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Surgical Site Infection Education SPECIAL SUPPLEMENT

Overview of Infections of Cardiac Rhythm Management Devices

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Overview of Infections of Cardiac Rhythm Management Devices

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Infection remains the most common serious complication of placing cardiac rhythm management devices (permanent pacemakers and implantable cardioverter-defibrillators). Despite advances in lead and generator design as well as improved understanding of risk factors for infection, the rate of cardiac device infection has been increasing out of proportion to that of device placement.^{1,3} These infections result in substantial morbidity and financial outlay due to the need for surgical procedures for system extraction, the need for parenteral antibiotics, and the cost of a new device for reimplantation. The estimated average cost of combined medical and surgical treatment of an infected medical device ranges from \$25,000 to \$50,000.^{4,5}

Several recent studies have suggested the cardiac device infection rate has dramatically increased over the past decade. A recent study¹ of Medicare beneficiaries from 1990 to 1999 noted cardiac device implantation rates increased from 3.26 per 1,000 beneficiaries in 1990 to 4.64 in 1999, or 42% growth over the 10-year period. Over the same time period, the incidence of infections of these devices increased from 0.94 to 2.11 infections per 1,000 beneficiaries, an increase of 124%. Another study² using the National Hospital Discharge Survey data found a 49% increase in the number of new cardiac device implantations from 1996 to 2003, and that the number of device infections increased by 3.1-fold during the same period. Specific etiologies for increasing infection rates are unknown, but may be related to changing demographic features and comorbidities of cardiac device recipients, evolving implantation practices, or increasing numbers of device revisions and multiple procedures.⁶

Clinical Features

In general, there are two distinct presenting syndromes of cardiac device infection.^{7,8} However, the signs and symptoms depend on the specific anatomic location of the infected portion of the device, and since the device traverses multiple tissue planes, the presenting syndromes may overlap considerably.

The first syndrome is a local surgical site infection at the generator pocket and subcutaneous segment of

the leads. These patients tend to present with only local symptoms at the generator-pocket site, such as purulent drainage, erythema, tenderness, and warmth. Systemic symptoms such as fever are frequently absent. Pocket infection typically occurs within the first several months after device implantation or revision, although delayed-onset pocket infection is a well-reported phenomenon that may occur even years after device manipulation. Late-onset infections are often due to low-virulence organisms such as coagulase-negative staphylococci. Occasionally patients present with chronic pain, poor wound healing, generator migration, or device erosion, but no other cardinal signs of infection. In some of these patients, low-grade indolent infection may cause what otherwise appear to be mechanical complications. If generator erosion occurs, the device is considered contaminated and is generally treated no differently than a pocket infection.⁹

The second clinical syndrome is less commonly seen. This is a deeper infection such as transvenous lead infection or lead-related infective endocarditis. These patients most commonly present with systemic symptoms such as fever or sepsis and often have positive blood cultures. Other findings may include embolic phenomena, particularly pulmonary emboli. Vegetations can often be detected on the leads; transesophageal echocardiography is by far the most sensitive imaging modality for detection of lead vegetations.¹⁰⁻¹³ *Staphylococcus aureus* causes the overwhelming majority of lead-related infective endocarditis. Lead involvement may occur as a consequence of a primary-pocket infection, with organisms migrating distally down the lead, or more commonly due to seeding of the lead as a secondary complication of bacteremia from another primary focus (for example, an infected central venous catheter).^{8,14-20} Recent data²¹⁻²⁴ suggest that rates of bacteremia due to *S. aureus* are increasing, with the rate of nosocomial *S. aureus* bacteremia more than doubling. *S. aureus* bacteremia is particularly common in elderly males, a population also more likely to receive implantable cardiac devices.^{23,25} A prospective study¹⁴ on *S. aureus* bacteremia in patients with cardiac devices found an incidence of confirmed device infection of 45.4%, with 60% of patients with device infection having no local signs or symptoms suggesting generator-pocket infection as the source for

bacteremia. Patients with *S. aureus* bacteremia in the setting of a cardiac device should undergo careful evaluation for lead involvement, potentially including transesophageal echocardiogram.

