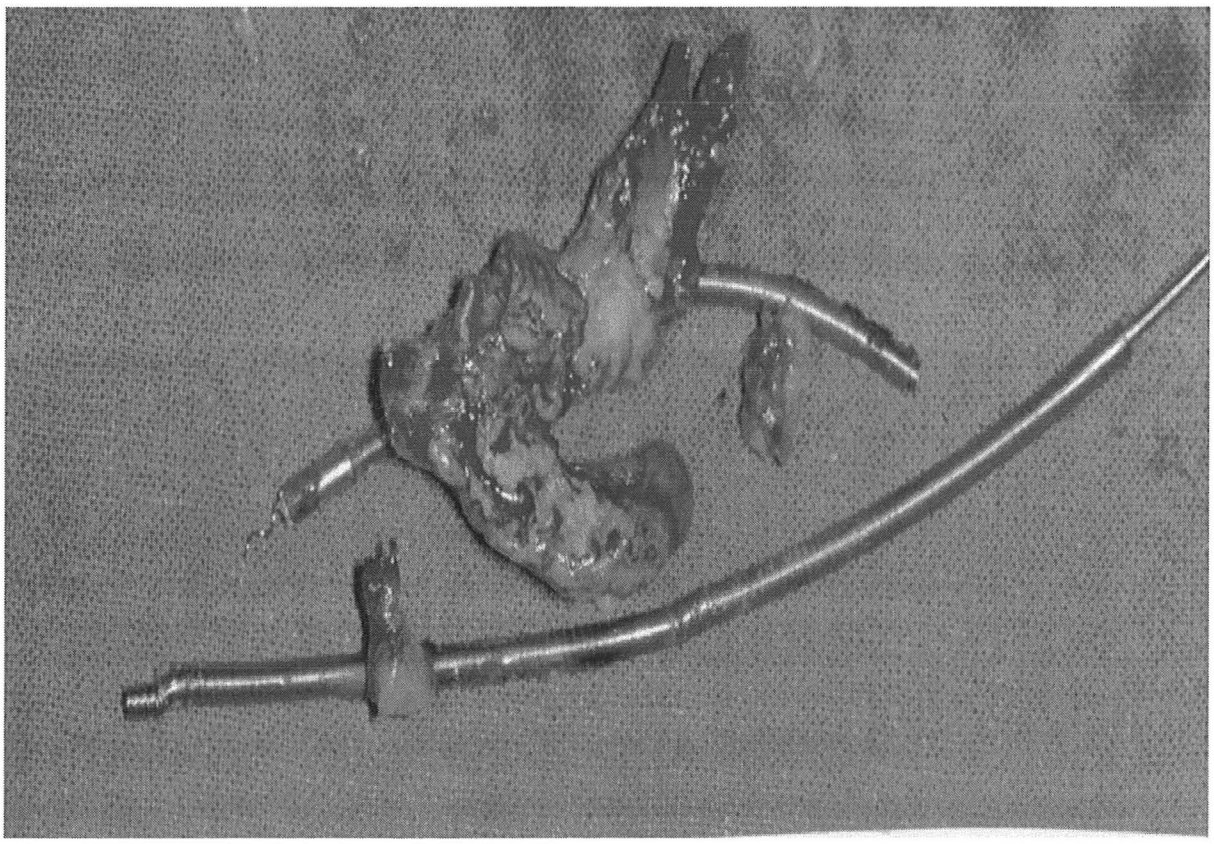
Cardiac Device Infections
When Good Devices Go Bad

Gail Peterson, MD
Associate Professor of Medicine
UT Southwestern Division of Cardiology
Internal Medicine Grand Rounds
November 9, 2007



This is to acknowledge that Gail Peterson, M.D. has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Peterson will be discussing off-label uses in this presentation.

Introduction

Cardiac devices have become an integral aspect of modern cardiovascular medicine. According to one estimate there are more than 3.25 million patients with permanent pacemakers (PPM) worldwide in the year 2000.[1] PPMs have well established indications for the treatment of arrhythmias. In recent years, there have been increasing numbers of implantations of PPMs and particularly of internal cardioverter-defibrillators (ICD) (Figure 1).

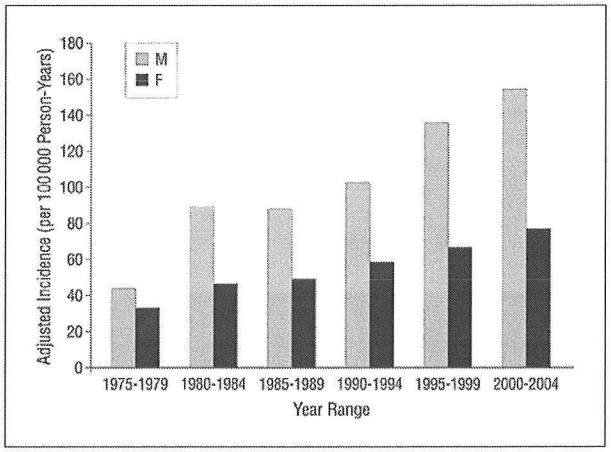


Figure 1. Incidence of cardiac device implantation, Olmsted County, Minnesota, 1975 2004 (age adjusted to the population of white individuals in the United States in 2000) From Uslan,D. Z. Arch Intern Med 2007

The rise in implanted devices can be attributed to expanded indications after encouraging results were observed in randomized controlled trials. These studies demonstrated that in selected populations, permanent pacemakers and implantable ICDs improve survival rates, symptoms or both.[2-7] In the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II) trial, patients with a history of myocardial infarction and left ventricular ejection fraction of 30% or less had significantly improved survival with an ICD.[3] Similar improvements in survival was evident in the Sudden Cardiac Death in Heart Failure trial (SCD-HeFT) in patients with ischemic or non-ischemic cardiomyopathy, left ventricular ejection fraction of 35% or less and New York Heart Association functional class II or III congestive symptoms were treated who were treated with an ICD.[8] Patients with heart failure, particularly the subset with left bundle branch block, have dyssynchronous left ventricular contraction with the intraventricular septum contracting prior to the left ventricular free wall. This dyssynchronous contraction leads to reduced left ventricular ejection fraction and cardiac output. Pacing both the left and right ventricle, or cardiac resynchronization therapy (CRT), is increasingly being used to reduce the effects of cardiac dyssynchrony on left ventricular function and functional status. CRT has been shown to improve symptoms, reduce hospitalizations and mortality from heart failure in subsets of patients with advanced heart failure.[2,5-7] These new indications, along with the aging US population, ensure that the number of cardiac device implants will continue to rise in the foreseeable future.

Despite the well documented benefits from these devices, they paradoxically place the same population at risk for device-related complications. The most common complication is infection. With the escalating number of devices implanted, it is not surprising that infections involving cardiac devices are increasingly encountered in clinical practice.

Epidemiology

The published incidence of pacemaker infections ranges from 0.6-5.6% in recent series.[9-

[12] The rate of ICD infections is less well described, but published rates range from 0.7-6.9% and may even be higher when the devices are implanted surgically.[11,13-15] The first population-based study to assess the cumulative probability of device infection (in the predominately white population of Olmstead County, Minnesota) found a higher incidence of ICD infection compared with PPM infection. In their cohort population of 1524 patients followed from 1975 to 2004, the incidence of pacemaker infection was 0.1% per year, and the incidence of ICD infection was 0.89% per year.[16]

Of patients with cardiac device infections (CDI), 10-23% will have device endocarditis, or infection involving an endocardial lead.[1,17,18] A population based study from France described the incidence of pacemaker endocarditis at 550 cases/million recipients per year.[19]

Two recent studies evaluating large databases (Medicare and the National Hospital Discharge survey) found an alarming increase in CDI in the United States, outpacing the number of device implantations. In a 20% random sample of Medicare beneficiaries there was a 42% increase in device implantation from 1990 to 1999.[20] During this same time period, there was a 124% increase in the rate of CDI infections in this population (from 0.9 to 2.1 cases per 1000 beneficiaries, $p<0.001$). In an evaluation of the National Hospital Discharge Survey from 1996 to 2003; there was a 49% rise in the number of new cardiac rhythm management devices in the US, from 159,585 in 1996 to 237,720 in 2003 (Figure 2).[21] Most of this increase was driven by ICD insertions (160% for ICDs and 31% for PPMs), although the absolute number of PPM implantations remained higher. There were no significant changes in the demographic characteristics of patients receiving cardiac device implantations. In the same period, the number of hospitalizations for CDIs increased 3.1 fold (2.8 fold for PPMs and 6 fold for ICDs). The authors also found that after correcting for age, gender, race, hospital size, presence of diabetes mellitus or renal failure, CDI increased the risk for hospital death more than 2 fold.

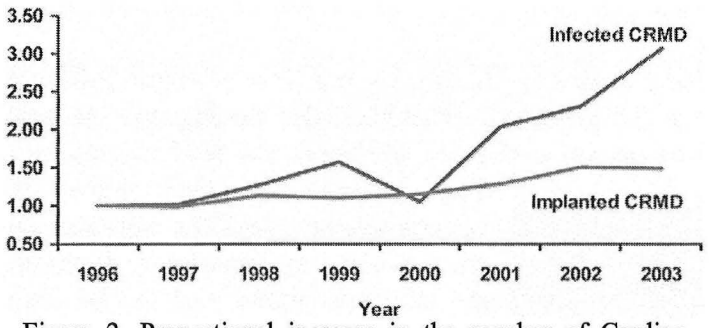


Figure 2. Proportional increase in the number of Cardiac Rhythm Management Devices (CRMD) implanted and those infected by the year of hospitalization, normalized to the number of devices implanted and infected in the year 1996. From Voigt, JACC, 2006.

