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Update on Cardiovascular Implantable Electronic Device Infections and Their Management: A Scientific Statement From the American Heart Association

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Update on Cardiovascular Implantable Electronic Device Infections and Their Management

A Scientific Statement From the American Heart Association

Endorsed by the Heart Rhythm Society

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Young; Council on Cardiovascular Surgery and Anesthesia; Council on Cardiovascular Nursing;
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and Outcomes Research

Abstract—Despite improvements in cardiovascular implantable electronic device (CIED) design, application of timely infection control practices, and administration of antibiotic prophylaxis at the time of device placement, CIED infections continue to occur and can be life-threatening. This has prompted the study of all aspects of CIED infections. Recognizing the recent advances in our understanding of the epidemiology, risk factors, microbiology, management, and prevention of CIED infections, the American Heart Association commissioned this scientific statement to educate clinicians about CIED infections, provide explicit recommendations for the care of patients with suspected or established CIED infections, and highlight areas of needed research. (*Circulation*. 2010;121:458-477.)

Key Words: AHA Scientific Statements ■ infection ■ device, cardiovascular ■ implantable electronic device ■ pacemaker ■ implantable cardioverter-defibrillator ■ endocarditis

In 2003, the American Heart Association published a scientific statement that reviewed a variety of nonvalvular cardiovascular device infections.¹ The document included an encyclopedic view of device infections involving cardiac, arterial, and venous structures. The primary focus of the statement was to formally recognize this group of cardiovascular infections and to highlight their clinical importance. The

document also included a limited number of recommendations regarding the prevention and management of nonvalvular device infections. Perhaps the most noteworthy recommendation in the statement emphasized that antibiotic prophylaxis for routine dental, gastrointestinal, and genitourinary procedures was not indicated in patients with these devices.

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Table 1. Applying Classification of Recommendations and Level of Evidence

		SIZE OF TREATMENT EFFECT →			
		CLASS I <i>Benefit >>> Risk</i> Procedure/Treatment SHOULD be performed/administered	CLASS IIa <i>Benefit >> Risk</i> Additional studies with <i>focused objectives</i> needed IT IS REASONABLE to perform procedure/administer treatment	CLASS IIb <i>Benefit ≥ Risk</i> Additional studies with <i>broad objectives</i> needed; additional registry data would be helpful Procedure/Treatment MAY BE CONSIDERED	CLASS III <i>Risk ≥ Benefit</i> Procedure/Treatment should NOT be performed/administered SINCE IT IS NOT HELPFUL AND MAY BE HARMFUL
ESTIMATE OF CERTAINTY (PRECISION) OF TREATMENT EFFECT	LEVEL A Multiple populations evaluated* Data derived from multiple randomized clinical trials or meta-analyses	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Sufficient evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from multiple randomized trials or meta-analyses 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Sufficient evidence from multiple randomized trials or meta-analyses
	LEVEL B Limited populations evaluated* Data derived from a single randomized trial or nonrandomized studies	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Some conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Greater conflicting evidence from single randomized trial or nonrandomized studies 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Evidence from single randomized trial or nonrandomized studies
	LEVEL C Very limited populations evaluated* Only consensus opinion of experts, case studies, or standard of care	<ul style="list-style-type: none"> Recommendation that procedure or treatment is useful/effective Only expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation in favor of treatment or procedure being useful/effective Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation's usefulness/efficacy less well established Only diverging expert opinion, case studies, or standard of care 	<ul style="list-style-type: none"> Recommendation that procedure or treatment is not useful/effective and may be harmful Only expert opinion, case studies, or standard of care
Suggested phrases for writing recommendations†		should is recommended is indicated is useful/effective/beneficial	is reasonable can be useful/effective/beneficial is probably recommended or indicated	may/might be considered may/might be reasonable usefulness/effectiveness is unknown/unclear/uncertain or not well established	is not recommended is not indicated should not is not useful/effective/beneficial may be harmful

*Data available from clinical trials or registries about the usefulness/efficacy in different subpopulations, such as gender, age, history of diabetes, history of prior myocardial infarction, history of heart failure, and prior aspirin use. A recommendation with Level of Evidence B or C does not imply that the recommendation is weak. Many important clinical questions addressed in the guidelines do not lend themselves to clinical trials. Even though randomized trials are not available, there may be a very clear clinical consensus that a particular test or therapy is useful or effective.

†In 2003, the ACCF/AHA Task Force on Practice Guidelines developed a list of suggested phrases to use when writing recommendations. All guideline recommendations have been written in full sentences that express a complete thought, such that a recommendation, even if separated and presented apart from the rest of the document (including headings above sets of recommendations), would still convey the full intent of the recommendation. It is hoped that this will increase readers' comprehension of the guidelines and will allow queries at the individual recommendation level.

The 6 years after the publication of the 2003 document¹ have witnessed exceptional advances in our understanding of several clinical aspects of cardiovascular device infections. In particular, CIED infections have received the bulk of the attention, with sentinel observations regarding the epidemiology, associated risk factors, and management and prevention of permanent pacemaker (PPM) and implantable cardioverter-defibrillator (ICD) infections. Findings from several key clinical investigations that were published after 2003 prompted the Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young of the American Heart Association to provide an updated document limited to CIED infections. Because of the rarity of infection of implantable loop recorders and cardiovascular monitors, these devices are not considered in the present document.

Classification System

The writing group was charged with the task of developing evidence-based recommendations for care and designating a classification and a level of evidence for each recommendation. The American College of Cardiology/American Heart Association classification system was used as shown in Table 1.

Background

CIEDs have become increasingly important in cardiac disease management over the past 5 decades in the United States and have dramatically improved both patient quality and quantity of life. PPMs have been implanted since the 1960s. Advances in PPM technology have provided a strong foundation for the accelerated development of ICD and cardiac resynchronization systems.² Over the years, CIEDs have become smaller in size despite a marked expansion of device functionality.

Guidelines from the American College of Cardiology/American Heart Association/Heart Rhythm Society are available and are updated serially; the guidelines provide specific recommendations for CIED implantation.³

In an analysis⁴ of CIED implantation in the United States between 1997 and 2004, implantation rates for PPMs and ICDs increased by 19% and 60%, respectively. Approximately 70% of device recipients were 65 years of age or older, and more than 75% of them had 1 or more coexisting illnesses. These data are consistent with findings from recent population-based surveys in Olmsted County, Minnesota,^{5,6} where patients undergoing PPM implantation between 1975 and 2004 had increasing numbers of coexisting illnesses. Simultaneously, dual-chamber pacing has become used much more frequently than single-chamber pacing.⁴ Similarly, the frequency of ICD implantation increased in the elderly (70 to 79 years of age) and very elderly (80 years of age or older).⁵ The 2001 World Survey⁷ found that in developed countries, between 20% and 35% of CIED recipients were more than 80 years old.

The National Hospital Discharge Survey⁸ found a 49% increase in the number of new CIED implantations, including both PPMs and ICDs, in the United States between 1999 and 2003. In 2003, although the absolute number of PPM implantations was higher than for ICDs (180 284 versus 57 436), more of the increase in CIED device implantation was driven by ICD implantations (160% and 31% increases in ICD and PPM implantations, respectively).⁸ In summary, the increased rates of CIED implantation coupled with increased implantation in older patients with more comorbid conditions have set the stage for higher rates of CIED infection.

Incidence and Epidemiology

PPM endocarditis has been recognized since the early 1970s.^{9,10} In earlier years, the rates of PPM infection ranged widely between 0.13%¹¹ and 19.9%.¹² Although most infections have been limited to the pocket, frank PPM endocarditis accounts for approximately 10% of PPM infections.¹³

The first ICD was implanted in 1980.¹⁴ Subsequent decreases in the size of ICDs permitted implantation without thoracotomy, although initially, abdominal implantation with tunneling was required. Subsequently, the entire device could be implanted prepectorally. The infection rate with these less extensive operations was lower (<7%).¹⁵ In a study of all ICD primary implantations, replacements, and revisions at a single center, there were 21 ICD-related infections (1.2%) among 1700 procedures, affecting 1.8% of 1170 patients. Among 959 patients with long-term follow-up, the infection rate was 3.2% with abdominal and 0.5% with pectoral systems.¹⁵

Despite the greater ease of device implantation with pectoral rather than other routes and increasing experience with implantation, the rate of CIED infection has been increasing. Cabell et al¹⁶ reported that among Medicare beneficiaries, the rate of cardiac device infections (PPMs, ICDs, valves, and ventricular assist devices) increased from 0.94 to 2.11 per 1000 beneficiaries between 1990 and 1999, a 124% increase during the study period. The rate of frank

endocarditis was relatively unchanged (0.26 and 0.39 cases/1000 beneficiaries, respectively).

These findings were mirrored when CIED implantations were analyzed in Olmsted County, Minnesota, from 1975 to 2004.¹⁷ A total of 1524 patients were included with a total person-time follow-up of 7578 years with device implantation. The incidence of CIED infection was 1.9/1000 device-years (95% confidence interval [CI] 1.1 to 3.1), with an incidence of pocket infection alone of 1.37/1000 device-years (95% CI 0.62 to 0.75) and an incidence of pocket infection with bloodstream infection or device-related endocarditis of 1.14/1000 device-years (95% CI 0.47 to 2.74). Notably, the cumulative probability of CIED infection was higher among patients with ICDs than among those with PPMs. The National Hospital Discharge Survey⁸ similarly showed that between 1996 and 2003, the number of hospitalizations for CIED infections increased 3.1-fold (2.8-fold for PPMs and 6.0-fold for ICDs). The numbers of CIED infection-related hospitalizations increased out of proportion to rates of new device implantation. Moreover, CIED infection increased the risk of in-hospital death by more than 2-fold.

Risk Factors

Several studies have identified characteristics associated with CIED infections. In a single-center case-control study,¹⁸ case subjects were more likely to have diabetes mellitus and heart failure and to have undergone generator replacement; renal dysfunction (glomerular filtration rate <60 mL · min⁻¹ · 1.72 m⁻²) had the strongest (odds ratio [OR] 4.8) association with CIED infection. Renal dysfunction was also associated with risk of CIED infection in a more recent nested case-control investigation.¹⁹ In addition, Lekkerkerker et al¹⁹ identified oral anticoagulant use as an associated risk factor for infection. In another single-center case-control study, 29 patients with PPM infection were included, and long-term corticosteroid use (OR=13.9) and the presence of more than 2 pacing leads (OR=5.41) were identified as independent correlates of device infection.²⁰

In addition to patient factors, procedural characteristics may also play an important role in the development of CIED infection. In a prospective cohort of 6319 patients receiving CIED implantation in 44 medical centers, Klug et al²¹ identified 42 patients who developed CIED infection during 1 year of follow-up. The factors associated with an increased risk of infection included fever within 24 hours before implantation (OR 5.83), use of preprocedural temporary pacing (OR 2.46), and early reintervention (OR=15.04). Implantation of a new system (OR=0.46 compared with partial or complete system replacement) and use of periprocedural antimicrobial prophylaxis (OR 0.40) were both associated with a lower risk of infection. The latter finding corroborated other evidence supporting perioperative antimicrobial prophylaxis for CIED infection prevention.^{20,22} Other small studies suggest that pectoral transvenous device placement is associated with significantly lower rates of CIED infection than for those implanted abdominally¹⁵ or by thoracotomy.^{23,24} Thus, the pervasive use of a pectoral approach is not only less invasive but also appears to confer an ancillary benefit of lower infection risk.

Physician experience in CIED implantation may also play a role in the rate of subsequent CIED infection. In a study of Medicare administrative data, Al-Khatib et al²⁵ found a significantly higher risk of ICD infection within 90 days of device implantation in patients whose device was placed by physicians in the lowest quartile of implantation volume (OR 2.47 compared with physicians in the highest-volume quartile). Rates of mechanical complications at 90 days were also higher for lower-volume physicians.

Finally, among patients with bloodstream infection, the organism involved is strongly associated with the likelihood of serving as a manifestation of CIED infection, even in patients with no other evidence of CIED infection. In a cohort of 33 patients with implanted devices and subsequent *Staphylococcus aureus* bacteremia,²⁶ nearly one half (45.4%) had confirmed CIED infection, and only a minority had local signs or symptoms that suggested generator-pocket infection. Similarly, in a cohort study from Olmsted County, Minnesota, 55% of 22 patients with cardiac devices and subsequent *S aureus* bacteremia had definite or possible CIED infection.¹⁷ In contrast, the risk of device infection with bacteremia with Gram-negative bacilli was substantially lower.²⁷

Johansen et al²⁸ followed up 36 076 patients in the Danish Pacemaker Register. The incidence of explantation due to infection was significantly higher after replacement procedures than after first implantation (2.06% versus 0.75%, $P < 0.01$). Device revision was associated with CIED infection in another investigation described recently.¹⁹ Although the incidence of infection decreased in the past 3 years of the study, the shorter follow-up of patients was thought to be a possible explanation. Whether multiple device revisions increase the risk of CIED infection exponentially is undefined.

