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Infections of Permanent Pacemakers and Implantable Cardioverter- Defibrillators

Metallidis Symeon – Pilalas Dimitris
Aristotle University of Thessaloniki
Greece

1. Introduction

The rapid evolution of technology in recent decades has led to the development of several new implantable devices that help to improve or sustain life. Both cardiovascular and orthopedic medicines are among the specialties most affected by these advances. New and improved versions of early devices are being introduced routinely.

Cardiac prosthetic devices have become an integral part of modern cardiovascular medicine. Since the initial use of prosthetic heart valves in 1953 as a treatment for aortic regurgitation, other permanent indwelling devices, including permanent pacemakers (PPMs) and implantable cardioverter defibrillators (ICDs), have been shown to improve survival rates, reduce symptoms, or both. The growing number of evidenced-based indications for cardiac devices coupled with an aging population ensures a continued increase in the implantation of cardiac devices for the foreseeable future.

Worldwide, there are approximately 3.25 million functioning pacemakers and 180000 functioning implantable cardioverter defibrillators (Chua, Wilkoff et al. 2000). Although cardiac devices have prolonged the lives of countless patients, they also paradoxically place these same patients at risk for a number of complications, including infection. Infection rates for these devices range from 1% to 7%, and the optimal method for management of such infection has yet to be defined.

In 2003, the American Heart Association published a scientific statement that reviewed a variety of nonvalvular cardiovascular device infections (Baddour, Bettmann et al. 2003). The 7 years after the publication of the 2003 document have witnessed exceptional advances 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.

In an analysis of CIED implantation in the United States between 1997 and 2004, implantation rates for PPMs and ICDs increased by 19% and 60%, respectively (Zhan, Baine et al. 2008). Approximately 70% of device recipients were 65 years of age or older and more than 75% of them had 1 or more coexisting illnesses. 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) (Uslan, Tleyjeh et al. 2008). The 2001 World Survey found that in developed countries, between 20% and 35% of CIED recipients were more than 80 years old. The

National Hospital Discharge Survey found a 49% increase in the number of new CIED implantations, including both PPMs and ICDs, in the United States between 1999 and 2003 (Voigt, Shalaby et al. 2006).

2. Incidence and epidemiology

PPM endocarditis has been recognized since the early 1970s. In earlier years, the rates of PPM infection ranged widely between 0.13% and 19.9% (Bluhm 1985). Although most infections have been limited to the pocket, PPM endocarditis accounts for approximately 10% of PPM infections (Arber, Pras et al. 1994).

The first ICD was implanted in 1980 (Mirowski, Reid et al. 1980). 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%) (Mela, McGovern et al. 2001).

Cabell et al 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 endocarditis was relatively unchanged (0.26 and 0.39 cases/ 1000 beneficiaries, respectively) (Cabell, Heidenreich et al. 2004).

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 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 (Voigt, Shalaby et al. 2006). The number of CIED implantations continued to increase after 2003 from 199516 in 2004 to 222940 in 2006, representing a 12% increment. In the same period the number of CIED infections increased from 8273 in 2004 to 12979 in 2006, representing a 57% increment as seen in figure 1. From 1996 to 2006, co morbid illnesses in recipients of new CIED devises became more prevalent with an increasing percentage of patients with end-organ failures (6.5% in 1996 vs 8% in 2006) and diabetes mellitus (14.5% in 1996 vs 16.5% in 2006) (Voigt, Shalaby et al. 2006) (Voigt, Shalaby et al. 2010).

It also results in significant financial costs, including prolonged hospitalization, prolonged antimicrobial therapy, management of systemic complications of sepsis, and the costs involved in device extraction and potential re-implantation. According to one US study, the mean hospital cost for treating a single PPM or ICD infection is $24 459 or $57 213, respectively.

3. Risk factors

In a prospective cohort of 6319 patients receiving CIED implantation in 44 medical centers, Klug et al 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 (Klug, Balde et al. 2007).