Managing Infected Cardiac Rhythm Management Devices

Generally, successfully treating infected cardiac rhythm management devices requires extraction of the entire device system in combination with parenteral antibiotics. While there are published case reports of successful treatment of infected devices with device retention, this approach is best reserved for very superficial infections or unusual circumstances, such as when the patient is unable to tolerate an extraction procedure.^{8,26-28}

Several case series of patients with infected cardiac devices have demonstrated the importance of system extraction. In a 1985 case series²⁹ of 75 patients with cardiac device infection, 32 patients were treated conservatively with antibiotics plus incision and drainage or aspiration of infected fluid. Only one of the 32 patients was successfully cured. All the remaining patients who initially failed conservative management were eventually cured after undergoing pacing system extraction. In a more recent case series³⁰ of 31 patients with lead-related infective endocarditis, medical therapy with antibiotics and device retention were attempted in seven patients. All seven patients had relapses of endocarditis; one died from the infection. The only factor predicting failure of treatment or mortality was the absence of surgery ($p < 0.0001$).

Therefore, complete system extraction is recommended to treat device-related infection, whether it is generator-pocket infection or lead-associated endocarditis. Even when the infection appears to be localized to the generator pocket, it is likely that the leads are involved as well.³¹ The cure rate is excellent with device extraction and parenteral antibiotics. In our recent Mayo Clinic study²⁸ of 189 patients meeting criteria for cardiac device infection, 98% of patients underwent complete system removal, with a 96% cure rate and a median follow-up duration of 175 days. The nature and duration of antimicrobial therapy after device extraction are beyond of the scope of this review.

Accurately diagnosing a patient with an infected cardiac device has crucial therapeutic implications. Diagnosis may be difficult, particularly for atypical cases, given the varying presentations noted above. In patients presenting only with generator migration or pocket discomfort, for example, an infection diagnosis may not initially be considered. Accurate diagnosis is essential to ensure that patients with cardiac device infection are treated appropriately, including with

complete device extraction, if necessary. A correct diagnosis is equally important among patients without device infection, so that unnecessary device removal does not occur, particularly as many patients are device-dependent. The risk of complications with percutaneous device removal has been linked to the duration of implantation, and serious complications of lead extraction, such as venous tears and myocardial rupture, are well-reported.^{9,30,32-34} In our case series,²⁸ 11% of patients undergoing percutaneous device extraction had complications from the procedure, including cardiac valvular damage, venous lacerations, hemorrhage, and fracture of the lead tip requiring surgical intervention. Despite the risk, removing an infected system is imperative to cure the infection, and the mortality rate among patients with infected retained leads is approximately 25%.³² The American Heart Association guidelines for management of nonvalvular cardiac device infections recommend complete device removal, including the generator and leads.⁹

Preventing Cardiac Rhythm Management Device Infection

Because infection of a cardiac rhythm device can be devastating, prevention of infection is crucial. Several recent studies^{35,36} have shed light on the risk factors associated with an increased risk of infection, including host-specific factors and procedural factors. Many of the risk factors are patient comorbidities such as hemodialysis, diabetes, or age.³⁵⁻³⁷ As such, these risk factors are non-modifiable with little opportunity for intervention to reduce the infection risk. Antibiotic prophylaxis, typically a single dose of a parenteral antibiotic such as cefazolin, is often administered before implantation. A meta-analysis³⁸ in 1998 showed a consistent protective effect with antibiotic pre-treatment (odds ratio 0.256 for infection), although numerous limitations were noted. A recent prospective, randomized, double-blind placebo-controlled study³⁹ of 1,000 consecutive patients in Brazil compared the incidence of cardiac device infection in subjects receiving parenteral cefazolin versus those receiving a placebo. The study was stopped after 649 patients were enrolled due to a significant difference noted in favor of the antibiotic arm: The incidence of infection in the antibiotic arm was 0.63% (two of 314) versus 3.28% in the placebo group (11 of 335, $p = 0.016$). The approach to device infection prophylaxis varies significantly between providers, in particular with regard to post-implantation antibiotics. Some centers continue parenteral antibiotics after the procedure, others discharge the patient on oral antibiotics, and still others do not provide any further antibiotics post-implantation after the initial dose. Several centers have switched to