The reasons for the disproportionate increase in CDI are not fully understood, but may reflect in part an improved understanding of the presentation and diagnosis of CDI. The advanced age, accompanying comorbidities, and inevitable contact with healthcare personnel all contribute to an increased likelihood of infection in this population. Patients with devices in place require hospitalization, often for congestive heart failure, and are therefore at increased risk for nosocomial bacteremia. The improved survival of device recipients results in more days at-risk for infection. In addition, the increased demand for devices may result in less experienced

operators placing the devices, as devices placed by lower volume operators are more likely to become infected.[22]

A more relevant question may be not the overall incidence of CDI among patients with these devices, but rather the incidence of CDI in patients who present with bacteremia. According to one survey, the incidence of blood stream infection (BSI) in patients with devices in place is 10.1 per 1000 device-years.[16] To assess the incidence of device infection during bacteremia, Chamis prospectively evaluated 782 consecutive patients with *S. aureus* bacteremia. Of these 782 patients, 33 had a cardiac device. Device involvement in the infection was confirmed in 45% (15 of 33), 58% were cured, 36% died and 6% relapsed. Of the 15 patients with confirmed CDI, nine showed no local signs or symptoms; such subclinical presentation could lead to delayed recognition of infection and delayed device removal. In this study, there was a nonsignificant but strong trend toward higher mortality in patients whose devices were not removed compared with those with complete device removal (48% vs. 17%). In a retrospective study of 21 patients with *S. aureus* or *S. epidermidis* bacteremia, 67% of cardiac devices were infected.[23] In a population-based Olmstead County survey, twelve of 22 cases of *S. aureus* bacteremia (54.6%) had definite or possible CDI, and 18% had confirmed device infection.[16]

In contrast to *S .aureus* BSI, device infection in patients with gram-negative bacteremia appears to be rare, with definite or possible CDI occurring in only 6% (4% confirmed) in one study and 12% (none confirmed) in another.[16,24] Despite infrequent system removal in patients with gram-negative bacteremia, relapsing bacteremia among surviving patients was rarely seen.[23] Complete removal of cardiac devices in patients with *S. aureus* bacteremia is recommended if there is clinical or echocardiographic evidence for CDI, if there is no clear source for *S. aureus* bacteremia, or if there is recurrent bacteremia after completion of antimicrobial therapy.[25] Device removal does not appear to be required in gram negative sepsis unless there is clear evidence of device infection.

Classification and Definitions

CDI have traditionally been classified anatomically and by the time of onset following implantation. Infection may involve the generator or defibrillator pocket, the electrode patches in the subcutaneous tissue or on the surface of the heart, the lead electrodes as they traverse the soft tissue and venous system, and the valvular and nonvalvular endocardium including the tricuspid valve and the insertion sites of the lead tips. Pocket infections are those where the infection is limited to the generator or defibrillator pocket or the subcutaneous portion of the lead. Infections may track from the pocket to the electrode or to the epicardial surface. When the infections involve

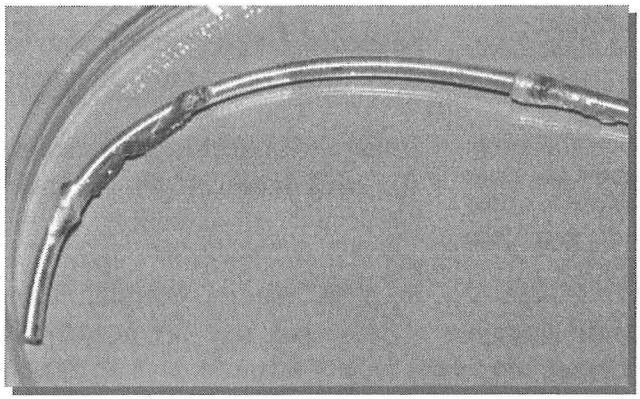


Figure 3. Pacemaker lead with vegetations. Courtesy of Vance Fowler

the intracardiac lead or endocardial surfaces, they are defined as device endocarditis (Figure 3).

Local (pocket) infections are the most common type, and usually develop within weeks of insertion or generator change. The generator pocket infection may occur with or without bacteremia. Those that develop within 2 weeks of implantation are usually caused by *S. aureus*, and may be associated with systemic features and bacteremia.

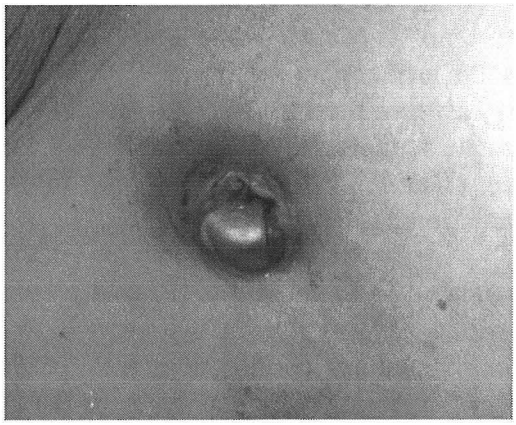


Figure 4. Erosion of a generator due to infection. Courtesy of Mike Jessen

Late infections often develop from erosions through traumatized skin (Figure 4). These are usually infected with skin flora, including *S. aureus*, *S. epidermidis*, other coagulase negative staphylococci and gram-negative organisms. They may be asymptomatic except for the erosion itself.

Device endocarditis may occur from a few days after implantation to years later, and most commonly presents with systemic signs and symptoms.

Early infections are usually defined as occurring in the first month after device implantation or generator exchange (although it has been variably defined by some authors as occurring within the first 12 weeks). Early infection most often arises from intraoperative contamination and is attributable to direct microbiologic seeding of the device or pocket. Late infections are defined as those occurring beyond this time (some authors have also added a delayed category of more than a year after implantation). The determination of origin of late infections is not always clear. Late infection occasionally develops from primary mechanical erosion of the generator or defibrillator through the skin with resultant seeding of the pocket. Infections more than one year after implantation are often related to manipulation of the device (such as battery changeout). In rare cases, late infection may be due to contamination that occurred during the implantation procedure. There have been reports of late infection with *Staphylococcus* species occurring up to 16 months after implantation that were identical to isolates obtained from the pocket site at the time of implantation.[26] Hematogenous seeding of the device from distant sites has been reported, but with the exception of *S. aureus* bacteremia appears to be relatively rare.

Risk Factors

There are many risk factors that have been associated with CDI[15,27,28]. Diabetes is frequently present, reported in up to 75% of infected patients. In one small study, diabetes was the strongest predictor of device infection;[28] In this study, 36% of patients with diabetes mellitus and a device in place developed ICD infection compared with 3.9% of patients without diabetes. However, larger and more recent studies have not found diabetes to be an independent risk factor.[29,30]

Other risk factors identified in descriptive studies include advanced patient age, female sex, malnutrition, malignancy, skin disorders (acne, rash with pruritis, dermatitis herpetiformis), the use of steroids or other immunosuppressive agents, use of anticoagulants, prolonged procedure time, placement of a subcutaneous defibrillator patch, postimplantation pocket hemorrhage or necrosis, and indwelling IV catheters.[10,15,27,31-33] Multiple pacemaker insertions are also associated with higher rates of infection.

In a case control study the presence of more than 2 pacing leads and long-term corticosteroid use were independent risk factors for subsequent infection.[30] Recently, renal insuffiency has been shown to dramatically increase the risk for CDI (OR 4.8).[34] Operator experience with implantation may also be a factor in subsequent risks. A relationship between physicians with lower volumes of ICD implantations and higher subsequent infection rates within 90 days of implantation has been shown.[22]

The Prospective Evaluation of Pacemaker Leads Related to Endocarditis (PEOPLE) trial evaluated 6319 consecutive patient receiving cardiac devices during the year 2000.[29] Over a mean follow-up of 12 months the rate of confirmed device infections was 0.68%. Factors independently related to the development of infection included fever in the 24 hours before implantation (OR 5.8), the use of temporary pacing prior to implantation (OR 2.5) and need for early reintervention (OR 15.0). This study also showed a reduced risk in patients with de novo implantation (OR 0.46) compared with patients undergoing a device revision or replacement.

Pathogenesis

After devices are implanted, they are rapidly coated by various proteins and fibronectin. The ability of staphylococci to adhere to polymer surfaces and their capacity for biofilm formation contribute to the pathogenesis of infections of implanted medical devices. The adherence of *S. aureus* to devices depends on the presence of extracellular and host plasma proteins that have coated the surface of indwelling devices (including fibronectin, fibrinogen and collagen). *S. aureus* adheres to the host-tissue ligands via genetically defined microbial surface proteins, referred to as "microbial surface components recognizing adhesive matrix molecules" (MSCRAMM). Examples of MSCRAMMs include *S. aureus* surface proteins such as fibronectin-binding protein A or B which bind to fibronectin, clumping factor A which binds to fibrinogen, and collagen-binding protein which binds to collagen.

S. aureus and coagulase negative staphylococci are capable of forming biofilm, although the bulk of investigative attention has been focused on *S. epidermidis*. The development of biofilm, a glycocalyx or slime substance is a unique aspect of foreign body infections. Biofilm is a structural community of bacterial cells enclosed in a self-produced glycocalyx or exopolysaccharides, and adherent to an inert or living surface.[35] Almost any surface is susceptible to biofilm formation, including rocks in a stream, teeth in the mouth, and pipes delivering water.