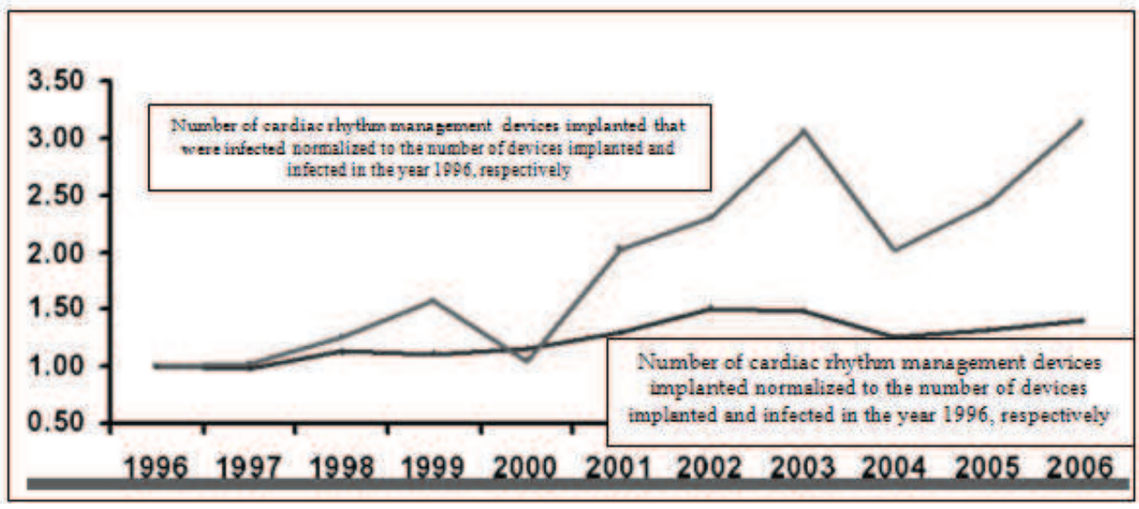

Fig. 1. Trends in Cardiovascular Implantable Devises and Infection in the United States (Adapted from Voigt, A., A. Shalaby, et al. (2010). "Continued rise in rates of cardiovascular implantable electronic device infections in the United States: temporal trends and causative insights." Pacing Clin Electrophysiol 33(4): 414-9.)

Johansen et al 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%). Device revision was associated with CIED infection in another investigation described recently. 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 increasethe risk of CIED infection exponentially is undefined (Johansen, Feychting et al. 2002).

Another retrospective study was contacted in Minnesota (Sohail, Uslan et al. 2007). From 1 January 1991 to 31 December 2003, 12,799 PPMs were implanted at the Mayo Clinic–Rochester. Potential study subjects among the patients who received these devices were identified by searching the aforementioned databases. Twenty-nine case patients and 58 control subjects met the inclusion criteria. On univariate analysis, previous PPM infection, malignancy, long-term corticosteroid use, multiple device revisions, a permanent central venous catheter, the presence of 12 pacing leads, and a lack of antibiotic prophylaxis at the time of PPM placement were associated with an increased risk of PPM infection. A multivariable logistic regression model identified long-term corticosteroid use (odds ratio [OR], 13.90; 95% confidence interval [CI], 1.27–151.7) and the presence of 12 pacing leads versus 2 leads (OR, 5.41; 95% CI, 1.44–20.29) as independent risk factors for PPM infection. In contrast, use of antibiotic prophylaxis prior to PPM implantation had a protective effect (OR, 0.087; 95% CI, 0.016–0.48).

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 (Chamis, Peterson et al. 2001).

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 al 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 (Al-Khatib, Lucas et al. 2005).

Finally Baman et al. evaluated risk factors for mortality in patients with cardiac-device related infection. Two hundred ten patients with cardiac-device related infection were identified at the University of Michigan between 1995 and 2006. Mean age for our study population was 63 ±17 years, and 72 (44%) were women. All-cause 6-month mortality was 18% (n=37). Independent variables associated with death were systemic embolization (hazard ratio 7.11; 95% CI 2.74 to 18.48), moderate or severe tricuspid regurgitation (hazard ratio 4.24; 95% CI 1.84 to 9.75), abnormal right ventricular function (hazard ratio 3.59; 95% CI 1.57 to 8.24), and abnormal renal function (hazard ratio 2.98; 95% CI 1.17 to 7.59). Size and mobility of cardiac device vegetations were not independently associated with mortality (Baman, Gupta et al. 2009).

In summary, several factors associated with a greater risk of CIED infection have been described in this section, including the following:

1. Fever within 24 hours of implantation
2. Lack of antibiotic prophylaxis before device implantation
3. Temporary pacing before permanent device placement
4. Presence of tunneled central venous catheter (such as hemodialysis catheter)
5. Operator inexperience
6. History of cardiac rhythm management device infection
7. History of multiple device-related procedures
8. Recent device manipulation (i.e., generator exchange or lead revision)
9. Presence of more than two electrode leads
10. Long-term corticosteroid therapy
11. Anticoagulation
12. Comorbid conditions (diabetes mellitus, heart failure, renal failure, malignancy)

4. Microbiology

Staphylococcal species cause the bulk of CIED infections and account for 60% to 80% of cases in most reported series. In a recent investigation, coagulase-negative staphylococci (42%), followed by S. aureus (29%) were responsible for more than two thirds of cases of device infection (2) (Sohail, Uslan et al. 2007). Early device infections (within 2 weeks of implantation) are primarily caused by S. aureus. Prevalence of oxacillin-resistant S. aureus is variable depending on the geographic location of reporting institutions. In one study, gram-negative bacteria, other gram-positive cocci (including enterococci, streptococci, and micrococci), and fungi (Candida spp. and Aspergillus fumigatus) were isolated in 9%, 4%, and 2% of cases, respectively. A variety of coagulase-negative *Staphylococcus* (CoNS) species have been described to cause CIED infections. 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. Distinguishing skin flora, particularly coagulase-negative

staphylococci, as either pathogen or culture contaminant is a frequent diagnostic dilemma. Multiple sets of blood cultures should yield the pathogen if endovascular infection is present. Skin flora that grow in culture from percutaneous aspirates of fluid or abscess collection should be considered as pathogens. Recovery of skin flora at driveline transcutaneous exit sites or in open wounds in proximity to a device is more difficult to define as pathogen versus contaminant; a Gram's stain may be helpful.

