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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), British Heart Rhythm Society (BHRS), British Cardiovascular Society (BCS), British Heart Valve Society (BHVS) and British Society for Echocardiography (BSE)

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Infections related to implantable cardiac electronic devices (ICEDs), including pacemakers, implantable cardiac defibrillators and cardiac resynchronization therapy devices, are increasing in incidence in the USA and are likely to increase in the UK, because more devices are being implanted. These devices have both intravascular and extravascular components and infection can involve the generator, device leads and native cardiac structures or various combinations. ICED infections can be life-threatening, particularly when associated with endocardial infection, and all-cause mortality of up to 35% has been reported. Like infective endocarditis, ICED infections can be difficult to diagnose and manage. This guideline aims to (i) improve the quality of care provided to patients with ICEDs, (ii) provide an educational resource for all relevant healthcare professionals, (iii) encourage a multidisciplinary approach to ICED infection management, (iv) promote a standardized approach to the diagnosis, management, surveillance and prevention of ICED infection through pragmatic evidence-rated recommendations, and (v) 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, 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.

Keywords: pacemaker, implantable cardiac device, defibrillator, infection, guidelines, antibiotics

Contents

1. Introduction
2. Methods
   2.1 Scope and purpose
   2.2 Stakeholder involvement
   2.3 Literature review
   2.4 Consensus process and guideline development
3. Epidemiology
   3.1 What is the incidence of ICED infection (in the UK)?
   3.2 Should the incidence of ICED infection be measured and reported?
   3.3 What are the risk factors for ICED infection?
   3.4 What is the mortality associated with ICED infection?
   3.5 What are the risk factors for mortality in ICED infections?
   3.6 What are the most common microbial causes of ICED infection?
   3.7 Which antimicrobial agents are they usually susceptible to?

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3.8 Does the aetiology vary with time of presentation after implantation?
4. Pathogenesis
5. Clinical diagnosis
5.1 What are the clinical features of ICED infection?
5.2 What is the risk of ICED infection in patients with bloodstream infection?
6. Echocardiography and other imaging modalities in ICED infection
6.1 What is the role of chest radiography?
6.2 What is the diagnostic accuracy of echocardiography?
6.3 When should echocardiography be performed?
6.4 What is the role of FDG-PET/CT scanning?
7. Microbiological sampling and processing
7.1 Which samples should be collected to establish the cause of ICED infection?
7.2 When should blood cultures be taken?
7.3 How should the generator pocket be sampled at the time of removal?
7.4 What laboratory methods should be used during processing?
8. Definitions
8.1 Early post-implantation inflammation
8.2 Uncomplicated generator pocket infection
8.3 Complicated generator pocket infection
8.4 ICED lead infection (ICED-LI)
8.5 ICED-associated native or prosthetic valve endocarditis (ICED-IE)
9. Management of ICED infection
9.1 How should the device be managed?
9.1.1 In early post-implantation inflammation?
9.1.2 In generator pocket infection, ICED-LI and ICED-IE?
9.1.3 What is the preferred means of device removal?
9.1.4 What proportion of patients are too unwell or refuse complete ICED removal?
9.1.5 How should an infected ICED be managed if removal is not an option?
9.1.6 Where should removal of infected ICEDs be undertaken?
9.1.7 How should the device be managed in skin erosion?
9.1.8 If required, when should device re-implantation take place?
9.1.9 How should temporary pacing be managed?
9.2 Principles of antimicrobial therapy
9.2.1 Biofilm and ICED infection
9.2.2 Which antimicrobials are recommended for early post-implantation inflammation?
9.2.3 Which antimicrobials are recommended for uncomplicated generator pocket infections?
9.2.4 Which antimicrobial agents are recommended for complicated generator pocket infections?
9.2.5 Which antimicrobial agents are recommended for ICED-LI or ICED-IE?
9.2.6 What regimens are recommended for attempted ICED salvage?
9.2.7 What is the optimal route of administration of antimicrobial therapy for ICED infection?
9.2.8 What is the optimal duration of therapy for ICED infection?
9.2.9 What therapy is recommended if ICED salvage fails?
10. Prevention of ICED infection
10.1 Where should ICED insertion take place?
10.2 Does operator experience affect infection rates?
10.3 Should temporary pacing be avoided to reduce infection?
10.4 Should ICED procedures be carried out in patients with signs of infection?
10.5 Should patients having ICED insertion or manipulation be screened for staphylococcal carriage or decolonized?
10.6 How should anticoagulation be managed during ICED insertion or manipulation?
10.7 Which infection control measures should be in place before ICED implantation?
10.8 How should skin be prepared before ICED insertion/manipulation?
10.9 Antimicrobial prophylaxis
10.9.1 Should systemic antimicrobial prophylaxis be used for ICED insertion?
10.9.2 When should prophylaxis be administered?
10.9.3 Which agent(s) should be given?
10.9.4 Should antimicrobials be instilled into the generator pocket after implantation?
10.10 Which operative factors influence risk of infection?
10.11 What represents ideal post-operative wound closure and care?

1. Introduction

Implantable cardiac electronic devices (ICEDs) were introduced into routine clinical use in the 1960s. Since then their use has increased worldwide and now includes implantable cardiac defibrillators (ICDs) and cardiac resynchronization therapy devices (CRTDs) in addition to permanent pacemakers (PPMs). Infection is an uncommon but serious complication, which can manifest as infection of the generator ('box') pocket and the leads and can also involve endocardial structures; ICED infections now constitute ~10% of all endocarditis cases.[1] Approximately 40 000 ICEDs were implanted in the UK in 2010, and the number of ICD and CRTD implantations increased by 12.5% and 15.8% compared with 2009, respectively.[2] The incidence of ICEDs that become infected is usually <2%,[3–6] 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.[7] Mortality rates continue to be a concern;[8–12] analyses of the mortality following generator pocket infection compared with lead-associated endocarditis have yielded conflicting results.[4,10,12] The incidence of infections involving ICEDs is increasing in the USA[5,13] and 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.[2]

Like endocarditis, ICED infections can be difficult to diagnose. In fact, diagnostic difficulties may be even greater than in infective endocarditis (IE) because echocardiography is less accurate,

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blood cultures are 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 death or significant complications.[11] Long hospital stays and multiple inpatient episodes are common[14] and attempts to salvage infected systems often result in unnecessarily prolonged courses of treatment.[15] 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.[16] The BSAC, BHRS and 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 synthesize 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 standardized 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 BHRS standards for implantation and follow-up of cardiac rhythm management devices in adults.[17]

2. Methods

The guideline was developed in accordance with AGREE II.[18]

2.1 Scope and purpose

The objectives can be summarized as follows: (i) to improve the quality of care provided to patients with ICEDs; (ii) to provide an educational resource for all relevant healthcare professionals; (iii) to encourage a multidisciplinary approach to ICED infection management; (iv) to promote a standardized approach to the diagnosis, management, surveillance and prevention of ICED infection through pragmatic evidence-rated recommendations; and (v) 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.

2.2 Stakeholder involvement

The BSAC was the host organization in collaboration with the BCS, BHRS, BHVS and BSE. The working party comprised members of all three organizations. The membership included a patient's representative, consultants in cardiology, medical microbiology, infectious diseases, clinical pharmacy and NHS management.

2.3 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 de-duplication, 991 references remained. Additional references were added following review of manuscripts identified from the original search. The working party agreed key questions and then used the results of the literature search when answering specific questions. The level of evidence available to support each recommendation was categorized as: A, high-quality randomized controlled trials (RCTs) and meta-analysis of RCTs; 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 causes and outcomes were confined to studies of over 100 patients. Restricting the review to larger studies had a risk of bias against pure lead infections, hence case reports were included to illustrate specific points.

2.4 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 were written. Each section was compiled into a draft guideline, which was circulated within the Working Party for comment. Consensus was reached by an iterative process. Any issues where consensus could not be reached were discussed in a face-to-face meeting and either a final decision was made or it was agreed that no consensus could be reached. A draft document was sent to a comprehensive list of stakeholders and uploaded to the BSAC web site for a 6 week period, after which final alterations were made to the document in response to the consultation process.

3. Epidemiology

3.1 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 following subsequent procedures (predominantly generator replacements).**

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[3,5–7,14,19–21,23–35,125] studies were 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% to 2.2% of patients in 18 studies with follow-up or study periods between 6 weeks and 11 years. Incidence was measured in different ways in different studies: an incidence of 1.82 per 1000 PPM years following primary PPM implantation was described in Denmark;[7] 1.9 per 1000 device years (85% PPM) in Minnesota, USA;[21] 3.1 per 1000 patient years in a global study of ICDs;[28] and 10.0 per 1000 patient years for cardiac resynchronization therapy with a defibrillator (CRTD) in Italy.[25] The Minnesota study showed a significantly higher incidence in patients with ICDs compared with PPMs (8.9 versus 1.0 per 1000 device years),[21] similar to the incidence found in the large CRTD study from Italy (n=3253).[25] However, in the Minnesota study only 15% of 1524 patients had an ICD.

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Two other large studies, which included a variety of devices, compared the proportion of patients developing infection in different device types over 6 and 11 year study periods.[32,33] There was no difference in the rate of lead-associated endocarditis (ICED-IE) in PPM versus ICD[32] and minimal differences in PPM versus ICD and CRTD.[33] 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.[28–30,34] In a study that included data from four RCTs (n=1903), 1% of patients receiving a CRTD developed infection over 6 months of follow-up.[31] A summary of incidence studies is provided in Table S1 (available as Supplementary data at *JAC* Online).

The incidence of infection associated with primary implantation is ~2- to 5-fold lower than for revision procedures (primary 0.5%–0.8%, revision 1%–4%) over follow-up periods of between 1 and 3 years.[19,23,35] Using different measures, infection rates for primary and revision procedures were 1.82 and 5.32 per 1000 PPM years, respectively,[7] and for CRTDs 9.0 and 18 per 1000 patient years, respectively.[25] 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 6 months of follow-up.[3]

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.[13] 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.[13] 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.[5] 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.[5]

Historically, the incidence of infection associated with devices sited in the wall of the abdomen or implanted at thoracotomy was higher than that associated with devices implanted at the pectoral site or transvenously; e.g. 3.2% versus 0.5% for primary abdominal versus pectoral implantation and 5.8% versus 0.8% for thoracotomy versus non-thoracotomy route of insertion.[34,36] Based on studies that reported the time of presentation, the majority of patients with infection present within 12 months of implantation (63%–77% in three studies with prolonged follow-up), 21%–31% within 1 month and 23%–37% after 1 year.[19,33,36] In an 11 year study that included only patients with lead-associated endocarditis, however, two-thirds of patients presented after 1 year.[32]

3.2 Should the incidence of ICED infection be measured and reported?

Summary:

- **Recommendation 3.2.1: Standardized definitions for ICED infection should be applied throughout the UK and data collected prospectively on infection rates per procedure at 6 months, 1 year and 2 years post-procedure and per 1000 device years. [C]**
- **Recommendation 3.2.2: Infection rates should be collated separately for primary and subsequent procedures. [C]**
- **Recommendation 3.2.3: 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 standardized definitions in Section 8. 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. Although infection rates per procedure are more easily collected, infection rates per 1000 device days are preferred and will enable more useful benchmarking. Data on risk factors for infection should include the number of previous ICED procedures, use of antimicrobial prophylaxis and a measure of procedure complexity, e.g. procedure time (Section 3.3). Table S4 provides appropriate ICD-10 codes for ICED infection.