The importance of reinterventions and device replacement is highlighted in the current era of increased safety alerts and device advisories. Gould and Krahn²⁹ reported that in Canada, the risk of major complications of ICD replacement in response to recalls that required reoperation was 5.8% (31 of 533 patients), which included 2 deaths after extraction for pocket infection. Kapa et al³⁰ reported a 1.4% complication risk at Mayo Clinic.

In summary, several factors associated with a greater risk of CIED infection have been described in this section, including the following: (1) Immunosuppression (renal dysfunction and corticosteroid use); (2) oral anticoagulation use; (3) patient coexisting illnesses; (4) periprocedural factors, including the failure to administer perioperative antimicrobial prophylaxis; (5) device revision/replacement; (6) the amount of indwelling hardware; (7) operator experience; and (8) the microbiology of bloodstream infection in patients with indwelling CIEDs. Future study of CIED infection pathogenesis should better define how associated factors contribute to infection risk and whether intervention can decrease the risk.

Risk factor analyses reported to date have noteworthy limitations, generally have included relatively small numbers of patients with CIED infections, and, with few exceptions, reflect the experience of single centers. Thus, although the existing literature provides some insight into CIED infection risk factors, larger, more representative studies would be useful in identifying and addressing the most important

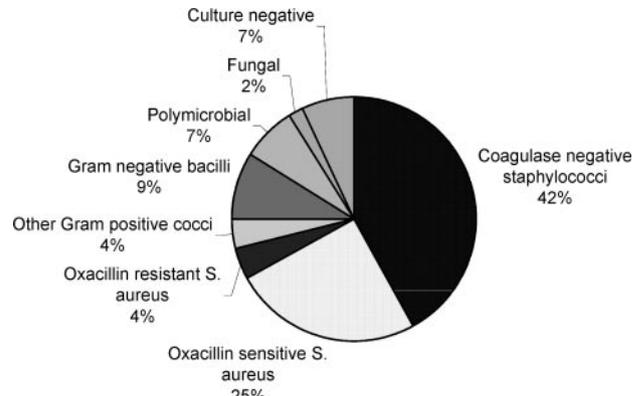


Figure 1. Microbiology of PPM/ICD infections (n=189). From Sohail et al,³⁸ with permission.

factors that are responsible for the development of CIED infection.

Financial Burden

Precise data regarding the actual healthcare burden of CIED infections are not available and are sorely needed. Considering the acquisition costs of CIED,³¹ it is not surprising that the economic consequences, including healthcare resource utilization, of CIED infections are substantial. The financial impact is due to multiple factors, including but not limited to the costs of device removal, a new device (which would be required in the majority of patients), cardiac and other medical evaluations, diagnostic procedures, surgical interventions for infected device removal, new device placement and certain infectious complications, medical therapy of infection, and critical care stays that are often prolonged. Even when a CIED is ultimately proven not to be infected, the cost of an evaluation for device infection among those with *S aureus* bacteremia is sizable.³²

Microbiology

Staphylococcal species cause the bulk of CIED infections^{17,33–40} and account for 60% to 80% of cases in most reported series (Figure 1). A variety of coagulase-negative *Staphylococcus* (CoNS) species have been described to cause CIED infections.⁴¹ CoNS is well recognized as a common cause of microbiological specimen contamination, and thus, repeated isolation of the same species of CoNS with an identical antibiotic susceptibility pattern is desired to support its role as an etiologic agent in CIED infections. Polymicrobial infection sometimes involves more than 1 species of CoNS.^{36,40,42} The prevalence of oxacillin resistance among staphylococcal strains has varied among studies, but it is prevalent and should influence initial empirical therapy decisions in CIED infections. *Corynebacterium* species, *Propionibacterium acnes*, Gram-negative bacilli^{37,38} including *Pseudomonas aeruginosa*,⁴³ and *Candida* species account for a minority of CIED infections. Fungi other than *Candida*⁴⁴ and nontuberculosis mycobacteria^{45,46} are rarely identified as pathogens in CIED infection.

The microorganisms that cause CIED infections may be acquired either endogenously from the skin of patients or

exogenously from the hospital inanimate environment or from the hands of hospital workers. In support of endogenous acquisition, an association has been noted between the presence of preaxillary skin flora and the pathogens isolated from pacemaker infection.³⁵ Although low concentrations of methicillin-resistant CoNS have been detected in individuals with no healthcare contact and no recent antibiotic exposure,⁴⁷ a disproportionate frequency of CIED infections due to multidrug-resistant staphylococci^{26,40} suggests that a healthcare environment is the site of infection acquisition.^{48,49}

Pathogenesis

The pocket may become infected at the time of implantation, during subsequent surgical manipulation of the pocket, or if the generator or subcutaneous electrodes erode through the skin. In the latter case, erosion can also occur as a secondary event due to underlying infection. Pocket infection may track along the intravascular portion of the electrode to involve the intracardiac portion of the pacemaker or ICD. Alternatively, the pocket or intracardiac portion of the electrode may become infected as a result of hematogenous seeding during a bout of bacteremia or fungemia secondary to a distant infected focus. Hematogenous seeding of a CIED is unlikely to occur in cases of Gram-negative bacillary bacteremia, as discussed below. Bacteremia due to *S aureus* can result in device infection, but the prevalence of this occurrence and the differentiation of this mechanism of device infection from intraoperative contamination at the time of device placement or manipulation are difficult to determine. There are no data that examine the likelihood of hematogenous seeding of a device due to other Gram-positive cocci that are more common causes of bloodstream infection or due to fungi, in particular *Candida* species.

Device-related infection is the result of the interaction between the device, the microbe, and the host. Initial attachment of bacteria to the device is mediated by physical-chemical properties, such as hydrophobicity, surface tension, and electrostatic charge, of the plastic surface of the device and the bacterial surface.⁵⁰ Bacteria, particularly Gram-positive cocci, can also adhere to and be engulfed by endothelial cells that can cover an endothelialized lead over a period of time, which is thought to be an important mechanism of device infection by the hematogenous route.

Device Factors

Device-related factors, such as the type of plastic polymer, irregularity of its surface, and its shape, can affect bacterial adherence to the device.⁵¹ Plastic polymers that encase medical devices, as well as the pathogens that adhere to them, are hydrophobic. The greater the degree of hydrophobicity, the greater is the adherence.⁵² Polyvinyl chloride favors more adherence than Teflon (duPont, Wilmington, Del), polyethylene more than polyurethane, silicone more than polytetrafluoroethylene, and latex more than silicone; some metals (eg, stainless steel) favor adherence more than others (eg, titanium). An irregular surface of the device favors microbial adherence more than a smooth surface. Indirect device factors previously addressed in this document as risk factors associ-

ated with CIED infection include subsequent invasive manipulation of an implanted CIED and a limited number of device implantations previously performed by the physician performing the procedure.

Microbial Factors

None of the major virulence factors or toxins of *S aureus* have been found in CoNS, and it seems clear that the development and persistence of CoNS infections, which are so often associated with foreign materials, are due to different mechanisms, such as adherence. The initial nonspecific attachment by means of physicochemical forces is followed or accompanied simultaneously by the specific interaction of bacterial surface adhesins with the uncoated device directly and with host proteins that coat the device. CoNS may adhere directly to plastic polymers on the surface of the device via fimbria-like surface protein structures⁵³ or via a capsular polysaccharide (polysaccharide/adhesin). Antibodies to polysaccharide/adhesin (either produced actively by immunization or infused passively as polyclonal or monoclonal antibodies) prevent experimental *S epidermidis* catheter infections⁵⁴ and experimental endocarditis⁵⁵ in animals.

Bacteria may also adhere to host matrix proteins that coat the surface of an implanted device.⁵⁶ Host extracellular matrix proteins include fibrinogen, fibronectin, and collagen that are deposited on newly implanted biomaterials.^{57,58} Staphylococci have a variety of surface adhesins, some known collectively by the acronym MSCRAMM (microbial surface components reacting with adherence matrix molecules), that allow the pathogen to establish a focus of infection.⁵⁹

Biofilm Formation

Subsequent accumulation of bacteria on top of bacteria that adhere to a device surface requires the production of so-called polysaccharide intercellular adhesin, which is strongly associated with the staphylococcal cell surface and mediates cell-to-cell adhesion.^{50,59} The layers of bacteria on the surface of an implanted device are encased in this extracellular slime⁶⁰ and constitute a biofilm. Biofilm is defined as a surface-associated community of 1 or more microbial species that are firmly attached to each other and the solid surface and are encased in an extracellular polymeric matrix that holds the biofilm together. Microbes in a biofilm are more resistant to antibiotics and host defenses, perhaps as a result of the dense extracellular matrix that protects the microbes secluded in the interior of the community. When a bacterial cell switches modes from free-floating (planktonic) organisms to biofilm, it undergoes a phenotypic shift in behavior in which large groups of genes are regulated.⁵⁰

Microbial Persistence

Phenotypic variation is also thought to be operative in supporting the persistence of infection due to staphylococci in a biofilm that coats the surface of a CIED. Small colony variants are phenotypes that have caused CIED infections^{61–63} and harbor several characteristics that are thought to enhance the survival of staphylococci either in a biofilm or

in endothelial cells that cover the device, including resistance to certain antibiotics.^{64–66}

Host Factors

Host factors associated with increased risk of CIED infection were outlined in a previous section of this document. These include renal failure, corticosteroid use, congestive heart failure, hematoma formation, diabetes mellitus, and anticoagulation use.

Diagnosis

CIED infection can present as different syndromes. In the majority of cases, local inflammatory changes of the generator-pocket site are present, or cutaneous erosion with percutaneous exposure of the generator and/or leads is seen. These local changes, often accompanied by pain or discomfort, usually prompt patients to seek medical attention. Fever and other signs of systemic toxicity are frequently absent. Some patients present with vague symptoms that include malaise, fatigue, anorexia, or decreased functional capacity. Less commonly, the diagnosis of CIED infection is suspected in patients with fever of undefined origin who harbor no local inflammatory changes at the generator-pocket site. At least 2 sets of blood cultures should be obtained before the initiation of antimicrobial therapy in all patients with suspected CIED infection; some patients with bloodstream infection may not manifest systemic toxicity or peripheral leukocytosis. Positive blood cultures, particularly due to staphylococcal species, provide a strong clue that the clinical syndrome is due to CIED infection. Patients should be educated about the need to be evaluated for CIED infection by cardiologists or specialists in infectious diseases if they develop fever or bloodstream infection for which there is no initial explanation.

Transesophageal echocardiography (TEE) may be useful in demonstrating CIED-related endocarditis in adults. Because of its poor sensitivity, transthoracic echocardiography is frequently not helpful in ruling out a diagnosis of lead-related endocarditis, particularly in adults. Moreover, patients can develop both right-sided (lead-related) and left-sided endocarditis; the sensitivity of TEE for left-sided involvement and for perivalvular extension of infection is superior to that of transthoracic echocardiography. Additionally, visualization of the lead in the proximal superior vena cava from TEE views may identify tissue along that region that is difficult to visualize by other methods. TEE examination is critical among patients with *S aureus* bacteremia, because the rate of endocarditis is significant.⁶⁷ Several prognostic features may be better defined on transthoracic echocardiography than on TEE, such as pericardial effusion, ventricular dysfunction and dyssynchrony, and pulmonary vascular pressure estimations. Concomitant or subsequent transthoracic echocardiography acquired at the time of diagnosis of CIED infection can serve as a baseline for additional studies that may be required during the course of the patient's illness or follow-up.

A mass adherent to the lead that is seen on echocardiography is usually a thrombus or infected vegetation. Because it is impossible to distinguish between the 2 with echocardiography and recognizing that 5% of adherent masses were

deemed thrombus in 1 retrospective survey,⁶⁸ there will be some patients who are labeled as manifesting CIED-related endocarditis who may not have a lead infection. Masses that are detected in patients without positive blood cultures or other suggestive features for infection are likely to represent thrombus and by themselves do not require lead removal or antibiotic treatment. In addition, the failure to visualize a mass adherent to a lead with TEE does not exclude lead infection.

Cultures of generator-pocket-site tissue and lead tips at the time of device removal are useful in identifying the causative organism and to support a diagnosis of CIED infection. The sensitivity of pocket-site tissue culture is higher than that of swab culture of the pocket.⁶⁹ Gram staining, in addition to both anaerobic and aerobic bacterial cultures, should be done. Both tissue and the lead tip should be cultured for fungi and mycobacteria if the initial Gram stain is negative; mycobacteria and fungal stains also should be obtained on resected pocket tissue. Percutaneous aspiration of the device pocket should not be done, in general, because of the lack of adequate diagnostic yield and the theoretical risk of introducing microorganisms into the pocket site and causing device infection.

Because leads are extracted through an open generator pocket in most cases, lead contamination can occur if a pocket is infected. This likely explains the lack of systemic manifestations and negative blood cultures in many cases in which a positive lead-tip culture is demonstrated.