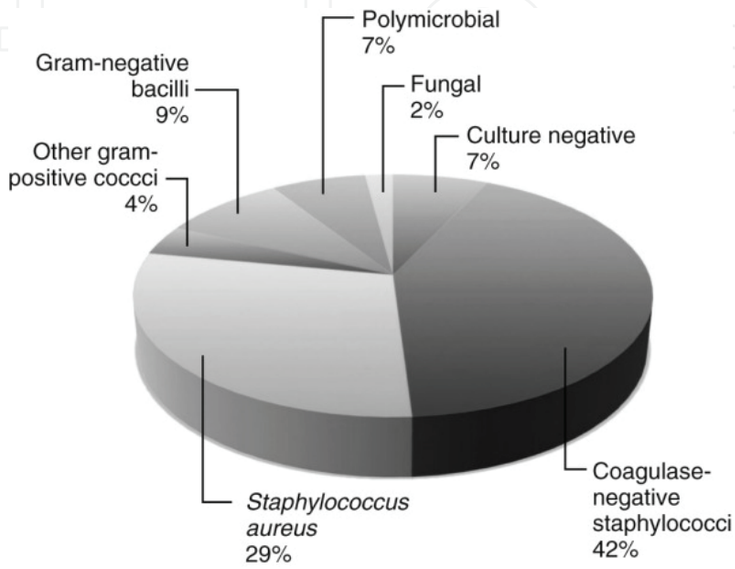

Fig. 2. Microbiology of cardiac rhythm management device infections. (Adapted from Sohail MR, Uslan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter defibrillator infections. J Am Coll Cardiol 2008;49;1851-1859.)

Polymicrobial infection sometimes involves more than 1 species of CoNS (Cacoub, Leprince et al. 1998). 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 including *Pseudomonas aeruginosa*, and *Candida* species account for a minority of CIED infections. Fungi other than *Candida (Metallidis, Chrysanthidis et al. 2008)* and nontuberculosis mycobacteria are rarely identified as pathogens in CIED infection. We have recently described a rare case of lead endocarditis caused by mucor sp.

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 pre-axillary skin flora and the pathogens isolated from pacemaker infection.

In a study by Da Costa et al specimens were collected at the site of implantation for culture from the skin and the pocket before and after insertion in a consecutive series of patients who underwent elective permanent pacemaker implantation. There were 103 patients (67 men and 36 women) whose age ranged from 16 to 93 years. At the time of pacemaker implantation, a total of 267 isolates were identified. The majority (85%) were staphylococci. During a mean follow-up of 16.5 months (range, 1 to 24), infection occurred in four patients (3.9%). In two of them, an isolate of *Staphylococcus schleiferi* was recognized by molecular

method as identical to the one previously found in the pacemaker pocket. In one patient, *Staphylococcus aureus*, an organism that was absent at the time of pacemaker insertion, was isolated. In another patient, a *Staphylococcus epidermidis* was identified both at the time of pacemaker insertion and when erosion occurred; however, their antibiotic resistance profiles were different (Da Costa, Lelievre et al. 1998).

Although low concentrations of methicillin-resistant CoNS have been detected in individuals with no healthcare contact and no recent antibiotic exposure, a disproportionate frequency of CIED infections due to multidrug-resistant staphylococci suggests that a healthcare environment is the site of infection acquisition.

5. Pathogenesis

Microbial contamination of a device generator or leads with skin flora at the time of implantation is the most likely mechanism of infection in the large majority of cases. This likely explains the preponderance of staphylococci as causative pathogens. Colonization and subsequent infection of CIEDs are facilitated by an ability of these organisms to adhere to device surfaces and produce biofilm. This causes an inability of the host's immune system to eliminate infection due to neutrophil dysfunction, poor penetration of antibiotics into the biofilm, and down regulation of metabolic activity in infecting organisms that makes them less susceptible to some antimicrobials, necessitating device removal for the best chance of infection cure. Once a generator or pocket is colonized, bacteria can migrate along the electrode leads and manifest as tunnel infection, bacteremia, or infected vegetations on electrode leads or cardiac valves. Incorporation of lead segments in the vascular endothelium or endocardial tissue may provide some protection from hematogenous seeding of microorganisms. Nevertheless, hematogenous seeding of leads is a major concern, particularly when Staphylococcus aureus is the pathogen

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 about 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 physicalchemical properties, such as hydrophobicity, surface tension, and electrostatic charge, of the plastic surface of the device and the bacterial surface (Vuong and Otto 2002). 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.