3.3 What are the risk factors for ICED infection?

Summary:

- **The number of prior procedures, their complexity and a lack of antimicrobial prophylaxis are the most consistently identified risk factors for ICED infection.**

Establishing the risk factors for ICED infection is important for the design of preventative strategies. Twelve studies were identified that employed multivariate statistical techniques.[6,7,20,23,25,33,35,37–41] A variety of patient characteristics and procedural issues have been associated with ICED infections. Male sex,[7,20] younger age,[6,7] anticoagulation,[20,33] COPD,[25,39] renal impairment,[20,33] lack of administration of antimicrobial prophylaxis,[7,35,38,41] the type of device,[6,23,38,40] the need for re-intervention prior to discharge[35,40] and a higher number of prior procedures[7,25,33,35] have all been identified as risk factors for ICED infection in at least two studies; the number of prior procedures and lack of antimicrobial prophylaxis have been the most consistently identified risk factors. A shorter time from implantation (within 1 year),[7] an earlier year of implantation (before 1985),[7] fever in the 24 h prior to implantation,[35] the use of a temporary pacemaker prior to implantation,[35] congestive heart failure,[20] azotaemia,[20] chronic corticosteroid therapy,[38] haemodialysis,[40] procedure time[40] and post-operative haematoma[41] were all associated with infection in one of several studies of various design and size (Table S2, available as Supplementary data at *JAC* Online).

Risk factors for early infection (within 6 months of implantation) in patients with ICDs appear to be different from risk factors for later infection.[39] The presence of epicardial leads or post-operative 'wound complications' was associated with early infection and the length of hospitalization (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

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site of infection, elevated white cell count, fever, malaise and the absence of pocket symptoms or signs were associated with ICED-IE.[37]

3.4 What is the mortality associated with ICED infection?

Summary:

- **All-cause mortality ranges between 0% and 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% to 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.[8–13,15,38,42–52] 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 e.g. 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,[8,9,11,43,45,49,50,52] 4%–29% at 6 months,[8,42,43,48] 9%–35% at 1 year,[9–11,44,52] and 6%–35% at 2 years or longer.[9,12,15,45,46]

3.5 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-IE has a higher mortality than localized generator pocket infection.**
- **Recommendation 3.5: ICED infection should be considered a medical emergency, and cases should be referred urgently to centres with expertise and facilities for removal if these are not available locally.**

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%.[8,11,43] In contrast, in the single study with at least 100 patients that included only PPM-associated infections with a local presentation, mortality was 6% over a follow-up period of 24 months (explantation rate 92%).[46] A small study of 52 patients found a significantly higher mortality in ICED-IE or bloodstream infection (29%) compared with only generator pocket infection (5%);[53] a larger study also found significantly lower mortality in those who did not have ICED-IE.[9] Likewise, Deharo *et al.*[12] found higher (albeit not statistically significant) mortality (15.5% versus 12.5%) in patients with endocarditis compared with pocket infection. Greenspon *et al.*[43] 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% and 15% in 12 studies including 100 patients or more reporting this outcome[8,9,12,15,42,44–49,51] and between 0% and 8% when the one study that included only patients with ICED-IE was excluded.[8] 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.[52] Mortality was also higher in the Deharo *et al.* study:[12] 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 with either ICD (24.4%) or CRTD (30%) infection,[52] in contrast to a smaller study,[9] 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.[9,12,42,45,49,50] The most consistently reported risk factors for mortality were abnormal renal function,[12,42,50] endocarditis or features likely to be associated with endocarditis (systemic embolization or moderate/severe tricuspid regurgitation),[42,50] and older age[12,50] (Table S3, available as Supplementary data at *JAC* Online). 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.[9,11,50] In a small study (n=52), significantly higher mortality was also found in those patients in whom explantation occurred after >3 days in hospital.[53] However, it is difficult to account for the possibility that patients who did not undergo explantation may have been considered too unwell to undergo the procedure in this type of analysis.

3.6 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.[8,10–12,15,37,42–44,46–48,51,54–58] Despite considerable heterogeneity in the design of studies, the microbial epidemiology of ICED infections was found to be remarkably consistent. Gram-positive bacteria were by far the most commonly isolated microorganisms (from 67.5% of patients to 92.5% of isolates across ten studies reporting the proportion of Gram-positives),[8,10–12,14,48,51,54,56,58] with CoNS the most consistently isolated bacteria followed closely by *Staphylococcus aureus*. Gram-negative bacilli were isolated in 1%–17% of patient episodes (6%–10.6% of isolates in studies using the total number of isolates as the denominator). Fungal

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Table 1. Summary of the microbiology of implantable cardiac electronic device infection

Pathogen (number of studies reporting this pathogen)	Range in studies using patients as the denominator	Range in studies using isolates as the denominator
CoNS (17)	10%[a]–68%	42%–77%
Staphylococcus aureus (16)	24%–59%	10%–30%
Gram-negative bacilli (11)	1%–17%	6%–11%
Enterococcus spp. (6)	5%–6%[b]	0.4%–10%[b]
Streptococcus spp. (5)	4%–6%[b]	3%–10%[b]
Propionibacterium spp. (3)	—	0.8%–8%
Fungi (5)	0.5%–2%	0.4%–1.4%

[a]This study only used blood cultures and had high culture negativity (49%).
[b]This study reported *Streptococcus* and *Enterococcus* spp. together.

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% to 24.5%.[15,44,46–48,54,56] Twelve studies reported the proportion of patients with clinical infection but negative cultures,[8,11,12,15,19,42,43,48,54–56,58] which ranged from 12% to 49% of patients. Table 1 summarizes the reported microbial epidemiology of ICED infections.

3.7 Which antimicrobial agents are they usually susceptible to?

Summary:

- **UK data on the antimicrobial susceptibility of ICED infection pathogens are not available.**
- **9% of *S. aureus* bloodstream isolates from England were methicillin resistant (surveillance data for 2013).**

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).[10,54] In four studies that included fewer than 100 patients but reported methicillin resistance in CoNS, between 12.5% (Australia) and 29% (France) of isolates were resistant.[14,19,32,59] In *S. aureus* [reported studies were from USA, Europe and 28 countries (one study)], between 2.6% (Germany) and 55% (USA) of isolates were methicillin resistant.[8,11,12,15,42,43,48,54] In over 1000 isolates, UK antimicrobial resistance surveillance data for the period 2001–06 found that 67% (range 54%–80%) of CoNS were methicillin resistant, but the relevance of these data to current practice is questionable. More up-to-date data for CoNS bloodstream isolates, in particular data for CoNS isolates causing ICED infection, are not available for the UK. Detailed data on the incidence and susceptibility of *S. aureus* bloodstream isolates for England are available because of mandatory surveillance. During 2013 the incidence of *S. aureus* bloodstream infection (all causes) was 18.8/100 000 population and 9% of these were methicillin resistant.[60]

3.8 Does the aetiology vary with time of presentation after implantation?

Summary:

- **There are no clinically useful differences in the pathogens causing ICED infection in relation to time after implantation.**
- **Recommendation 3.8: The 1 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,[37] this is not a consistent finding.[56] 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%).[8,11,43] Gram-negative bacteria were only reported in two studies (1% and 4.5%).[8,11]

Two studies were identified that had compared the microbiology of early (within 6 months of implantation) and later infections,[39,43] although the reasoning behind a 6 month cut-off is not described. *S. aureus* was the cause of 35%–48% of early infections compared with 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 1 year of implantation, indicating that the 1 year cut-off often applied to procedure-related acquisition in device implantation surgery may not be applicable to ICED infections.[61]

4. 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 this may develop into symptomatic infection at a later stage.**

A concise discussion of pathogenesis is included because it informs diagnostic, therapeutic and preventative strategies. Microbial contamination of a device during manufacture and packaging 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 squamae 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

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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*.[46] 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.[24]

The theories above are supported by the identification of 'asymptomatic colonization' 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.[62–66] Between 21% and 47% of patients had microbes isolated from various specimen types with CoNS, *Propionibacterium* spp. 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[66] but no significant difference in ICED infection rates was seen between patients with positive and negative cultures.[66] 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.[65] 'Asymptomatic colonization' may represent an early stage of infection but difficulties with microbiological sampling and potential contamination cloud the picture.

The role of biofilm in infection and treatment is outlined in Section 9.2.1. The reason why ICDs and CRTDs have been associated with a higher incidence of infection (Section 3.1) 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 10 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.

5. Clinical diagnosis

5.1 What are the clinical features of ICED infection?

Summary:

- **Generator pocket infection is characterized by localized 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 lead infection (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 characterized by localized erythema, localized cellulitis, swelling or pain over the pocket.[21,46] The severity of symptoms can vary considerably. This may progress to wound dehiscence, purulent discharge, skin erosion or sinus formation.[67] Symptoms and signs may fluctuate and can be insidious in onset.[68] 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 (Figures S1 and S2, available as Supplementary data at *JAC* Online). 'Superficial cellulitis' may be an early presentation of generator pocket infection.[24,46] 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 ('under-sizing'), or other anatomical restriction, should therefore be resolved before the skin is breached. However, tethering around a device with threatened erosion is usually indicative of infection. No amount of operating to 'make the pocket bigger' takes the problem away, and it often postpones decisions about the need for device removal. 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.[46] Where reported, concurrent generator pocket infection in patients with ICED-IE and ICED-LI varies between 6% and 58% of cases,[14,15,19,42,69,70] 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.[59] 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 C-reactive protein (CRP) is often elevated (96%).[11,59,67,68,71] 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;[69] vascular and embolic phenomena occurred in fewer than 5% of cases of ICED-IE or ICED-LI[69] but clinical (e.g. dyspnoea, pleuritic chest pain) or radiological evidence of pulmonary involvement has occurred in 38%–44% of cases.[59] 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.[59,72]

The role of the modified Duke criteria[73,74] 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,[67] and the latter is often used in practice. Laboratory analysis of samples taken at device removal can also support the diagnosis (Section 7). 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.

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5.2 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 5.2: 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]**

Of patients with ICEDs *in situ* whose blood cultures grow a *Staphylococcus* spp., at least 35% will ultimately have ICED infection confirmed.[75,76] Regardless of 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%)[76,77] and other Gram-positive cocci (30%),[78] with a much lower risk in Gram-negative bacteraemia (6%).[79] 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. The need for system removal will depend on the results of further investigations and response to therapy.

6. Echocardiography and other imaging modalities in ICED infection

6.1 What is the role of chest radiography?

Summary:

- **Recommendation 6.1.1: A chest X-ray should be carried out in all patients with suspected ICED infection. [C]**
- **Recommendation 6.1.2: 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 (CXR) suggestive of embolic foci of infection may support a diagnosis of ICED infection in difficult cases[80] and pulmonary involvement occurs in 10%–45% of patients with ICED infection.[11,59,69] A plain 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.[80,81] Septic pulmonary emboli are a minor Duke criterion.[73]

6.2 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 valve infection. Echocardiographic diagnostic parameters should include valve (Figure S3) and lead vegetations in addition to new valve regurgitation and abscess formation.[73] Valve involvement is often not limited to the tricuspid valve. Aortic or mitral valve vegetations are present in 10%–15% of patients with ICED endocarditis and valve involvement in ICED infection is associated with higher in-hospital mortality (Section 3.4). 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 with 90%–96% with TOE.[43,59,69,71,82] 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 visualize 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 artefact 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.[83] Echocardiographic images must therefore be interpreted in conjunction with the clinical features and on an individual case basis. It should be noted that leads can be infected without lead vegetations being seen on echocardiography (Figure S4); a negative scan cannot therefore exclude the diagnosis.

6.3 When should echocardiography be performed?

Summary:

- **Recommendation 6.3.1: Echocardiography should be carried out as soon as possible (within 24 h) after a diagnosis of ICED infection is considered. [C]**
- **Recommendation 6.3.2: 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 6.3.3: Echocardiography should be performed in all patients in whom ICED-LI or ICED-IE infection is suspected clinically (according to Section 5.1). [B]**
- **Recommendation 6.3.4: 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]**

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- **Recommendation 6.3.5: Repeat echocardiographic imaging is recommended after ICED removal to identify persisting valve or mural vegetations. [C]**

See Sections 5.1, 5.2 and 6.2. No studies have specifically examined the effect of the timing of echocardiography on outcome but early removal (within 3 days of admission) of ICEDs has been associated with better survival[53] and therefore the need 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. Serial echocardiograms may be required to confirm or exclude ICED-LI or ICED-IE.[59] 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.[84] 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. Intra-cardiac echocardiography (ICE) may provide enhanced diagnostic accuracy compared with TOE,[85] but its availability is limited and it remains unable to distinguish between infected and non-infected masses, such as thrombus, Lambl's excrescences or fibrin strands. There is no evidence to support ultrasound evaluation of a potentially infected device pocket over and above clinical examination.