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parenteral vancomycin due to high institutional rates of methicillin-resistant *S. aureus* infection. Some implantation centers have attempted novel methods for reducing the infection rate, including intraoperative pocket lavage with antibiotic solution or antibiotics applied directly to the pocket. There are inadequate published data on the utility of any of these approaches.

Conclusions

Cardiac rhythm management device infection remains the most common serious complication after implantation, and the problem appears to be increasing as the indications for implantation and comorbidities of recipients increase. Further studies identifying patient- and procedure-specific risk factors will allow development of novel interventions. Awareness of the presenting signs and symptoms and need for appropriate management will hopefully result in improved outcomes and reduced morbidity.

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Prevention of Biofilm-Associated Infections of Implants

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Half of the almost 2 million cases of healthcare-acquired infections that occur each year in the United States are associated with implantable devices. Device-related infections are on the rise due to the more frequent use of medical devices and the longer survival of patients who have inherently high infection risks. The relationship between implanted devices and occurrence of nosocomial infection is particularly prominent in critically ill patients, cancer subjects, and in those who require sophisticated implants such as cardiac rhythm management devices (CRMD).^{1,2} Despite adherence to basic infection control practices, infections of implantable permanent pacemakers (PPM) and intracardiac cardioverter defibrillators (ICD) continue to occur at unacceptably high rates of 1% to 7%,¹ and the absolute number of annual cases of infection has increased out of proportion to the rising utilization of such cardiac devices.³

Because managing device-associated infections can be both difficult and expensive,⁴ prevention remains a priority. In general, potentially protective antimicrobial-utilizing practices comprise systemic antibiotic prophylaxis in the case of surgical implants and various modes of local applications for both catheters and surgical implants.⁵ This paper delineates the pathogenesis of device-related infection and assesses the potential preventive efficacy of antimicrobial-utilizing approaches.

Pathogenesis of Device-Related Infection

Implanted-device infections center on the universal formation of a layer of biofilm around the indwelling device. Biofilms are heterogeneous structures that comprise organisms encased in a substance known as extracellular polymeric substance (EPS) or extracellular matrix (ECM) and host elements that include platelets and tissue ligands such as fibronectin, fibrinogen, and fibrin.^{6,7} In addition to acting as a barrier that protects embedded organisms from host immune defenses, including phagocytosis and opsonization,⁸ the biofilm also can impair the activity⁹ and penetration¹⁰ of some antibiotics. This unique biofilm environment may help explain why certain antimicrobial modifications are likely to be clinically protective; these modifications let local leaching of antimicrobials

provide effective zones of inhibition and ensure killing of the biofilm-embedded organisms.

The nature of the infecting pathogens depends on the type of the device and mode of insertion. For example, devices that are implanted either percutaneously (such as vascular catheters) or subcutaneously (such as CRMDs) are typically infected by skin organisms, namely staphylococci. In contrast, gram-negative bacteria are responsible for a large portion of infections of devices that are inserted into the urologic (such as bladder catheters) or gastrointestinal (such as biliary stents) tracts. Biofilm's role is increasingly recognized in infections that are not even device-related, including wound infections, otitis, sinusitis, and pulmonary infections associated with cystic fibrosis.