Biofilm formation may be divided into phases (Figure 5). First, the attachment involves adhesion molecules, physiochemical, protein and polysaccharade factors. Adherent bacterial cells produce exopolysaccharides and then proliferate within the self-produced biofilm, largely protected from antibiodies, phagocytes and antibiotics. Phagocytes are attracted to the biofilm and release phagocytic enzymes. Although the biofilms are protected, the phagocytic enzymes damage tissue around the biofilm and bacteria are released; this release may cause dissemination and acute infection in the neighboring tissue. Adherence of S. epi is mediated by specific adhesions such as the proteinaceous autolysin encoded by the *altE* gene, the capsular polysaccharide adhesion (PSA) thought to be encoded by the *ica* operon, and the fibrinogen binding protein encoded by the *fbe* gene.[36,37] The initial adherence phase is followed by accumulation of bacteria and adherence to one another, which is mediated by the polysaccharide intercellular adhesion (PIA) also encoded by the *ica* operon.[38]

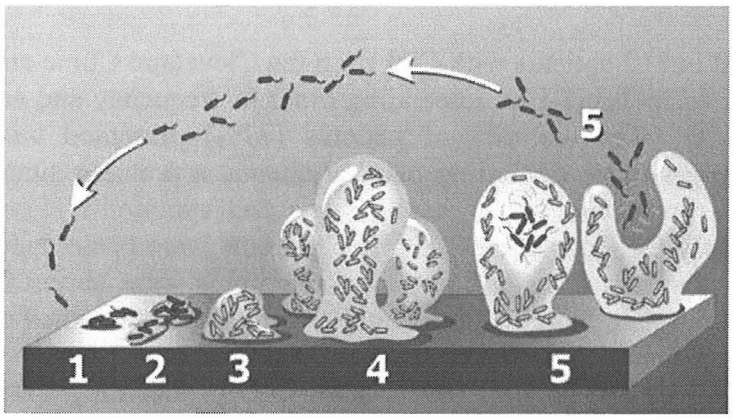


Figure 5. Biofilm formation
From: biology.binghamton.edu/davies/images/biofilm.jpg

S. epidermidis strains involved in pacemaker and intravascular catheter related infections are much more likely to have fbe, altE and ica genes compared to saprophytic strains found on the hands of nonmedical personnel.[39] These genes and their products may be useful for future targets for diagnosis and therapy. There is data that antibodies to purified PSA prevent catheter-related bacteremia and endocarditis in an animal model.[40]

Biofilm not only enhances the pathogen's ability to adhere to foreign material, it limits host defenses. Neutrophils, mononuclear cells and natural killer cells do not function normally in this environment.[41] Neutrophils have decreased phagocytic and bactericidal ability, decreased opsonization and increased release of oxygen-free radicals and lysosomal enzymes, resulting in local tissue damage.[41] Biofilm also increases bacterial resistance to antibiotics 500 fold.[42] It is the presence of biofilms that make device infections difficult to eradicate with antibiotics and the host immune response alone.

Clinical Presentation

The diagnosis of CDI is hampered by the variable clinical presentation and lack of sufficient diagnostic critiera.[43] The clinical presentation is highly variable both in regard to time of onset and clinical severity. Several studies have examined the timing of infection with regard to device implantation and all have defined early and late infections slightly differently. Still it is apparent that 25-35% of device infections occur in the early

weeks to months after implantation while the majority of infections, approximately 70%, occur 6 months or more after implantation.[1,12,44-46]

The clinical manifestations found in 312 patients with CDI from the Cleveland Clinic and Mayo Clinic series are summarized in Table 1 in descending order of frequency and are consistent with earlier reports.[1,47] The majority of patients (77%) presented with symptoms localized to the pulse generator (including pain, erythema, a draining sinus, erosion, and warmth), and 11% presented with systemic signs and symptoms alone. Documented fever occurred in only 34% of patients. 37% of patients were bacteremic, but among the patients with bacteremia, fever and systemic symptoms were absent in 40%. Therefore, it is important to obtain blood cultures in all patients with suspected or proven device infections. In this patient population systematic echocardiograms were not performed on all patients. A total of 216 patients (69%) underwent echocardiography, and 57 had vegetations. Therefore, 18% of the population was diagnosed with device endocarditis.

Table 1. Clinical manifestations of device endocarditis. From dy Chua, Ann Intern Med 2000; Sohail, JACC, 2007.

	dy Chua n=123		Sohail n=189		Total n=312	
Manifestation	n	%	n	%	n	%
pocket erythema	67	55%	128	68%	195	63%
pocket swelling	44	36%	127	67%	171	55%
pocket pain	68	55%	93	49%	161	52%
draining sinus	52	42%	95	50%	147	47%
bacteremia	40	33%	76	40%	116	37%
fever documented	23	19%	82	43%	105	34%
chills	27	22	73	39%	100	32%
pocket warmth	28	23%	71	38%	99	32%
purulent drainage	28	23%	65	34%	93	30%
pocket erosion	39	32	48	25%	87	28%
malaise	26	21	79	42%	81	26%
anorexia	14	12%	32	17%	46	15%

The presentation of patients with lead infection is differs from the presentation of device infections. In studies confined to the analysis of patients with device endocarditis, fever is more common, occurring in 78-100% of patients.[12,18,44,45,48] A new or changing murmur was present in 13-20% of patients.[12,18] Local symptoms may be present in only 24-52%.[44,45,48] Increased erythrocyte sedimentation rate, leukocytosis, and microscopic

hematuria are the most common laboratory findings.[18,44,48] Evidence for pulmonary embolism is present in 12-30% on presentation.[12,44,45,48]

The diagnosis is not difficult in patients who develop systemic features of infection (including fever, pain, chills, and swelling localizing the infection to the device). However, in more than 1/3 of cases, fever and septic shock may be the only sign. Acute severe disease is usually associated with *S. aureus*, although infections with coagulase negative staphylococcus may cause similar manifestations. In one series of late-onset cases (*S. aureus* 14%, coagulase-negative staphylococci 81%) the mean time from onset of symptoms to diagnosis was 8 months (range 1-48 months).[44]

Diagnosis

Identification of CDI can be challenging given the wide array of presenting symptoms and lack of a gold standard. Most investigators now use local signs of inflammation at the generator pocket (erythema, warmth, fluctulance, wound dehiscence, drainage or erosion) as clinical evidence supporting device infection.[16,25,47] Endocarditis is diagnosed if valvular or lead vegetations are found by echocardiographic imaging, or if modified Duke criteria for infective endocarditis is met.[16,25,47,49,50] Duke criteria have been used for device IE, but do not incorporate coagulase negative staphylococcus as a major criterion. Additional criteria have been proposed specifically for device endocarditis that include CP, pulmonary scintigraphy and pulmonary and local symptoms to increase the sensitivity for the Duke criteria.[43] Device infection can be confirmed microbiologically if culture or gram stain from the generator pocket or lead is positive for organisms. Infection can be rejected if there is no evidence for device infection, the device is not removed, and there is no evidence for relapse within 12 weeks.[16,25]

All patients suspected of pacemaker infection should have at least 2 sets of blood cultures performed. Those with bacteremia or suspected endocarditis (such as patient with septic pulmonary emboli) should also undergo TEE as an initial study due to the low sensitivity of chest wall echocardiography in this setting. A bubble study should be performed in patients in whom percutaneous lead extraction is planned, to exclude a patent foramen ovale or atrial septal defect which could place the patient at risk for systemic embolism during device removal. At the time of device removal cultures should be obtained from the device pocket and from all lead tips and mesh.

In ambiguous cases, ultrasound of the pocket site can identify fluid collections in the area. Some fluid may be present early after implantation of the generator or defibrillator, but accumulation months to years after implantation is uncommon. If the diagnosis remains in question, ultrasound directed percutaneous aspiration may be considered, but can also lead to secondary infections.[51] Tagged leukocyte or gallium scanning may also be helpful distinguished infection from a noninfected fluid collection.

Microbiology

The microbiologic profile of CDI (Figure 6) is different from valvular infective endocarditis. The majority of infections of cardiac devices are caused by staphylococcal species, which account for 70-90% of infections in most series.[1,17,52] Polymicrobial

infections are present in 8% of cases, and appear to be more frequent in patients on corticosteroids or diabetes mellitus.[1]

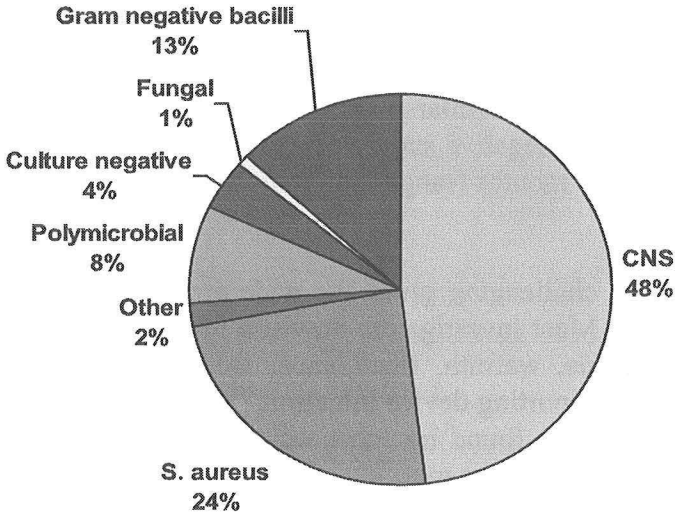


Figure 6. Microbiologic profile of cardiac device infections. From Chua, Ann Intern Med, 2000; Sohail, JACC, 2007

Cultures from the generator pocket yield microorganisms in 75%. Blood cultures are positive in 40% of all cases. Some studies have suggested that infections occurring early after implantation are more likely due to *S. aureus* and late infections are more commonly caused by CNS[12,18,44,53] although other studies found the opposite to be true.[53] The microorganisms causing device endocarditis are similar to the group of CDI as a whole.

