>
<tr>
<td>Post-operative haematoma</td>
<td>1</td>
</tr>
<tr>
<td>Post-operative wound infection (early infection)</td>
<td>1</td>
</tr>
<tr>
<td>Temporary pacemaker pre-implantation</td>
<td>1</td>
</tr>
<tr>
<td><strong>Patient characteristics</strong></td>
<td></td>
</tr>
<tr>
<td>Number of prior procedures</td>
<td>5</td>
</tr>
<tr>
<td>Anticoagulation</td>
<td>2</td>
</tr>
<tr>
<td>Chronic obstructive pulmonary disease</td>
<td>2</td>
</tr>
<tr>
<td>Male sex</td>
<td>2</td>
</tr>
<tr>
<td>Renal impairment</td>
<td>2</td>
</tr>
<tr>
<td>Younger age</td>
<td>2</td>
</tr>
<tr>
<td>Azotemia</td>
<td>1</td>
</tr>
<tr>
<td>Chronic corticosteroid therapy</td>
<td>1</td>
</tr>
<tr>
<td>Duration of hospitalisation (late infection)</td>
<td>1</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Earlier year of implantation (before 1985)</td>
<td>1</td>
</tr>
<tr>
<td>Fever in 24 hours pre-implantation</td>
<td>1</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>1</td>
</tr>
<tr>
<td>Shorter time from implantation (&lt;1 year)</td>
<td>1</td>
</tr>
</tbody>
</table>

CRT-D, cardiac resynchronisation therapy with defibrillator; CRT-P, cardiac resynchronisation therapy with pacing.
### Table 3. Summary of the microbiology of implantable cardiac electronic device infection.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>Range (%) in studies using patients as the denominator</th>
<th>Range (%) in studies using isolates as the denominator</th>
</tr>
</thead>
<tbody>
<tr>
<td>Coagulase negative staphylococci [17]</td>
<td>10% to 68%</td>
<td>42% to 77%</td>
</tr>
<tr>
<td>Staphylococcus aureus [16]</td>
<td>24% to 59%</td>
<td>10% to 30%</td>
</tr>
<tr>
<td>Gram-negative bacilli [11]</td>
<td>1% to 17%</td>
<td>6% to 11%</td>
</tr>
<tr>
<td>Enterococcus spp. [6]</td>
<td>5% to 6%</td>
<td>0.4% to 10%</td>
</tr>
<tr>
<td>Streptococcus spp. [5]</td>
<td>4% to 6%</td>
<td>3% to 10%</td>
</tr>
<tr>
<td>Propionibacterium spp. [3]</td>
<td>-</td>
<td>0.8% to 8</td>
</tr>
<tr>
<td>Fungi [5]</td>
<td>0.5% to 2%</td>
<td>0.4% to 1.4%</td>
</tr>
</tbody>
</table>

*This study only used blood cultures and had high culture negativity (49%)

**This study reported *Streptococcus* and *Enterococcus* spp. together
Table 4 Risk factors for mortality in implantable cardiac electronic device (ICED) infection.

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Number of studies identifying risk factor</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Procedure related risk factors for ICED infection mortality</strong></td>
<td></td>
</tr>
<tr>
<td>CRT device</td>
<td>1</td>
</tr>
<tr>
<td>Complicated device removal</td>
<td>1</td>
</tr>
<tr>
<td>De novo implant</td>
<td>1</td>
</tr>
<tr>
<td>Epicardial right ventricular pacing system in those undergoing reimplantation</td>
<td>1</td>
</tr>
<tr>
<td>Late removal (versus immediate)</td>
<td>1</td>
</tr>
<tr>
<td>System upgrade/revision</td>
<td>1</td>
</tr>
<tr>
<td><strong>Patient characteristics associated with ICED infection mortality</strong></td>
<td></td>
</tr>
<tr>
<td>Abnormal renal function</td>
<td>3</td>
</tr>
<tr>
<td>Older age</td>
<td>2</td>
</tr>
<tr>
<td>Abnormal right ventricular function</td>
<td>1</td>
</tr>
<tr>
<td>Corticosteroid therapy</td>
<td>1</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>1</td>
</tr>
<tr>
<td>Heart failure</td>
<td>1</td>
</tr>
<tr>
<td>Length of time lead in-situ</td>
<td>1</td>
</tr>
<tr>
<td>Medical therapy</td>
<td>1</td>
</tr>
<tr>
<td>Metastatic malignancy</td>
<td>1</td>
</tr>
<tr>
<td>Moderate/severe tricuspid regurgitation</td>
<td>1</td>
</tr>
<tr>
<td>Pathogen other than a coagulase negative staphylococcus</td>
<td>1</td>
</tr>
<tr>
<td>Pre-reimplantation C-reactive protein</td>
<td>1</td>
</tr>
<tr>
<td>Systemic embolisation</td>
<td>1</td>
</tr>
<tr>
<td>Thrombocytopenia on admission</td>
<td>1</td>
</tr>
</tbody>
</table>