Approaches for Preventing Device-Associated Infections

Because device colonization is a prelude to catheter-associated infection, preventing bacterial adherence to the device can potentially lower the risk of clinical infection.¹¹ In general, antimicrobial-based strategies aim to prevent implant-associated infections by impeding bacterial adherence to the device surface and/or reducing bacterial concentration in the immediate vicinity of the device.

- 1. Systemic antibiotic prophylaxis.** Although systemic antibiotic prophylaxis plays an important role in preventing infections associated with surgically-placed implants,¹² it has no confirmed benefit for vascular or urinary catheters. The rising prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA) coupled with the fact that most coagulase-negative staphylococci are methicillin-resistant has prompted clinicians to increasingly utilize vancomycin instead of cephalosporins (cefazolin or cefuroxime) for systemic antibiotic prophylaxis against infection of surgical implants including CRMDs. Clinicians sometimes expand the antimicrobial spectrum of perioperatively administered antibiotics to help prevent organisms that asymptotically reside at distant

Table 1. Comparison of Antimicrobial Dipping of Devices With Antibacterial Envelope

	Dipping	Envelope
Durability of activity	Hours	Days
Determined amounts of antimicrobials bound to device	No	Yes
Determined amounts of antimicrobials that leach off device	No	Yes
Uses agents that are not usually given to treat infection	No	Yes
Demonstrated <i>in vivo</i> efficacy	No	Yes

sites from hematogenously seeding the surgical implant. This seeding may theoretically occur during pacemaker implantation in a patient who requires intraoperative placement of a foley catheter into a bladder that contains gram-negative bacteria. Although no prospective pertinent data exist, retrospective analysis showed that, in sharp contrast to MRSA, CRMD infection in patients with gram-negative bacteremia is rare.¹³

- 2. Antiseptic cleansing of the skin.** The recent CDC guidelines prefer cleansing of the skin with a 2%-chlorhexidine solution to using povidone-iodine or alcohol for the insertion and maintenance of central venous catheters.¹⁴ The advantages of using chlorhexidine include its relatively strong, broad-spectrum, durable, and persistent bactericidal activity that is not inhibited by exposure to bodily fluids. Although no published results of prospective, randomized clinical trials compare antiseptic cleansing of the skin with chlorhexidine to cleansing with povidone iodine for surgical implant-associated infection prevention, chlorhexidine likely may also protect more against such infections which, like vascular catheters, are mostly infected by staphylococci.
- 3. Antimicrobial irrigation of the surgical field.** In contrast to antiseptic cleansing of the skin, which is applicable to both surgical implants and catheters, antimicrobial irrigation is practiced only in the context of surgical implantation of devices. The governing principle is that organisms that initially adhere not only to the surface of the device but also to adjacent tissues can cause implant infection. Although this clinical practice constitutes a prevailing standard of care at the time of placing many types of surgical implants, no prospective, randomized trial has demonstrated the clinical efficacy of this potentially preventive approach that ensures antimicrobial activity for up to several

hours. Moreover, the application of this approach is hampered by a number of factors, including inter-surgeon differences as to the choice (frequently vancomycin or bacitracin), concentration, volume, pressure, and flow (pulsatile versus constant) of antimicrobial irrigation.⁵

- 4. Dipping devices in antimicrobial solutions.** Because this approach incorporates relatively small amounts of antimicrobials on the surface of the implant as compared with the irrigation strategy, it results in short-term local antimicrobial activity (usually up to few hours) and no detectable systemic antimicrobial levels. Although central venous and arterial catheters dipped in either vancomycin¹⁵ or cefazolin¹⁶ were less likely to become colonized than undipped catheters, there was no reported reduction in the rate of catheter-related bloodstream infection. A single prospective, randomized clinical trial had reported significantly lower rates of prosthetic valve endocarditis associated with antibiotic-dipped versus undipped valves, but the study conclusion was limited by the large variety of tested antibiotics.¹⁷ Furthermore, early results from a prospective, randomized clinical trial¹⁸ showed no significant benefit from using rifampin-dipped versus undipped vascular grafts. As with antimicrobial irrigation of the surgical field, the approach of dipping implants in antimicrobial solution is limited by the use of variable types of antimicrobials (including antibiotics that are commonly used to treat established infection), lack of a standardized method of application, and unknown amounts of locally available antimicrobials.
- 5. Coating devices with antimicrobials.** The objective of both antimicrobial coating and dipping of the device is to inhibit bacterial colonization of both surgical and non-surgical devices and, hopefully, protect against device-