6.4 What is the role of FDG PET/CT scanning?

Summary:

- **Recommendation 6.4: Routine use of FDG PET/CT scanning outside research studies is not currently recommended. [C]**

In case reports[86–96] and pilot series[97–99] fluorodeoxyglucose positron emission tomography combined with CT (FDG PET/CT) has been used to assist the diagnosis of ICED infection. In many of these cases FDG PET/CT confirmed generator pocket infection when there were already clinical features to suggest infection, raising doubts about the added value of the test. Early reports indicate that FDG PET/CT is not a sensitive tool for the diagnosis of ICED-LI/IE but may be useful when there is uncertainty about generator pocket infection, which would be a clear clinical benefit. Optimal timing, acquisition and processing of images are currently unclear.[100] At the present time there is insufficient evidence of what FDG PET/CT adds to a clinical diagnosis, and this investigation cannot be recommended as a routine clinical test but may be useful in selected cases where there is diagnostic uncertainty.

7. Microbiological sampling and processing

Identification of the causative microorganism(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. Negative blood cultures appear to be more common in ICED infection than in native valve endocarditis and do not exclude a diagnosis of infection.

7.1 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 the 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.

7.2 When should blood cultures be taken?

Summary:

- **Recommendation 7.2.1: Blood cultures should be taken prior to starting antimicrobial therapy. [B]**
- **Recommendation 7.2.2: On clinical suspicion of ICED infection in patients with a chronic or subacute presentation, three sets of aseptically collected, optimally filled blood cultures should be taken from peripheral sites with ≥6 h between them. [C]**
- **Recommendation 7.2.3: 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 h and prior to commencement of empirical antimicrobial therapy. [C]**
- **Recommendation 7.2.4: Blood cultures should be taken 48–72 h after removal of an infected ICED. [C]**
- **Recommendation 7.2.5: 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.[6,24,41,54] Consistently positive blood cultures with the same microorganism are highly specific for an intravascular source of infection but lack sensitivity.[46] 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,[54] 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—re-implantation 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

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cultures taken following ICED removal should therefore be interpreted carefully and in their clinical context.

7.3 How should the generator pocket be sampled at the time of removal?

Summary:

- **Recommendation 7.3: In patients with clinical evidence of infection, tissue (~2 cm^2) 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.[62] In the microbiology laboratory, tissue should be subjected to Gram's stain and culture. It is recommended that pocket site tissue is only taken from patients who show clinical evidence of ICED infection, as detection of colonization (or contamination) in the absence of signs of infection is of little clinical value and may lead to unnecessary antimicrobial therapy or even surgery.

7.4 What laboratory methods should be used during processing?

Pus samples or fluid (e.g. 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 (Table 1). Suitable culture media and incubation conditions are as follows: chocolate agar (35–37°C in 5% CO_2 for 48 h), cysteine lactose electrolyte deficient (CLED) or MacConkey agar (35–37°C in air for 24 h), blood agar (35–37°C in an anaerobic cabinet for 48 h) 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 h before subculture onto the same media. These media should recover the vast majority of bacteria and fungi that have been implicated in ICED infection.[48,101]

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.,[102,103] *Nocardia* spp.[48] and auxotrophic staphylococci.[104] 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 not detected by routine culture. The use of sonication for the recovery of bacteria from ICEDs may have a useful role to play in patients with clinical signs of infection and this merits further study.[64]

8. Definitions

There are no universally agreed definitions of ICED infection so these definitions have been synthesized from current available evidence, those used previously[19,21,35,57,74] 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.

8.1 Early post-implantation inflammation

Erythema affecting the box implantation incision site, without purulent exudate, dehiscence, fluctuance or systemic signs of infection and occurring within 30 days of implantation. The term 'inflammation' here implies that a definite diagnosis of infection has not been established and starting antimicrobial therapy is not necessarily indicated. There should be clinical resolution with removal of the cause within 2 weeks (e.g. if allergic reaction to local dressing/skin preparation, removing or changing the dressing/preparation) so a period of close observation may be required (Figures S1 and S2). A small localized area (<1 cm) of erythema and or purulence associated with a suture ('stitch abscess') is included in this group and this should resolve with removal of the suture and a short course of antimicrobial therapy, if clinically indicated.

8.2 Uncomplicated generator pocket infection

(i) Spreading cellulitis affecting the generator site; OR (ii) incision site purulent exudate (excluding simple stitch abscess); OR (iii) wound dehiscence; OR (iv) erosion through skin with exposure of the generator or leads; OR (v) fluctuance (abscess) or fistula formation; AND 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 time frame. A microbiological cause may be identified from pus samples.

8.3 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.

8.4 ICED lead infection

Definite ICED-LI:

(i) Symptoms/signs of systemic infection (Section 5), NO signs of generator pocket infection (Section 8.2) AND echocardiography consistent with vegetation(s) attached to lead(s) AND presence of major Duke microbiological criteria.[74]
(ii) Symptoms/signs of systemic infection (Section 5), NO signs of generator pocket infection (Section 8.2) AND culture, histology or molecular evidence of infection on explanted lead.

Possible ICED-LI:

(i) Symptoms/signs of systemic infection (Section 5.1) AND echocardiography consistent with vegetation(s) attached to lead(s) BUT no major Duke microbiological criteria present.[74]
(ii) Symptoms/signs of systemic infection (Section 5.1) AND major Duke microbiological criteria present[74] BUT no echocardiographic evidence of lead vegetations.

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Note: ICED-LI can occur with or without evidence of generator pocket infection. Possible ICED-LI is a common problem; the diagnosis of ICED-LI may be strengthened by evidence of pulmonary emboli (Section 5). Diagnosis of isolated ICED-LI, i.e. exclusion of 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.[55] If there is uncertainty, manage as for ICED-IE.

8.5 ICED-associated native or prosthetic valve endocarditis (ICED-IE)

Duke criteria for definite endocarditis satisfied, with echocardiographic evidence of valve involvement,[74] in a patient with an ICED *in situ*.

9. Management of ICED infection

The aim of managing ICED infection is to cure the patient of infection, as efficiently as possible, while minimizing the risk of harm. Efficiency in this context would include reducing: (i) 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) colonization and infection with antimicrobial-resistant microorganisms. Management of ICED infection should be individualized to each patient but there are clear principles, supported by varying degrees of evidence, to guide management plans. Figures 1–3 summarize the management pathways for early post-implantation inflammation, generator pocket infection and suspected ICED-IE/ICED lead infection, respectively. This section contains principles of device management and antimicrobial therapy and scenario-based management recommendations.

9.1 How should the device be managed?

The options for ICED management when infection is diagnosed or suspected are summarized in Table 2. 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. Methods of removal are outlined in Appendix 2 and Table S5.

9.1.1 In early post-implantation inflammation?

Summary:

- **Recommendation 9.1.1: In early post-implantation inflammation the ICED can initially be left *in situ*. [B]**

Although 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).

9.1.2 In generator pocket infection, ICED-LI and ICED-IE?

Summary:

- **Recommendation 9.1.2: Complete and early (as soon as possible, but not more than 2 weeks after diagnosis) 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 9.2.1) means that device removal is usually required to enable cure. The majority (usually >90%) of large, single-centre reports of ICED infections managed with device removal and appropriate antimicrobial therapy demonstrate cure with this approach,[6,19,23,32,34,44,47,105,106] although relapse of infection was reported in 0%–7% of episodes.[8,15,38,44,46–48] Relapse is more common when devices are not removed; e.g. over half of patients who did not have complete removal demonstrated relapse.[6,32,46] Case series describe success in 82%–98% of attempted system removals for ICED infection.[9,44,51,107] Furthermore, removal techniques have evolved with improved success rates and lower interventional thresholds, casting doubt on the current relevance of older studies.[108] The likelihood of failure of percutaneous removal increases with the length 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.[70] The risk of mortality associated with device extraction is multifactorial, but appears to vary with the indication for removal. Nevertheless, the presence of current infection increases the risk of death (Section 3.4). A 2.7% in-hospital mortality from severe sepsis was reported following device removal in one series.[45] In a prospective cohort study of patients from the International Collaboration on Endocarditis,[11] device removal during the initial hospitalization 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 3-fold higher in patients managed conservatively.[9] A single-centre analysis has demonstrated similar results.[71] 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 (USA) cites infection as the strongest indication for complete system removal.[109] During the consultation process on the first draft of this guideline, several cardiologists commented on the negative impact of delayed device removal on their patients and the resulting unnecessary prolongation of antimicrobial therapy. Although there is no specific evidence on which to base recommendations, to have an impact on the duration of antimicrobial therapy and avoid unnecessary prolongation of antimicrobials (a key consideration in the current climate[110]), the Working Party felt that the device should be removed as soon as possible, but within 2 weeks, of a diagnosis being made.

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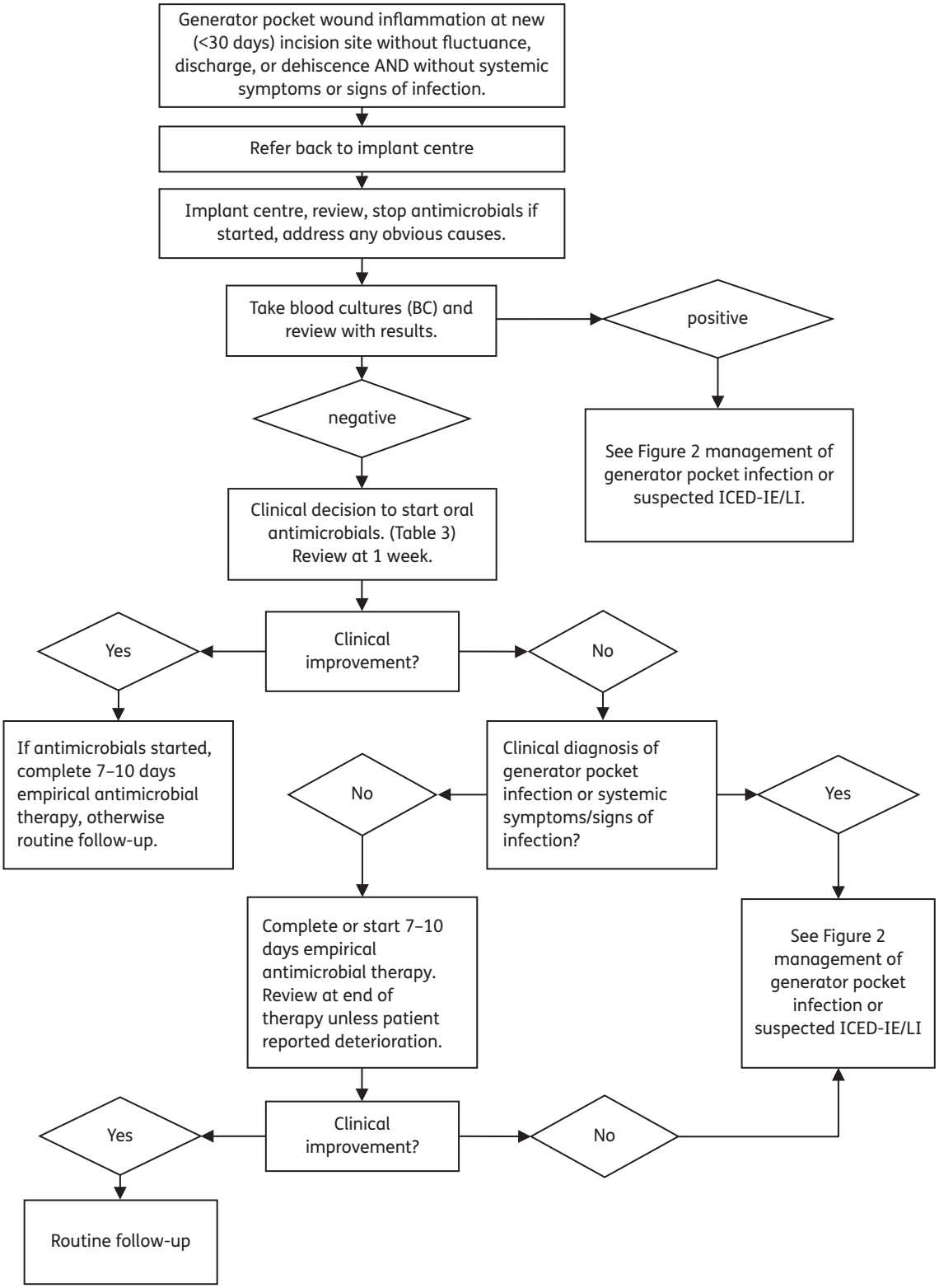

Figure 1. Management of early post-implantation inflammation.

