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

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A summary of the update on cardiovascular implantable electronic device infections and their management

A scientific statement from the American Heart Association

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Editor's note: This is a reprinting of a scientific statement from the American Heart Association (AHA) that was published in Circulation in 2010. A note at the end of this article provides the complete citation for the original publication, which JADA is reproducing here with permission of the AHA as a service to its readers.

In 2003, the American Heart Association (AHA) 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 in the pre-

ABSTRACT

Background. The purpose of this statement is to update the recommendations by the American Heart Association (AHA) for cardiovascular implantable electronic device (CIED) infections and their management, which were last published in 2003.

Methods and Results. The AHA 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. The recommendations in this statement reflect analyses of relevant literature, to include recent advances in our understanding of the epidemiology, risk factors, microbiology, management and prevention of CIED infections.

Conclusion. There are no scientific data to support the use of antimicrobial prophylaxis for dental or other invasive procedures.

Clinical Implications. The concerns about life-threatening drug reactions, the development of resistant strains of bacterial pathogens, medicolegal issues and cost to the health care system are, thus, avoided.

Key Words. American Heart Association scientific statements; infection; device; cardiovascular implantable electronic device; pacemaker; defibrillator; endocarditis; bacteremia; antibiotic prophylaxis.

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vention 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.

The years since the publication of the 2003 document[1] have witnessed exceptional advances in our understanding of several clinical aspects of cardiovascular device infections. In particular, cardiovascular implantable electronic device (CIED) infections have received the bulk of attention with sentinel observations in the epidemiology, associated risk factors, 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 of Cardiovascular Disease for the Young of the American Heart Association to provide an updated document limited to CIED infections. Due to the rarity of infection of implantable loop recorders and cardiovascular monitors, these devices are not considered in this 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 (LOE) to each recommendation.

BACKGROUND

CIEDs have become increasingly important in cardiac disease management over the past five 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, are serially updated and provide specific recommendations for CIED implantation.[3]

In an analysis of CIED implantation in the United States between 1997 and 2004, implantation rates for PPM and ICD increased by 19 percent and 60 percent, respectively.[4] Approximately 70 percent of device recipients were 65 years of age or older and more than 75 percent of them had one or more coexisting illnesses.[5,6] Simultaneously, dual-chamber pacing has become much more frequently used than single-chamber pacing.[4] Similarly, the frequency of ICD implantation increased in the elderly (70-79 years of age) and very elderly (≥ 80 years of age).[5]

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.[7,8] In earlier years, the rates of PPM infection ranged widely between 0.13 percent[9] and 19.9 percent.[10] Although most infections have been limited to the pocket, frank PPM endocarditis accounts for approximately 10 percent of PPM infections.[11]

The first ICD was implanted in 1980.[12] Subsequent decreases in the size of ICDs permitted implantation without thoracotomy. Subsequently, the entire device could be implanted prepectorally.[13]

Despite the greater ease of device implantation utilizing pectoral rather than other routes, and increasing experience with implantation, the rate of CIED infection has been increasing.[14,15] The National Hospital Discharge Survey similarly showed that between 1996 and 2003, the number of hospitalizations for CIED infections increased 3.1-fold (2.8-fold for PPM and 6.0-fold for ICD).[16] 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 greater than twofold.

RISK FACTORS

Several studies have identified characteristics associated with CIED infections. In a single-center case-control study,[17] cases were more likely to have diabetes mellitus, heart failure, and will have undergone generator replacement; renal dysfunction (glomerular filtration rate < 60 milliliters per minute per 1.72 square meters) had the strongest (odds ratio = 4.8) association with CIED infection.

Oral anticoagulant use, long-term cortico-

ABBREVIATION KEY. AHA: American Heart Association. **CIED:** Cardiovascular implantable electronic device. **CoNS:** Coagulase-negative streptococci. **ICD:** Implantable cardioverter-defibrillator. **LOE:** Level of evidence. **PIA:** Polysaccharide intercellular adhesin. **PPM:** Permanent pacemaker. **PS/A:** Polysaccharide/adhesin. **SCV:** Small colony variants. **TEE:** Transesophageal echocardiography. **TTE:** Transthoracic echocardiography.

steroid use and the presence of more than two pacing leads have also been identified as independent correlates of device infection.[18,19]

In addition to patient factors, procedural characteristics may also play an important role in the development of CIED infection. The factors associated with an increased risk of infection included fever within 24 hours prior to implantation, use of preprocedural temporary pacing and early reintervention.[20] Implantation of a new system and use of periprocedural antimicrobial prophylaxis were both associated with lower risk of infection.[19,21] Other small studies suggest that pectoral transvenous device placement is associated with significantly lower rates of CIED infection compared with those implanted abdominally[13] or by thoracotomy.[22,23]

In summary, several factors associated with a greater risk of CIED infection have been described in this section and include 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 CIED. Future study of CIED infection pathogenesis should better define how associated factors contribute to infection risk and whether intervention can decrease the risk.