CRT, cardiac resynchronisation therapy.
<table>
<thead>
<tr>
<th>Diagnosis/scenario</th>
<th>ICED management (recommendation)</th>
<th>Antimicrobial strategy</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncomplicated generator pocket wound inflammation</td>
<td>Leave device in situ J.1.1</td>
<td>Case by case, consider oral therapy (see Table 6 and Figure 1)</td>
<td>This entity may represent early infection, but other possible explanations.</td>
</tr>
<tr>
<td>Generator pocket infection AND no absolute requirement for ICED* AND device removable.</td>
<td>Complete device removal without replacement ICED.</td>
<td>10-14 days (IV and PO) therapy (see Table 6)</td>
<td>Preferred option with greatest chance of cure.</td>
</tr>
<tr>
<td>Generator pocket infection AND absolute requirement for ICED* AND device removable.</td>
<td>Complete device removal, temporary pacing and delayed replacement ICED until signs of infection resolved.</td>
<td>10-14 days IV antimicrobials. (see Table 6 and Table 7)</td>
<td>Risk of cross infection to temporary system and permanent system.</td>
</tr>
<tr>
<td>Generator pocket infection when attempted lead extraction considered too risky/or declined by patient AND no absolute requirement for ICED*.</td>
<td>Removal of generator and proximal leads leaving intravascular/cardiac portion in situ (H3), without replacement ICED.</td>
<td>6 weeks IV therapy (see )</td>
<td>Bioburden of infection reduced by generator removal, small possibility of eradicating residual lead infection.</td>
</tr>
<tr>
<td>Generator pocket infection when attempted lead extraction considered too risky/or declined by patient AND no absolute requirement for ICED*.</td>
<td>Removal of generator and proximal leads leaving intravascular/cardiac portion in situ (H3), with early/single stage replacement ICED.</td>
<td>6 weeks IV therapy (see Table W)</td>
<td>Bioburden of infection reduced; small possibility of eradicating residual lead infection, high risk of infecting new system, but risk probably persists longer than temporary system could be used.</td>
</tr>
<tr>
<td>ICED-associated IE (without clinical evidence of generator pocket infection) AND no absolute requirement for ICED* AND device removable.</td>
<td>Prompt and complete device removal (H1) without replacement ICED.</td>
<td>If native valves affected: total 4 weeks IV therapy (See table) If prosthetic valves affected, secondary brain abscess or spinal infection: 6 weeks IV therapy (See table)</td>
<td>Consider day 1 as the first day of appropriate antibiotics, timing of ICED removal does not affect duration.</td>
</tr>
<tr>
<td>ICED-associated IE or lead infection (without generator pocket infection) when attempted lead extraction considered too risky/or declined by patient AND absolute requirement for ICED.</td>
<td>Prompt and complete device removal (H1) without replacement ICED.</td>
<td>Prolonged therapy post removal not usually required. Review therapy 1 week after removal.</td>
<td>This approach is possible, if tricuspid valve is structurally normal, no “ghost lesions” present post system removal and rapid clinical response to device removal. If in doubt, treat as ICED-IE.</td>
</tr>
<tr>
<td>Leave entire device in situ (H2).</td>
<td>6 weeks IV therapy (see Table 8)</td>
<td>High risk of failure. Stop antimicrobials after 6 weeks if good clinical response, consider long term oral suppressive therapy if relapse occurs.</td>
<td></td>
</tr>
</tbody>
</table>

ICED-LI, implantable cardiac electronic device lead infection; ICED-IE, implantable cardiac electronic device associated endocarditis.
Table 6. Empirical treatment regimens for ICED infection. All doses require review if renal function is impaired.