Recommendations for Diagnosis of CIED Infection and Associated Complications

Class I

1. All patients should have at least 2 sets of blood cultures drawn at the initial evaluation before prompt initiation of antimicrobial therapy for CIED infection. (*Level of Evidence: C*)
2. Generator-pocket tissue Gram's stain and culture and lead-tip culture should be obtained when the CIED is explanted. (*Level of Evidence: C*)
3. Patients with suspected CIED infection who either have positive blood cultures or who have negative blood cultures but have had recent antimicrobial therapy before blood cultures were obtained should undergo TEE for CIED infection or valvular endocarditis. (*Level of Evidence: C*)
4. All adults suspected of having CIED-related endocarditis should undergo TEE to evaluate the left-sided heart valves, even if transthoracic views have demonstrated lead-adherent masses. In pediatric patients with good views, transthoracic echocardiography may be sufficient. (*Level of Evidence: B*)

Class IIa

1. Patients should seek evaluation for CIED infection by cardiologists or infectious disease specialists if they develop fever or bloodstream infection for which there is no initial explanation. (*Level of Evidence: C*)

Class III

1. Percutaneous aspiration of the generator pocket should not be performed as part of the diagnostic evaluation of CIED infection. (*Level of Evidence: C*)

Management

CIED removal is not required for superficial or incisional infection at the pocket site if there is no involvement of the device. Seven to 10 days of antibiotic therapy with an oral agent with activity against staphylococci is reasonable.

Complete removal of all hardware, regardless of location (subcutaneous, transvenous, or epicardial), is the recommended treatment for patients with established CIED infection.^{37,38,70} This includes cases in which a localized pocket infection occurs in the absence of signs of systemic infection. Complete removal of hardware is needed because infection relapse rates due to retained hardware are high.^{1,37,38,71,72} Erosion of any part of the CIED should imply contamination of the entire system, including the intravascular portion of leads, and complete device removal should be performed.

Complete CIED removal should be performed when patients undergo valve replacement or repair for infective endocarditis, because the CIED could serve as a nidus for relapsing infection and subsequent seeding of the surgically treated heart valve. An epicardial system should be considered if a new CIED is required after valve surgery with initial CIED removal.

The first issue to address in the treatment of CIED infections is the approach to hardware removal. As newer technologies have emerged and the experience has grown, percutaneous lead extraction has become the preferred method for removal of CIED hardware. However, these procedures involve significant risks, including cardiac tamponade, hemothorax, pulmonary embolism, lead migration, and death, even in experienced hands. Thus, the performance of these procedures should be limited to centers with the appropriate facilities and training, which includes the presence and imminent availability of cardiothoracic surgery on site to provide backup in the event of complications. In high-volume centers, percutaneous lead removal can be accomplished relatively safely with a high rate of success.⁷³ A primary surgical approach to lead removal in patients with CIED infection should be limited to patients who have significant retained hardware after attempts at percutaneous removal. Another scenario in which a preference for surgical lead removal has been advocated⁷⁴ is in patients with lead vegetations >2 cm in diameter, because of concerns about the risk of pulmonary embolism with percutaneous lead extraction. Experience suggests, however, that percutaneous removal in patients with large vegetations can be done without precipitating a clinically apparent pulmonary embolism.^{38,72} Until additional data are available, decisions regarding percutaneous versus surgical removal of leads with vegetations larger than 2 cm in diameter should be individualized and based on a patient's clinical parameters and the extractor's evaluation.

Antimicrobial therapy is adjunctive in patients with CIED infection, and complete device removal should not be delayed, regardless of timing of initiation of antimicrobial therapy. Selection of the appropriate antimicrobial agent should be based on identification and in vitro susceptibility testing results. Because the bulk of infections are due to staphylococcal species, and some of them will be oxacillin resistant, vancomycin should be administered initially as

empirical antibiotic coverage until microbiological results are known. Patients with infections due to oxacillin-susceptible staphylococcal strains can be given cefazolin or nafcillin alone with discontinuation of vancomycin. Vancomycin should be continued in patients who are not candidates for β -lactam antibiotic therapy and those with infections due to oxacillin-resistant staphylococci. Pathogen identification and in vitro susceptibility testing can be used to direct treatment in the minority of patients with nonstaphylococcal CIED infections.

There are no clinical trial data to define the optimal duration of antimicrobial therapy for CIED infections, regardless of the extent of infection, or to determine when conversion to an oral agent is appropriate once complete device removal has been achieved. Factors that influence medical decision making include the extent of device infection, the causative organism, the presence and duration of bloodstream infection, and associated complications such as valvular involvement, septic thrombophlebitis, or osteomyelitis (Figure 2A). Blood cultures should be obtained from all patients after device removal. When CIED infection is limited to the pocket site, 7 to 10 days of therapy after device removal is reasonable if the presentation is device erosion without inflammatory changes; otherwise, 10 to 14 days of antimicrobial treatment is recommended. Therapy can be switched to an oral regimen once susceptibility results are known if there is an oral agent available that is active against the pathogen and the infected CIED has been removed.

At least 2 weeks of parenteral therapy is recommended after extraction of an infected device for patients with bloodstream infection. Patients with sustained (>24 hours) positive blood cultures despite CIED removal and appropriate antimicrobial therapy should receive parenteral therapy for at least 4 weeks, even if TEE is negative for valvular vegetations.

It is intuitive that adequate debridement and control of infection at all sites, both at the generator site and metastatic, if present, be achieved before new device placement. The contralateral side is preferred for new device placement, if required.

There are several aspects of CIED removal for which data are needed so that management recommendations can be provided. These include whether the infected pocket site should be closed before new device placement, whether generator-capsule debridement is appropriate, and how to manage patients who have undergone device removal but have a remaining lead remnant.

Patients with bloodstream infection and no localizing evidence of either generator-site infection or lead or endocardial involvement represent a difficult management group. Although bloodstream infection can be a manifestation of CIED infection, it can occur without CIED infection. There are several clinical parameters^{26,75} that may better characterize patients who have CIED infection and *S aureus* bacteremia but no localizing evidence of infection. These include the following: (1) Relapsing bacteremia after a course of appropriate antibiotic therapy; (2) if there is no other identified source for bacteremia; (3) if bacteremia persists more than 24 hours; (4) if the CIED is an ICD; (5) presence of a prosthetic cardiac valve; and (6) bacteremia within 3 months of device placement.

On the basis of findings from 1 investigation,²⁷ CIED infection is unlikely in patients with Gram-negative bacteremia.

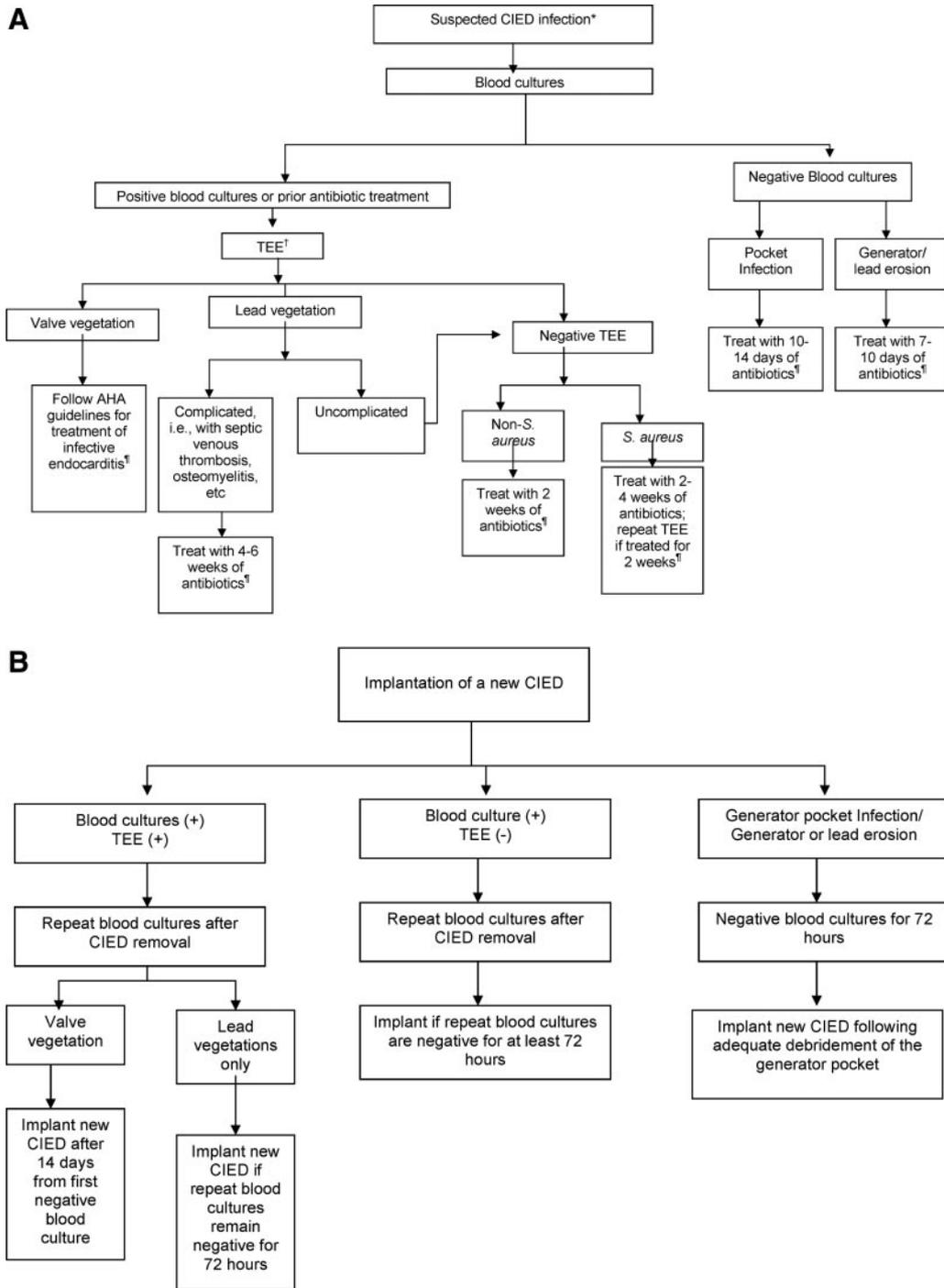


Figure 2. A, Approach to management of adults with CIED infection. AHA indicates American Heart Association. Modified from Sohail et al³⁸ with permission. *A history, physical examination, chest radiograph, electrocardiogram, and device interrogation are standard baseline procedures before CIED removal. †Duration of antibiotics should be counted from the day of device explantation. ‡Treatment can be extended to 4 or more weeks if there are metastatic septic complications (ie, osteomyelitis, organ or deep abscess, etc) or sustained bloodstream infection despite CIED removal. B, Approach to implantation of a new device in patients after removal of an infected CIED. Modified from Sohail et al³⁸ with permission.

mia and no other evidence of device infection; thus, CIED removal is not recommended in this setting. In contrast, patients who have Gram-negative bacteremia that has relapsed despite administration of appropriate antibiotic therapy and with no other defined focus of infection should undergo CIED removal. CIED removal should also be performed in patients with sustained or persistent Gram-negative

bacteremia despite administration of appropriate antibiotic therapy and no other defined source of infection.

The likelihood of CIED infection in patients with bacteremia or fungemia due to organisms other than *S aureus* or Gram-negative bacilli that more commonly cause bloodstream infection (coagulase-negative staphylococci, streptococci, enterococci, and *Candida* species) and no other evi-

dence of CIED infection has received limited attention. Results of 2 relatively small case series^{33,76} suggest that the risk of CIED infection in these patients is low; however, more data are clearly needed in this clinical setting to permit recommendations on whether device removal is warranted.

Recommendations for Antimicrobial Management of CIED Infection

Class I

1. Choice of antimicrobial therapy should be based on the identification and in vitro susceptibility results of the infecting pathogen. (*Level of Evidence: B*)
2. Duration of antimicrobial therapy should be 10 to 14 days after CIED removal for pocket-site infection. (*Level of Evidence: C*)
3. Duration of antimicrobial therapy should be at least 14 days after CIED removal for bloodstream infection. (*Level of Evidence: C*)
4. Duration of antimicrobial therapy should be at least 4 to 6 weeks for complicated infection (ie, endocarditis, septic thrombophlebitis, or osteomyelitis or if bloodstream infection persists despite device removal and appropriate initial antimicrobial therapy. (*Level of Evidence: C*)

Recommendations for Removal of Infected CIED

Class I

1. Complete device and lead removal is recommended for all patients with definite CIED infection, as evidenced by valvular and/or lead endocarditis or sepsis. (*Level of Evidence: A*)
2. Complete device and lead removal is recommended for all patients with CIED pocket infection as evidenced by abscess formation, device erosion, skin adherence, or chronic draining sinus without clinically evident involvement of the transvenous portion of the lead system. (*Level of Evidence: B*)
3. Complete device and lead removal is recommended for all patients with valvular endocarditis without definite involvement of the lead(s) and/or device. (*Level of Evidence: B*)
4. Complete device and lead removal is recommended for patients with occult staphylococcal bacteremia. (*Level of Evidence: B*)

Class IIa

1. Complete device and lead removal is reasonable in patients with persistent occult Gram-negative bacteremia despite appropriate antibiotic therapy. (*Level of Evidence: B*)

Class III

1. CIED removal is not indicated for a superficial or incisional infection without involvement of the device and/or leads. (*Level of Evidence: C*)
2. CIED removal is not indicated for relapsing bloodstream infection due to a source other than a CIED and for which long-term suppressive antimicrobials are required. (*Level of Evidence: C*)

New Device Implantation

It is imperative that there be an assessment of the need for new device placement in each patient with an infected CIED.