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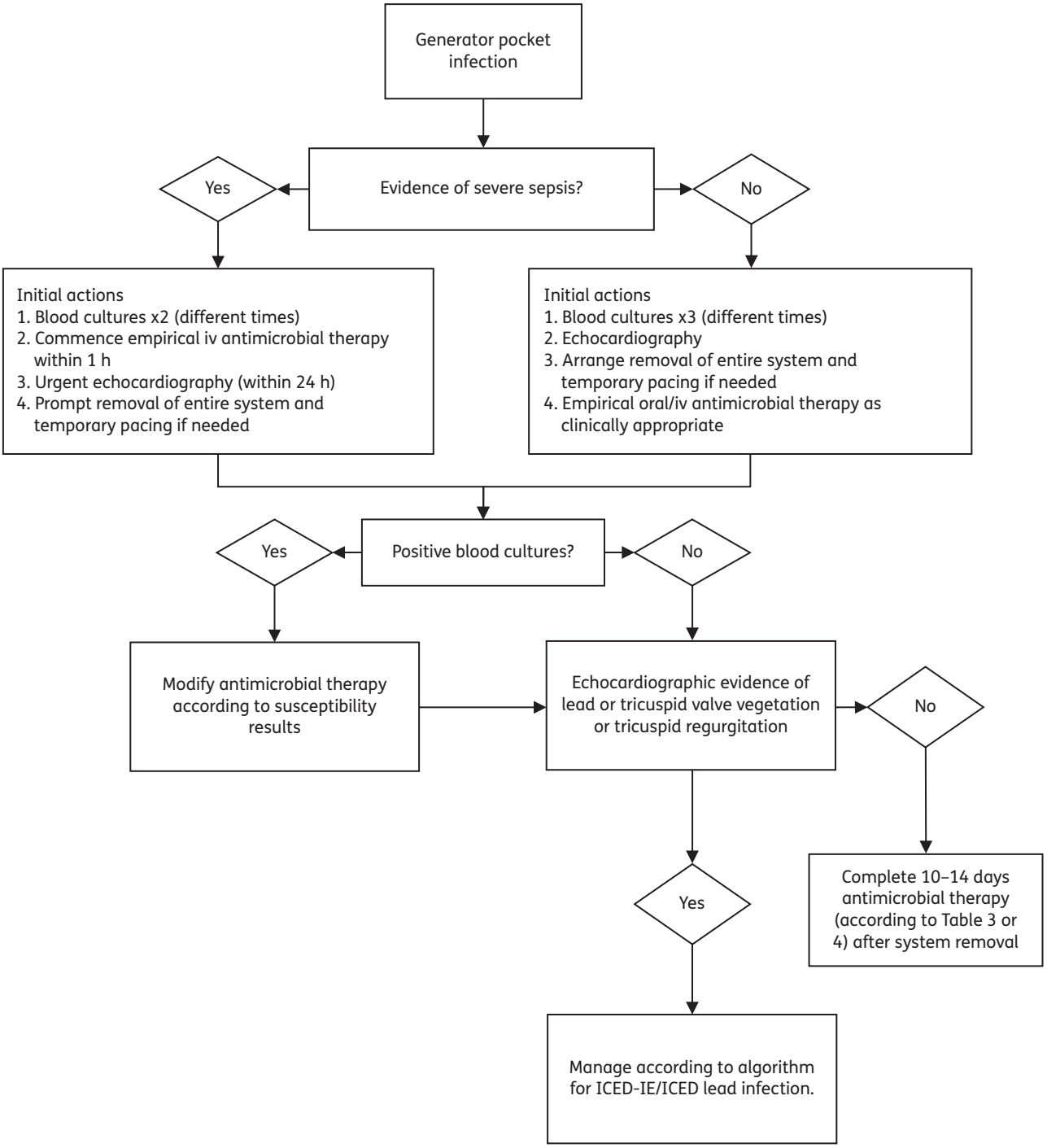

Figure 2. Management of generator pocket infection.

9.1.3 What is the preferred means of device removal?

Summary:

- **Recommendation 9.1.3.1: Percutaneous methods of lead removal are preferred for infected leads, combined with complete removal of the generator. [B]**
- **Recommendation 9.1.3.2: Open surgical removal should be considered for large lead-associated vegetations (>20 mm) 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.[107] Only the time a device had remained *in situ* was a risk factor for

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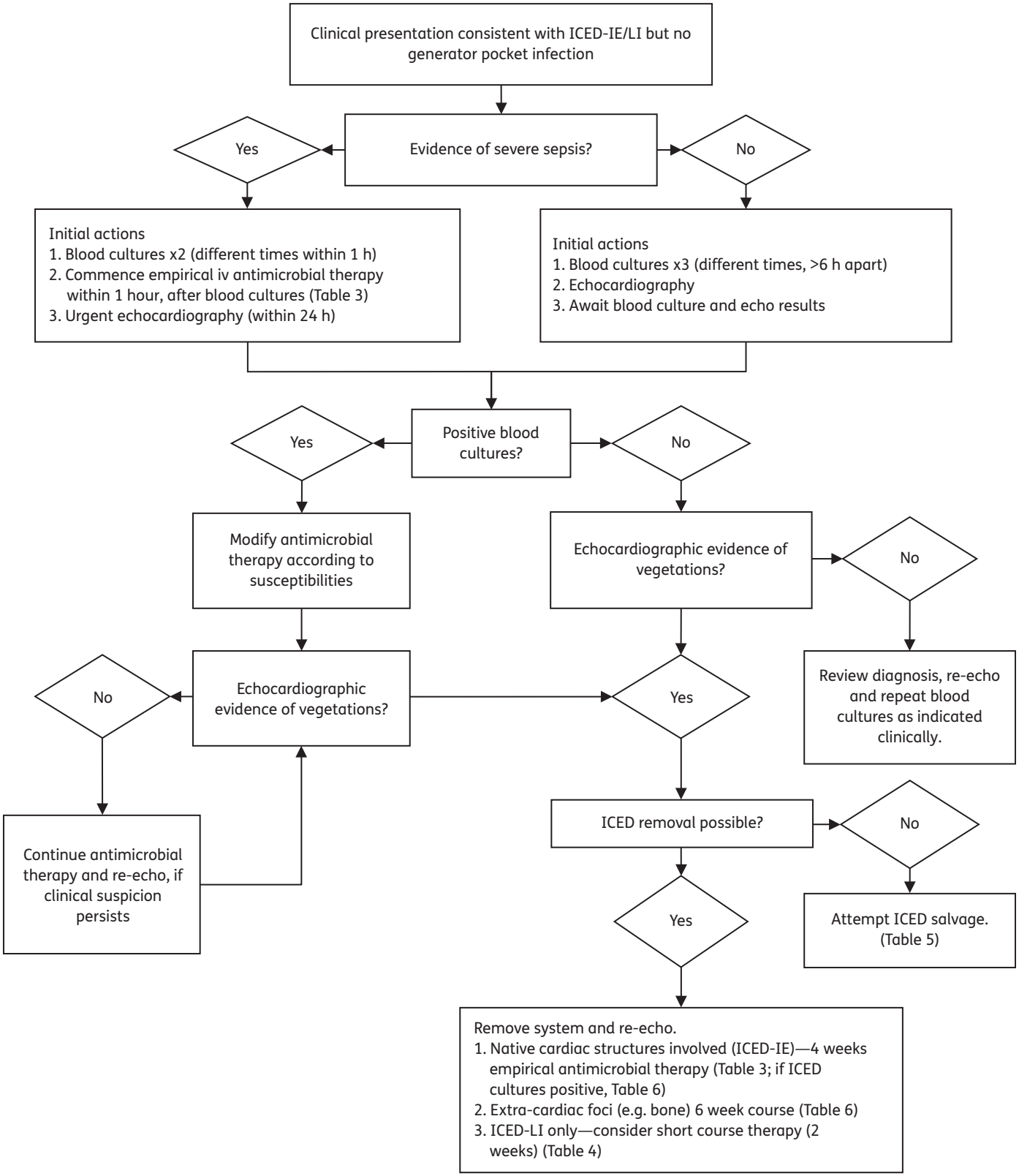

Figure 3. Management of suspected ICED-IE/ICED lead infection.

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Table 2. Options for device management and antimicrobial strategies in ICED infection

Diagnosis/scenario	ICED management (recommendation)	Antimicrobial strategy	Comment
Early post-implantation inflammation	leave device *in situ*	case by case, consider observation or oral therapy 7–10 days (Table 3 and Figure 1)	this entity may represent early infection, but other possible explanations
Uncomplicated generator pocket infection AND no absolute requirement for ICED AND device removable	complete device removal without replacement ICED	10–14 days (iv and po) therapy (Tables 3 and 4)	preferred option with greatest chance of cure
Uncomplicated generator pocket infection AND absolute requirement for ICED AND device removable	complete device removal, temporary pacing, delayed replacement ICED until signs of infection resolved	10–14 days iv antimicrobials. (Tables 3 and 4)	risk of cross infection to temporary system and permanent system
Generator pocket infection when attempted lead extraction considered too risky/or declined by patient AND no absolute requirement for ICED	removal of generator leaving leads *in situ* without replacement ICED	6 weeks iv therapy (Table 5)	bioburden of infection reduced by generator removal, small possibility of eradicating residual lead infection
Generator pocket infection when attempted extraction considered too risky or declined by patient AND absolute requirement for ICED	removal of generator leaving leads *in situ* with early/ single-stage replacement ICED	6 weeks iv therapy (Table 5)	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
ICED-IE (with or without clinical evidence of generator pocket infection) AND no absolute requirement for ICED AND device removable	prompt and complete device removal without replacement ICED	if native valves affected: total 4 weeks iv therapy (Table 6). If prosthetic valves affected, secondary brain abscess or spinal infection: 6 weeks iv therapy (Table 6)	consider day 1 as the first day of appropriate antimicrobials, timing of ICED removal does not affect duration, unless persistently bacteraemic on therapy
ICED-LI (with or without clinical evidence of generator pocket infection or IE) AND no absolute requirement for ICED AND device removable	prompt and complete device removal without replacement ICED	prolonged therapy post removal not usually required. Review therapy 1 week after removal	this approach is possible if tricuspid valve is structurally normal, no ghost lesions present after system removal and rapid clinical response to device removal. If in doubt, treat as ICED-IE
ICED-IE or ICED-LI (without generator pocket infection) when extraction considered too risky/or declined by patient AND absolute requirement for ICED	leave entire device *in situ*	6 weeks iv therapy (Table 5)	high risk of failure. Stop antimicrobials after 6 weeks if good clinical response, consider long term oral suppressive therapy if relapse occurs

iv, intravenous; po, *per os*.

failed percutaneous removal in this series, but it is unclear whether vegetation size was included in the analysis.[107] One case with a 15 mm vegetation required surgical lead removal.[107] Size of vegetation was not associated with mortality in one single-centre series, but data on vegetation size were unavailable in 80% of cases.[42] Some clinicians have routinely listed patients with vegetations over 10 mm for surgical lead extraction,[8] others use a 20 mm cut-off,[111] while some are wary of 'large vegetations' without specifying a cut-off dimension.[70] Major complications are more common after open surgical lead removal than percutaneous techniques,[70] but percutaneous removal can also be complicated; five (55%) of nine patients with large vegetations (10–38 mm) and percutaneous removal suffered pulmonary embolism, although this complication did not appear to affect mortality or inpatient stay.[112] 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 10 and 40 mm, highlighting this as an area for further study.