<table>
<thead>
<tr>
<th>Diagnosis/scenario</th>
<th>Antimicrobial</th>
<th>Dose/route</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Generator pocket wound inflammation.</td>
<td>Flucloxacillin</td>
<td>500mg 6-hourly po</td>
<td>Benefit of and need for antimicrobial therapy is unclear.</td>
</tr>
<tr>
<td>2. Generator pocket wound inflammation in penicillin allergic or MRSA colonised patient</td>
<td>Doxycycline OR Linezolid OR Clindamycin</td>
<td>100mg 12-hourly po 600mg 12-hourly po 450mg 6-hourly po</td>
<td>Benefit of and need for antimicrobial therapy is unclear. If possible, avoid clindamycin in patients at risk of <em>Clostridium difficile</em> infection.</td>
</tr>
<tr>
<td>3. Generator pocket infection.</td>
<td>Vancomycin OR Daptomycin OR Teicoplanin</td>
<td>15mg/kg 12-hourly* iv 6 mg/kg 24-hourly iv 10mg/kg to a maximum of 1g given at 0, 12 and 24 hours and then 24 hourly.</td>
<td>*or dose vancomycin according to local protocols. Use daptomycin in glycopeptide intolerant patient or when nephrotoxicity is a concern.</td>
</tr>
<tr>
<td>4. ICED-LI or ICED-IE pending blood cultures, e.g. in severe sepsis.</td>
<td>Vancomycin AND Meropenem</td>
<td>1g 12-hourly* IV 1g 8-hourly IV</td>
<td>Appropriate spectrum but risk of nephrotoxicity. Gentamicin (high dose) or other agents may be appropriate depending on local epidemiology.</td>
</tr>
<tr>
<td>5. ICED-LI or ICED-IE with negative blood cultures.</td>
<td>Vancomycin AND Gentamicin$</td>
<td>1g 12-hourly* IV 1mg/kg 12-hourly IV</td>
<td>Appropriate spectrum but risk of nephrotoxicity. $Aim for pre-dose levels &lt;1mg/L and post dose levels 3-5mg/L. meropenem is an alternative to gentamicin.</td>
</tr>
<tr>
<td>                                                                                                                                                                                                                                                                                                                           &amp;nbs...</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

See BNF for drug interactions and cautions. Po, oral; iv intravenous; ICED-LI, implantable cardiac electronic device lead infection; ICED-IE, implantable cardiac electronic device associated endocarditis.
### Table 7. Directed antimicrobial regimens for uncomplicated generator pocket infections.

<table>
<thead>
<tr>
<th>Pathogen</th>
<th>First line (IV) (depending on susceptibility)</th>
<th>Oral switch (depending on susceptibility) usually after device removal.</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus</em> spp. (methicillin susceptible).</td>
<td>Flucloxacillin 2g 6-hourly.</td>
<td>Flucloxacillin 1g 6-hourly.</td>
</tr>
<tr>
<td><em>Staphylococcus</em> spp. (methicillin resistant, penicillin allergic patient)</td>
<td>Vancomycin 1g 12-hourly. Or Teicoplanin 10mg/kg to a maximum of 1g given at 0, 12 and 24 hours and then 24 hourly. Or Daptomycin 6mg/kg 24-hourly.</td>
<td>Linezolid 600mg 12-hourly. Or Clindamycin 450mg 6-hourly. Or Doxycycline 100mg 12-hourly.</td>
</tr>
<tr>
<td><em>Streptococcus</em> spp. (penicillin susceptible)</td>
<td>Benzylpenicillin 1.2g 4-hourly.</td>
<td>Amoxicillin 1g 6-hourly.</td>
</tr>
<tr>
<td><em>Streptococcus</em> spp. (penicillin resistant or penicillin allergic patient)</td>
<td>Vancomycin 1g 12-hourly. Or Teicoplanin 10mg/kg to a maximum of 1g given at 0, 12 and 24 hours and then 24 hourly.</td>
<td>Linezolid 600mg 12-hourly.</td>
</tr>
<tr>
<td><em>Enterococcus</em> (amoxicillin susceptible)</td>
<td>Amoxicillin 2g 6-hourly.</td>
<td>Amoxicillin 1g 6-hourly.</td>
</tr>
<tr>
<td><em>Enterococcus</em> (amoxicillin resistant, but vancomycin susceptible or penicillin allergic)</td>
<td>Vancomycin 1g 12-hourly. Or Teicoplanin 10mg/kg to a maximum of 1g given at 0, 12 and 24 hours and then 24 hourly.</td>
<td>Linezolid 600mg 12-hourly.</td>
</tr>
<tr>
<td><em>Enterococcus</em> (amoxicillin and vancomycin resistant)</td>
<td>Daptomycin 6mg/kg 24-hourly. Or Linezolid 600mg 12-hourly.</td>
<td>Linezolid 600mg 12-hourly.</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em> (&quot;coli forms&quot;)</td>
<td>Case-by-case depending on susceptibility, monotherapy advised.</td>
<td>Case-by-case depending on susceptibility, monotherapy advised.</td>
</tr>
</tbody>
</table>

Review dosing regimens in patients with renal impairment. IV, intravenous.
Table 8 Antimicrobial regimens for treatment (salvage) of ICED-IE/ICED lead infection when system cannot be removed.