One third to one half of patients in some series will not require new CIED placement.³⁸ There are several factors, including reversal of the pathological processes that precipitated the need for CIED implantation, changing clinical circumstances, and lack of appropriate clinical indication initially, that obviate the need for new CIED placement and thus result in avoidance of new device infection.

Removal of infected hardware should not be attempted until a careful assessment of a new implantation strategy has been performed, particularly in patients with pacemakers for complete heart block and resynchronization therapy devices. When implantation of a new device is necessary, it should be performed on the contralateral side if possible to avoid relapsing device infection. If this is not possible, a transvenous lead can be tunneled to a device placed subcutaneously in the abdomen. Implantation is usually postponed to allow for resolution of infection, but patients who are PPM dependent represent a challenge, because they cannot be discharged home with a temporary pacemaker.

Because of complications with passive-fixation leads that have been used in the past for temporary pacing in CIED infection cases, active-fixation leads attached to pacing generators or defibrillators are now being used as a "bridge" until PPM implantation is deemed appropriate. Use of active-fixation leads connected to external devices in stimulation-dependent patients with infection permits earlier mobilization of the patient and has been associated with a reduced risk of pacing-related adverse events, including lead dislocation, resuscitation due to severe bradycardia, and local infection.⁷⁷

The optimal timing of device replacement is unknown. Some have advocated proceeding 24 hours after removal.^{23,38,71,78} Sohail et al³⁸ demonstrated a difference in timing of replacement based on (1) blood culture results (median time of 13 days for bacteremic patients versus 7 days for nonbacteremic patients) and (2) type of pathogen identified (median 7 days for CoNS versus 12 days for *S aureus*). There have been no prospective trial data that examined timing of new device replacement and risk of relapsing infection; however, several investigators recommend waiting for blood cultures to be negative before a new device is placed^{23,38,71} (Figure 2B).

Only 1 medical center has described simultaneous contralateral (side-to-side) replacement of an infected CIED.⁷⁹ A 1-stage exchange was performed in 68 consecutive patients over almost a 14-year period by 1 cardiologist, and two thirds of patients had dual-chamber devices. Clinical presentations included device erosion (41%), cellulitis or abscess (35%), and endocarditis (24%). Fifty-nine patients (87%) were followed up for more than 1 year, and 9 patients were lost to follow-up after 1 to 10 months after 1-stage contralateral device exchange, with no new identified CIED infections. Additional experience with 1-stage contralateral device exchange is needed, however, before it can be recommended for routine use.

There are reports of successful implantations of previously implanted devices from either deceased patients or from the same patient with a prior PPM infection.^{78,80} Mansour and coworkers⁷⁸ described 17 patients with a previously infected PPM who underwent successful implantation (at a new site and

after resterilization) without relapsing infection. The practice of reusing CIEDs after sterilization is not advocated, however.

Recommendations for New CIED Implantation After Removal of an Infected CIED

Class I

1. Each patient should be evaluated carefully to determine whether there is a continued need for a new CIED. (*Level of Evidence: C*)
2. The replacement device implantation should not be ipsilateral to the extraction site. Preferred alternative locations include the contralateral side, the iliac vein, and epicardial implantation. (*Level of Evidence: C*)

Class IIa

1. When positive before extraction, blood cultures should be drawn after device removal and should be negative for at least 72 hours before new device placement is performed. (*Level of Evidence: C*)
2. New transvenous lead placement should be delayed for at least 14 days after CIED system removal when there is evidence of valvular infection. (*Level of Evidence: C*)

Long-Term Suppressive Antimicrobial Therapy

Long-term antimicrobial suppressive therapy is used in selected patients with CIED infections who, for a variety of reasons, are not candidates for device removal either by percutaneous or surgical methods.⁸¹ Often, these patients have a limited life expectancy or refuse device removal. Long-term suppressive therapy can be attempted in these cases if they meet several criteria, which include a stable cardiovascular status, clinical improvement with initial antimicrobial therapy, and clearance of bloodstream infection. Because there are no comparative trials, the optimal choice of antimicrobial therapy and its dosing are undefined. Moreover, treatment options are frequently limited, because many CIED infections are caused by multidrug-resistant pathogens that are acquired in the healthcare or nosocomial environment. Thus, prolonged suppression of infection can be difficult to achieve with oral antimicrobial therapy.

Little is known about CIED infection relapse rates despite use of long-term suppressive therapy. Other factors that are relevant to the use of long-term suppressive therapy include the likelihood for selection of resistant organisms, both for the identified pathogen being suppressed and for normal colonizing strains; safety profile; patient compliance; and financial expense.

Recommendations for Use of Long-Term Suppressive Antimicrobial Therapy

Class IIb

1. Long-term suppressive therapy should be considered for patients who have CIED infection and who are not candidates for complete device removal. (*Level of Evidence: C*)

Class III

1. Long-term suppressive therapy should not be administered to patients who are candidates for infected CIED removal. (*Level of Evidence: C*)

Complications of Device Infection

Complications of CIED infection can be either contiguous to the device or anatomically remote. Contiguous complications include chest wall abscess, septic thrombophlebitis, and right-sided heart endocarditis. More remote complications include skeletal complications, both local (clavicular osteomyelitis and sternoclavicular arthritis) and remote (metastatic osteomyelitis, discitis, and septic arthritis); cardiopulmonary complications (septic pulmonary emboli, mycotic pulmonary artery aneurysm, and left-sided endocarditis with its potential complications); metastatic complications, including soft tissue and organ or muscle abscess formation; and sepsis, with its potential complications.

Outcomes

CIED infection is a serious complication associated with substantial morbidity, mortality, and cost.^{8,28,56,82} Reported mortality rates for these infections range widely and tend to be higher in patients with confirmed device-related endocarditis and in those treated without device removal (Table 2).^{23,24,28,56,83–87} Because of a lack of adequate comparison groups, substantial heterogeneity among studies, and marked differences in populations who do and do not receive device removal, precise estimates of the benefits of device removal are not available.

A risk factor analysis⁸⁸ was conducted that examined clinical and echocardiographic variables that identified patients with CIED infections who were at increased risk of mortality. All-cause mortality at 6 months among 210 patients with CIED infections was 18%. Variables associated with increased mortality risk among this cohort included systemic embolization, moderate to severe tricuspid regurgitation, abnormal right ventricular function, and abnormal renal function. Size and mobility of lead vegetations were not independently associated with mortality.

Prevention

Prophylaxis at CIED Implantation

Prevention of CIED infection can be addressed before, during, and after device implantation. Before device implantation, it is important to ensure that patients do not have clinical signs of infection. A parenterally administered antibiotic is recommended 1 hour before the procedure. Data from a meta-analysis,²² 2 case-control studies that examined purported risk factors of CIED infection,^{20,21} and a large, prospective, randomized, double-blinded, placebo-controlled trial strongly support the administration of antibiotic prophylaxis for CIED implantation.⁸⁹ Most experts continue to advocate a first-generation cephalosporin, such as cefazolin, for use as prophylaxis. Although not generally recommended, some advocate the use of vancomycin instead of cefazolin, particularly in centers where oxacillin resistance among staphylococci is high. If vancomycin is used, then it should be administered 90 to 120 minutes before the procedure. Vancomycin also represents an alternative to a first-generation cephalosporin in patients who are allergic to cephalosporins. In patients who are allergic to both cephalosporins and vancomycin, daptomycin and linezolid represent prophylaxis

Table 2. Published Case Series That Report Outcomes of CIED Infection

Reference	Year	n	Population	Treatment	Follow-Up, y	Outcomes
Arber et al ¹³	1994	44	Pacemaker endocarditis categorized as definite (n=25), probable (n=12), or possible (n=7)	?	?	?
Klug et al ⁵⁴	1997	57	Pacemaker lead endocarditis	Plan for initial device removal and parenteral antibiotic therapy	1.67	7% Predischarge mortality (2 before removal 2 after removal); 26.9% mortality at end of follow-up
O'Nunain et al ⁸⁴	1997	21	ICD infection	Total system removal in 15; partial system removal in 2; no explantation in 4. All received parenteral antibiotics	1.75	No clinical recurrence of infection; 1 sudden death
Molina ⁸⁵	1997	38	Pacemaker infection (n=21) or ICD infection (n=17)	(1) IV antibiotics without device removal (n=12); (2) complete system removal with 2 weeks of parenteral antimicrobials (n=19); (3) complete removal with 6 weeks of parenteral antimicrobials (n=7)	0.75 to 5 y	100% Failure and 17% mortality in those treated conservatively; no deaths or recurrent infections in the groups treated with device removal
Cacoub et al ⁴²	1998	33	Definite pacemaker endocarditis	Lead removal and prolonged subsequent antibiotic therapy	1.83	24% Mortality
Chua et al ³⁷	2000	123	Patients with either pacemaker (n=87) or ICD (n=36) infections	Extraction in 95% with antibiotic therapy (median 28 days)	1.08	8% Mortality, 3% relapse
Baddour ⁸¹	2001	51	Patients with device-related infections not candidates for surgery (from survey of providers)	Long-term suppressive antibiotics (3 mo to 10 y)	Not specified	3 Developed relapsing infection
del Rio et al ⁴⁰	2003	31	Pacemaker or ICD endocarditis	Initial conservative therapy (n=7); surgical removal (n=24)	3.17	Initial conservative therapy: 100% relapse, 1 death; initial surgical therapy: 1 relapse, 3 deaths
Rundstrom et al ⁸⁶	2004	38	Pacemaker endocarditis (44 episodes in 38 patients)	Pacemaker removal in 28 episodes, conservative therapy in 16 episodes	Not specified	64% Infection-free in group with pacemaker removal; 19% infection-free in conservative-therapy group
Sohail et al ³⁷	2007	189	Patients with CDI	Initial surgical removal in 183 (96%); removal after failure of medical therapy in 3 (2%); all received parenteral antimicrobial therapy, most for at least 2 wk	0.48	3.7% In-hospital mortality; of those followed up after discharge, 5% relapse or persistent pocket infection; 95% infection-free at end of follow-up
Sohail et al ⁸⁷	2008	44	Pacemaker or ICD endocarditis (from 2007 series with CDI)	Surgical removal in 43 (98%) with parenteral antimicrobial therapy	0.5	14% In-hospital mortality

options. Antibiotic prophylaxis is also recommended if subsequent invasive manipulation of the CIED is required.

Preoperative antiseptic preparation of the skin of the surgical site should be done. Intraoperatively, compulsive attention to sterile technique is mandatory. If a patient has limited subcutaneous tissue and/or poor nutrition and is at increased risk for erosion, a retropectoral pocket should be considered. In a survey of pediatric patients, 9 (13.8%) of 65 with subcutaneously placed device-pocket transvenous systems developed infection compared with none of the 82 who underwent retropectoral placed systems.⁹⁰

Hematoma within the pocket that complicates CIED placement or invasive manipulation has been identified as a risk factor associated with device placement.¹⁹ Therefore, prevention of hematoma during the procedure is desirable, and several interventions have been used, although there are no data to support their use. This can be achieved by meticulous cautery of bleeding sites and consideration of packing the pocket with antibiotic-soaked sponges to provide tamponade while leads are being placed. The application of topical thrombin may be helpful, particularly in anticoagulated patients. Irrigation of the pocket is useful to remove debris and may reveal persistent

bleeding that could lead to a pocket hematoma. In addition, irrigation with an antimicrobial-containing solution for pocket cleansing has been used. Use of monofilament suture for closure of the subcuticular layer may avoid superficial postoperative cellulitis. A pressure dressing applied for 12 to 24 hours after skin closure and dressing may further decrease the risk of hematoma formation.

In the immediate postoperative period, recent data indicate that low-molecular-weight heparin predisposes to hematoma formation and should be avoided.⁹¹ A hematoma should be evacuated only when there is increased tension on the skin. Needle aspiration should otherwise be avoided because of the risk of introducing skin flora into the pocket and subsequent development of infection.