associated infection. Although dozens of antimicrobial-coated surfaces have been reported to reduce bacterial colonization of the device *in vitro*, only several have been tested in animals, and an even smaller number have been clinically assessed. Incorporation of silver alone on the device surface has not been demonstrated to be clinically beneficial and, in some instances, has been associated with adverse events.¹⁹⁻²⁵ In contrast, coating vascular catheters with the combination of chlorhexidine and silver sulfadiazine was found to protect against clinical infection.²⁶ Incorporating the combination of minocycline and rifampin on vascular catheters,²⁷⁻³⁰ ventricular catheters,³¹ and surgical implants^{32,33} has been demonstrated to protect against clinical infection, even more so than chlorhexidine and silver sulfadiazine.³⁴ The fact that minocycline (inhibits protein synthesis) and rifampin (inhibits DNA-dependent RNA polymerase) possess different mechanisms of activity may help explain why there have been no reported cases of antibiotic resistance when using this combination.^{27,30}

6. Placement of antimicrobial envelope. The best example of this strategy is placing around a CRMD an antibacterial envelope consisting of a bioresorbable polymer that contains minocycline and rifampin — an antimicrobial combination that has been consistently shown to protect against infection when used to coat a variety of devices. No prospective, randomized clinical trial has assessed the clinical efficacy of this innovative strategy because such a large number (thousands) of patients would be needed to conduct a sufficiently powered trial. However, this approach has demonstrated a broad-spectrum antimicrobial activity *in vitro* and strong efficacy in preventing device colonization and infection *in vivo*.³⁵ As shown in **Table 1 on p. 7**, using the antibacterial envelope appears to be more advantageous than dipping devices in antimicrobial solution.

Conclusion

In summary, different antimicrobial-utilizing approaches have variously succeeded in preventing device-associated infections. The characteristics of individual antimicrobial interventions can help predict the likelihood and degree of clinical protection against infection. Since infection is the most common serious complication of implanted devices, there is a pressing need to use strategies that have either been demonstrated to prevent clinical infection or possess certain characteristics that make

them likely to reduce infection. Such characteristics include broad-spectrum activity against most potential pathogens; antimicrobial efficacy during the time period at highest risk for inoculating pathogens; leaching of antimicrobial agents to produce effective zones of inhibition that protect against organisms that not only adhere directly to the device surface but are also embedded deep within the biofilm; low likelihood for developing resistance; and lack of toxicity in humans.

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The Health Economic Consequences of Cardiac Rhythm Device Infections

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Cardiac rhythm management devices (CRMDs) play an important role in treating both bradyarrhythmias and tachyarrhythmias. Given the clinical benefits of CRMDs, they are used with increasing frequency. Last year, more than 100,000 implantable cardioverter defibrillators (ICDs) alone were implanted in the US.¹ However, like all surgeries, CRMD implant and replacement/revision procedures carry a small but serious risk of infection, the resolution of which is hindered by the presence of prosthetic material within the body. Because CRMD systems usually include transvenous leads, CRMD infection can also occur as a consequence of bacteremia from some other source unrelated to primary implant or revision procedures.

As with all implanted devices, infections of CRMD systems often cannot be eradicated with antimicrobial drugs alone. Excepting the most superficial surgical wound infections (eg, “stitch abscess”), successfully treating CRMD infections generally requires the extraction of all implanted hardware.^{2,3} As a result, infections of CRMDs not only pose serious clinical risks for patients, but are also associated with substantial costs to the health-care system.