<table>
<thead>
<tr>
<th>Organism</th>
<th>Agent</th>
<th>Dose/route</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus</em> sp. (methicillin-susceptible)</td>
<td>Flucloxacillin* AND Rifampicin* AND Gentamicin*</td>
<td>2g 4–6-hourly IV and 600mg 12-hourly orally and 1mg/kg IV, 12-hourly</td>
<td>Use 4-hourly regimen if weight &gt;85kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>For all organisms: Continue gentamicin for the first two weeks provided there are no signs or symptoms of toxicity. Aim for pre-dose &lt;1mg/L and 1 hour post dose 3-5mg/L. Dose according to ideal body weight if obese.</td>
</tr>
<tr>
<td><em>Staphylococcus</em> sp. (methicillin-resistant, glycopeptide susceptible) or penicillin-allergic patient</td>
<td>Vancomycin* OR Teicoplanin* AND Rifampicin* AND Gentamicin*</td>
<td>1g* IV 12-hourly and 10mg/kg to a maximum of 1g given at 0, 12 and 24 hours and then 24 hourly and 1mg/kg IV, 12-hourly</td>
<td>Dose glycopeptides according to local guidelines. Maintain pre-dose vancomycin and teicoplanin levels 15-20 and 20-40mg/L, respectively. See comment <em>Staphylococcus</em> sp. (methicillin-susceptible).</td>
</tr>
<tr>
<td><em>Staphylococcus</em> sp. Alternative regimen e.g. glycopeptide resistant isolate; vancomycin intolerant patient or where nephrotoxicity is a concern</td>
<td>Daptomycin* AND Rifampicin* AND Gentamicin*</td>
<td>6-8mg/kg 24-hourly IV and 600mg 12-hourly orally and 1mg/kg 12-hourly IV</td>
<td>Because resistance can develop on daptomycin, combination therapy is advised. If isolate is resistant to rifampicin and gentamicin, linezolid can be used. High doses based on.124 See comment <em>Staphylococcus</em> sp. (methicillin-susceptible).</td>
</tr>
<tr>
<td><em>Streptococcus</em> sp. (penicillin-susceptible)</td>
<td>Benzylpenicillin* AND Gentamicin*</td>
<td>1.2g 4-hourly IV and 1mg/kg 12 hourly IV</td>
<td>See comment <em>Staphylococcus</em> sp. (methicillin-susceptible).</td>
</tr>
<tr>
<td><em>Streptococcus</em> sp. (penicillin-resistant) or penicillin allergic patient</td>
<td>Vancomycin* OR Teicoplanin* AND Gentamicin*</td>
<td>1g 12-hourly IV and 10mg/kg to a maximum of 1g given at 0, 12 and 24 hours and then 24 hourly and 1mg/kg 12 hourly IV</td>
<td>See comment <em>Staphylococcus</em> sp. (methicillin-susceptible). See comment <em>Staphylococcus</em> sp. (methicillin-susceptible).</td>
</tr>
<tr>
<td><em>Enterococcus</em> sp. (penicillin-susceptible)</td>
<td>Amoxicillin* AND Gentamicin*</td>
<td>2g 4-hourly IV and 1mg/kg 12 hourly IV</td>
<td>See comment <em>Staphylococcus</em> sp. (methicillin-susceptible).</td>
</tr>
<tr>
<td><em>Enterococcus</em> sp. (penicillin-resistant) or penicillin allergic patient</td>
<td>Vancomycin* OR Teicoplanin* AND Gentamicin*</td>
<td>1.2g 12-hourly IV and 10mg/kg IV 24-hourly</td>
<td>See comment <em>Staphylococcus</em> sp. (methicillin-susceptible).</td>
</tr>
<tr>
<td><em>Enterococcus</em> sp. (vancomycin-resistant) or glycopeptide allergic patient</td>
<td>Daptomycin* AND Gentamicin*</td>
<td>6-8mg/kg 24-hourly IV and 1mg/kg 12 hourly IV</td>
<td>Because resistance can develop on daptomycin, combination therapy is advised. Continue gentamicin for the first two weeks provided there are no signs or symptoms of toxicity If isolate is resistant to gentamicin, linezolid can be used. High doses based on pharmacokinetic data and case series.124 See comment <em>Staphylococcus</em> sp. (methicillin-susceptible).</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>Meropenem AND Gentamicin*</td>
<td>2g 8-hourly IV and 1mg/kg 12 hourly IV</td>
<td>Alternative regimens may be appropriate according to susceptibility or local epidemiology. See comment <em>Staphylococcus</em> sp. (methicillin-susceptible).</td>
</tr>
</tbody>
</table>