Echocardiography

Several studies have examined the role of echocardiography in the diagnosis of CDI.[12,44,45,53] Table 2 shows a comparison of transthoracic (TTE) and transesophageal (TEE) studies in patients with confirmed pathologic device endocarditis who had both studies performed. In five studies TTE detected vegetations in 22-43% of cases compared with TEE which detected 87-96% of cases.[12,44,45,48,53] These and other studies have demonstrated the superiority of TEE for detecting vegetations on endocardial leads.[25,44,53] Transesophageal echocardiography allows excellent visualization of the device leads from the superior vena cava through to the attachment sites in the right atrium and ventricle (Figure 7). Two studies

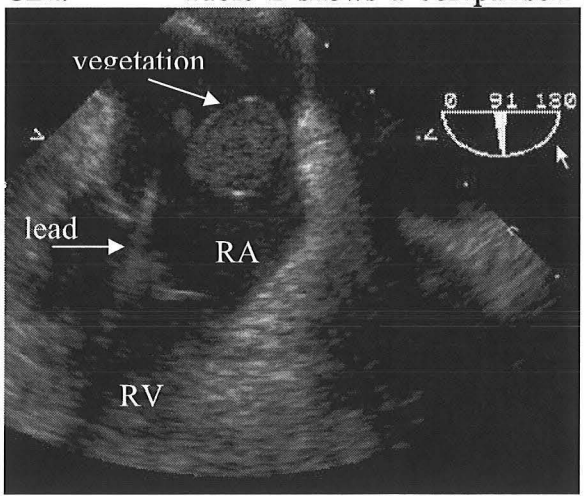


Figure 7. Transesophageal echocardiogram of a pacemaker vegetation.

compared TEE to surgical findings, and found a high concordance (84%-92%).[44,53]

Table 2. Sensitivity of echocardiography in device endocarditis

AUTHOR	N	TTE	TEE
Del Rio 2003	23	9 (39%)	20 (87%)
Victor 1999	23	7 (30%)	22 (96%)
Cacoub 1998	33 with TTE, 24 with TEE	9 (22%)	23 (96%)
Klug 1997	52	12 (23%)	49 (94%)
Massoure 2007	60 with TTE, 56 with TEE	26 (43%)	50 (89%

One difficulty in evaluating these patients is that we don't have good data on the normal echocardiographic appearance of noninfected leads. In one study, TEE was also performed on a control group of 17 noninfected patients, and small strands were evident in 29%.[45] These strands differed from those occurring in patients with clinical evidence for CDI by being much smaller in their measurements (1-2 mm x 3-5 mm in the noninfected controls versus 2-25 mm x 15-30mm in device endocarditis).

Complications of Infection

Pulmonary lesions including pleural effusions, pneumonia, pulmonary abscess, pulmonary embolism and recurrent bronchitis may be present in 32-43% of patients with device endocarditis.[44,53] In one series, 7 of 17 patients had positive findings on V/Q scans, although it was not clear why the perfusion studies were performed.[53] In another series, 30% (13 of 36 patients) had positive V/Q scans, including 5 patients with no suggestive history of pulmonary embolism.[44] Published experienced regarding the role of CT angiography in patients with CDI is lacking.

Septic arthritis, osteomyelitis, lung, brain, liver, splenic and perinephric abscesses have all been described as complications of CDI.[47] Thrombosis of a vein where leads were in place can also occur. The procoagulant effect of bacteria and leucocytes is known, and thrombi present within the intravascular device can harbor and protect microorganisms. In an evaluation of patients with *S. aureus* bacteremia and indwelling intravascular catheters, the incidence of probable or definite intravascular catheter-associated thrombus was 71%.[54]

Management

Antibiotic Therapy

There are no prospective studies evaluating antimicrobial treatment protocols in patients with CDI. The AHA guidelines recommend only that antibiotic therapy should be directed against an identified pathogen and guided by susceptibility testing.[55] If no pathogen is recovered, empiric therapy should be broad-spectrum to cover nosocomial and skin-colonizing microbes, and should include vancomycin. According to the AHA scientific statement, a minimum of 14 days of intravenous antibiotics should be used after the removal of the device and the first negative blood culture. Four weeks of antibiotics after the device is removed should be given for patients with *S. aureus* bacteremia or if

vegetations are present. For patients with complicating osteomyelitis or left-sided endocarditis, a 6-week parenteral treatment course is used widely.

Chambers provided recommendations for therapy for staphylococcal device infections in a recent and comprehensive review. (Table 3)[52] Linezolid and the combination of quinupristin/dalfopristin offer options for methicillin-resistant staphylococci, but should be reserved for patients with vancomycin-resistant organisms or when patients are intolerant to vancomycin.

Table 3. Recommended antibiotic therapy for staphylococcal CDI. Adapted from Chambers, Intern Med J, 2005

Clinical Context	**Treatment***
Empirical Therapy	Vancomycin (IV)
Organism known and infected leads able to be removed	Treat 2-4 weeks once leads removed
S. aureus, coagulase negative staphylococci	Flucoxacillin or dicloxicillin 2 gm IV q 4 hr *or* Cefazolin 2 gm q 8hr IV *or* Vancomycin (IV) *plus* gentamicin 1 mg/kg q 8hr IV**
Organisms known and infected leads unable to be removed	Treat for 4-6 weeks IV then suppress
S. aureus, coagulase negative staphylococci	Flucloxacillin or dicloxacillin 2 g IV q 4 hr IV *or* Cefazolin 2 gm q 8 hr IV *or* Vancomycin (IV) *plus* gentamicin 1 mg/kg q 8hr IV
Suppressive therapy	Treat long-term Flucoxacillin or dicloxicillin 500-1000 mg po TID or QID *or* Cefalexin 500-1000 mg po TID or QID *or* Floroquinolone plus rifampin

*Recommendations are dependent on susceptibility testing of pathogen. Doses should be modified according to renal function and occurrence of adverse events.
**Peak gentamicin plasma concentractions should be 2-4 mg/L, troughs < 1 mg/L

Recently the Mayo clinic suggested guidelines for duration of antibiotic therapy based on their own experience and a review of the literature (Figure 8).[17] Cases with only pocket infection may be treated with 10-14 days of antimicrobials, and those with blood stream infection for 4 weeks after device removal. A small number of patients have a positive culture of the lead tip, but do not have bacteremia, systemic features of infection or echocardiographic evidence of endocarditis. Although there is no data supporting a specific duration of therapy, patients should probably receive 4 weeks of parenteral antimicrobial therapy and considered as having endocarditis.

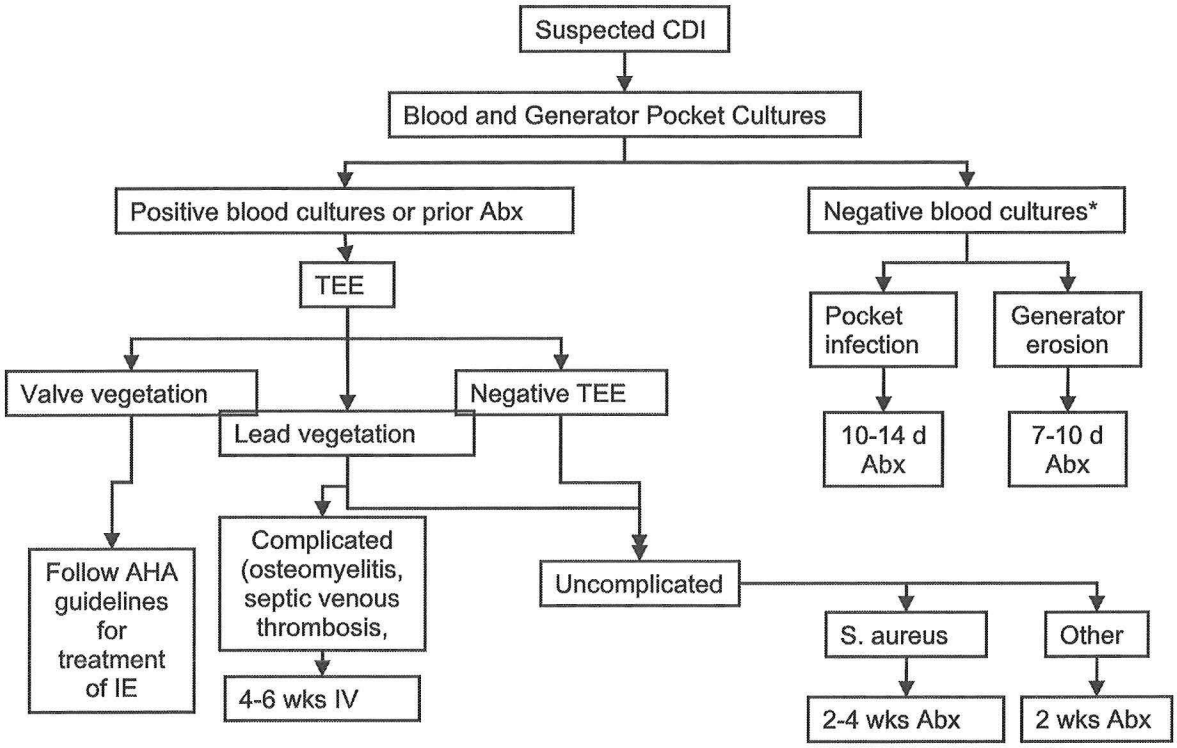


Figure 8. Suggested approach to diagnosis and duration of antimicrobial therapy for device infections. Adapted from Sohail 2007
*TEE should also be performed on patients with suspected IE such as those with septic pulmonary emboli

System Removal

Lead removal can be difficult due to the endotheliazation and fibrocollagenous sheath formation that occurs within months of implantation. Two techniques for removing cardiac devices are available: invasive thoracotomy and percutaneous extraction.