Pathogen Virulence Factors: Two major areas of investigation of microbial virulence factors are (1) tissue and foreign body adherence molecules and (2) foreign body surface biofilm formation.

There are several *S aureus* adhesins that are operative in the binding of microorganisms to extracellular and host plasma proteins that coat the surface of indwelling medical devices. These host proteins are exposed in areas where endothelium has been denuded by contact with or attachment to indwelling devices. The adhesins, known as extracellular matrix-binding proteins or microbial surface components recognizing adhesive matrix molecules (MSCRAMM), have been studied in a number of in vitro adherence assays and in animal models of infection and have demonstrated their importance in microbial virulence. Much of the work has examined *S aureus* surface proteins, including fibronectin-binding protein A or B, clumping factor A or B, and collagen-binding protein (Veenstra, Cremers et al. 1996). The only experimental model of cardiovascular infection that has been used to examine these putative virulence factors is the animal endocarditis model. Findings derived from experimental endocarditis investigations may be applicable to cardiovascular device–related infections in humans.

The layers of bacteria on the surface of an implanted device are encased in this extracellular slime 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 (Francois, Vaudaux et al. 1998).

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. 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. 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.

6. Clinical manifestations

CRMD infection has three important presentations (Sohail, Uslan et al. 2007). The most common presentation is pocket site infection (>60%). Patients generally present with localized inflammatory changes at the generator pocket site including erythema, pain, swelling, warmth, drainage, or dehiscence of overlying skin. Systemic signs of sepsis or positive blood cultures are present in less than one half of these cases. The second presentation is occult bacteremia or fungemia and no local changes at the pocket site. The third presentation is CRMD-related endocarditis (lead and/or valvular vegetations) in 10% to 23% of cases. Patients with device-related endocarditis are defined by modified Duke criteria (Arber, Pras et al. 1994). When vegetations are visualized on cardiac structures, the tricuspid valve is the most common site of infection (as many as 25% of cases with CRMD-related endocarditis). However, vegetations can develop on the pulmonic or left-sided

valves, especially in the setting of *S. aureus* bacteremia (SAB). Patients who are bacteremic with *S. aureus* have radiographic or computed tomography (CT) findings of multiple focal pulmonary infiltrates or abscesses due to septic emboli in as many as 40% (Klug, Lacroix et al. 1997). Patients with CRMD-related endocarditis have a higher mortality (14% to 21%) compared with those without it (<5%), even with percutaneous device extraction. A small proportion (<5%) of patients can present with erosion of a device lead or generator only in the absence of inflammatory signs at the pocket and positive blood cultures. Whether erosion is caused by low-grade infection or purely by mechanical factors may not be entirely clear in all patients. Median time from device implantation to infection was much shorter for ICD recipients (125 days) compared with those with PPM implantation (414 days) in a recent investigation. Early onset of infection in patients with ICDs may be, in part, due to higher prevalence of comorbid conditions and an increased rate of *S. aureus* infection in this group of patients (Uslan, Tleyjeh et al. 2008).

7. Diagnosis

A diagnosis of CRMD infection is apparent when pocket site inflammatory changes are present. For some patients, a diagnosis is more difficult to confirm. Blood cultures should be obtained in all cases before starting empirical antibiotics. If drainage is present, swab specimens should be submitted for cultures. Abnormal laboratory findings (leukocytosis, anemia, high erythrocyte sedimentation rate or C-reactive protein) are present in 50% or less of cases, and the absence of these findings should not dissuade clinicians from considering a possibility of CIED infection in the appropriate setting. 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.

Laboratory, radiological, and echocardiographic procedures are helpful in making a diagnosis of cardiovascular device-related infection. Occult bacteremia or fungemia with no other evidence of infection should prompt serious concerns of device infection. In patients with SAB, concomitant CIED infection is present in as many as 50% of the patients (Klug, Balde et al. 2007). Risk is especially high within the first year after device implantation. Local signs or symptoms of pocket or tunnel infection may be absent in more than 50% of cases. A thorough evaluation for focal infection, including echocardiography and possibly an ultrasound scan of the generator pocket (to evaluate for fluid collection) in patients with SAB and the presence of CIED is recommended. Although fluid can be present early after surgical implantation of the device generator, its accumulation months to years after device placement would be unusual. Ultrasonography-directed diagnostic aspiration could be considered. However, it carries a risk of introducing infection in an otherwise sterile collection during this procedure. Indium-labeled leukocyte or gallium scanning may be helpful in differentiating an inflammatory fluid collection from a noninfected pocket site fluid collection. A technetium-labeled white blood cell scan may aid in the differentiation of noninfected versus septic thrombi attached to pacing leads. CIED removal may also be considered in patients who have no identified focus of SAB. Failure to remove an infected device is associated with an increased risk of treatment failure with relapsing bacteremia. In patients with no evidence of CIED infection (after a thorough evaluation) at the time of SAB