*All these antimicrobials may need dose adjustment in renal impairment. IV, intravenous.
Table 9: Commonly employed extraction tools and their indications [Adapted from^{104}]

<table>
<thead>
<tr>
<th>Tool</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locking stylet</td>
<td>Stylet inserted into the central lumen of the lead and passed as distal as possible into the lead, preferably to the tip, and secured. Traction applied on stylet rather than lead which keeps it intact. Usually used in combination with other methods.</td>
</tr>
<tr>
<td>Mechanical telescoping sheaths</td>
<td>Composed of Teflon, polypropylene or metal. Sheaths are passed over the lead and rotation used to dissect adhesions from the lead. Sheath can be advanced all the way to the heart, and counter traction used to free the tip from the endocardium. Large bore outer sheath usually passed over inner sheath to support the latter.</td>
</tr>
<tr>
<td>Laser or electrosurgical sheaths</td>
<td>Tubular sheath that passes over lead and distal tip delivers either laser or radiofrequency energy that dissects fibrous adhesions.</td>
</tr>
<tr>
<td>Femoral or trans-jugular workstations</td>
<td>If leads cannot be removed from the site of insertion for example if it has been fractured, additional venous access is gained usually from the femoral route. Long sheaths are used to deliver snares that can grasp the leads. Once secured, manual counter traction can be applied to free the leads</td>
</tr>
</tbody>
</table>
Generator pocket wound inflammation, without fluctuance, discharge, or dehiscence AND without systemic symptoms or signs of infection.

- Take blood cultures (BC) and review with results.
  - positive
    - See Figure 2 management of generator pocket infection or suspected ICED-IE/lead infection.
  - negative
    - Clinical decision to start oral antimicrobials. Review at 1 week.
      - Yes
        - Clinical diagnosis of generator pocket infection or systemic symptoms/signs of infection?
          - Yes
            - See Figure 2 management of generator pocket infection or suspected ICED-IE/lead infection
          - No
            - Complete 7-10 days empirical antimicrobial therapy, if started. Routine follow-up unless patient reported deterioration.
              - No
                - Clinical improvement?
                  - Yes
                    - Routine follow-up
                  - No
                    - Clinical improvement?
                      - Yes
                        - Routine follow-up
                      - No
                        - Complete/start 7-10 days empirical antimicrobial therapy. Review at end of therapy unless patient reported deterioration.

Figure 1. Management of uncomplicated generator pocket wound inflammation
Figure 2. Management of generator pocket infection

- Yes: Evidence of severe sepsis?
  - Initial actions:
    1. Blood cultures x2 (different times)
    2. Commence empirical IV antimicrobial therapy within 1 hour
    3. Urgent echocardiography (within 24 hours)
    4. Prompt removal of entire system and temporary pacing if needed
  - Yes: Positive blood cultures?
    - Modify antimicrobial therapy according to table X
    - Yes: Echocardiographic evidence of lead or tricuspid valve vegetation or tricuspid regurgitation
      - Yes: Complete 10-14 days antimicrobial therapy (according to Table X) after system removal
      - No: Manage according to algorithm for ICED-IE/ICED lead infection.
    - No: Echocardiographic evidence of lead or tricuspid valve vegetation or tricuspid regurgitation
      - No: Initial actions:
        1. Blood cultures x3 (different times)
        2. Echocardiography
        3. Arrange removal of entire system and temporary pacing if needed
        4. Empirical oral/IV antimicrobial therapy as clinically appropriate
Figure 3. Management of suspected ICED-IE/ICED lead infection.
Figure 4. Implantable cardiac defibrillator tip removed surgically from a patient with *Staphylococcus warneri* device infection.
Figure 5. Local skin reaction to chlorhexidine following implantable cardiac electronic device insertion.
Figure 6. Local skin reaction to Liquiband flex following implantable cardiac electronic device insertion.
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