Routine ambulatory care follow-up after CIED placement to detect early infectious complications has been performed in many centers. Recent data from 1 investigation⁹² failed to demonstrate the utility of early follow-up and advocated that instead, patients should be instructed to call their implanting physician for development of fever or incision findings of inflammation. The writing group believes that both early follow-up in a clinic setting and

thorough patient education should be conducted for early identification of CIED-related infectious complications. Currently, there are no data to support the administration of postoperative antibiotic therapy, and it is not recommended because of the risk of drug adverse events, selection of drug-resistant organisms, and cost.

Recommendations for Antimicrobial Prophylaxis at the Time of CIED Placement

Class I

1. Prophylaxis with an antibiotic that has in vitro activity against staphylococci should be administered. If cefazolin is selected for use, then it should be administered intravenously within 1 hour before incision; if vancomycin is given, then it should be administered intravenously within 2 hours before incision. (*Level of Evidence: A*)

Antibiotic Prophylaxis for Invasive Procedures

Bacterial pathogens commonly gain entrance to the circulation, whether from routine daily activities such as toothbrushing or from invasive procedures.⁹³ There is a general and longstanding focus on secondary antibiotic prophylaxis to prevent hematogenous infections from invasive procedures in patients with a wide variety of medical devices and conditions. However, controversy surrounds this practice because there are few data to show efficacy, and the risk from prophylaxis likely outweighs any benefit. For example, there is concern about the development of antibiotic-resistant bacterial pathogens, the possibility of a fatal allergic reaction, and the costs associated with this practice, which include malpractice litigation and, additional medical and dental office visits.

Since the original American Heart Association recommendations were made more than 50 years ago, there has been a proliferation of purported indications for the use of prophylactic antibiotics for patients thought to be at risk for distant site infection from invasive procedures.^{94–97} There is little, if any, scientific justification for administration of antibiotic prophylaxis for invasive procedures, although there is a wide range of opinions.⁹⁶ A review of the literature from 1950 to 2007 for publications on cardiac electrophysiological device infections reveals more than 140 articles, none of which report hematologic infection from dental, gastrointestinal, genitourinary, dermatologic, or other procedures.

The predominance of staphylococci as pathogens in CIED infections rather than oral flora⁹⁸ suggests that antibiotic prophylaxis for dental procedures is of little or no value.^{1,89,99,100} In the rare event of a device infection due to an oral pathogen, it is most likely to have arisen from a bacteremia from a common daily event such as toothbrushing or chewing food.⁹⁸ Therefore, there is currently no scientific basis for the use of prophylactic antibiotics before routine invasive dental, gastrointestinal, or genitourinary procedures to prevent CIED infection.

Recommendations for Antimicrobial Prophylaxis for Invasive Procedures in Patients With CIEDs

Class III

1. Antimicrobial prophylaxis is not recommended for dental or other invasive procedures not directly related

to device manipulation to prevent CIED infection. (*Level of Evidence: C*)

Emerging Technology

Advances in molecular, gene, and cell therapies make the development of a biological pacemaker, a tissue that could be implanted in the heart, a future possibility.¹⁰¹ As pointed out in a recent report,¹⁰² our total dependence on a biological pacemaker will have to await the demonstration of the safety and long-term efficacy of the biological tissue.

Advancement in the development of gene and cell-transfer therapies to restore myocardial function in a failing heart and to inhibit ventricular arrhythmias^{103,104} could potentially impact the need for ICDs in the future. Technical advances could also impact the risk of infection in cases in which a device, rather than a biological therapy, is required. These include development of a totally subcutaneous ICD and a leadless pacing system.

Pediatric Concerns

Pediatric and young adult patients with congenital heart disease represent a population with unique medical and surgical issues. These include smaller body size, vascular anomalies, congenital heart defects with and without surgical correction or palliation, and arrhythmias due to congenital disease or surgical repair. The decision to place a CIED in 1 of these patients requires long-term planning with the expectation of prolonged survival that will include numerous generator changes and lead replacement due to lead fracture or stress related to somatic growth. In addition, adults with some forms of congenital heart disease that do not allow traditional transvenous access to cardiac chambers will require modified pacemaker/ICD systems. With that in mind, a variety of approaches to implantation of these systems are required. Epicardial implants are frequently preferred or necessary because of a patient's size and growth potential, the presence of intracardiac shunts that allow the possibility of right-to-left shunting, and anatomic or surgical barriers to a transvenous approach. Biventricular pacing often requires epicardial placement of a left ventricular lead because of the small size of the coronary sinus. ICD implants are particularly challenging in a patient who weighs less than 15 kg and usually require novel and nonstandard approaches with nonthoracotomy ICD coil arrays, epicardial patches, or shock leads placed in or adjacent to the pericardial space (Figures 3A and 3B). Another technique that is occasionally used to obtain the advantage of an endocardial lead while preserving the integrity of small veins is to perform a thoracotomy with placement of a lead through an atrial wall via a purse-string suture, with the lead connector extended to an abdominal device.

Klug et al¹⁰⁵ demonstrated that young patients with or without congenital defects have a greater prevalence of PPM lead infections than older (>40 years of age) individuals. They speculated that several factors could be operative in causing an increased infection rate among younger patients, including a higher rate of reinterventions at the generator site, placement of a relatively larger device based on a higher ratio between the volume of the generator and body size, and the likelihood of local trauma to the generator site in younger,

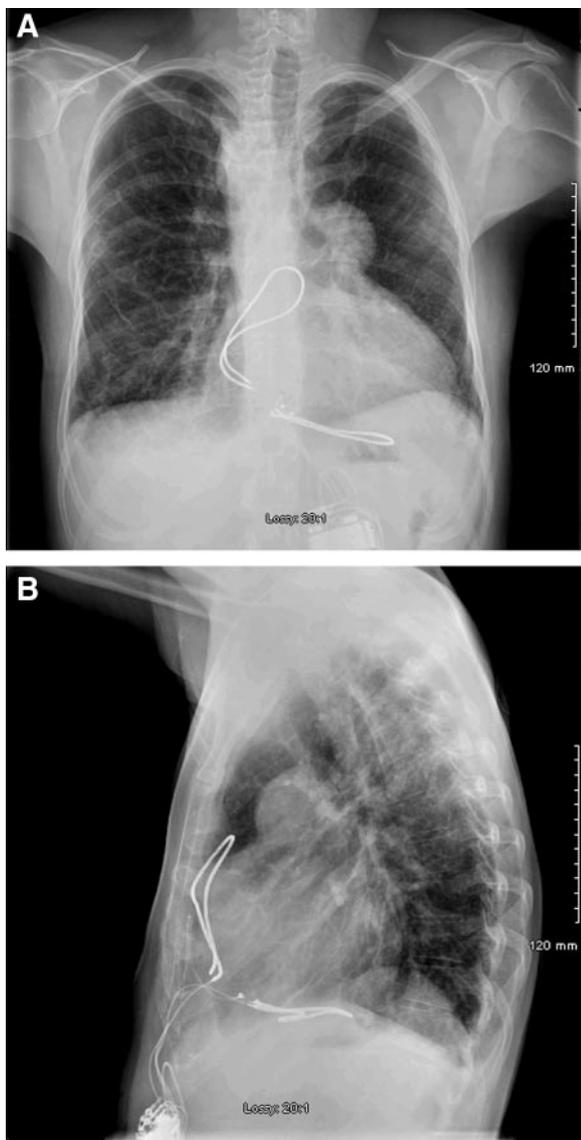


Figure 3. A and B, Nonthoracotomy ICD system placed in a 39-year-old man with inoperable pulmonary atresia with ventricular septal defect who had ventricular tachycardia with syncope. Note the retrosternal and intrapericardial coil arrays, the epicardial pace/sense leads, and the abdominal ICD.

more active individuals. A number of studies^{86,106–114} of infected PPMs in the pediatric population have demonstrated that congenital heart disease is present in a large percentage (44% to 83%) of young patients, with overall infection rates that ranged between 1% and 8%. Patients with endocardial and epicardial leads composed 70% and 30%, respectively, of reported cases. With the exception of 1 study, there were no differences in rates of epicardial and transvenous pacemaker infections. In the largest review of pediatric pacemaker infections, Cohen et al⁹⁰ analyzed 385 pacemaker procedures over a 20-year period and identified 30 infections (7.8%). Of these infections, 19 (4.9%) were superficial and were treated successfully with antibiotics only, whereas 9 (2.3%) were deep pocket infections that required removal of the generator and leads. By multivariable analysis, the only risk factors for infection were the presence of Down syndrome and reinter-

vention for revision of the pacing system. Although the numbers were small, the authors suggested that a subpectoral placement of a device yielded a reduced infection risk compared with a prepectoral location.

No study has compared rates of pacemaker and ICD infections in a pediatric population, although several investigations have examined pediatric and congenital heart disease patients after ICD implantation. Silka et al¹¹⁵ described 125 pediatric patients with 4 ICD wound infections and 2 pocket erosions. A recent 4-center survey¹¹⁵ reported 7 infections (1.5%) and 3 erosions in the first 30 days after device implantation and 13 (2.9%) chronic infections among 443 patients. One study¹¹⁶ compared ICD complications between adults and pediatric patients (<21 years of age) at the same institution. The infection rate in the pediatric group was 18% (2 of 11) compared with 1.2% (4 of 309) among the adults ($P=0.003$). There was 1 epicardial and 1 transvenous system infection in the pediatric group. There was no specific information provided in the report to indicate how many of the systems in adults were epicardial.¹¹⁷ The authors speculated that pediatric patients may have had a higher infection rate due to returning to activity sooner and less than optimal wound care.

The same principles of diagnosis and management of device infections in the general population apply to pediatric and congenital heart disease patients; however, there are some additional considerations. The excellent imaging provided by standard transthoracic echocardiography may supplant the need for a transesophageal study in some pediatric patients. Because of the high prevalence of nontransvenous systems and the unique configurations required to implant CIEDs in some pediatric patients and individuals with congenital heart disease, there must be a thorough evaluation of the need to remove all components of a device. This includes a review of a patient's ongoing need for the device; if the device therapy is no longer required, it should be removed. Epicardial and other nontransvenous systems in use can necessitate extensive surgical procedures for complete device removal, including a full or limited sternotomy or thoracotomy. Therefore, the suspicion of device-component infection must be balanced against the risk of surgical removal. An experienced team of physicians with expertise in cardiac electrophysiology, infectious diseases, pediatrics and congenital heart disease, and cardiothoracic surgery is pivotal in CIED infection management.

Ethical Considerations

Consideration for withdrawal of CIED support in terminally ill patients is common and will become more frequent as the age and accompanying comorbid conditions increase among recipients of these devices. Although a thorough review of related ethical considerations is beyond the scope of the present statement, the topic is important to highlight, because the occurrence of a device infection has prompted some patients to refuse implantation of a new device after removal of an infected device. Many of the same ethical concerns that apply to deactivation of a noninfected implanted CIED apply to removal of an infected device without new CIED placement. The American College of Cardiology/American Heart Association/Heart Rhythm Society 2008 guidelines³ for device-based therapy of cardiac rhythm abnormalities outlines specific recommendations regarding terminal

Table 3. Summary of Recommendations

Recommendation	Class and Level of Evidence
A. Recommendations for diagnosis of CIED infection and associated complications	
1. All patients should have at least 2 sets of blood cultures drawn at the initial evaluation before prompt initiation of antimicrobial therapy for CIED infection.	IC
2. Generator-pocket tissue Gram stain and culture and lead-tip culture should be obtained when the CIED is explanted.	IC
3. Patients with suspected CIED infection who either have positive blood cultures or have negative blood cultures but have had recent antimicrobial therapy before blood cultures were obtained should undergo TEE for CIED infection or valvular endocarditis.	IC
4. All adults suspected of having CIED-related endocarditis should undergo TEE to evaluate the left-sided heart valves, even if transthoracic views have demonstrated lead-adherent masses. In pediatric patients with good views, TTE may be sufficient.	IB
5. Patients should seek evaluation for CIED infection by cardiologists or infectious disease specialists if they develop fever or bloodstream infection for which there is no initial explanation.	IIaC
6. Percutaneous aspiration of the generator pocket should not be performed as part of the diagnostic evaluation of CIED infection.	IIIC
B. Recommendations for antimicrobial management of CIED infection	
1. Choice of antimicrobial therapy should be based on the identification and in vitro susceptibility results of the infecting pathogen.	IB
2. Duration of antimicrobial therapy should be 10 to 14 days after CIED removal for pocket-site infection.	1C
3. Duration of antimicrobial therapy should be at least 14 days after CIED removal for bloodstream infection.	1C
4. Duration of antimicrobial therapy should be at least 4 to 6 weeks for complicated infection (ie, endocarditis, septic thrombophlebitis, or osteomyelitis or if bloodstream infection persists despite device removal and appropriate initial antimicrobial therapy).	1C
C. Recommendations for removal of infected CIED	
1. Complete device and lead removal is recommended for all patients with definite CIED infection, as evidenced by valvular and/or lead endocarditis or sepsis.	IA
2. Complete device and lead removal is recommended for all patients with CIED pocket infection, as evidenced by abscess formation, device erosion, skin adherence, or chronic draining sinus without clinically evident involvement of the transvenous portion of the lead system.	1B
3. Complete device and lead removal is recommended for all patients with valvular endocarditis without definite involvement of the lead(s) and/or device.	1B
4. Complete device and lead removal is recommended for patients with occult staphylococcal bacteremia.	1B
5. Complete device and lead removal is reasonable in patients with persistent occult Gram-negative bacteremia despite appropriate antibiotic therapy.	IIaB
6. CIED removal is not indicated for a superficial or incisional infection without involvement of the device and/or leads.	IIIC
7. CIED removal is not indicated for relapsing bloodstream infection due to a source other than a CIED and for which long-term suppressive antimicrobials are required.	IIIC
D. Recommendations for new CIED implantation after removal of an infected CIED	
1. Each patient should be evaluated carefully to determine whether there is a continued need for a new CIED.	IC
2. The replacement device implantation should not be ipsilateral to the extraction site. Preferred alternative locations include the contralateral side, the iliac vein, and epicardial implantation.	1C
3. When positive before extraction, blood cultures should be drawn after device removal and should be negative for at least 72 hours before new device placement is performed.	IIaC
4. New transvenous lead placement should be delayed for at least 14 days after CIED system removal when there is evidence of valvular infection.	IIaC
E. Recommendations for use of long-term suppressive antimicrobial therapy	
1. Long-term suppressive therapy should be considered for patients who have CIED infection and who are not candidates for complete device removal.	IIbC
2. Long-term suppressive therapy should not be administered to patients who are candidates for infected CIED removal.	IIIC