and for whom a decision is made to treat conservatively, there should be close follow-up over the next 12 weeks to monitor for relapsing bacteremia. In untreated patients with bacteremia, blood cultures are usually positive. Culture of purulent drainage from a percutaneous driveline exit site or from a subcutaneous pocket or other site identifies a specific pathogen. Gram's stain of the drainage material is useful in demonstrating neutrophils and infecting bacteria. Despite collection of clinical specimens for microbiological examination, stains and cultures fail to demonstrate a pathogen in some patients with nonvalvular cardiovascular device–related infections. These culture-negative cases, much like those seen with infective endocarditis, are often due to recent antibiotic administration, which may diminish the sensitivity of subsequent microbiological studies. Unlike infective endocarditis, fastidious and uncommon microorganisms that do not grow or stain positive by routinely used laboratory methods have not been identified as pathogens in nonvalvular device-related infections. These groups of rare pathogens that are now being identified as causes of culture-negative endocarditis by technical advances in the laboratory have not accounted for culture-negative nonvalvular infections.

Lead tip cultures are frequently used to confirm the diagnosis of CRMD-related infective endocarditis. However, most transvenous leads are extracted percutaneously in current practice, and lead tips may be contaminated during removal through the incision of an infected pocket (Sohail 2007). Lead tip cultures are more reliable if they are extracted using a sterile technique (via protected sleeve) or if removed from a different incision than that used at the generator pocket site.

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 (Fowler, Li et al. 1997). 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.

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, there will be some patients who are labeled as manifesting CIED-related endocarditis who may not have a lead infection (Vilacosta, Sarria et al. 1994; Victor, De Place et al. 1999). 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. In a study by Chua et al seventy-one patients with implantable pacemaker (n = 49, 69%), implantable defibrillator (n

= 18, 25%), or both devices (n = 4, 6%) requiring lead extraction had pocket swab and tissue cultures for analysis. Infection was evident clinically in 35 (49%) of the patients and absent in the remainder. Patients with clinical infection had positive cultures more frequently (P = 0.002) by pocket tissue culture (n = 24, 69%) than by swab culture (n = 11, 31%). However, patients without clinical infections had positive cultures at similar rates by pocket tissue culture (n = 10, 28%) and by swab culture (n = 8, 22%). Gram staining, in addition to both anaerobic and aerobic bacterial cultures, should be done (Chua, Wilkoff et al. 2000).

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.

8. Management

The primary focus of treatment should be complete removal of the PPM or ICD system. Although no prospective, randomized trials have been conducted to evaluate the role of medical (antimicrobial) therapy alone versus a combined medical-surgical treatment approach, data from several retrospective analyses show a clear and clinically important advantage of complete device removal. For example, the reported mortality rate of CRMD-related endocarditis ranges from 31% to 66% if the infected device is retained compared with 18% or less in patients managed with a combined approach of complete device removal and parenteral antibiotics. Patients with partial device removal (generator only) or those treated conservatively with antibiotics alone have a higher risk of treatment failure or relapse.

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 (Love, Wilkoff et al. 2000). 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 (Gaynor, Zierer et al. 2006; Field, Jones et al. 2007). 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.

In a study by Anna del Rio a total of 31 patients, 25 men and 6 women aged 61 ±15 years (mean ±SD), with pacemaker or ICD endocarditis were identified among 669 consecutive patients (4.6%) with IE. Medical treatment without removal of the pacing system was initially performed on seven patients; all of them (100%) had relapses of endocarditis, and one patient died. The remaining 24 patients underwent surgical removal of the pacing system; 1 patient had one relapse, 3 patients died after surgical treatment, and the others were successfully cured with no relapses after a mean follow-up of 38 ±9 months. The only prognostic factor for failure of treatment or mortality was the absence of surgical treatment (del Rio, Anguera et al. 2003).

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 (Jones, Eckart et al. 2008).

In a study by Grammes et al a total of 984 patients underwent extraction of 1,838 leads; local or systemic infection occurred in 480 patients. One hundred patients had intracardiac vegetations identified by transesophageal echocardiogram, and all underwent percutaneous lead extraction (215 leads). Mean age was 67 years. Median extraction time was 3 min per lead; median implant duration was 34 months. During the index hospitalization, a new device was implanted in 54 patients at a median of 7 days after extraction. Post-operative 30-day mortality was 10%; no deaths were related directly to the extraction procedure (Grammes, Schulze et al. 2010).

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 advocated is in patients with lead vegetations >2 cm in diameter, because of concerns about the risk of pulmonary embolism with percutaneous lead extraction (Smith and Love 2008). Experience suggests, however, that percutaneous removal in patients with large vegetations can be done without precipitating a clinically apparent pulmonary embolism. 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 b-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. 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 (Sohail, Uslan et al. 2007).