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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.[113–116]

9.1.4 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[19,35,111,117] and others may decline system removal.[46,118] Of the seven studies that reported on this outcome, 3%–15% of patients were either unsuitable or refused ICED removal.[6,14,19,34,35,41,57]

9.1.5 How should an infected ICED be managed if removal is not an option?

Summary:

- **Recommendation 9.1.5.1: In a patient with ICED-LI, 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 9.1.5.2: 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 should be given. [C]**

Salvage of infected ICEDs with antimicrobial therapy alone has been reported,[19,44,117,119] as has success with partial system removal.[19,118] Excluding 'superficial infections', seven studies reported cure rates ranging between 13% and 71% for patients managed with partial device removal.[6,14,44,46,57,106,120] A recent series of ICD-associated IE reported a 100% failure rate with attempted salvage.[32] 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.[19] 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 with just 9% of the 16 patients managed with the device *in situ*.[105] 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.[19] Recurrence of infection is associated with failure to remove all prosthetic material.[106] 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.[120]

When there is evidence of generator pocket infection but the risks of ICED removal are considered very high (or a patient declines system removal), 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 risk of removing leads (which increases with the length of time that leads have been *in situ*) and the generator often represents the bulk of the infection burden.[70,107,111] However, this approach has a high risk of relapse and also re-infection of any newly implanted system, so it is not appropriate for patients who are dependent on their ICED. In patients who are exceedingly frail or terminally ill, palliative care with suppressive oral antimicrobial therapy may be the most appropriate management strategy (Section 9.2.9).

9.1.6 Where should removal of infected ICEDs be undertaken?

Summary:

- **Recommendation 9.1.6: Removal of infected ICEDs should only be undertaken in recognized centres with expertise in the procedure and with appropriate surgical facilities immediately available. [C]**

This recommendation reinforces standards developed by BHRS.[17] Myocardial and vascular tears and cardiac tamponade are recognized complications of lead extraction, which require the immediate availability of appropriate cardiac, vascular and/or thoracic surgical facilities. Lead removal 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.[70,121]

9.1.7 How should the device be managed in skin erosion?

Summary:

- **Recommendation 9.1.7: Erosion of skin to expose either leads or generator to the air requires removal of the entire system. [C]**

Leads or the generator can erode through the skin, often as a result of superficial positioning of the device, e.g. 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.[111] Pre-erosion may also be a manifestation of infection and if skin integrity is lost (e.g. if granulation tissue is present over a superficial portion of lead) microbial contamination or infection is 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.[122] However, a 62.5% infection rate has been documented with erosion or pre-erosion associated with skin inflammation or granulation of the scar.[123] 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.

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9.1.8 If required, when should device re-implantation take place?

Summary:

- **The need for and timing of a replacement ICED after removal of an infected device will depend on the indications for its use.**
- **Recommendation 9.1.8.1: Wherever possible, re-implantation should be avoided or delayed until symptoms and signs of systemic and local infection have resolved. [B]**
- **Recommendation 9.1.8.2: 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]**
- **Recommendation 9.1.8.3: No part of an ICED that has been removed because of infection should be reimplanted. [C]**

An episode of ICED infection should prompt a review of the need for a replacement device; in many instances the initial indication was equivocal and does not justify the risk of re-implantation. Robust evidence to support this recommendation is lacking but it is well recognized that sepsis is a contraindication to permanent device implantation.[124] In case series, 70%–77% of patients required a new device after removal of an infected ICED, indicating that this is a common dilemma.[14,71] Re-implantation was usually undertaken when systemic symptoms had resolved. Fever at the time of device implantation is a described risk factor for subsequent device infection,[35] 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 not known but some advocate an interval of 7–10 days.[14,19] If symptoms and signs have resolved at the time of device removal, earlier reimplantation may be appropriate—further research is needed.

If the patient is not PPM 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 permanent ICED after removal of an infected system, but re-implantation should occur at a new site if this is necessary. 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 or has persistent generator pocket soft tissue infection.

During the consultation process the practice of removing an infected ICED, placing new leads and then re-attaching the old generator after cleaning with chlorhexidine or hydrogen peroxide was described. Given current knowledge of sterilization procedures and the biofilm nature of ICED infection, the Working Party doubts that sterilization of an infected generator can be achieved by either of these methods and there is a high risk of transferring bacteria to the new leads.

9.1.9 How should temporary pacing be managed?

In patients who are pacemaker dependent, it seems sensible to use temporary pacing until symptoms and signs of systemic infection (including fever) have resolved before implanting a permanent device.[124] However, temporary pacing has been associated with an increased risk of subsequent infection.[27,35,125] This may be a marker of the urgency of the procedure rather than a true causal relationship, but temporary leads are usually inserted via temporary central venous catheters, often with poor fixation and frequent line handling, both of which are risk factors for infection. To reduce these infection risks as well as ensuring more reliable pacing, some cardiologists are using permanent-type pacing leads for temporary pacing.[126] The 'permanent' lead is tunnelled under the skin and attached to an external pacemaker which is secured to the skin for the period of temporary pacing; when it is considered appropriate to site a permanent system the external pacemaker and permanent lead that has been used for temporary pacing are removed.

If temporary pacing via a central venous catheter is used, the choice of the venous access site for temporary pacing should take into consideration the need for a future ICED; the pre-pectoral region contralateral to the infected site should therefore be avoided for temporary pacing access if possible.

9.2 Principles of antimicrobial therapy

Summary:

- **Recommendation 9.2: Antimicrobial treatment strategies should be discussed by the multidisciplinary team and should be 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 following: the severity of illness at presentation; plans for device management (Table 2); 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. There is no robust trial evidence to support these antimicrobial regimens; they are made on the basis of *in vitro* susceptibility data, observational studies, pharmacokinetic and pharmacodynamic data and clinical experience. These recommendations should not preclude patients from inclusion in clinical trials to test the effectiveness of different antimicrobial treatment regimens.

9.2.1 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 in the body of prosthetic materials, if contaminated, allows 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

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than traditional *in vitro* susceptibility testing would suggest. Some bacteria are far more adept at sticking to non-biological materials than others, which explains e.g. the predominance of staphylococci in ICED infection and the rarity of 'coliform' lead infections (Section 3.6).[79]

Like other medical devices, ICEDs are susceptible to biofilm formation but, unlike other devices (such as intravascular catheters, prosthetic heart valves and some orthopaedic implants), eradication of infection can rarely be achieved.[32,127] 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 lumen[128]) 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 sections of leads were culture positive in 72% of cases,[46] 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 antimicrobial therapy.[129]

Native valve endocarditis can occur in patients with ICEDs *in situ* without lead involvement,[21] 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.[19,69] 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. This summary highlights the need for swift and complete removal of infected ICEDs as a key element of therapy.

9.2.2 Which antimicrobials are recommended for early post-implantation inflammation?

Summary:

- **Recommendation 9.2.2: The decision to commence antimicrobials for early post-implantation inflammation should be determined on a case-by-case basis—either using a short course of an oral antimicrobial appropriate for soft tissue infection or monitoring closely without antimicrobials (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.[46] Six studies describe superficial infections, with a wide variation in the proportion of infections falling in this category (5%–86%).[22–24,29,34,41,125] 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[24] and the Working Party therefore recommends 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%).[23,24,29,34,41,125] 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 microorganism to cause superficial infection and cefazolin for 10 days has been effective in this setting,[41] but treatment regimens are often not reported. Flucloxacillin 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 3. The recommended duration of 7–10 days is pragmatic.

9.2.3 Which antimicrobials are recommended for uncomplicated generator pocket infections?

Summary:

- **Recommendation 9.2.3.1: When there is clinical evidence of generator pocket infection empirical antimicrobial therapy should be commenced (Table 3, Figure 2). [C]**
- **Recommendation 9.2.3.2: Directed (or targeted) antimicrobial regimens for treatment of generator pocket infection when the microbial cause is known are shown in Table 4. [C]**
- **Recommendation 9.2.3.3: Local antimicrobial instillation into an infected generator pocket is not recommended. [C]**

Please also see the discussion in Section 9.2.4. There are no RCTs to guide therapy in this situation, so recommendations are based on anecdotal reports of success, the 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,[24] 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 3). 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 bacterial infections will depend on susceptibility testing. Once the device has been

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Table 3. Empirical treatment regimens for ICED infection

Diagnosis/scenario	Antimicrobial	Dose/route[a]	Comment
1. Early post-implantation inflammation	flucloxacillin	0.5–1 g q6h po	benefit of and need for antimicrobial therapy is unclear
2. Early post-implantation inflammation in penicillin-allergic or MRSA-colonized patient	doxycycline OR	100 mg q12h po	benefit of and need for antimicrobial therapy is unclear
	linezolid OR	600 mg q12h po	
	clindamycin	450 mg q6h po	if possible, avoid clindamycin in patients at risk of *Clostridium difficile* infection
3. Uncomplicated generator pocket infection	vancomycin OR	1 g q12h[b] iv	
	daptomycin OR	4 mg/kg q24h iv	
	teicoplanin	6 mg/kg to a maximum of 1 g given at 0, 12 and 24 h and then q24h[183]	
4. ICED-LI or ICED-IE or complicated generator pocket infection pending blood cultures, e.g. in severe sepsis	vancomycin AND	1 g q12h[b] iv	appropriate spectrum but risk of nephrotoxicity
	meropenem OR	1 g q8h iv	gentamicin (high dose, according to local guidelines) or other agents may be appropriate depending on local epidemiology
	daptomycin AND	8–10 mg/kg q24h iv	less risk of nephrotoxicity than vancomycin
	meropenem	1 g q8h iv	
5. ICED-LI or ICED-IE or generator pocket infection with negative blood cultures	vancomycin AND	1 g q12h[b] iv	appropriate spectrum but risk of nephrotoxicity
	gentamicin[c] OR	1 mg/kg q12h iv	
	daptomycin AND	8–10 mg/kg q24h iv	
	gentamicin[c]	1 mg/kg q12h iv	

iv, intravenous; po, *per os*; q6h, every 6 h; q12h, every 12 h; q8h, every 8 h; q24h, every 24 h.
[a]All doses require review if renal function is impaired. See British National Formulary (BNF) for drug interactions and cautions.
[b]Or dose vancomycin according to local protocols. Use daptomycin in glycopeptide-intolerant patient or when nephrotoxicity is a concern.
[c]Aim for pre-dose levels <1 mg/L and post-dose levels 3–5 mg/L. Meropenem is an alternative to gentamicin.

removed, residual infection involves only soft tissues and antimicrobial regimens can be kept short (Section 9.2.8).

Local delivery of antimicrobials into or around the generator has been investigated.[130,131] This approach has no role in the management of an infected ICED and we recommend complete removal of infected devices, positioning of any new system in a different anatomical location and systemic antimicrobial therapy as per guideline recommendations.

9.2.4 Which antimicrobial agents are recommended for complicated generator pocket infections?

Summary:

- **Recommendation 9.2.4: Treat complicated generator pocket infection as for ICED-LI or ICED-IE depending on final diagnosis. [C]**

See Section 9.2.5.