Until relatively recently, simple traction was the only means available for percutanous removal. This method had a relatively low success rate, particularly with longer duration between lead implantation and extraction. More recent developments in lead extraction have improved the success of percutaneous removal. A locking stylet is now available to lock within the lumen all the way to the tip so that the entire lead can be removed when traction is applied.[56] A telescoping sheath can be advanced over the lead to apply counterpressure along the lead body, advancing over the lead to shear off the fibrous tissue binding the wires to the endocardium or vein. The sheath can then be used to apply countertraction during lead extraction, preventing inversion of the myocardium.[57] More recently, sheaths powered by

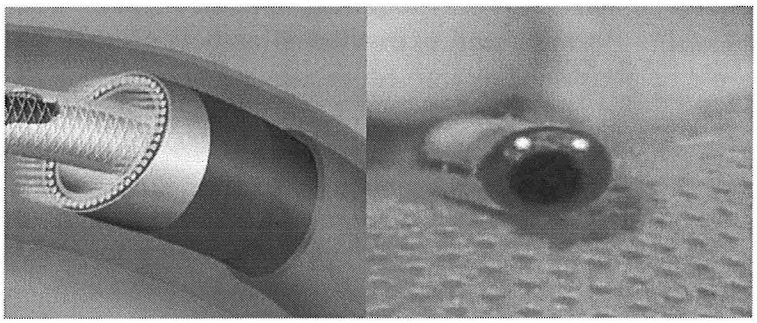


Figure 9. Laser sheath on left, electrosurgical sheath on right. From Verma, 2004

various ablative energy sources have been developed as an alternative to using mechanical force (Figure 9). In the PLEXES study, the use of the excimer laser was shown to result in a better rate of complete lead removal compared to unpowered mechanical sheaths in patients whose leads were in place for at least one year.[58] An electrosurgical sheath that uses radiofrequency energy is also available, which is less expensive and appears to be as effective as the laser sheath. Successful percutaneous extraction may be performed in 74-95% of patients.[44,45] Using the above mentioned techniques, complete extraction success rate is as high as 95%.

Indications for surgical removal are failed percutaneous extraction, and suspected infection of epicardial leads. Pericarditis and evidence for deep mediastinal infection on imaging studies (CT or leucocyte-labelled scans) should prompt surgical removal of the entire device. Surgery involves a thoracotomy or sternotomy, which involves additional risks. A minimally invasive video-assisted technique under thoracoscopic vision has also been described.[59]

Complications of removal

Major complications can occur in as many as 3.3% of patients.[60,61] Major complications of percutaneous extraction include myocardial avulsion, vascular tears, pulmonary embolism, pneumothorax, arterovenous fistula, and death. Additional complications include pericardial effusion, hematoma, arrhythmias, and venous thrombosis.[60]

In an evaluation of consecutive patients from the US Extraction Database, major complications occurred in 1.9% of patients, including death (0.4%), urgent cardiovascular surgery (0.8%), and pericardial or pleural drainage (0.5%).[60,62] The risk of failed extraction is greater the longer the lead has been in place, most likely because scar tissue formation increases over time. Data on whether infected leads may be easier to remove are conflicting, but complication rates in these patients may be higher.[60,63,64]

In a recent survey of infected leads, 20 of 163 patients (12%) had complications with percutaneous removal, including tricuspid valve damage requiring surgery, subclavian vein laceration, fracture of lead tip requiring surgerical intervention, hemorrhage, and hemothorax.[17] One patient died from hemorrhage. In the same survey, 5 of 19 patients (26%) had complications with surgical removal including hemorrhage, postoperative cardiac arrest, subclavian laceration and ventriculotomy requiring operative repair. There was one death in this group as well. Because lead extraction is associated with life-threatening complications, it should be performed by trained, experienced physicians.

Management of Large Vegetations

In the past there were concerns that patients with vegetations greater than 1 cm in dimension undergo surgical removal of the leads over concern that large vegetations will result in hemodynamically significant pulmonary embolism. However, there have been no randomized studies comparing surgical versus percutaneous removal of infected devices. When considering the means of removal the incremental risk of causing pulmonary embolism, or further pulmonary embolism must be weighed against the risks associated with cardiopulmonary bypass surgery. There have been several authors

advocating percutaneous removal regardless of vegetation size. In two studies percutaneous removal of large vegetations (>1 cm) was performed and no patient had clinical signs or symptoms of pulmonary embolus, although systematic diagnostic evaluation was not performed.[12,45] One group of investigators performed pulmonary scintigraphy on all patients with lead vegetations following device removal and found evidence for pulmonary emboli in 55%, although survival and hospital length of stay were not affected by these findings.[46] Since evaluation for pulmonary emboli only occurred after lead extraction, the investigators could not determine when the embolism occurred (prior to and/or following device removal). Another study systematically evaluated patients with device endocarditis before and after device removal with pulmonary scintigraphy.[44] Evidence of vegetation migration occurred in 30%, but only one had clinical evidence for embolism.

More recently percutaneous extraction of even large vegetations (up to 7 cm) was shown to be associated with no clinical evidence of embolism.[17,65] Some authors advocate percutaneous removal of large vegetations in the operating room with full equipment for immediate extracorporeal bypass if acute right heart failure or severe embolism occurs.[65]

Importance of Device Removal

Because of the expense of replacing devices and potential complications associated with percutaneous or surgical removal, physicians may be tempted to leave part or all of the device in place and treat with antibiotics alone. There have been no prospective or randomized trials to examine antimicrobials alone with complete device extraction in addition to antimicrobials. However, there is compelling evidence for complete system removal in patients with CDI, as relapse rates in patients with incomplete device removal are unacceptably high in comparison.[1,12,31,53,66] In a review of 75 patients with CDI (17 with bacteremia) all of the patients treated with complete device removal initially were cured.[31] Thirty-two were treated conservatively with antibiotics and local incision and drainage, and only one was cured. After subsequent device removal of the system, all remaining 31 patients were cured. In a review of 123 cases of CDI, 3 of 6 patients without compete hardware removal relapsed.[1] In Chamis' study, patients in whom the device was left in place were more likely to die or fail therapy compared to those whose device was completely removed.[25] Patients with device endocarditis without complete system removal have been consistently shown to have a higher mortality rate.[12,48,53] Although there is only retrospective data, most guidelines including a recent American Heart Association statement[55] recommend complete device removal along with antibiotic therapy in patients with documented CDI.

Device-dependent patients

Before the new implantation is placed, the cardiac rhythm can be controlled by a temporary transvenous pacemaker if needed. Recently a technique was described which would allow patients in this situation to ambulate freely. In the ipsilateral side of the infection and proximal to the infected site, a permanent bipolar lead is inserted transcutaneously via jugular or subclavian vein and placed in the right ventricle. The lead is fixed into the skin and then is connected to the infected explanted pulse generator, which can be taped externally to the chest wall. This results in the patient having a more

stable system than traditional temporary systems.[67] For patients at risk of ventricular arrhythmias with ICD infections, a wearable external defibrillator is commercially available and should be considered as an option to allow for patients to complete antibiotic therapy as an outpatient.

Timing of Reimplantation

The timing of reimplantation of a new device, if needed, remains a subject of debate among experts, and depends in part on the infecting microorganism and clinical presentation. Some investigators have suggested delaying the implantation of a new device for 10-14 days in the setting of a pocket infection without BSI, and up to 6 weeks in bacteremic patients.[68] Others suggest that the device may be safely reimplanted once the pocket has been adequately debrided and follow-up blood cultures are negative.[1,17]

In a recent series, the median time between explantation and reimplantation was 5 days.[1] In another series, the median time was 13 days in patients with bacteremia versus 7 days in those with negative blood cultures.[47] Both series had low rates of relapse. Recommendations based on the Mayo clinic experience are shown in Figure 10. The device reimplantation should be in a different site (the contralateral side, if possible) once blood cultures show no growth. The need for ongoing device therapy should be considered carefully before reimplantation, since 13-52% of patients may no longer require pacemaker or ICD support.[1,17,53,61,64]

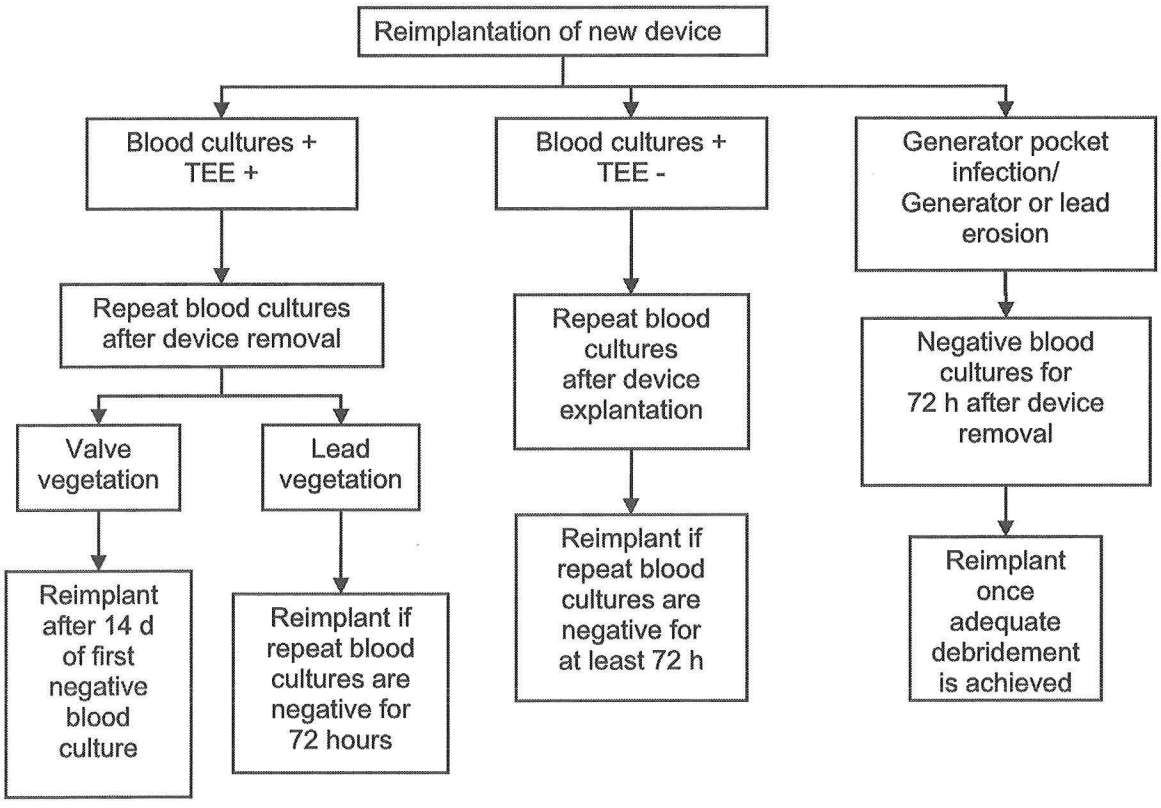


Figure 10. Suggested approach for timing of new device reimplantation. From Sohail, JACC, 2007

Some authors advocate a single-staged exchange with infected device removal and implantation of a new device at the same setting, provided the new device can be implanted in a new pocket site.[69] However, this technique raises concern over the risk of seeding a new device if unrecognized bacteremia is still present.[52]

Suppressive Therapy

There are no well-designed prospective studies providing guidelines for optimal management for patients who are not candidates for percutaneous or surgical device removal. There exists one retrospective study of 51 patients treated with a variety of long-term oral antibiotics, after a minimum of 4 weeks of intravenous antimicrobial; 51% of patients received suppressive therapy for one year or more and only 7% relapsed.[70] In another study of four patients with infected ICDs, long-term beta-lactam based antimicrobial therapy was associated with no clinical recurrences over 21 months of follow-up.[71] An attractive approach is to use a combination of rifampin and a fluoroquinolone as used in patients with infected joint prostheses,[72] although this combination has not been evaluated for CDI in published studies. Long-term suppressive therapy should be reserved only for patients in whom device removal poses unacceptable risks.