(Continued)

Table 3. Continued

Recommendation	Class and Level of Evidence
F. Recommendations for antimicrobial prophylaxis at the time of CIED placement	
1. Prophylaxis with an antibiotic that has in vitro activity against staphylococci should be administered. If cefazolin is selected for use, then it should be administered intravenously within 1 hour before incision; if vancomycin is given, then it should be administered intravenously within 2 hours before incision.	IA
G. Recommendations for antimicrobial prophylaxis for invasive procedures in patients with CIEDs	
1. Antimicrobial prophylaxis is not recommended for dental or other invasive procedures not directly related to device manipulation to prevent CIED infection.	IIIC
H. Recommendations to avoid microbiological studies in cases of CIED removal for noninfectious reasons	
1. Routine microbiological studies should not be conducted on CIEDs that have been removed for noninfectious reasons.	IIIB

TTE indicates transthoracic echocardiography.

care of dying patients and device deactivation. In addition, there will be a thorough addressing of the ethics of CIED use in a pending statement on CIED extraction from the Heart Rhythm Society.

Removal of Noninfected CIEDs

Avoidance of Microbiological Studies

Noninfectious device-related complications or device malfunction may occur that requires CIED removal with new device placement. At the time of device removal, specimens from the generator pocket or the explanted device should not be routinely sent for microbiological studies unless there are intraoperative findings to suggest concurrent infection. As evidenced in a previous investigation,⁶⁹ intraoperative culture specimens frequently yield bacteria, although there is no other evidence of infection. In these cases, it is presumed that contamination during device explantation and processing of specimens likely account for the majority of positive cultures. In these cases, no antimicrobial therapy has been administered, and the rate of subsequent device infection has been no greater than expected. Thus, cultures should not be obtained routinely, because if positive, they could be misinterpreted as being clinically significant and lead to the inappropriate administration of antimicrobials, or worse, removal of the newly implanted device.

Recommendations to Avoid Microbiological Studies in Cases of CIED Removal for Noninfectious Reasons

Class III

1. Routine microbiological studies should not be conducted on CIEDs that have been removed for noninfectious reasons. (*Level of Evidence: B*)

Areas in Need of Further Research

Tremendous gains in our knowledge of CIED infections have occurred over the past 5 years. Because of the increasing rate of these infections among an increasing pool of device recipients, it is imperative that aggressive investigation of all aspects of device infection be conducted. The following topics represent areas that the writing group identified as critical for further study:

1. Determine the safety of 1-stage contralateral device replacement compared with delayed device replacement as a management scheme.

2. Define a scoring system that distinguishes patients with *S aureus* bacteremia and no other evidence of device infection who prove to have CIED infection from those who do not, so that unnecessary device removal can be avoided.
3. Develop CIEDs that are less prone to infection.
4. Develop adjunctive therapies that eliminate biofilm-laden microorganisms.
5. Determine whether there is a “floor” of vegetation size, among other characteristics, that reliably predicts the occurrence of clinically significant pulmonary embolism with percutaneous extraction of an infected lead.
6. Define more clearly the circumstances in which vancomycin should be used as primary prophylaxis for CIED implantation.
7. Identify risk factors and characterize outcomes of CIED infections in large populations that are representative of those treated in clinical practice.
8. Develop a scoring system to assess the risk of serious complications associated with percutaneous removal that will identify a subset of patients for whom median sternotomy for CIED removal is recommended.
9. Assess implantation strategies in infants and children for CIED with respect to both leads and generators that will reduce both short- and long-term infection rates.
10. Develop gene and cell therapies to obviate the need for CIED devices.
11. Define the current financial cost of CIED infection in the United States.
12. Determine whether generator capsule excision and pocket closure before new device placement are beneficial in reducing the likelihood of new CIED infection.
13. Determine the risk of CIED infection among patients with bloodstream infection due to coagulase-negative staphylococci, streptococci, enterococci, and *Candida* species and no other evidence of device infection.

Summary of Recommendations

This document has addressed critical aspects of CIED infections. In particular, management strategies have been presented, and a summary of recommendations is outlined in Table 3.

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Writing Group Disclosures

Writing Group Member	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
Larry M. Baddour	Mayo Clinic	None	None	None	None	None	Cardinal Health*; Talecris Biotherapeutics*	None
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Ann F. Bolger	UCSF	None	None	None	None	None	None	None
Andrew E. Epstein	University of Pennsylvania	Biotronik*; Boston Scientific*; Medtronic*; St Jude Medical†	None	Biotronik*; Boston Scientific*; Medtronic*; St Jude Medical†	Yes, in cases involving ICDs*	None	None	None
Christopher C. Erickson	University of Nebraska	St. Jude Medical†	None	Received honorarium from Medtronic to give a lecture in 2007*	None	None	None	None
N.A. Mark Estes III	Tufts-New England Medical Center	None	None	Boston Scientific*; Medtronic*; St. Jude Medical*	None	None	None	None
Michael Gewitz	New York Medical College	None	None	None	None	None	NDTI*; Jefferson University*	None
Bradley P. Knight	University of Chicago	Two of my electrophysiology fellows are supported by industry. One grant from Boston Scientific† and 1 from St. Jude†	None	Medtronic, for speaking at fellow educational courses, often exceeds \$10 000 in 1 year†	None	None	None	None
Matthew E. Levison	Drexel University	None	None	None	None	None	None	Editor, Infectious Disease Section, <i>Merck Manual</i>
Peter B. Lockhart	Carolinas Medical Center	None	None	None	None	None	None	None
Frederick A. Masoudi	Denver Health Medical Center	AHRQ†; NHLBI†	None	None	None	None	None	American College of Cardiology (contract)*
Jane W. Newburger	Harvard	None	None	None	None	None	None	None
Eric J. Okum	Rush University, Chicago	None	None	Two speaking engagements for training staff of Sanofi-Aventis in the role of Lantus insulin use in cardiac surgery patients (total \$1000)*	None	None	None	None
Eleanor B. Schron	Was with NIH but retired	None	None	None	None	None	InCirculation.net Advisory Board, an international educational Web site for dissemination of findings from studies in cardiovascular disease. I have provided advice concerning groups of nurses who may be interested in the Web site and identified nurse researchers with expertise in cardiovascular nursing. Payment zero to no more than \$1000 in a particular year*	None
Kathryn A. Taubert	American Heart Association	None	None	None	None	None	None	None
Walter R. Wilson	Mayo Clinic	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (1) the person receives \$10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (2) the person owns 5% or more of the voting stock or share of the entity, or owns \$10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

*Modest.

†Significant.

Reviewer Disclosures

Reviewer	Employment	Research Grant	Other Research Support	Speakers' Bureau/Honoraria	Expert Witness	Ownership Interest	Consultant/Advisory Board	Other
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Anne Dubin	Stanford University	None	None	None	None	None	None	None
Loren Hiratzka	Bethesda North Hospital	None	None	None	None	None	None	None
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*Modest.

†Significant.

References

- Baddour LM, Bettmann MA, Bolger AF, Epstein AE, Ferrieri P, Gerber MA, Gewitz MH, Jacobs AK, Levison ME, Newburger JW, Pallasch TJ, Wilson WR, Baltimore RS, Falace DA, Shulman ST, Tani LY, Taubert KA. Nonvalvular cardiovascular device-related infections. *Circulation*. 2003;108:2015–2031.
- Hayes DL, Furman S. Cardiac pacing: how it started, where we are, where we are going. *Pacing Clin Electrophysiol*. 2004;27:693–704.
- Epstein AE, DiMarco JP, Ellenbogen KA, Estes NA III, Freedman RA, Gettes LS, Gillinov AM, Gregoratos G, Hammill SC, Hayes DL, Hlatky MA, Newby LK, Page RL, Schoenfeld MH, Silka MJ, Stevenson LW, Sweeney MO, Smith SC Jr, Jacobs AK, Adams CD, Anderson JL, Buller CE, Creager MA, Ettinger SM, Faxon DP, Halperin JL, Hiratzka LF, Hunt SA, Krumholz HM, Kushner FG, Lytle BW, Nishimura RA, Ornato JP, Page RL, Riegel B, Tarkington LG, Yancy CW; American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices); American Association for Thoracic Surgery; Society of Thoracic Surgeons. ACC/AHA/HRS 2008 guidelines for device-based therapy of cardiac rhythm abnormalities: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the ACC/AHA/NASPE 2002 Guideline Update for Implantation of Cardiac Pacemakers and Antiarrhythmia Devices): developed in collaboration with the American Association for Thoracic Surgery and Society of Thoracic Surgeons [published correction appears in *Circulation*. 2009;120:e34–e35]. *Circulation*. 2008;117:e350–e408.
- Zhan C, Baine WB, Sedrakyan A, Steiner C. Cardiac device implantation in the United States from 1997 through 2004: a population-based analysis. *J Gen Intern Med*. 2007;23(suppl 1):13–19.
- Uslan DZ, Tleyjeh IM, Baddour LM, Friedman PA, Jenkins SM, St Sauver JL, Hayes DL. Temporal trends in permanent pacemaker implantation: a population-based study. *Am Heart J*. 2008;155:896–903.
- Lin G, Meverden RA, Hodge DO, Uslan DZ, Hayes DL, Brady PA. Age and gender trends in implantable cardioverter defibrillator utilization: a population based study. *J Interv Card Electrophysiol*. 2008;22:65–70.
- Mond HG, Irwin M, Morillo C, Ector H. The world survey of cardiac pacing and cardioverter defibrillators: calendar year 2001. *Pacing Clin Electrophysiol*. 2004;27:955–964.
- Voigt A, Shalaby A, Saba S. Rising rates of cardiac rhythm management device infections in the United States: 1996 through 2003. *J Am Coll Cardiol*. 2006;48:590–591.
- Schwartz IS, Pervez N. Bacterial endocarditis associated with a permanent transvenous cardiac pacemaker. *JAMA*. 1971;218:736–737.
- Corman LC, Levison ME. Sustained bacteremia and transvenous cardiac pacemakers. *JAMA*. 1975;233:264–266.
- Conklin EF, Giannelli S Jr, Nealon TF Jr. Four hundred consecutive patients with permanent transvenous pacemakers. *J Thorac Cardiovasc Surg*. 1975;69:1–7.
- Bluhm G. Pacemaker infections: a clinical study with special reference to prophylactic use of some isoxazolyl penicillins. *Acta Med Scand Suppl*. 1985;699:1–62.
- Arber N, Pras E, Copperman Y, Schapiro JM, Meiner V, Lossos IS, Militianu A, Hassin D, Pras E, Shai A, Moshkowitz M, Sidi Y. Pacemaker endocarditis: report of 44 cases and review of the literature. *Medicine (Baltimore)*. 1994;73:299–305.
- Mirowski M, Reid PR, Mower MM, Watkins L, Gott VL, Schauble JF, Langer A, Heilman MS, Kolenik SA, Fischell RE, Weisfeldt ML. Termination of malignant ventricular arrhythmias with an implanted automatic defibrillator in human beings. *N Engl J Med*. 1980;303:322–324.
- Mela T, McGovern BA, Garan H, Vlahakes GJ, Torchiana DF, Ruskin J, Galvin JM. Long-term infection rates associated with pectoral versus abdominal approach to cardioverter-defibrillator implants. *Am J Cardiol*. 2001;88:750–753.
- Cabell CH, Heidenreich PA, Chu VH, Moore CM, Stryjewski ME, Corey GR, Fowler VG Jr. Increasing rates of cardiac device infections among Medicare beneficiaries: 1990–1999. *Am Heart J*. 2004;147:582–586.
- Uslan DZ, Sohail MR, St Sauver JL, Friedman PA, Hayes DL, Stoner SM, Wilson WR, Steckelberg JM, Baddour LM. Permanent pacemaker and implantable cardioverter-defibrillator infection: a population-based study. *Arch Intern Med*. 2007;167:669–675.
- Bloom H, Heeke B, Leon A, Mera F, Delurgio D, Beshai J, Langberg J. Renal insufficiency and the risk of infection from pacemaker or defibrillator surgery. *Pacing Clin Electrophysiol*. 2006;29:142–145.
- Lekkerkerker JC, van Nieuwkoop C, Trines SA, van der Bom JG, Bernards A, van de Velde ET, Bootsma M, Zeppenfeld K, Jukema JW, Borleffs JW, Schalij MJ, van Erven L. Risk factors and time delay