9.2.5 Which antimicrobial agents are recommended for ICED-LI or ICED-IE?

- **Recommendation 9.2.5.1: Empirical regimens for ICED-LI or ICED-IE are shown in Table 3. [C]**
- **Recommendation 9.2.5.2: 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 9.2.5.3: 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]**

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Table 4. Directed antimicrobial regimens for uncomplicated generator pocket infections or ICED-LI/generator pocket infections assuming device removal

Pathogen	First line (iv) (depending on susceptibility)[a]	Oral switch (depending on susceptibility) usually after device removal[a]
Staphylococcus spp. (methicillin-susceptible isolate)	flucloxacillin 2 g q6h	flucloxacillin 1 g q6h
Staphylococcus spp. (methicillin-resistant isolate or penicillin-allergic patient)[184]	vancomycin[b] 1 g q12h OR teicoplanin 6 mg/kg to a maximum of 1 g given at 0, 12 and 24 h and then q24h[183] OR daptomycin 4 mg/kg q24h	linezolid 600 mg q12h OR clindamycin 450 mg q6h OR doxycycline 100 mg q12h
Streptococcus spp. (penicillin-susceptible isolate)	benzyl penicillin 1.2 g q4h	amoxicillin 1 g q6h
Streptococcus spp. (penicillin-resistant or penicillin-allergic patient)	vancomycin[b] 1 g q12h OR teicoplanin 6 mg/kg to a maximum of 1 g given at 0, 12 and 24 h and then q24h[183]	linezolid 600 mg q12h
Enterococcus spp. (amoxicillin susceptible)	amoxicillin 2 g q6h	amoxicillin 1 g q6h
Enterococcus (amoxicillin resistant, but vancomycin susceptible or penicillin-allergic patient)	vancomycin[b] 1 g q12h OR teicoplanin 6 mg/kg to a maximum of 1 g given at 0, 12 and 24 h and then q24h[183]	linezolid 600 mg q12h
Enterococcus spp. (amoxicillin- and vancomycin-resistant, daptomycin-susceptible isolate)	daptomycin 4 mg/kg q24h OR linezolid 600 mg q12h	linezolid 600 mg q12h
Enterobacteriaceae ('coliforms')	case-by-case depending on susceptibility, monotherapy advised	case-by-case depending on susceptibility, monotherapy advised

For abbreviations of dosing routes and regimens see footnote to Table 3.
[a]All doses require review if renal function is impaired. See BNF for drug interactions and cautions.
[b]Or dose vancomycin according to local protocols. After device removal, residual infection is a skin and soft tissue infection, hence lower dosing regimens.

- **Recommendation 9.2.5.4: Vancomycin or daptomycin are suitable anti-Gram-positive agents for empirical treatment or for culture-negative ICED infection. [B]**
- **Recommendation 9.2.5.5: Local resistance patterns should be considered in choosing anti-Gram-negative agents for empirical treatment of suspected ICED infection. Aminoglycosides (e.g. gentamicin) and meropenem are both usually appropriate. [C]**
- **Recommendation 9.2.5.6: Modify treatment regimens once the microbial cause is identified (Tables 4 and 5). [C]**

Gram-positive bacteria (usually staphylococci) account for more than 80% of ICED infections while Gram-negative bacteria cause a significant minority (<20%, Table 1). 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 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.[72] 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 whether 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 should be completed, even if the ICED is removed. For this indication see BSAC endocarditis guidelines.[132] The indications for surgery on an infected prosthetic valve are as described in BSAC endocarditis guidelines.[132]

Microbiological details have often been omitted in multivariate analyses of risk factors for mortality (Section 3.5). However, positive blood cultures with *S. aureus* or methicillin-resistant *S. epidermidis* have been associated with increased 6 month mortality.[42]

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).[7,14,19,24,35] In some the types of antimicrobial regimen are described but not the outcomes. The regimens

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Table 5. Antimicrobial regimens for treatment of ICED-IE when system can be removed and no prosthetic valves are involved

Organism	Agent	Dose/route[a]	Comment
Staphylococcus spp. (methicillin-susceptible isolate)	flucloxacillin	2 g every 4–6 h iv	use q4h regimen if weight >85 kg.
Staphylococcus spp. (methicillin-resistant, glycopeptide-susceptible isolate or penicillin-allergic patient)	vancomycin OR	1 g q12h iv	dose glycopeptides according to local guidelines. Maintain pre-dose vancomycin and teicoplanin levels at 15–20 and 30–40 mg/L, respectively.
	teicoplanin	12 mg/kg iv to a maximum of 1 g given at 0, 12 and 24 h and then q24h[183]	
	AND		
	rifampicin OR	600 mg orally q12h	
	gentamicin	1 mg/kg iv q12h	for all organisms: continue gentamicin for the first 2 weeks provided there are no signs or symptoms of toxicity. Aim for pre-dose <1 mg/L and 1 h post-dose level 3–5 mg/L. Dose according to ideal body weight if obese.
Staphylococcus spp. (alternative regimen, e.g. glycopeptide-resistant isolate; vancomycin-intolerant patient or where nephrotoxicity is a concern)	daptomycin AND	6–8 mg/kg q24h iv	because resistance can develop on daptomycin,[132] combination therapy is currently advised. If isolate is resistant to rifampicin and gentamicin, linezolid can be used. High daptomycin doses based on reference 135, doses up to 10 mg/kg have been given (see ref 185).
	rifampicin OR	600 mg q12h orally	
	gentamicin	1 mg/kg q12h iv	see gentamicin comment for *Staphylococcus* spp. (methicillin-resistant).
Streptococcus spp. (penicillin-susceptible isolate)	benzyl penicillin AND	1.2 g q4 h iv	depending on penicillin MIC, as per endocarditis guidelines.[132]
	gentamicin	1 mg/kg q12h iv	see gentamicin comment for *Staphylococcus* spp. (methicillin-resistant).
Streptococcus spp. (penicillin-resistant isolate or penicillin-allergic patient)	vancomycin OR	1 g q12h iv	
	teicoplanin	12 mg/kg iv to a maximum of 1 g given at 0, 12 and 24 h and then q24h[183]	
	AND		
	gentamicin	1 mg/kg q12h iv	see gentamicin comment for *Staphylococcus* spp. (methicillin-resistant).
Enterococcus spp. (penicillin and gentamicin-susceptible isolate)	amoxicillin AND	2 g 4-hourly iv	
	gentamicin	1 mg/kg q12h iv	see gentamicin comment for *Staphylococcus* spp. (methicillin-resistant). A longer duration of treatment may be appropriate.
Enterococcus spp. (penicillin-resistant isolate or penicillin-allergic patient)	vancomycin OR	1.2 g q12h iv	
	teicoplanin AND	12 mg/kg iv to a maximum of 1 g given at 0, 12 and 24 h and then q24h[183]	
	gentamicin	1 mg/kg q12h iv	see gentamicin comment for *Staphylococcus* spp. (methicillin-resistant). A longer duration of treatment may be appropriate.

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Table 5. *Continued*

Organism	Agent	Dose/route[a]	Comment
Enterococcus spp. (vancomycin-resistant, daptomycin-susceptible isolate or glycopeptide-allergic/intolerant patient)	daptomycin AND	8–10 mg/kg q24h iv	because resistance can develop on daptomycin,[186] high-dose combination therapy is advised.[185–188] Continue gentamicin for duration of therapy provided there are no signs or symptoms of toxicity. If isolate is resistant to gentamicin or toxicity occurs, linezolid or amoxicillin can be used with daptomycin, but supporting data are limited[186–188] High doses are based on pharmacokinetic data and case series.[135]
	gentamicin OR	1 mg/kg q12h iv	
	amoxicillin OR	2 g q4 h iv	
	linezolid	600 mg q12h iv/po	
Enterobacteriaceae	meropenem	2 g q8h iv	alternative regimens may be appropriate according to susceptibility.
	AND gentamicin	1 mg/kg q12h iv	see gentamicin comment for *Staphylococcus* spp. (methicillin-resistant).

For abbreviations of dosing routes and regimens see footnote to Table 3.
[a]All doses need review if renal function is impaired.

included in Table 3 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 6).

Antimicrobial regimens that have been used successfully in the treatment of ICED-IE infection after removal of the system include vancomycin and aminoglycosides,[12,32,69] vancomycin monotherapy,[29] cloxacillin plus gentamicin,[32] ceftaroline,[133] cephalothin and aminoglycoside,[134] methicillin,[69,134] methicillin combined with an aminoglycoside,[69,134] daptomycin monotherapy,[135] daptomycin combined with gentamicin[135] and daptomycin combined with rifampicin.[135] 'β-Lactams' and vancomycin were the predominant agents used in one study but success rates were not reported.[6] Meropenem maintains a very broad spectrum of activity against Gram-negative bacteria, but there is little published experience of its use in ICED infection. Carbapenemase-producing Gram-negative organisms are more prevalent in some locations and may preclude the empirical use of carbapenems.

9.2.6 What regimens are recommended for attempted ICED salvage?

Summary:

- **Recommendation 9.2.6.1: Regimens for attempted salvage of ICED infection are summarized in Table 6. [D]**
- **Recommendation 9.2.6.2: 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 is recommended for treatment of prosthetic valve endocarditis because of the enhanced activity of such regimens against biofilms and concerns about resistance developing during therapy.[132,136] For example, daptomycin and vancomycin had superior activity *in vitro* against biofilm-associated MRSA when compared with linezolid, tigecycline and clindamycin.[137] In a different model, daptomycin, tigecycline and minocycline demonstrated superior activity against MRSA biofilms when compared with vancomycin, linezolid and rifampicin (monotherapy).[138] However, addition of rifampicin to the other five antimicrobials resulted in eradication of the biofilm.[138] Combination therapy has therefore been used in a number of reports.[72] Anecdotal success in curing ICED infection with the device *in situ* has been reported with vancomycin and aminoglycosides,[12,69] anidulafungin (*Candida* ICED infection),[139] daptomycin[135] and ciprofloxacin plus flucloxacillin.[118] Recommended regimens are summarized in Table 6.

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.

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Table 6. Antimicrobial regimens for treatment (salvage) of ICED-IE/ICED-LI and complicated generator pocket infection when entire system CANNOT be removed or prosthetic valves are involved

Cause	Agent	Dose/route[a]	Comment
Staphylococcus spp. (methicillin-susceptible isolate)	flucloxacillin AND	2 g every 4–6 h iv	use q4h regimen if weight >85 kg.
	rifampicin AND	600 mg q12 h orally	
	gentamicin	1 mg/kg q12h iv	for all microorganisms: continue gentamicin for the first 2 weeks provided there are no signs or symptoms of toxicity. Aim for pre-dose <1 mg/L and 1 h post-dose level 3–5 mg/L. Dose according to ideal body weight if obese.
Staphylococcus spp. (methicillin-resistant, glycopeptide-susceptible isolate or penicillin-allergic patient.)	vancomycin[b] OR	1 g[a] q12h iv	maintain pre-dose vancomycin and teicoplanin levels at 15–20 and 30–40 mg/L,[183] respectively.
	teicoplanin	12 mg/kg iv to a maximum of 1 g given at 0, 12 and 24 h and then q24h	
	AND rifampicin AND	600 mg q12h orally	
	gentamicin	1 mg/kg q12h iv	see gentamicin comment for *Staphylococcus* spp. (methicillin-susceptible).
Staphylococcus spp. Alternative regimen e.g. glycopeptide-resistant isolate; vancomycin-intolerant patient or where nephrotoxicity is a concern	daptomycin AND	6–8 mg/kg q24h iv	because resistance can develop on daptomycin,[132] combination therapy is advised. If isolate is resistant to rifampicin and gentamicin, linezolid can be used. High doses based on references 135 and 185.
	rifampicin AND	600 mg q12h orally	
	gentamicin	1 mg/kg q12h iv	see gentamicin comment for *Staphylococcus* spp. (methicillin-susceptible).
Streptococcus spp. (penicillin-susceptible isolate)	benzyl penicillin AND	1.2 g q4h iv	
	gentamicin	1 mg/kg q12h iv	see gentamicin comment for *Staphylococcus* spp. (methicillin-susceptible).
Streptococcus spp. (penicillin-resistant isolate or penicillin-allergic patient)	vancomycin[b] OR	1 g q12h iv	see levels above.
	teicoplanin AND	12 mg/kg iv to a maximum of 1 g given at 0, 12 and 24 h and then q24h[183]	
	gentamicin	1 mg/kg q12h iv	see gentamicin comment for *Staphylococcus* spp. (methicillin-susceptible).
Enterococcus spp. (penicillin-susceptible)	amoxicillin AND	2 g q4h iv	
	gentamicin	1 mg/kg q12h iv	see gentamicin comment for *Staphylococcus* spp. (methicillin-susceptible).
Enterococcus spp. (penicillin-resistant or penicillin-allergic patient)	vancomycin[b] OR	1 g q12h iv	see gentamicin comment for *Staphylococcus* spp. (methicillin-susceptible).
	teicoplanin AND	12 mg/kg iv to a maximum of 1 g given at 0, 12 and 24 h and then q24h[183]	
	gentamicin	1 mg/kg q12h iv	