Summary of Management

In the absence of prospective studies the consensus therapeutic approach recommends early removal of the entire device system plus appropriate antibiotics for 10-14 days in patients without bloodstream infection, and for 4-6 weeks in patients with lead-associated endocarditis. Surgical instead of percutaneous removal is performed in the setting of epicardial leads, right to left shunts, and may be considered in the setting of large vegetations (>2 cm). When surgical removal is not possible for clinical reasons (such as in high risk patients) prolonged chronic suppressive oral antibiotics have been given successfully.[70]

Outcomes

Mortality

Death rates are higher in the setting of device endocarditis compared with CDI in the absence of vegetations. Of 189 patients with CDI, 9 (5%) died, of whom 7 died during the index hospitalization.[17] Five of the nine deaths had device-related endocarditis. *S. aureus* was the most common organism in patients who died. Two late deaths were among the 5 patients with relapse of infection (one who had incomplete device removal, and the other who had a temporary pacing wire before insertion of a new device)

Table 4 shows mortality in patients with device endocarditis treated by medical intervention alone compared with those treated by a combination of antibiotics and complete device removal in several series.

Table 4. Complete device removal with antimicrobial therapy compared with antimicrobial therapy alone in the management of device endocarditis. (adapted from Cacoub, AJC, 1998, del Rios 2003, Massoure, 2007)

Author	DEVICE IE		Electrode removal (%)	Medical Mortality (%)	Medical/surgical mortality (%)
	Definite	Probable			
Corman 1975	4	1	60	50	33
Morgan 1979	0	12	67	50	25
Bluhm 1982	4	10	57	33	13
Choo 1981	14	0	100	-	0
Glock 1986	0	7	100	-	29
Loffler 1988	0	9	100	-	0
Arber 1994	25	12	57	31	20
Cacoub 1998	33	0	100	-	24
Del Rio 2003	31	0	77	14	12
Massoure 2007	60	0	95	66	16
Total	**80**	**51**	**81**	**41**	**17**

It is difficult to accurately compare treatment strategies since randomization of therapy was not performed and most of the series did not specify the inclusion and exclusion criteria for surgery. However, medical therapy without complete removal consistently is associated with a worse outcome, with overall mortality rate of 41% in the group treated with antibiotics alone compared with 17% in those treated with antibiotics along with system removal.[12,48,53] Therefore while there remain case reports of patients treated successfully with antibiotics alone or with incomplete device removal, most experts agree that complete device removal must be performed in the setting of device infections (regardless of whether there is evidence for endocarditis).

Relapse of infection

In one study, relapse occurred in 1/117 patients (0.86%) after device removal and in 50% (3 of 6) patients without complete device removal.[1] The patient who relapsed after complete device removal had the second generator implanted into the old pocket. In a more recent study, relapse occurred in 5 of 189 patients (2.6%). Three of the patients with relapse had incomplete device removal, and the other two had temporary wires as bridges between explantation of the infected device and reimplantation of a new device.

Economic Consequences

The economic consequences of device infection are underscored by the fact that treatment of CDIs not only requires complete removal of the system, but in most cases replacement with a new system. Costs include hospitalization, diagnostic procedures, antibiotic delivery, two surgical procedures and a new device. The average cost of treatment has been estimated at $25,000 for PPM infection and $50,000 for ICD

infection.[68,73] A prospective study with prosthetic devices (including PPMs, ICDs, prosthetic heart valves, ventricular assist devices) and *S. aureus* bacteremia found the average cost of *S. aureus* bacteremia in these patients ranged from $40,000 to $84,000.[74] Of these patients, 44% had additional complications, and the 12 week mortality was high (35%).

Prevention

A meta-analysis of 7 randomized studies examining the impact of systemic antibiotics on the risk of pacemaker-related infection was published in 1998. [75] Overall the selected studies included 2023 patients, of whom 1011 received systemic antibiotic prophylaxis and 1012 none. The meta-analysis showed a consistent protective effect of antibiotic pretreatment (p=0.0046) decreasing the incidence of pocket infections and pacer IE over a mean follow-up of approximately 2 years, from 3.7% to 0.49%. A single dose of intravenous cefazolin is sufficient in most cases to prevent infection.[76] Vancomycin should be used when the patient has documented colonization with methicillin-resistent *S. aureus*, or in those with significant beta-lactam allergies. A recent risk factor analysis showed convincing evidence that antibiotic prophylaxis was effective in reducing infection over a 12 month follow-up.[29]

Secondary prophylaxis is not recommended for patients undergoing dental, respiratory, gastrointestinal or genitourologic procedures. Secondary prophylaxis is recommended by the American Heart Association for patients who undergo incision and drainage of infection at other sites.[55]

Future Directions

A potential strategy is to target staphylococcal virulence factors via adjunctive therapy. There are two immunotherapeutic phase II trials in the literature. In a double-blind randomized controlled trial involving 60 patients with *S. aureus* bacteremia, the safety and efficacy of tefibazumab, a humanized monoclonal antibody that binds to the surface-expressed adhesion protein clumping factor A, was evaluated.[77] Clumping factor A is one of the MSCRAMMs found on virtually all strains of *S. aureus*, and mediates the binding of *S. aureus* to fibrinogen. Progression to severe sepsis occurred in 4 patients in the placebo group, and in no tefibazumab patients. There were 3 more deaths in the placebo group, but this difference was not statistically significant. There was no difference in overall adverse clinical events, although two patients developed serious adverse events (including one hypersensitivity reaction definitely related to the study drug). The drug half-life in the study was 14 days. The second trial evaluated a polyclonal human IgG against capsular polysaccharide type 5 and type 8.[78] This antibody has been shown to offer passive protection in various animal models of staphylococcal sepsis. The trial enrolled 40 patients (21 to the study drug and 18 to placebo) and found a shorter time to resolution of fever and shorter length of hospital stay in the study drug group. More patients died in the study group (5 vs. 2) but this difference did not reach statistical significance (p=0.42). Further investigations of these adjunctive agents are planned. While these agents were tested in therapeutics due to cost, their long-term niche may be in the realm of prophylaxis.

One possible direction in the future is the use of vaccines in high risk patients. StaphVAX is a vaccine with *S. aureus* type 5 and 8 capsular polysaccarides which are the strains that account for more than 80% of *S. aureus* infections. In a double-blind placebo controlled trial, hemodialysis patients were vaccinated with StaphVAX. While the study didn't meet a priori endpoints at 54 weeks, post-hoc analysis identified a significant reduction in the occurrences of *S. aureus* bacteremia at 40 weeks.[79] A follow-up study with new endpoints was performed, and contrary to prior observations showed no reduction in *S. aureus* infections.[80] Other vaccines are being developed; vaccines using fibronectin binding proteins and other bacterial surface adhesion proteins such as fim A. These vaccines have been shown to reduce endocarditis in animal models. Such vaccines could have important clinical applications, particularly among patients at high risk for infection such as those with diabetes or indwelling intravascular catheters.

Conclusions

The explosive growth in the use of cardiac devices has resulted in a significant number of infections complications. Infectious complications appear to be increasing at a greater rate than the device implantation rates. Early diagnosis and appropriate therapy are necessary, although the diagnosis remains challenging. Evidence supporting various treatment modalities is primarily limited to retrospective case series and expert opinion. Intensive antimicrobial therapy and removal of the device remain the cornerstones of therapy. The morbidity and cost associated with these infections is substantial, because standard therapy for such infections generally involves removal of the entire device, intravenous antibiotics and in many cases reimplantation of the device. For a potential new therapeutic approach such as prophylaxis or adjunctive treatment of staphylococcal infections of a cardiac device, clinical trials are needed to determine whether the intervention provides a clinical benefit. If results of these trials are favorable, new therapies can be incorporated into clinical practice guidelines and ultimately improve outcomes.

References

1. dy Chua JD, Wilkoff BL, Lee I, Juratli N, Longworth DL, Gordon SM. Diagnosis and management of infections involving implantable electrophysiologic cardiac devices. *Ann Intern Med* 2000;133:604-8.

2. Cleland JG, Daubert JC, Erdmann E, Freemantle N, Gras D, Kappenberger L, Tavazzi L. The effect of cardiac resynchronization on morbidity and mortality in heart failure. *N Engl J Med* 2005;352:1539-49.

3. Moss AJ, Zareba W, Hall WJ, Klein H, Wilber DJ, Cannom DS, Daubert JP, Higgins SL, Brown MW, Andrews ML. Prophylactic implantation of a defibrillator in patients with myocardial infarction and reduced ejection fraction. *N Engl J Med* 2002;346:877-83.