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. A practical approach to CIED infections is provided in figure 3.

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 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 within3 months of device placement.

As reported by Uslan et al from forty-nine patients with gram-negative bacteremia who had PPM/ICD only 3 (6%) had either definite (2 patients) or possible (1 patient) PPM/ICD infection. Both patients with definite PPM/ICD infection had clear infection of the generator pocket. None of the other patients with alternate sources of bacteremia developed PPM/ICD infection. Thirty four patients with retained PPM/ICD were observed for 112 weeks (median time, 759 days), and 2 (6%) developed relapsing bacteremia, although they each had alternative sources of relapse. In sharp contrast to *S. aureus* infection, PPM/ICD infection in patients with gram-negative bacteremia was rare, and no patients appeared to have secondary PPM/ICD infection due to hematogenous seeding of the system. Despite infrequent system removal in these patients, relapsing bacteremia among patients who survived initial bacteremia was rarely seen. If secondary PPM/ICD infection occurs in patients with gram-negative bacteremia, it is either uncommon or it is cured with antimicrobial therapy despite device retention (Uslan, Sohail et al. 2006).

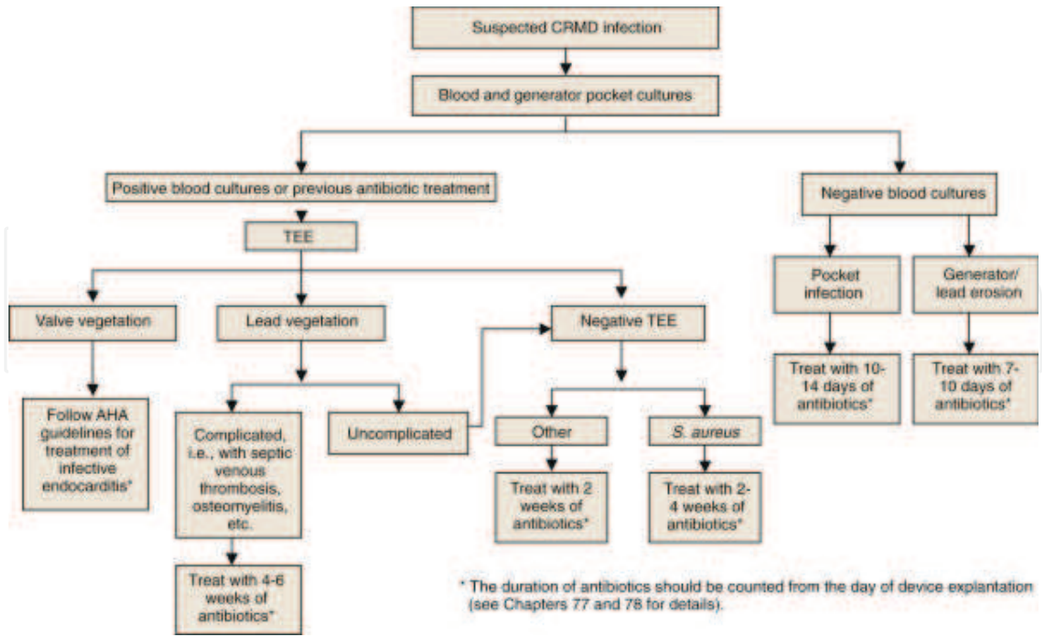

Fig. 3. Approach to the management of adults with cardiac rhythm management device infection. This algorithm applies only to the patients who are managed with complete device removal. AHA, American Heart Association; CRMD, cardiac rhythm management device; TEE, transesophageal echocardiogram.(Adapted from Sohail MR, Uslan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter defibrillator infections. J Am Coll Cardiol. 2008;49;1851-1859.)

Chamis et al evaluated prospectively in a cohort all adult patients with SAB and permanent pacemakers or implantable cardioverterdefibrillators over a 6-year period. The overall incidence of confirmed CDI was 15 of 33 (45.4%). Confirmed CDI occurred in 9 of the 12 patients (75%) with early SAB (1 year after device placement). Fifteen of 21 patients (71.5%) with late SAB (1 year after device placement) had either confirmed (6 of 21, 28.5%) or possible (9 of 21, 43%) CDI. In 60% of the patients (9 of 15) with confirmed CDI, no local signs or symptoms suggesting generator pocket infection were noted (Chamis, Peterson et al. 2001). The incidence of CDI among patients with SAB and cardiac devices is high. Neither physical examination nor echocardiography can exclude the possibility of CDI. In patients with early SAB, the device is usually involved, and '40% of these patients have obvious clinical signs of cardiac device involvement. Conversely, in patients with late SAB, the cardiac device is rarely the initial source of bacteremia, and there is a paucity of local signs of device involvement. The cardiac device is involved, however, in 28% of these patients.