Continued

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Table 6. *Continued*

Cause	Agent	Dose/route[a]	Comment
Enterococcus spp. (vancomycin-resistant, daptomycin-susceptible isolate or glycopeptide-allergic/intolerant patient)	daptomycin AND	8–10 mg/kg q24h iv	because resistance can develop on daptomycin,[186] high-dose combination therapy is advised.[185–188] Continue gentamicin for the duration of therapy provided there are no signs or symptoms of toxicity. If isolate is resistant to gentamicin, or toxicity develops, linezolid or amoxicillin can be used with daptomycin (supporting data are limited[186–188]). High doses are based on pharmacokinetic data and case series.[135]
	gentamicin OR	1 mg/kg q12h iv	
	amoxicillin OR	2 g q4h iv	
	linezolid	600 mg q12h iv/po	
Enterobacteriaceae	meropenem AND	2 g q8h iv	alternative regimens may be appropriate according to isolate susceptibility.
	gentamicin	1 mg/kg q12h iv	see gentamicin comment for *Staphylococcus* spp. (methicillin-susceptible).

For abbreviations of dosing routes and regimens see footnote to Table 3.
[a]All doses need review if renal function is impaired.
[b]Or dose vancomycin according to local protocols.

9.2.7 What is the optimal route of administration of antimicrobial therapy for ICED infection?

Summary:

- **Recommendation 9.2.7.1: 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 9.2.7.2: Peripheral cannulae carry the lowest infection risk and reduce the risk of damaging future sites for ICED implantation. [B/C]**
- **Recommendation 9.2.7.3: A peripherally inserted central catheter (PICC) or 'midline' is preferred for long-term intravenous access and should be inserted and maintained according to national guidelines. [C]**
- **Recommendation 9.2.7.4: A switch to oral antimicrobials is appropriate for generator pocket infections after device removal but intravenous therapy is recommended for ICED-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).[140] CRBSI acquired during treatment of IE is associated with increased mortality and is influenced by the type of vascular access device.[140] Patients can be managed with peripheral cannulae (that are changed every 72 h) for long periods.[140] Cuffed, tunnelled central venous catheters may not be the most appropriate device for delivering antimicrobials to patients with IE.[140] PICCs or midlines 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 length of time they remain *in situ*, so the choice between rotating peripheral cannulae and PICCs/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 as siting cannulae becomes problematic.

An early series of pacemaker infections describes treatment of a generator pocket wound infection with oral antimicrobials, subsequent relapse of infection and death of the patient.[134] 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-IE cases and attempted ICED salvage.

9.2.8 What is the optimal duration of therapy for ICED infection?

Summary:

- **Recommendation 9.2.8: Duration of therapy should be determined by the type of ICED infection, proposed device**

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management, involvement of other cardiac structures and the presence of extra-cardiac foci of infection (Table 2). [C]

An overview of the recommended duration of therapy in different clinical situations is given in Table 2. A blanket approach to the duration of therapy will result in considerable inappropriate antimicrobial exposure in a vulnerable patient population. Recommendations for duration of therapy therefore vary with the clinical situation. 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 6 weeks;[19] 4–6 weeks;[6,106] 28.5 days;[23] 26 days;[47] median 25.7 days;[14] 2–4 weeks;[34] or 2 weeks of intravenous therapy followed by 4 weeks of oral antimicrobials).[59]

Where reported, the duration of therapy used for generator pocket infections is reasonably consistent: 10 days[12,41] to 2 weeks.[24] 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). Removal of the ICED as soon as possible (but within 2 weeks) is necessary to avoid discomfort for the patient, risk of progression to ICED-IE/LI, unnecessarily prolonged antimicrobial treatment, side effects and the development of antimicrobial resistance.

ICED-IE (and ICED-LI) has been treated with 6 weeks,[12,15,32,43] 5.4 weeks[55] or 14–28 days of therapy.[57] In cases of ICED-IE/LI, the Working Party agreed that the key factors determining the total duration of antimicrobial therapy are as follows: (i) the decision to attempt ICED salvage or not; (ii) rapidity of ICED removal; (iii) concurrent involvement of native or prosthetic heart valves, or just lead involvement; (iv) initial clinical response to antimicrobials; and (v) the presence of extra-cardiac foci of infection (such as haematogenous vertebral osteomyelitis).

(a) If ICED salvage is to be attempted, 6 weeks of therapy is recommended. There are no reliable tests of cure so therapy should normally be stopped at 6 weeks and the patient observed closely for relapse and blood cultures should be taken as clinically indicated. The patient should be counselled regarding the high risk of relapse.

(b) Delay in ICED removal beyond 4 weeks will likely impact on the total duration of therapy, with all the associated risks.

(c) 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 (see points iii–v). Where there has been a good initial clinical response to antimicrobial therapy, there is no evidence of extracardiac infection and the ICED has been removed, a total of 4 weeks of therapy is usually sufficient to treat any residual 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 4 weeks of therapy after system removal is appropriate. Six weeks of therapy is advised for prosthetic valve endocarditis and for attempted salvage of ICEDs in the setting of associated IE or lead infection.[12,117] Prolonged antimicrobial therapy after device removal may not be required for isolated lead infection.

(d) The initial response to antimicrobial therapy can be slow in endocarditis but if an antimicrobial regimen is changed because of suspected failure of therapy, duration should be counted from the start of the new regimen.

(e) The total duration of therapy needs to be adequate to treat any secondary extra-cardiac foci of infection. If e.g. vertebral osteomyelitis and discitis are present a 6 week course of therapy will be needed, even if the primary diagnosis is ICED-LI and the system has been removed.

9.2.9 What therapy is recommended if ICED salvage fails?

Summary:

- **Recommendation 9.2.9: 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;[19] this should be considered a last resort and involvement of an infection specialist is advised.

10. Prevention of ICED infection

10.1 Where should ICED insertion take place?

Summary:

- **Recommendation 10.1: ICED insertion should take in place in an appropriately ventilated (at least 15 but ideally 25 air changes/h), equipped and cleaned room. [C]**

Design recommendations for cardiac catheter laboratories or operating theatres vary from country to country and ICED insertion should be carried out in a room that meets local standards. The Working Party agreed with the previous proposal that the ideal environment to implant ICEDs would be a dedicated ICED laboratory,[141] but acknowledged that this is aspirational. Health Technology Memorandum 03-01[142] specifies ventilation and air change requirements for cardiac catheterization laboratories and operating theatres while Health Building Note 01-01[143] gives 'best practice' guidance on the design and planning of new cardiac facilities. The air requirements specified for cardiac catheterization laboratories (15 air changes/h) are less than the 25 air changes/h recommended for operating theatres.[142] The BHRS guidelines highlight the importance of implantation occurring in an environment appropriate for sterile procedures but do not provide further detail.[17] Because there is direct evidence that ICEDs can become contaminated in the room where the device is implanted[46] and because the procedure involves a medical device, which is intended to remain in place throughout life, the Working Party felt that operating theatre standards of

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ventilation are appropriate for ICED implantation. There was complete agreement with the previous statement that a cardiac catheterization laboratory is not an ideal environment for implantation of ICEDs.[141] There are currently no published minimum standards for the environment in which implantable devices are inserted.

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.

10.2 Does operator experience affect infection rates?

Summary:

- **Recommendation 10.2: Procedures, including generator change, should be performed or supervised by experienced operators as per BHRS guidelines. [B]**

Operator experience did not appear as a risk factor for ICED infection in the review of multivariate studies in Section 3.3 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 focused 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% versus 0.4%; 90 days, 1.3% versus 0.6%, $P=0.01$).[144] 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.[145] Devices implanted by thoracic surgeons had a higher 90 day infection rate than those that were implanted percutaneously (5.1% versus 2.1%), although the total number of surgical implants was very low (311 versus 8062).[145] 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 (2006–08): the overall complication rate was 3.82% in centres performing fewer than 24 implants per year versus 3.08% in those implanting more than 110 devices a year ($P<0.0001$).[146] A smaller, more recent registry of 1744 patients with ICED implants and followed up prospectively for 6 months detected higher complication rates in lower-volume centres.[4] 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.[33] 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 (Section 3.3). It has been suggested that this is related to bacterial contamination of the avascular pocket that forms around the generator, which may 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 BHRS on this issue.[17]

10.3 Should temporary pacing be avoided to reduce infection?

Summary:

- **Recommendation 10.3: 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% to 18%.[147] In the light of these 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 1 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*.[35] 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 atrioventricular node ablation in a non-emergency setting.[38] It is increasingly common to implant PPMs in the acute setting, in order to avoid the risks of temporary pacing. The Working Party endorses this approach from an infection prevention perspective.

10.4 Should ICED procedures be carried out in patients with signs of infection?

Summary:

- **Recommendation 10.4: 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 (Section 3.3). 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.

10.5 Should patients having ICED insertion or manipulation be screened for staphylococcal carriage or decolonized?

Summary:

- **There are no studies specifically investigating the impact of pre-procedure screening for *S. aureus* or decolonization therapy on ICED infection rates.**
- **Recommendation 10.5.1: Current national guidelines for screening for MRSA colonization prior to elective procedures should be followed, as a minimum. [C]**

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- **Recommendation 10.5.2: Pre-procedural topical antimicrobial agents aimed at eliminating *S. aureus* are recommended for patients who are known to be colonized with *S. aureus*. [C]**

S. aureus colonizes the anterior nares of approximately one-third of people and appears intermittently in an additional third.[148] *S. aureus* can colonize other body sites or contaminate other body sites from the anterior nares. It has been common practice to try and reduce surgical site infection (SSI) caused by *S. aureus* by applying topical antimicrobials to the anterior nares or skin. This is clearly pertinent to ICED implantation, where *S. aureus* is a prominent pathogen. The National Institute for Health and Care Excellence (NICE) reviewed the evidence for the use of mupirocin or chlorhexidine for nasal decontamination (five RCTs) and concluded it does not reduce the overall rate of SSI.[148] NICE did highlight a non-statistically significant reduction in SSI caused by *S. aureus* in *S. aureus* carriers when mupirocin was used. None of these studies was undertaken in an ICED population.

The NICE guideline development group also modelled the cost effectiveness of three strategies for the use of nasal mupirocin to prevent SSI: no treatment; screen for *S. aureus* and treat identified carriers with mupirocin; or treat all patients with mupirocin.[148] Their model suggested screening for *S. aureus* carriage was not as cost effective as treating all patients empirically. However, the consensus was that routine treatment of all patients with mupirocin should not be recommended, especially as the potential harm of increased antimicrobial resistance had not been factored into the model.[148] Washing with chlorhexidine was also of uncertain benefit in terms of SSI reduction and washing with soap prior to surgery was advised by NICE.[148] Both of these areas warrant prospective evaluation in ICED patients.