4. Gregoratos G, Abrams J, Epstein AE, Freedman RA, Hayes DL, Hlatky MA, Kerber RE, Naccarelli GV, Schoenfeld MH, Silka MJ, Winters SL, Gibbons RJ, Antman EM, Alpert JS, Hiratzka LF, Faxon DP, Jacobs AK, Fuster V, Smith SC, Jr. ACC/AHA/NASPE 2002 guideline update for implantation of cardiac pacemakers and antiarrhythmia devices: summary article: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (ACC/AHA/NASPE Committee to Update the 1998 Pacemaker Guidelines). *Circulation* 2002;106:2145-61.

5. Abraham WT, Fisher WG, Smith AL, Delurgio DB, Leon AR, Loh E, Kocovic DZ, Packer M, Clavell AL, Hayes DL, Ellestad M, Trupp RJ, Underwood J, Pickering F, Truex C, McAtee P, Messenger J. Cardiac resynchronization in chronic heart failure. *N Engl J Med* 2002;346:1845-53.

6. Bristow MR, Saxon LA, Boehmer J, Krueger S, Kass DA, De Marco T, Carson P, DiCarlo L, DeMets D, White BG, DeVries DW, Feldman AM. Cardiac-resynchronization therapy with or without an implantable defibrillator in advanced chronic heart failure. *N Engl J Med* 2004;350:2140-50.

7. Bradley DJ, Bradley EA, Baughman KL, Berger RD, Calkins H, Goodman SN, Kass DA, Powe NR. Cardiac resynchronization and death from progressive heart failure: a meta-analysis of randomized controlled trials. *JAMA* 2003;289:730-40.

8. Bardy GH, Lee KL, Mark DB, Poole JE, Packer DL, Boineau R, Domanski M, Troutman C, Anderson J, Johnson G, McNulty SE, Clapp-Channing N, Davidson-Ray LD, Fraulo ES, Fishbein DP, Luceri RM, Ip JH. Amiodarone or an implantable cardioverter-defibrillator for congestive heart failure. *N Engl J Med* 2005;352:225-37.

9. Gold MR, Peters RW, Johnson JW, Shorofsky SR. Complications associated with pectoral implantation of cardioverter defibrillators. World-Wide Jewel Investigators. *Pacing Clin Electrophysiol* 1997;20:208-11.

10. Smith PN, Vidaillet HJ, Hayes JJ, Wethington PJ, Stahl L, Hull M, Broste SK. Infections with nonthoracotomy implantable cardioverter defibrillators: can these be prevented? Endotak Lead Clinical Investigators. *Pacing Clin Electrophysiol* 1998;21:42-55.

11. Mela T, McGovern BA, Garan H, Vlahakes GJ, Torchiana DF, Ruskin J, Galvin JM. Long-term infection rates associated with the pectoral versus abdominal approach to cardioverter- defibrillator implants. *Am J Cardiol* 2001;88:750-3.

12. del Rio A, Anguera I, Miro JM, Mont L, Fowler VG, Jr., Azqueta M, Mestres CA. Surgical treatment of pacemaker and defibrillator lead endocarditis: the impact of electrode lead extraction on outcome. *Chest* 2003;124:1451-9.
13. Moss AJ, Hall WJ, Cannom DS, Daubert JP, Higgins SL, Klein H, Levine JH, Saksena S, Waldo AL, Wilber D, Brown MW, Heo M. Improved survival with an implanted defibrillator in patients with coronary disease at high risk for ventricular arrhythmia. Multicenter Automatic Defibrillator Implantation Trial Investigators. *N Engl J Med* 1996;335:1933-40.
14. Trappe HJ, Pfitzner P, Klein H, Wenzlaff P. Infections after cardioverter-defibrillator implantation: observations in 335 patients over 10 years. *Br Heart J* 1995;73:20-4.
15. Lai KK, Fontecchio SA. Infections associated with implantable cardioverter defibrillators placed transvenously and via thoracotomies: epidemiology, infection control, and management. *Clin Infect Dis* 1998;27:265-9.
16. Uslan DZ, Sohail MR, St Sauver JL, Friedman PA, Hayes DL, Stoner SM, Wilson WR, Steckelberg JM, Baddour LM. Permanent pacemaker and implantable cardioverter defibrillator infection: a population-based study. *Arch Intern Med* 2007;167:669-75.
17. Sohail MR, Uslan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR, Steckelberg JM, Stoner S, Baddour LM. Management and outcome of permanent pacemaker and implantable cardioverter-defibrillator infections. *J Am Coll Cardiol* 2007;49:1851-9.
18. Arber N, Pras E, Copperman Y, Schapiro JM, Meiner V, Lossos IS, Militianu A, Hassin D, Shai A, et al. Pacemaker endocarditis. Report of 44 cases and review of the literature. *Medicine.* 1994;73:299-305.
19. Duval X, Selton-Suty C, Alla F, Salvador-Mazenq M, Bernard Y, Weber M, Lacassin F, Nazeyrolas P, Chidiac C, Hoen B, Leport C. Endocarditis in patients with a permanent pacemaker: a 1-year epidemiological survey on infective endocarditis due to valvular and/or pacemaker infection. *Clin Infect Dis* 2004;39:68-74.
20. Cabell CH, Heidenreich PA, Chu VH, Moore CM, Stryjewski ME, Corey GR, Fowler VG, Jr. Increasing rates of cardiac device infections among Medicare beneficiaries: 1990-1999. *Am Heart J* 2004;147:582-6.
21. Voigt A, Shalaby A, Saba S. Rising rates of cardiac rhythm management device infections in the United States: 1996 through 2003. *J Am Coll Cardiol* 2006;48:590-1.
22. Al-Khatib SM, Lucas FL, Jollis JG, Malenka DJ, Wennberg DE. The relation between patients' outcomes and the volume of cardioverter-defibrillator implantation procedures performed by physicians treating Medicare beneficiaries. *J Am Coll Cardiol* 2005;46:1536-40.
23. Camus C, Leport C, Raffi F, Michelet C, Cartier F, Vilde JL. Sustained bacteremia in 26 patients with a permanent endocardial pacemaker: assessment of wire removal. *Clin Infect Dis* 1993;17:46-55.
24. Uslan DZ, Sohail MR, Friedman PA, Hayes DL, Wilson WR, Steckelberg JM, Baddour LM. Frequency of permanent pacemaker or implantable cardioverter-defibrillator infection in patients with gram-negative bacteremia. *Clin Infect Dis* 2006;43:731-6.
25. Chamis AL, Peterson GE, Cabell CH, Corey GR, Sorrentino RA, Greenfield RA, Ryan T, Reller LB, Fowler VG, Jr. Staphylococcus aureus bacteremia in patients with permanent pacemakers or implantable cardioverter-defibrillators. *Circulation* 2001;104:1029-33.

26. Da Costa A, Lelievre H, Kirkorian G, Celard M, Chevalier P, Vandenesch F, Etienne J, Touboul P. Role of the preaxillary flora in pacemaker infections: a prospective study. *Circulation* 1998;97:1791-5.
27. Karchmer AW, Longworth DL. Infections of intracardiac devices. *Infect Dis Clin North Am* 2002;16:477-505, xii.
28. Spinler SA, Nawarskas JJ, Foote EF, Sabapathi D, Connors JE, Marchlinski FE. Clinical presentation and analysis of risk factors for infectious complications of implantable cardioverter-defibrillator implantations at a university medical center. *Clin Infect Dis* 1998;26:1111-6.
29. Klug D, Balde M, Pavin D, Hidden-Lucet F, Clementy J, Sadoul N, Rey JL, Lande G, Lazarus A, Victor J, Barnay C, Grandbastien B, Kacet S. Risk factors related to infections of implanted pacemakers and cardioverter-defibrillators: results of a large prospective study. *Circulation* 2007;116:1349-55.
30. Sohail MR, Uslan DZ, Khan AH, Friedman PA, Hayes DL, Wilson WR, Steckelberg JM, Stoner SM, Baddour LM. Risk factor analysis of permanent pacemaker infection. *Clin Infect Dis* 2007;45:166-73.
31. Lewis AB, Hayes DL, Holmes DR, Jr., Vlietstra RE, Pluth JR, Osborn MJ. Update on infections involving permanent pacemakers. Characterization and management. *J Thorac Cardiovasc Surg* 1985;89:758-63.
32. Bluhm G. Pacemaker infections. A clinical study with special reference to prophylactic use of some isoxazolyl penicillins. *Acta Med Scand Suppl* 1985;699:1-62.
33. Wunderly D, Maloney J, Edel T, McHenry M, McCarthy PM. Infections in implantable cardioverter defibrillator patients. *Pacing Clin Electrophysiol* 1990;13:1360-4.
34. Bloom H, Heeke B, Leon A, Mera F, Delurgio D, Beshai J, Langberg J. Renal insufficiency and the risk of infection from pacemaker or defibrillator surgery. *Pacing Clin Electrophysiol* 2006;29:142-5.
35. Donlan RM. Biofilm formation: A clinically relevant microbiological process. *Clin Infect Dis* 2001;33:1387-1392.
36. Nilsson M, Frykberg L, Flock JI, Pei L, Lindberg M, Guss B. A fibrinogen-binding protein of Staphylococcus epidermidis. *Infect Immun* 1998;66:2666-73.
37. Cramton SE, Gerke C, Schnell NF, Nichols WW, Gotz F. The intercellular adhesion (ica) locus is present in Staphylococcus aureus and is required for biofilm formation. *Infect Immun* 1999;67:5427-33.
38. Rupp ME, Ulphani JS, Fey PD, Mack D. Characterization of Staphylococcus epidermidis polysaccharide intercellular adhesin/hemagglutinin in the pathogenesis of intravascular catheter-associated infection in a rat model. *Infect Immun* 1999;67:2656-9.
39. Klug D, Wallet F, Kacet S, Courcol RJ. Involvement of adherence and adhesion Staphylococcus epidermidis genes in pacemaker lead-associated infections. *J Clin Microbiol* 2003;41:3348-50.
40. Takeda S, Pier GB, Kojima Y, Tojo M, Muller E, Tosteson T, Goldmann DA. Protection against endocarditis due to Staphylococcus epidermidis by immunization with capsular polysaccharide/adhesin. *Circulation* 1991;84:2539-46.
41. Chaudhary R, Simmons RL. Pathogenesis of vascular graft infections. *J Vasc Surg* 1991;13:755-6.