Treating CRMD Infections

Briefly considering the clinical steps involved in managing CRMD infections provides insight into how these events can quickly become quite expensive. First, some diagnostic workup is required to confirm that device infection is present, and to characterize the nature and extent of the infection. While some cases (eg, erosions of the device pocket) are easily diagnosed based on physical examination alone, most require additional evaluation, usually including blood cultures, basic laboratory tests and, often, imaging studies. Transesophageal echocardiography is frequently recommended to define whether infection grossly involves the intracardiac portion of the leads and/or the right-sided heart valves.³

Once CRMD infection is diagnosed, additional — in some cases, extensive — resources are consumed in treatment. This almost always includes a course of

intravenous antibiotics, the duration of which varies depending on the nature of the infection. Managing medical complications related to the CRMD infection can require long hospitalization and high-intensity care, particularly for endovascular infections, which can lead to septic shock, heart failure, septic embolization, and other morbid and sometimes-fatal events.

Cost of CRMD Infections

Device extraction, which is recommended whenever infection is proven or likely to involve implanted hardware, generates additional costs. Although extracting recently implanted hardware is straightforward and can be done in the electrophysiology laboratory, removing chronic leads is both riskier and more difficult, and may require specialized extraction tools such as locking stylets and laser-assisted extraction sheaths. Experts in lead extraction recommend that operators perform these procedures in an operating room environment under general anesthesia,⁴ steps that improve the safety of difficult lead-extraction cases, but also increase the cost.

Assuming that the patient has an ongoing need for a CRMD device, the cost of re-implanting a new device also must be considered as a component of cost for the overall episode of care. This cost ranges from approximately \$5,000 to \$35,000 (for hardware alone), depending on the type of device implanted.

From the preceding discussion, it should be apparent that the costs of treating CRMD infections are highly variable, but on average quite significant. Few investigators have reported empirical estimates of the true costs of these events in literature. A carefully done analysis⁵ from a single center in the mid-1990s reported an average cost of ~\$25,000 to manage pacemaker infections, based on detailed review of the medical records and billing data from 16 cases. A single case of an infected ICD in that series cost the hospital more than \$50,000 to treat. Another single-center report⁶ of *Staphylococcus aureus* infections in patients with cardiac prosthetic devices estimated the 12-week cost of community-acquired infections at ~\$41,000 and of hospital-acquired infections at ~\$83,000. However, this analysis included patients with prosthetic heart

valves and circulatory support devices in addition to those with CRMDs. Therefore, the costs of CRMD infections are likely lower than these estimates.

A study of ICD recipients in the Medicare program in fiscal year 2003 also estimated the incremental costs associated with a discharge diagnosis of implant-associated infection during the same hospital admission in which an ICD was implanted.⁷ Based on multivariate regression models comparing patients with and without infections, the authors estimated the incremental length of stay associated with ICD infection at 9.6 days and the incremental costs at ~\$18,500 — on top of average hospital costs of \$40,000 for an uncomplicated ICD implantation.

Based on these limited data, one can conclude that the average cost of managing an infected CRM device is probably at least \$20,000 to \$25,000, and possibly much higher. Factors likely to be associated with higher costs include greater hardware costs of ICD compared with pacemaker systems; ICD use being associated with a patient population with more structural heart disease; infections occurring after generator replacements as opposed to *de novo* system implants (the removal of chronic leads is more likely to require advanced extraction methods compared with recently implanted leads); and the occurrence of endovascular compared with isolated pocket infections, given the serious clinical sequelae associated with bacteremia and endocarditis.

Conclusion

The considerable costs of CRMD infections highlight the importance of undertaking clinical measures to prevent these problematic events. Closely consider those patients in whom infection is most likely to occur, as well as those in whom device infection is like-

ly to be most costly from both clinical and economic perspectives, to help identify scenarios in which extra efforts to avoid device infection provide the most cost-effective bang for the buck.

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