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 evidence of CIED infection has received limited attention. Results of 2 relatively small case series 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 (Camus, Leport et al. 1993; Sopena, Crespo et al. 2010).

9. 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 (Sohail, Uslan et al. 2007). 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 (Braun, Rauwolf et al. 2006).

The optimal timing of device replacement is unknown (Mansour, Kauten et al. 1985). Some have advocated proceeding 24 hours after removal. Sohail et al 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*) (Sohail, Uslan et al. 2007).

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 (Figure 4).

Only 1 medical center has described simultaneous contralateral (side-to-side) replacement of an infected CIED. 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 (Nandyala and Parsonnet 2006). 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 (Panja, Sarkar et al. 1996). Mansour and coworkers 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 (Mansour, Kauten et al. 1985).

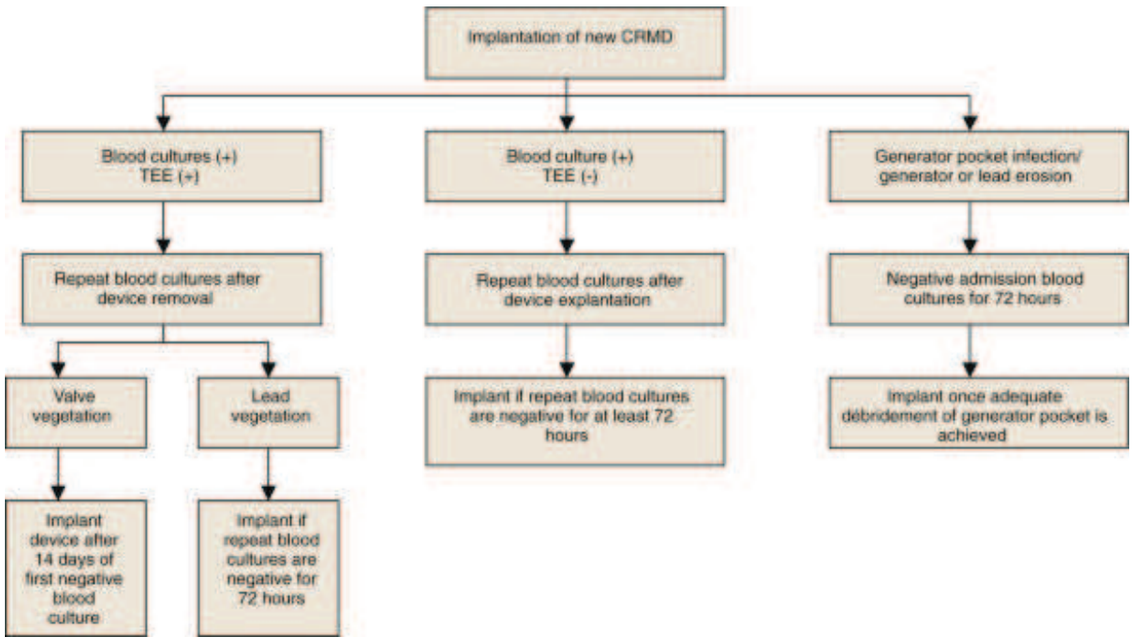

Fig. 4. Guidelines for implantation of a new device in patients with cardiac rhythm management device infection. CRMD, cardiac rhythm management device; TEE, transesophageal echocardiogram.(Adapted from Sohail MR, Uslan DZ, Khan AH, et al. Management and outcome of permanent pacemaker and implantable cardioverter defibrillator infections. J Am Coll Cardiol. 2008;49;1851-1859.)

10. 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 (Baddour 2001). 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.

11. Complications of device infection

Complications of CRMD infection may include valvular endocarditis (mostly right sided), septic arthritis, vertebral osteomyelitis, sternal wound infection, metastatic abscesses (lung,

liver, spleen, brain, renal), and thrombosis of a subclavian vein or superior vena cava. In patients with metastatic abscesses or osteomyelitis, it may be difficult to decipher whether an ectopic site is the source of bacteremia with hematogenous seeding of a cardiac device or vice versa.

12. Outcomes

CIED infection is a serious complication associated with substantial morbidity, mortality, and cost. 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 (Molina 1997; Bracke, Meijer et al. 2002; Rundstrom, Kennergren et al. 2004; Sohail, Uslan et al. 2008). 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 analysis 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% (Baman, Gupta et al. 2009). 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.

13. 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 (Da Costa, Kirkorian et al. 1998), 2 case-control studies (Klug, Balde et al. 2007; Sohail, Uslan et al. 2007) that examined purported risk factors of CIED infection, and a large, prospective, randomized, double-blinded, placebo-controlled trial (de Oliveira, Martinelli et al. 2009) strongly support the administration of antibiotic prophylaxis for CIED implantation. 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 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. Intraprocedurally, 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 retropectorally placed systems. Hematoma

within the pocket that complicates CIED placement or invasive manipulation has been identified as a risk factor associated with device placement (Cohen, Bush et al. 2002). 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 (Robinson, Healey et al. 2009). 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 investigation (Deuling, Smit et al. 2009) 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.