- associated with cardiac device infections: Leiden Device Registry. *Heart*. 2009;95:715–720.
20. Sohail MR, Uslan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR, Steckelberg JM, Stoner SM, Baddour LM. Risk factor analysis of permanent pacemaker infection. *Clin Infect Dis*. 2007;45:166–173.
 21. Klug D, Balde M, Pavin D, Hidden-Lucet F, Clementy J, Sadoul N, Rey JL, Lande G, Lazarus A, Victor J, Barnay C, Grandbastien B, Kacet S; PEOPLE Study Group. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. *Circulation*. 2007;116:1349–1355.
 22. Da Costa A, Kirkorian G, Cucherat M, Delahaye F, Chevalier P, Cerisier A, Isaaz K, Touboul P. Antibiotic prophylaxis for permanent pacemaker implantation: a meta-analysis. *Circulation*. 1998;97:1796–1801.
 23. Trappe HJ, Pfitzner P, Klein H, Wenzlaff P. Infections after cardioverter-defibrillator implantation: observations in 335 patients over 10 years. *Br Heart J*. 1995;73:20–24.
 24. Lai KK, Fontecchio SA. Infections associated with implantable cardioverter defibrillators placed transvenously and via thoracotomies: epidemiology, infection control, and management. *Clin Infect Dis*. 1998;27:265–269.
 25. Al-Khatib SM, Lucas FL, Jollis JG, Malenka DJ, Wennberg DE. The relation between patients' outcomes and the volume of cardioverter-defibrillator implantation procedures performed by physicians treating Medicare beneficiaries [published correction appears in *J Am Coll Cardiol*. 2005;46:1964]. *J Am Coll Cardiol*. 2005;46:1536–1540.
 26. Chamis AL, Peterson GE, Cabell CH, Corey GR, Sorrentino RA, Greenfield RA, Ryan T, Reller LB, Fowler VG Jr. *Staphylococcus aureus* bacteremia in patients with permanent pacemakers or implantable cardioverter-defibrillators. *Circulation*. 2001;104:1029–1033.
 27. Uslan DZ, Sohail MR, Friedman PA, Hayes DL, Wilson WR, Steckelberg JM, Baddour LM. Frequency of permanent pacemaker or implantable cardioverter-defibrillator infection in patients with gram-negative bacteremia. *Clin Infect Dis*. 2006;43:731–736.
 28. Johansen JB, Nielsen JC, Arnsbo P, Moller M, Pedersen AK, Mortensen PT. Higher incidence of pacemaker infection after replacement than after first implantation: experiences from 36,076 consecutive patients. *Heart Rhythm*. 2006;3(suppl 1):S102–S103.
 29. Gould PA, Krahn AD; Canadian Heart Rhythm Society Working Group on Device Advisories. Complications associated with implantable cardioverter-defibrillator replacement in response to device advisories. *JAMA*. 2006;295:1907–1911.
 30. Kapa S, Hyberger L, Rea RF, Hayes DL. Complication risk with pulse generator change: implications when reacting to a device advisory or recall. *Pacing Clin Electrophysiol*. 2007;30:730–733.
 31. Darouiche R. Treatment of infections associated with surgical implants. *N Engl J Med*. 2004;350:1422–1429.
 32. Chu VH, Crosslin DR, Friedman JY, Reed SD, Cabell CH, Griffiths RI, Masselink LE, Kaye KS, Corey GR, Reller LB, Stryjewski ME, Schulman KA, Fowler VG Jr. *Staphylococcus aureus* bacteremia in patients with prosthetic devices: costs and outcomes. *Am J Med*. 2005;118:1416.e19–1416.e24.
 33. Camus C, Lepout C, Raffi F, Michelet C, Cartier F, Vilde JL. Sustained bacteremia in patients with a permanent endocardial pacemaker: assessment of wire removal. *Clin Infect Dis*. 1993;17:46–55.
 34. Klug D, Lacroix D, Savoye C, Goullard L, Grandmougin D, Hennequin JL, Kacet S, Lekieffre J. Systemic infection related to endocarditis on pacemaker leads: clinical presentation and management. *Circulation*. 1997;95:2098–2107.
 35. Da Costa A, Lelièvre H, Kirkorian G, Célard M, Chevalier P, Vandenesch F, Etienne J, Touboul P. Role of the preaxillary flora in pacemaker infections: a prospective study. *Circulation*. 1998;97:1791–1795.
 36. Fu EY, Shepard RK. Permanent pacemaker infections. *Card Electrophysiol Rev*. 1999;3:39–41.
 37. Chua JD, Wilkoff BL, Lee I, Juratli N, Longworth DL, Gordon SM. Diagnosis and management of infections involving implantable electrophysiologic cardiac devices. *Ann Intern Med*. 2000;133:604–608.
 38. Sohail MR, Uslan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR, Steckelberg JM, Stoner S, Baddour LM. Management and outcome of permanent and implantable cardioverter-defibrillator infections. *J Am Coll Cardiol*. 2007;49:1851–1859.
 39. Villamil Cajoto I, Rodríguez Framil M, Van den Eynde Collado A, José Villacián Vicedo M, Canedo Romero C. Permanent transvenous pacemaker infections: an analysis of 59 cases. *Eur J Intern Med*. 2007;18:484–488.
 40. del Rio A, Anguera I, Miró JM, Mont L, Fowler VG Jr, Azqueta M, Mestres CA; Hospital Clinic Endocarditis Study Group. Surgical treatment of pacemaker and defibrillator lead endocarditis: the impact of electrode lead extraction on outcome. *Chest*. 2003;124:1451–1459.
 41. Kloos WE, Bannermann TL. Update on the clinical significance of coagulase-negative staphylococci. *Clin Microbiol Rev*. 1994;7:117–140.
 42. Cacoub P, Leprince P, Nataf P, Hausfater P, Dorent R, Wechsler B, Bors V, Pavie A, Piette JC, Gandjbakhch I. Pacemaker infective endocarditis. *Am J Cardiol*. 1998;82:480–484.
 43. Chacko ST, Chandy ST, Abraham OC, Swaminathan S, Varghese GM, Priscilla R, Mathai. Pacemaker endocarditis caused by *Pseudomonas aeruginosa* treated successfully. *JAPI*. 2003;51:1021–1022.
 44. Kouvousis NM, Lazaros GA, Christoforatu EG, Deftereos SG, Milona-Petropoulou DE, Lelekis MG, Zacharoulis AA. *Acremonium* species pacemaker site infection. *Hellenic J Cardiol*. 2003;44:83–87.
 45. Amin M, Gross J, Andrews C, Furman S. Pacemaker infection with *Mycobacterium avium* complex. *Pacing Clin Electrophysiol*. 1991;14:152–154.
 46. Giannella M, Valerio M, Franco J, Marin M, Bouza E, Muñoz P. Pacemaker infection due to *Mycobacterium fortuitum*: the role of universal 16S rRNA gene PCR and sequencing. *Diagn Microbiol Infect Dis*. 2007;57:337–339.
 47. Kernodle DS, Barg NL, Kaiser AB. Low-level colonization of hospitalized patients with methicillin-resistant coagulase-negative staphylococci and emergence of the organisms during surgical antimicrobial prophylaxis. *Antimicrob Agents Chemother*. 1988;32:202–208.
 48. Archer GL, Climo MW. Antimicrobial susceptibility of coagulase-negative staphylococci. *Antimicrob Agents Chemother*. 1994;38:2231–2237.
 49. Abraham J, Mansour C, Veledar E, Khan B, Lerakis S. *Staphylococcus aureus* bacteremia and endocarditis: the Grady Memorial Hospital experience with methicillin-sensitive *S aureus* and methicillin-resistant *S aureus* bacteremia. *Am Heart J*. 2004;147:536–539.
 50. Vuong C, Otto M. *Staphylococcus epidermidis* infections. *Microbes Infect*. 2002;4:481–489.
 51. Darouiche RO. Device-associated infections: a macroproblem that starts with microadherence. *Clin Infect Dis*. 2001;33:1567–1572.
 52. Phaller MA, Herwaldt LA. Laboratory, clinical, and epidemiological aspects of coagulase-negative staphylococci. *Clin Microbiol Rev*. 1988;1:281–299.
 53. Veenstra GJ, Cremers FF, van Dijk H, Fleer A. Ultrastructural organization and regulation of a biomaterial adhesion of *Staphylococcus epidermidis*. *J Bacteriol*. 1996;178:537–541.
 54. Kojima Y, Tojo M, Goldmann DA, Tosteson TD, Pier GB. Antibody to the capsular polysaccharide/adhesin protects rabbits against catheter-related bacteremia due to coagulase-negative staphylococci. *J Infect Dis*. 1990;162:435–441.
 55. Takeda S, Pier GB, Kojima Y, Tojo M, Muller E, Tosteson T, Goldmann DA. Protection against endocarditis due to *Staphylococcus epidermidis* by immunization with capsular polysaccharide/adhesin. *Circulation*. 1991;84:2539–2546.
 56. Wilkinson BJ. Biology. In: *The Staphylococci in Human Disease*. Crossley KB, Archer GL, eds. New York, NY: Churchill Livingstone; 1997.
 57. Francois P, Vaudaux P, Lew PD. Role of plasma and extracellular matrix proteins in the pathophysiology of foreign body infections. *Ann Vasc Surg*. 1998;12:34–40.
 58. Vaudaux P, François P, Proctor RA, McDevitt D, Foster TJ, Albrecht RM, Lew DP, Wabers H, Cooper SL. Use of adhesion-defective mutants of *Staphylococcus aureus* to define the role of specific plasma proteins in promoting bacterial adhesion to canine arteriovenous shunts [published correction appears in *Infect Immun*. 1995;63:3239]. *Infect Immun*. 1995;63:585–590.
 59. Heilmann C, Schweitzer O, Gerke C, Vanittanakom N, Mack D, Götz F. Molecular basis of intercellular adhesion in the biofilm-forming *Staphylococcus epidermidis*. *Mol Microbiol*. 1996;20:1083–1091.
 60. Bayston R, Penny SR. Excessive production of mucoid substance in staphylococcus SIIA: a possible factor in colonisation of Holter shunts. *Dev Med Child Neurol Suppl*. 1972;27:25–28.
 61. Baddour LM, Barker LP, Christensen GS, Parisi JT, Simson WA. Phenotypic variation of *Staphylococcus epidermidis* in infection of transvenous endocardial pacemaker electrodes. *J Clin Microbiol*. 1990;28:676–679.