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 and are in a state of flux. The Working Party therefore recommends adherence to national guidelines. If a patient is known to be colonized with MRSA (or MSSA) before a proposed ICED procedure, topical agents should be used to suppress carriage pre-procedure (e.g. nasal mupirocin and topical chlorhexidine washes[149]). Where high-level mupirocin resistance exists, other alternative regimens to which the microorganism is sensitive should be used, e.g. nasal neomycin/chlorhexidine (Naseptin or Prontoderm).

10.6 How should anticoagulation be managed during ICED insertion or manipulation?

Summary:

- **Recommendation 10.6.1: Uninterrupted warfarin [with careful international normalized ratio (INR) monitoring] is preferable to bridging with heparin in those patients in whom interruption of anticoagulation is contraindicated. [B]**
- **Recommendation 10.6.2: Where feasible (see notes below), 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 recognized risk factor for ICED infection.[4] The use of dual antiplatelet agents such as clopidogrel in combination with aspirin has been shown to increase the risk of bleeding at least 3-fold.[150,151] In addition, when 'bridging' patients with intravenous heparin, the incidence of bleeding was 14.3% compared with 4.3% in patients in whom warfarin was stopped and no heparin was given.[150] When patients with an annual risk of thromboembolic events of 5% or more were randomly assigned to continued warfarin treatment or to bridging therapy with heparin, clinically significant device pocket haematoma was significantly more common in the heparin group (relative risk 0.19; 95% CI 0.10–0.36; $P<0.001$).[152] Meticulous attention to detail and good surgical technique are important to ensure all haemostasis has been achieved prior to wound closure. In those patients in whom antithrombotic or anticoagulants can be stopped, they should be discontinued before the procedure (in practice ~5 days beforehand).

Feasibility. 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 INR of 2 rather than bridge with heparin. In patients on warfarin with an INR of 2–2.5, there was no statistically increased risk of bleeding compared with patients with an INR lower than 1.5, but an INR higher than 2.5 significantly increased the risk of bleeding.[150,153] Another study showed no increased risk of bleeding when warfarin was continued with an INR of 1.5 or higher.[150] 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.[153]

10.7 Which infection control measures should be in place before ICED implantation?

Summary:

- **Recommendation 10.7.1: ICED insertion should be carried out using an aseptic technique, in an environment observing operating theatre discipline, including appropriate clothing. [C]**
- **Recommendation 10.7.2: Bathing or showering with soap is recommended prior to ICED insertion. [C]**
- **Recommendation 10.7.3: Patients should be given specific theatre wear (including a hat) that allows easy access to the operative site and intravenous cannulae, and provides for the patient's comfort and dignity. [C]**
- **Recommendation 10.7.4: 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 10.7.5: 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 or the patient is known to have a chronic blood-borne viral infection. [C]**
- **Recommendation 10.7.6: Staff number and movements should be kept to a minimum in the operating theatre. [C]**
- **Recommendation 10.7.7: The operating team should remove hand/wrist jewellery, artificial nails and nail polish before procedures. [C]**

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- **Recommendation 10.7.8: 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 10.7.9: 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 they should be washed again with an antiseptic surgical solution. [B]**
- **Recommendation 10.7.10: Any equipment brought into the operating field should be covered to reduce the risk of contamination. [C]**
- **Recommendation 10.7.11: Devices and surgical equipment should be left uncovered for the minimum possible time. [C]**

We have extracted or adapted these recommendations from NICE guidelines,[148] 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. Details of structure, materials and implantation methods are provided in Appendix 1 and 2 for reference. All staff in the operating theatre, and the patient, can potentially shed skin squamae harbouring staphylococci (and other skin microorganisms) into the environment and operative field; this includes the hair, hence the recommendation for both staff and patients to wear a hat.

Because of the potential for contamination of devices in the operating room (Section 4), 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.

10.8 How should skin be prepared before ICED insertion/ manipulation?

Summary:

- **Recommendation 10.8.1: 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 10.8.2: The skin over the operative site should be prepared using an alcoholic chlorhexidine preparation containing a minimum of 2% chlorhexidine (or povidone iodine in alcohol for patients unable to tolerate chlorhexidine) [B]. The skin preparation should be left on for a minimum contact time of 30 s and should not be allowed to pool. [C]**
- **Recommendation 10.8.3: A pragmatic approach to draping is recommended i.e. one large fenestrated drape can be used to cover the patient, including the head. [C]**
- **Recommendation 10.8.4: If using incise drapes for ICED insertion, use iodophor-impregnated drapes; avoid incise drapes in patients with iodine allergy. [A]**

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.[148]

A meta-analysis of peri-operative prophylaxis and skin antisepsis concluded that there was evidence for the use of both.[154] We also found one prospective, observational, multicentre evaluation that examined skin preparation prior to ICED insertion.[4] This study found higher infection rates with povidone iodine compared with chlorhexidine.[4] 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 chlorhexidine,[148] but a systematic review concluded chlorhexidine was superior.[155] There has only been one good-quality RCT that demonstrated superiority of alcoholic chlorhexidine over povidone iodine for surgical skin antisepsis.[156] However, this trial did not include details of the length of application of the agents. The recent EPIC3 guidelines have recommended single use application of 2% chlorhexidine in 70% isopropyl alcohol for central line insertion. 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 s.[157] Pooling of alcoholic solutions should be avoided as there is a fire risk from diathermy during the procedure.[158] 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 Working Party cardiologists did not use incised drapes for ICED insertion and a systematic review of incise drapes found an increased risk of SSI when incised drapes (non-iodophor) were compared with non-incised drapes, for a variety of procedures.[159] However, if an incised drape is used, NICE guidelines recommend use of an iodophor-impregnated drape unless the patient has an iodine allergy.[148]

10.9 Antimicrobial prophylaxis

10.9.1 Should systemic antimicrobial prophylaxis be used for ICED insertion?

Summary:

- **Recommendation 10.9.1: Systemic antimicrobial prophylaxis should be used prior to ICED implantation. [A]**

Two meta-analyses of RCTs of antimicrobial prophylaxis prior to ICED insertion concluded that prophylaxis was potentially beneficial,[154,160] but the limitations of collating studies with different definitions, antimicrobial regimens and follow-up periods have been highlighted.[160] The best evidence of benefit of antimicrobial prophylaxis comes from a trial using cefazolin as the active agent.[41] This study included superficial infections as an outcome and only followed patients for 6 months. The meta-analysis included eight studies. A placebo-controlled RCT of 5 days of flucloxacillin did not show any benefit of prophylaxis.[161] A trial of flucloxacillin plus benzylpenicillin did show benefit, but this study excluded infections related to wound dehiscence or erosion, making interpretation difficult.[162] Cloxacillin prophylaxis significantly reduced infections while not affecting pocket culture results.[163]

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10.9.2 When should prophylaxis be administered?

Summary:

- **Recommendation 10.9.2.1: Intravenous antimicrobials should be administered within 1 h prior to skin incision. [A]**
- **Recommendation 10.9.2.2: 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.[154] Antimicrobial prophylaxis should be given at a time that ensures tissue and plasma concentrations exceed the MIC for the microorganisms commonly associated with infection at the time of incision and throughout the procedure. This would normally be within 1 h for intravenous drugs given as a bolus or short infusion, but some longer infusions that are given over 30 min or more may need to be started earlier to ensure that the infusion is completed at least 20 min before incision, e.g. vancomycin and fluoroquinolones.[164,165] 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.[154,166]

10.9.3 Which agent(s) should be given?

Summary:

- **Recommendation 10.9.3.1: The choice of prophylactic agent should cover the most likely pathogens in ICED infection. [C]**
- **Recommendation 10.9.3.2: 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 antimicrobial agent(s) in use—flucloxacillin was the most common.[16] The Working Party agreed that the agent used for prophylaxis should have activity against the most common causative microorganisms. In this respect, flucloxacillin 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 flucloxacillin) 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 flucloxacillin has been associated with nephrotoxicity in orthopaedic surgery.[167] If a glycopeptide is to be used, teicoplanin has some practical advantages over vancomycin in terms of administration as it can be given as a bolus[168] rather than a long infusion. Teicoplanin resistance is more frequent than vancomycin resistance among staphylococci (including CoNS), but both are uncommon.[169] Although teicoplanin was inferior to cefazolin in preventing Gram-positive infections in cardiac surgical patients,[170] a combination of teicoplanin and gentamicin was as effective as a multidose cephalosporin-based regimen in a similar patient population.[171] Further randomized 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.[172,173] Therapeutic usage of gentamicin has been associated with a 24.4% rate of acute kidney injury and 2.4% risk of renal failure,[148,174] but an increase in nephrotoxicity was not seen with a 2 mg/kg single-dose prophylaxis regimen in cardiac surgical patients.[171] 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.

10.9.4 Should antimicrobials be instilled into the generator pocket after implantation?

Summary:

- **Recommendation 10.9.4: Local instillation of antimicrobials or antiseptics should be avoided until evidence of benefit has been demonstrated. [C]**

A recent meta-analysis[154] pooled data from two studies to compare pre-operative systemic antimicrobial prophylaxis with locally instilled antimicrobials [rifampicin[175] in one and cloxacillin[176] (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[154] and concluded that local instillation of antimicrobials did not reduce infection rates.

Antimicrobial 'envelopes' have been developed to deliver antimicrobial agents locally into the generator pocket at the time of implantation or generator replacement. A product that delivers rifampicin and minocycline locally has been used in an uncontrolled clinical setting,[131] in an animal model[130,177] and *in vitro*,[178] but efficacy data from clinical trials are awaited.

10.10 Which operative factors influence risk of infection?

Summary:

- **There is no evidence to guide the method of haemostasis or the use of capsulectomy during ICED implantation or replacement and further research is warranted.**

Haematoma formation (after implantation) is a recognized risk factor for ICED infection (Section 3.3), and haemostasis is therefore important. Although diathermy can be used to achieve

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haemostasis during ICED implantation, there remains the possibility of interference with ICED function in patients with existing ICEDs,[179] this can be managed by using short pulses. It is often quoted that tissue damage resulting from diathermy use may paradoxically increase the risk of infection; however, the meta-analysis of six trials undertaken by NICE found no significant difference in SSI rates when diathermy was compared with scissors or scalpel for skin incision for a range of procedures.[148] There are no data comparing ICED infection rates with and without diathermy. Use of alternative cautery devices in small numbers of patients has been reported in the literature.[180–182]

Optimal management of haematoma formation post-ICED insertion is not known. Compression and evacuation are both used clinically. While haematoma formation is a risk factor for infection, so is re-operation, so it is unclear which approach is best. If the skin is tense and the wound is at risk of opening it may be better to re-operate.

The fibrous capsule that forms around the generator is believed by some to limit the penetration of systemically administered prophylactic antimicrobials and host defences during generator replacement. Capsulectomy, or disruption of the capsule, is therefore advocated by some cardiologists, although there is no evidence to support or refute this practice; it makes theoretical sense and warrants further investigation.

10.11 What represents ideal post-operative wound closure and care?

Summary:

- **Recommendation 10.11: No specific recommendations concerning wound closure and care can be made. [C]**

There is no evidence to support specific recommendations on wound closure and post-operative care following insertion of an ICED. NICE clinical guideline 74[148] found no evidence that the type of suture material, or wound closure methods had an impact on rates of SSI, but the evidence is limited and further research was advised. Common clinical practice is outlined in Appendix 2 (see Supplementary data). Attention to good surgical technique and attendance at appropriate training courses are advised.

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Supplementary data

Tables S1, S2, S3, S4 and S5 and Figures S1, S2, S3 and S4 are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/). In addition there three Appendices covering (i) outline of structure and materials used in ICEDs; (ii) methods of implantation and removal of ICED; and (iii) coding ICED infection.

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