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.

14. Antibiotic prophylaxis for invasive procedures

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. 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 (Tong and Rothwell 2000; Lockhart, Brennan et al. 2002; Wilson, Taubert et al. 2008).

The predominance of staphylococci as pathogens in CIED infections rather than oral flora suggests that antibiotic prophylaxis for dental procedures is of little or no value (Aas, Paster et al. 2005). 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. 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.

15. Conclusion

As the number of CIED implantations continued to increases, the numbers of CIED infections are following the increment (57% increment from 2004 to 2006). All physicians must be aware of the potential role of implantable cardiovascular devices in infection. Diagnosis and management might be difficult, so guidelines must be followed. As conclusion we will provide the recommendations made by the American Heart Association (Baddour, Epstein et al. 2010).

Diagnosis:

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.
2. Generator-pocket tissue Gram's stain and culture and lead-tip culture should be obtained when the CIED is explanted.
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.
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.

Management:

5. Choice of antimicrobial therapy should be based on the identification and in vitro susceptibility results of the infecting pathogen.
6. Duration of antimicrobial therapy should be 10 to 14 days after CIED removal for pocket-site infection.
7. Duration of antimicrobial therapy should be at least 14 days after CIED removal for bloodstream infection.
8. 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.
9. Complete device and lead removal is recommended for all patients with definite CIED infection, as evidenced by valvular and/or lead endocarditis or sepsis.
10. 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.
11. Complete device and lead removal is recommended for all patients with valvular endocarditis without definite involvement of the lead(s) and/or device.
12. Complete device and lead removal is recommended for patients with occult staphylococcal bacteremia.

New device implantation:

1. Each patient should be evaluated carefully to determine whether there is a continued need for a new CIED.
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.

Prevention:

1. A parenterally administrated antibiotic is recommended 1 hour before the implantation of the device
2. Cefazolin is the preferred regimen
3. Vancomycin must be use particularly in centers where oxacillin resistance among staphylococci is high
4. Preoperative antiseptic preparation of the skin and sterile technique is mandatory.
5. Antimicrobial prophylaxis is not recommended for dental or other invasive procedures not directly related to device manipulation to prevent CIED infection.
6. Clinical trials and large nationals registries must be done in order to increase the knowledge of handling such infections.

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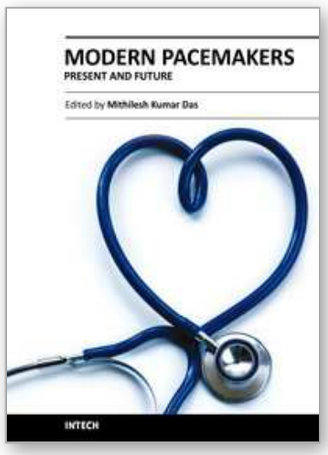

Modern Pacemakers - Present and Future

Edited by Prof. Mithilesh R Das

ISBN 978-953-307-214-2
Hard cover, 610 pages
Publisher InTech
Published online 14, February, 2011
Published in print edition February, 2011

The book focuses upon clinical as well as engineering aspects of modern cardiac pacemakers. Modern pacemaker functions, implant techniques, various complications related to implant and complications during follow-up are covered. The issue of interaction between magnetic resonance imaging and pacemakers are well discussed. Chapters are also included discussing the role of pacemakers in congenital and acquired conduction disease. Apart from pacing for bradycardia, the role of pacemakers in cardiac resynchronization therapy has been an important aspect of management of advanced heart failure. The book provides an excellent overview of implantation techniques as well as benefits and limitations of cardiac resynchronization therapy. Pacemaker follow-up with remote monitoring is getting more and more acceptance in clinical practice; therefore, chapters related to various aspects of remote monitoring are also incorporated in the book. The current aspect of cardiac pacemaker physiology and role of cardiac ion channels, as well as the present and future of biopacemakers are included to glimpse into the future management of conductions system diseases. We have also included chapters regarding gut pacemakers as well as pacemaker mechanisms of neural networks. Therefore, the book covers the entire spectrum of modern pacemaker therapy including implant techniques, device related complications, interactions, limitations, and benefits (including the role of pacing role in heart failure), as well as future prospects of cardiac pacing.

How to reference

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Metallidis Symeon and Pilalas Dimitris (2011). Infections of Permanent Pacemakers and Implantable Cardioverter-Defibrillators, Modern Pacemakers - Present and Future, Prof. Mithilesh R Das (Ed.), ISBN: 978-953-307-214-2, InTech, Available from: http://www.intechopen.com/books/modern-pacemakers-present-and-future/infections-of-permanent-pacemakers-and-implantable-cardioverter-defibrillators

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InTech Europe
University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
Fax: +385 (51) 686 166

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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