62. Seifert H, Wisplinghoff H, Schnabel P, von Eiff C. Small colony variants of *Staphylococcus aureus* and pacemaker-related infection. *Emerg Infect Dis*. 2003;9:1316–1318.
63. Seifert H, Oltmanns D, Becker K, Wisplinghoff H, von Eiff C. *Staphylococcus lugdunensis* pacemaker-related infection. *Emerg Infect Dis*. 2005;11:1283–1286.
64. Boelens JJ, Dankert J, Murk JL, Weening JJ, van der Poll T, Dingemans KP, Koole L, Laman JD, Zaat SA. Biomaterial-associated persistence of *Staphylococcus epidermidis* in pericatheter macrophages. *J Infect Dis*. 2000;181:1337–1349.
65. von Eiff C, Heilmann C, Proctor RA, Woltz C, Peters G, Götz F. A site-directed *Staphylococcus aureus hemB* mutant is a small colony variant which persists intracellularly. *J Bacteriol*. 1997;179:4706–4712.
66. Balwit JM, van Langevelde P, Vann JM, Proctor RA. Gentamicin-resistant menadione and hemin auxotrophic *Staphylococcus aureus* persist within cultured endothelial cells. *J Infect Dis*. 1994;170:1033–1037.
67. Fowler VG Jr, Li J, Corey GR, Boley J, Marr KA, Gopal AK, Kong LK, Gottlieb G, Donovan CL, Sexton DJ, Ryan T. Role of echocardiography in evaluation of patients with *Staphylococcus aureus* bacteremia: experience in 103 patients. *J Am Coll Cardiol*. 1997;30:1072–1078.
68. Lo R, D'Anca M, Cohen T, Kerwin T. Incidence and prognosis of pacemaker lead-associated masses: a study of 1,569 transepophageal echocardiograms. *J Invasive Cardiol*. 2006;18:599–601.
69. Dy Chua J, Abdul-Karim A, Mawhorter S, Procop GW, Tchou P, Niebauer M, Saliba W, Schweikert R, Wilkoff BL. The role of swab and tissue culture in the diagnosis of implantable cardiac device infection. *Pacing Clin Electrophysiol*. 2005;28:1276–1281.
70. Love CJ, Wilkoff BL, Byrd CL, Belott PH, Brinker JA, Fearnot NE, Friedman RA, Furman S, Goode LB, Hayes DL, Kawanishi DT, Parsonnet V, Reiser C, Van Zandt HJ. Recommendations for extraction of chronically implanted transvenous pacing and defibrillator leads: indications, facilities, training. *Pacing Clin Electrophysiol*. 2000;23:544–551.
71. Gaynor SL, Zierer A, Lawton JS, Gleva MJ, Damiano RJ, Moon MR. Laser assistance for extraction of chronically implanted endocardial leads: infectious versus noninfectious indications. *Pacing Clin Electrophysiol*. 2006;29:1352–1358.
72. Field ME, Jones SO, Epstein LM. How to select patients for lead extraction. *Heart Rhythm*. 2007;4:978–985.
73. Jones SO IV, Eckart RE, Albert CM, Epstein LM. Large, single-center, single-operator experience with transvenous lead extraction: outcomes and changing indications. *Heart Rhythm*. 2008;5:520–525.
74. Smith MC, Love CJ. Extraction of transvenous pacing and ICD leads. *Pacing Clin Electrophysiol*. 2008;31:736–752.
75. Usilan DZ, Dowsley TF, Sohail MR, Hayes DL, Friedman PA, Wilson WR, Steckelberg JM, Baddour LM. Cardiovascular implantable electronic device infection in patients with *Staphylococcus aureus* bacteremia. *Pacing Clin Electrophysiol*. September 30, 2009. doi: 10.1111/j.1540-8159.2009.02565.x. Accessed October 21, 2009.
76. Sopena B, Crespo M, Beiras X, del Campo EG, Rivera A, Gimena B, Maure B, Martínez-Vásquez C. Individualized management of bacteraemia in patients with a permanent endocardial pacemaker. *Clin Microbiol Infect*. Published online before print May 16, 2009. doi: 10.1111/j.1469-0691.2009.02787.x. Available at: <http://www3.interscience.wiley.com/journal/122387704/abstract?CRETRY=1&SRETRY=0>. Accessed October 21, 2009.
77. Braun MU, Rauwolf T, Bock M, Kappert U, Boscheri A, Schnabel A, Strasser RH. Percutaneous lead implantation connected to an external device in stimulation-dependent patients with systemic infection: a prospective and controlled study. *Pacing Clin Electrophysiol*. 2006;29:875–879.
78. Mansour KA, Kauten JR, Hatcher CR Jr. Management of the infected pacemaker: explantation, sterilization, and reimplantation. *Ann Thorac Surg*. 1985;40:617–619.
79. Nandyala R, Parsonnet V. One stage side-to-side replacement of infected pulse generators and leads. *Pacing Clin Electrophysiol*. 2006;29:393–396.
80. Panja M, Sarkar CN, Kumar S, Kar AK, Mitra S, Sinha DP, Chatterjee A, Roy S, Sarkar NC, Majumder B. Reuse of pacemaker. *Indian Heart J*. 1996;48:677–680.
81. Baddour LM; Infectious Diseases Society of America's Emerging Infections Network. Long-term suppressive antimicrobial therapy for intravascular device-related infections. *Am J Med Sci*. 2001;322:209–212.
82. Kay GN, Brinker JA, Kawanishi DT, Love CJ, Lloyd MA, Reeves RC, Pioger G, Fee J, Overland MK, Ensign LG, Grunkemeier GL. Risks of spontaneous injury and extraction of an active fixation pacemaker lead: report of the Accufix Multicenter Clinical Study and Worldwide Registry. *Circulation*. 1999;100:2344–2352.
83. Bracke F, Meijer A, Van Gelder B. Extraction of pacemaker and implantable cardioverter defibrillator leads: patient and lead characteristics in relation to the requirement of extraction tools. *Pacing Clin Electrophysiol*. 2002;23:1037–1040.
84. O'Nunain S, Perez I, Roelke M, Osswald S, McGovern BA, Brooks DR, Torchiana DF, Vlahakes GJ, Ruskin J, Garan H. The treatment of patients with infected cardioverter-defibrillator systems. *J Thorac Cardiovasc Surg*. 1997;113:121–129.
85. Molina JE. Undertreatment and overtreatment of patients with infected antiarrhythmic implantable devices. *Ann Thorac Surg*. 1997;63:504–509.
86. Rundstrom H, Kennergren C, Andersson R, Alestig K, Hogevik H. Pacemaker endocarditis during 18 years in Goteborg. *Scand J Infect Dis*. 2004;36:674–679.
87. Sohail MR, Usilan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR, Steckelberg JM, Jenkins SM, Baddour LM. Infective endocarditis complicating permanent pacemaker and implantable cardioverter-defibrillator infection. *Mayo Clin Proceed*. 2008;83:46–53.
88. Baman TS, Gupta SK, Valle JA, Yamada E. Risk factors for mortality in patients with cardiac device-related infection. *Circ Arrhythm Electrophysiol*. 2009;2:129–134.
89. de Oliveira JC, Martinelli M, D'Orio Nishioka SA, Varejão T, Uipe D, Andrade Pedrosa AA, Costa R, Danik SB. Efficacy of antibiotic prophylaxis before the implantation of pacemakers and cardioverter-defibrillators: results of a large, prospective, randomized, double-blinded, placebo-controlled trial. *Circ Arrhythm Electrophysiol*. 2009;2:29–34.
90. Cohen MI, Bush DM, Gaynor JW, Vetter VL, Tanel RE, Rhodes LA. Pediatric pacemaker infections: twenty years of experience. *J Thorac Cardiovasc Surg*. 2002;124:821–827.
91. Robinson M, Healey JS, Eikelboom J, Schulman S, Morillo CA, Nair GM, Branchuk A, Ribas S, Evans G, Connolly SJ, Turpie AG. Post-operative low-molecular-weight heparin bridging is associated with an increase in wound hematoma following surgery for pacemakers and implantable defibrillators. *Pacing Clin Electrophysiol*. 2009;32:378–382.
92. Deuling JH, Smit MD, Maass AH, Van den Heuvel AF, Nieuwland W, Zijlstra F, Van Gelder IC. The value and limitations of a wound inspection clinic after cardiac device implantation. *Eur J Cardiovasc Nurs*. 2009;8:288–292.
93. Lockhart PB, Brennan MT, Sasser HC, Fox PC, Paster BJ, Bahrani-Mougeot FK. Bacteremia associated with toothbrushing and dental extraction. *Circulation*. 2008;117:3118–3125.
94. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, Bolger A, Cabell CH, Takahashi M, Baltimore RS, Newburger JW, Strom BL, Tani LY, Gerber M, Bonow RO, Pallasch T, Shulman ST, Rowley AH, Burns JC, Ferrieri P, Gardner T, Goff D, Durack DT. Prevention of infective endocarditis: guideline from the American Heart Association: a guideline from the American Heart Association's Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council of Clinical Cardiology, Council on Cardiovascular Surgery, and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group [published correction appears in *Circulation*. 2007;116:e376–e377]. *Circulation*. 2007;116:1736–1754.
95. Tong DC, Rothwell BR. Antibiotic prophylaxis in dentistry: a review and practice recommendations. *J Am Dent Assoc*. 2000;131:366–374.
96. Pallasch TJ. Antibiotic prophylaxis. *Endod Topics*. 2003;4:46–59.
97. Lockhart PB, Brennan MT, Fox PC, Norton HJ, Jernigan DB, Strausbaugh LJ. Decision-making on the use of antimicrobial prophylaxis for dental procedures: a survey of infectious disease consultants and review. *Clin Infect Dis*. 2002;34:1621–1626.
98. Aas JA, Paster BJ, Stokes LN, Olsen I, Dewhirst FE. Defining the normal bacterial flora of the oral cavity. *J Clin Microbiol*. 2005;43:5721–5732.
99. Lockhart PB, Loven B, Brennan MT, Fox PC. The evidence base for the efficacy of antibiotic prophylaxis in dental practice. *J Am Dent Assoc*. 2007;138:458–474.

100. Bahrani-Mougeot FK, Paster BJ, Coleman S, Ashar J, Barbuto S, Lockhart PB. Diverse and novel oral bacterial species in blood following dental procedures. *J Clin Microbiol.* 2008;46:2129–2132.
101. Rosen MR, Brink PR, Cohen IS, Danilo P Jr, Robinson RB, Rosen AB, Szabolcs MJ. Regenerative therapies in electrophysiology and pacing. *J Interv Card Electrophysiol.* 2008;22:87–98.
102. Gepstein L. Experimental molecular and stem cell therapies in cardiac electrophysiology. *Ann NY Acad Sci.* 2008;1123:224–231.
103. Kizana E. Therapeutic prospects of cardiac gene transfer. *Heart Lung Circ.* 2007;16:180–184.
104. Rissanen TT, Ylä-Herttua S. Current status of cardiovascular gene therapy. *Mol Ther.* 2007;15:1233–1247.
105. Klug K, Vaksman G, Jarwé M, Wallet F, Francart C, Kacet S, Rey C. Pacemaker lead infection in young patients. *Pacing Clin Electrophysiol.* 2003;26:1489–1493.
106. Kammeraad JAE, Rosenthal E, Bostock J, Rogers J, Sreeram N. Endocardial pacemaker implantation in infants weighing ≤ 10 kilograms. *Pacing Clin Electrophysiol.* 2004;27:1466–1474.
107. Costa R, Filho MM, Tamaki WT, Crevelari ES, Nishioka SD, Moreira LF, Oliveira SA. Transfemoral pediatric permanent pacing: long-term results. *Pacing Clin Electrophysiol.* 2003;26(part II):487–491.
108. Lau YR, Gillette PC, Buckles DS, Zeigler VL. Actuarial survival of transvenous pacing leads in a pediatric population. *Pacing Clin Electrophysiol.* 1993;16(part I):1363–1367.
109. Walsh CA, McAlister HF, Andrews CA, Steeg CN, Eisenberg R, Furman S. Pacemaker implantation in children: a 21-year experience. *Pacing Clin Electrophysiol.* 1988;11(part II):1940–1944.
110. Till JA, Jones S, Rowland E, Shinebourne EA, Ward DE. Endocardial pacing in infants and children 15 kg or less in weight: medium-term follow-up. *Pacing Clin Electrophysiol.* 1990;13(part 1):1385–1392.
111. Noiseux N, Khairy P, Fournier A, Vobecky SJ. Thirty years of experience with epicardial pacing in children. *Cardiol Young.* 2004;14:512–519.
112. Dodge-Khatami A, Kadner A, Dave H, Rahn M, Prêtre R, Bauersfeld U. Left heart atrial and ventricular epicardial pacing through a left lateral thoracotomy in children: a safe approach with excellent functional and cosmetic results. *Eur J Cardiothorac Surg.* 2005;28:541–545.
113. Villain E, Martelli H, Bonnet D, Iserin L, Butera G, Kachaner J. Characteristics and results of epicardial pacing in neonates and infants. *Pacing Clin Electrophysiol.* 2000;23:2052–2056.
114. Silveti MS, Drago F, Grutter G, DeSantis A, DiCiommo V, Ravà L. Twenty years of paediatric cardiac pacing: 515 pacemakers and 480 leads implanted in 292 patients. *Europace.* 2006;8:530–536.
115. Silka MJ, Kron J, Dunnigan A, Dick M II. Sudden cardiac death and the use of implantable cardioverter-defibrillators in pediatric patients: the Pediatric Electrophysiology Society. *Circulation.* 1993;87:800–807.
116. Berul CI, Van Hare GF, Kertesz NJ, Dubin AM, Cecchin F, Collins KK, Cannon BC, Alexander ME, Triedman JK, Walsh EP, Friedman RA. Results of a multicenter retrospective implantable cardioverter-defibrillator registry of pediatric and congenital heart disease patients. *J Am Coll Cardiol.* 2008;51:1685–1691.
117. Link MS, Hill SL, Cliff DL, Swygman CA, Foote CB, Homoud MK, Wang PJ, Estes NAM III, Berul CI. Comparison of frequency of complications of implantable cardioverter-defibrillators in children versus adults. *Am J Cardiol.* 1999;83:263–266.