MICROBIOLOGY

Staphylococcal species cause the bulk of CIED infections[15,24-31] and account for 60 percent to 80 percent of cases in most reported series. A variety of coagulase-negative streptococci (CoNS) species have been described as causing CIED infections.[32] *Corynebacterium* species, *Propionibacterium acnes*, gram-negative bacilli,[28,29] including *Pseudomonas aeruginosa,*[33] and *Candida* species account for a minority of CIED infections. Fungi other than *Candida*[34] and nontuberculosis mycobacteria[35,36] 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. Supporting endogenous acquisition, an association has been noted between the presence of preaxillary skin flora and the pathogens isolated from pacemaker infection.[26] Although low concentrations of methicillin-resistant CoNS have been detected in individuals with no health care contact and no recent antibiotic exposure,[37] a disproportionate frequency of CIED due to multidrug resistant staphylococci[31,38] suggests that a health care environment is the site of infection acquisition.[39,40]

PATHOGENESIS

The pocket may become infected 1) at the time of implantation, 2) during subsequent surgical manipulation of the pocket, or 3) 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. Alternately, 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 *Staphylococcus aureus* can result in device infection, but the prevalence of this occurrence and differentiating this mechanism of device infection from intraoperative contamination at the time of device placement or manipulation is 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 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.[41] 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 and 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.[42] 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.[43] An irregular surface of the device favors microbial adherence more than a smooth surface.

Microbial factors. None of the major virulence factors or toxins of *S. aureus* has been found in CoNS, and it seems clear that 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 structures[44] or via a capsular polysaccharide, PS/A (polysaccharide/adhesin).

Bacteria may also adhere to host matrix proteins that coat the surface of an implanted device.[45] Host extracellular matrix proteins include fibrinogen, fibronectin and collagen that are deposited on newly implanted biomaterials.[46,47] 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.[47]

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 (PIA) that is strongly associated with the staphylococcal cell surface and mediates cell-to-cell adhesion.[41,48]

The layers of bacteria on the surface of an implanted device are encased in this extracellular "slime"[49] and constitute a biofilm. Biofilm is defined as a surface-associated community of one 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.[41]

Microbial persistence. Phenotypic variation is also thought to be operative in supporting persistence of infection due to staphylococci in a biofilm that coats the surface of a CIED. Small colony variants (SCV) are phenotypes that have caused CIED infections[50-52] 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.[53-55]

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. 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 to be seen for evaluation for CIED infection by cardiologists or infectious diseases specialists if they develop fever and/or blood stream infection for which there is no initial explanation.

Transesophageal echocardiography (TEE) may be useful in demonstrating CIED-related endocarditis in adults. Due to its poor sensitivity, transthoracic echocardiography (TTE) is frequently not helpful in ruling out a diagnosis of lead-related endocarditis, particularly in adults. A mass adherent to the lead seen on echocardiography is usually a thrombus or infected vegetation. Masses that are detected in patients without positive blood cultures or other suggestive features for infection are likely to represent thrombus and are 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.

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.[28,29,56] Complete removal of hardware is needed because infection relapse rates due to retained hardware are high.[1,28,29,57,58]

Outcomes. CIED infection is a serious complication associated with substantial morbidity, mortality and cost.[16,45,59,60] 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.[22,23,45,59,61] Due to 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 benefits of device removal are not available.

Prophylaxis at CIED implantation. Prevention of CIED infection can be addressed prior to, during and after device implantation. A parenterally administered antibiotic is recommended one hour before the procedure.[19-21,62]

Currently, there are no data to support the administration of postoperative antibiotic therapy and it is not recommended due to risk of drug adverse events, selection of drug-resistance organisms and cost.

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.63 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, to include malpractice litigation, additional medical and dental office visits. The cost of prescription antibiotics alone would exceed $80 million in the United States each year if prescribed for various cardiovascular conditions that are at risk for infection (P. Lockhart, unpublished data, January 2011). (More details on this calculation appear in the supplemental data to the online version of this article [found at "http://jada.ada.org"].)

Since the original American Heart Association recommendations over 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.[64-47] There is little, if any, scientific justification for any of these medical conditions, and there is a wide range of opinions from experts and reflects the lack of scientific data on the aspect of efficacy.[68] A review of the literature from 1950-2007 for publications on cardiac electrophysiologic device infections reveals over 140 articles, none of which report hematological infection from dental, gastrointestinal, genitourinary, dermatologic, or other procedures.

The predominance of staphylococci as pathogens in CIED infections rather than oral flora[69] suggests that antibiotic prophylaxis for dental procedures is of little or no value.[1,63,68,70] 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.[69] Therefore, there is currently no scientific basis for the use of prophylactic antibiotics prior to routine invasive dental, gastrointestinal, or genitourinary procedures to prevent CIED infection.

TABLE

Summary of recommendations.

RECOMMENDATION	CLASS AND LEVEL OF EVIDENCE
G. Recommendations for Antimicrobial Prophylaxis for Invasive Procedures in Patients With Cardiovascular Implantable Electronic Devices	
1. Antimicrobial prophylaxis is not recommended for dental or other invasive procedures not directly related to device manipulation to prevent cardiovascular implantable electronic device infection.	IIIC

RECOMMENDATIONS FOR ANTIMICROBIAL PROPHYLAXIS FOR INVASIVE PROCEDURES IN PATIENTS WITH CARDIOVASCULAR IMPLANTABLE ELECTRONIC DEVICES

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) (Table). ■

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