42. Khoury AE, Lam KY, Ellis B, Costerton JW. Prevention and control of bacterial infections associated with medical devices. *ASAIO* 1992;38:M174-M178.
43. Klug D, Messaoudene SA, Marquie C, Mizon F, Cordova H, Lacroix D, Kacet S. Prospective evaluation of new criteria for the diagnosis of pacemaker lead infection: limitation of the clnical duke criteria for the diagnosis of endocarditis. *Heart Rhythm* 2005;2:S241.
44. Klug D, Lacroix D, Savoye C, Goullard L, Grandmougin D, Hennequin JL, Kacet S, Lekieffre J. Systemic infection related to endocarditis on pacemaker leads: clinical presentation and management. *Circulation.* 1997;95:2098-107.
45. Victor F, De Place C, Camus C, Le Breton H, Leclercq C, Pavin D, Mabo P, Daubert C. Pacemaker lead infection: echocardiographic features, management, and outcome. *Heart.* 1999;81:82-7.
46. Meier-Ewert HK, Gray ME, John RM. Endocardial pacemaker or defibrillator leads with infected vegetations: a single-center experience and consequences of transvenous extraction. *Am Heart J* 2003;146:339-44.
47. Sohail MR. Management of infected pacemakers and implantable cardioverter-defibrillators. *Intern Med J* 2007;37:509-10; author reply 510.
48. Massoure PL, Reuter S, Lafitte S, Laborderie J, Bordachard P, Clementy J, Roudaut R. Pacemaker endocarditis: clinical features and management of 60 consecutive cases. *Pacing Clin Electrophysiol* 2007;30:12-9.
49. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service.[comment]. *American Journal of Medicine.* 1994;96:200-9.
50. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Jr., Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;30:633-8.
51. Karchmer AW. Infections of prosthetic valves and intravascular devices. In: Mandell GL, Bennett JE, Dolin R, eds. Principles and Practice of Infectious Diseases. New York: Churchill Livingstone, 2000:911-917.
52. Chambers ST. Diagnosis and management of staphylococcal infections of pacemakers and cardiac defibrillators. *Intern Med J* 2005;35 Suppl 2:S63-71.
53. Cacoub P, Leprince P, Nataf P, Hausfater P, Dorent R, Wechsler B, Bors V, Pavie A, Piette JC, Gandjbakhch I. Pacemaker infective endocarditis. *American Journal of Cardiology.* 1998;82:480-4.
54. Crowley AL, Peterson GE, Benjamin DK, Jr., Rimmer SH, Todd C, Mayhood JS, Cabell CH, Reller LB, Ryan T, Corey GR, Fowler VG. Venous thrombosis in patients with central venous catheter-associated *Staphylococcus aureus* bacteremia. *Crit Care Med* 2007;In press.
55. Baddour LM, Bettmann MA, Bolger AF, Epstein AE, Ferrieri P, Gerber MA, Gewitz MH, Jacobs AK, Levison ME, Newburger JW, Pallasch TJ, Wilson WR, Baltimore RS, Falace DA, Shulman ST, Tani LY, Taubert KA. Nonvalvular cardiovascular device-related infections. *Circulation* 2003;108:2015-31.
56. Alt E, Neuzner J, Binner L, Gohl K, Res JC, Knabe UH, Zehender M, Reinhardt J. Three-year experience with a stylet for lead extraction: a multicenter study. *Pacing Clin Electrophysiol* 1996;19:18-25.

57. Smith HJ, Fearnot NE, Byrd CL, Wilkoff BL, Love CJ, Sellers TD. Five-years experience with intravascular lead extraction. U.S. Lead Extraction Database. *Pacing Clin Electrophysiol* 1994;17:2016-20.
58. Wilkoff BL, Byrd CL, Love CJ, Hayes DL, Sellers TD, Schaerf R, Parsonnet V, Epstein LM, Sorrentino RA, Reiser C. Pacemaker lead extraction with the laser sheath: results of the pacing lead extraction with the excimer sheath (PLEXES) trial. *J Am Coll Cardiol* 1999;33:1671-6.
59. Robin J, Tronc F, Vedrinne C, Champsaur G. Video-assisted tricuspid valve surgery: a new surgical option in endocarditis on pacemaker. *Eur J Cardiothorac Surg* 1999;16:243-5.
60. Verma A, Wilkoff BL. Intravascular pacemaker and defibrillator lead extraction: a state-of-the-art review. *Heart Rhythm* 2004;1:739-45.
61. Bracke FA, Meijer A, van Gelder LM. Pacemaker lead complications: when is extraction appropriate and what can we learn from published data? *Heart* 2001;85:254-9.
62. Byrd CL, Wilkoff BL, Love CJ, Sellers TD, Reiser C. Clinical study of the laser sheath for lead extraction: the total experience in the United States. *Pacing Clin Electrophysiol* 2002;25:804-8.
63. Kantharia BK, Padder FA, Pennington JC, 3rd, Wilbur SL, Samuels FL, Maquilan M, Kutalek SP. Feasibility, safety, and determinants of extraction time of percutaneous extraction of endocardial implantable cardioverter defibrillator leads by intravascular countertraction method. *Am J Cardiol* 2000;85:593-7.
64. Bracke FA, Meijer A, van Gelder LM. Lead extraction for device related infections: a single-centre experience. *Europace* 2004;6:243-7.
65. Ruttmann E, Hangler HB, Kilo J, Hofer D, Muller LC, Hintringer F, Muller S, Laufer G, Antretter H. Transvenous pacemaker lead removal is safe and effective even in large vegetations: an analysis of 53 cases of pacemaker lead endocarditis. *Pacing Clin Electrophysiol* 2006;29:231-6.
66. Molina JE. Undertreatment and overtreatment of patients with infected antiarrhythmic implantable devices. *Ann Thorac Surg* 1997;63:504-9.
67. Rastan AJ, Doll N, Walther T, Mohr FW. Pacemaker dependent patients with device infection--a modified approach. *Eur J Cardiothorac Surg* 2005;27:1116-8.
68. Darouiche RO. Treatment of infections associated with surgical implants. *N Engl J Med* 2004;350:1422-9.
69. Eggimann P, Waldvogel F. Pacemaker and defibrillator infections. In: Waldvogel FA, Bison AL, eds. Infections Associated with Indwelling Medical Devices. Washington, DC: ASM Press, 2000:247-264.
70. Baddour LM. Long-term suppressive antimicrobial therapy for intravascular device-related infections. *Am J Med Sci* 2001;322:209-12.
71. O'Nunain S, Perez I, Roelke M, Osswald S, McGovern BA, Brooks DR, Torchiana DF, Vlahakes GJ, Ruskin J, Garan H. The treatment of patients with infected implantable cardioverter-defibrillator systems. *J Thorac Cardiovasc Surg* 1997;113:121-9.
72. Zimmerli W, Widmer AF, Blatter M, Frei R, Ochsner PE. Role of rifampin for treatment of orthopedic implant-related staphylococcal infections: a randomized controlled trial. Foreign-Body Infection (FBI) Study Group. *JAMA* 1998;279:1537-41.

73. Ferguson TB, Jr., Ferguson CL, Crites K, Crimmins-Reda P. The additional hospital costs generated in the management of complications of pacemaker and defibrillator implantations. *J Thorac Cardiovasc Surg* 1996;111:742-51;discussion 751-2.
74. Chu VH, Crosslin DR, Friedman JY, Reed SD, Cabell CH, Griffiths RI, Masselink LE, Kaye KS, Corey GR, Reller LB, Stryjewski ME, Schulman KA, Fowler VG, Jr. Staphylococcus aureus bacteremia in patients with prosthetic devices: costs and outcomes. *Am J Med* 2005;118:1416.
75. Da Costa A, Kirkorian G, Cucherat M, Delahaye F, Chevalier P, Cerisier A, Isaaz K, Touboul P. Antibiotic prophylaxis for permanent pacemaker implantation: a meta-analysis. *Circulation* 1998;97:1796-801.
76. Bertaglia E, Zerbo F, Zardo S, Barzan D, Zoppo F, Pascotto P. Antibiotic prophylaxis with a single dose of cefazolin during pacemaker implantation: incidence of long-term infective complications. *Pacing Clin Electrophysiol* 2006;29:29-33.
77. Weems JJ, Steinberg JP, Filler SG, Baddley JW, Corey GR, Sampathkumar P, Winston L, John JF, Kubin CJ, Talwani R, Moore T, Patti JM, Hetherington S, Texter M, Wenzel E, Kelley VA, Fowler VG. Phase II, randomized, double-blind, multicenter study comparing the safety and pharmacokinetics of tefibazumab to placebo for treatment of *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother* 2006;80:2751-2755.
78. Rupp ME, Holley HPJ, Lutz J, Dicpinigatis PV, Woods CW, Levine DP, Veney N, Fowler VG. A phase II, randomized, multicenter, double-blind, placebo-controlled, trial of a polyclonal anti-*Staphylococcus aureus* capsular polysaccharide immune globulin in the treatment of *Staphylococcus aureus* bacteremia. *Antimicrob Agents Chemother* 2007;In press.
79. Shinefield H, Black S, Fattom A, Horwith G, Rasgon S, Ordonez J, Yeoh H, Law D, Robbins JB, Schneerson R, Muenz L, Fuller S, Johnson J, Fireman B, Alcorn H, Naso R. Use of a Staphylococcus aureus conjugate vaccine in patients receiving hemodialysis. *N Engl J Med* 2002;346:491-6.
80. Rathjen TE. Nabi Biopharmaceuticals announces results of StaphVAX confirmatory Phase II clincial trial. Available at: http://phx.corporate-ir.net/phoenix/zhtml, 2005.