Nonstaphylococcal Infections of Cardiac Implantable Electronic Devices

George M. Viola, MD; Leah L. Awan, BS; Rabih O. Darouiche, MD

Background—Along with the rising use of cardiac implantable electronic devices (CIEDs), there has been a disproportional increase in the number of infections of such devices. Little is known about nonstaphylococcal CIED-related infections, which make up ≈10% to 30% of all CIED infections.

Methods and Results—A retrospective review of hospital records of patients admitted with a CIED-related infection was conducted in 4 academic hospitals in Houston, Tex, between 2002 and 2009. Of the 504 identified patients with CIED-related infection, 80 (16%) had a nonstaphylococcal infection and were the focus of this study. The mean duration of CIED placement before infection was 109±27 weeks, whereas 44% had their device previously manipulated within a mean of 29.5±6 weeks. The mean duration of clinical symptoms before admission was 48±12.8 days. Furthermore, 13 patients (16%) presented with CIED-related endocarditis. Although not described in prior reports, we identified 3 definite and 2 suspected cases of secondary Gram-negative bacteria seeding of the CIED. Inappropriate antimicrobial coverage was provided in ≈50% of the cases with a mean period of 2.1 days. The overall mortality rate was 4%.

Conclusions—Nonstaphylococcal CIED-related infections are prevalent and diverse with a relatively low virulence and mortality rate. Because nonstaphylococcal organisms are capable of secondarily seeding the CIED, a high suspicion for CIED-related infection is warranted in patients with bloodstream infection. In patients with suspected CIED infection, adequate Gram-positive and Gram-negative antibacterial coverage should be administered until microbiological data become available. (Circulation. 2010;121:2085-2091.)

Key Words: epidemiology • infection • pacemakers

The use of permanent pacemakers and implantable cardioverter-defibrillators, collectively known as cardiac implantable electronic devices (CIEDs), has greatly increased over the past few decades. Unfortunately, a National Hospital Discharge Survey from 1996 to 2006 indicated that along with the rising use of cardiac medical devices, there has been a disproportional increase in the number of infections of such devices. The rates of infection of CIED range from 0.1% to 19.9%, with an average rate of 4%. The reported average cost of combined medical-surgical treatment of an infected permanent pacemaker or implantable cardioverter-defibrillator is $24 459 and $57 213, respectively.

Clinical Perspective on p 2091

Staphylococcus epidermidis and S aureus, which collectively account for 70% to 90% of all CIED infections, have been studied extensively in the past. Unfortunately, nonstaphylococcal organisms, which cause 10% to 30% of all CIED infections, are so diverse that they have been reported only as case reports or small case series, and even when they have been analyzed, their impact was diluted by the most common staphylococcal species. We performed a large multicenter retrospective analysis to identify the most common causative nonstaphylococcal pathogens and to elucidate the epidemiological parameters, risk factors, and patient outcomes.

Methods

Hospital records of patients admitted with a CIED-related infection to 1 of 4 large teaching hospitals in Houston, Tex, between 2002 and 2009 were retrospectively identified electronically through the use of International Classification of Disease, ninth revision, codes 996.61 and 996.72. All identified records were individually reviewed, and subjects were included in the analysis if they fulfilled strict definition criteria for CIED-related infections. The study proposal was approved by the individual Institutional Review boards at each participating center.

Patients’ collected data included demographics, cardiac device characteristics, time of placement and manipulation, prior bouts of CIED-related infection, and history of bloodstream infection in the past 12-months, as well as clinical, laboratory, echocardiographic, and microbiological data. Additionally, we collected data regarding duration of hospitalization, necessity for intensive care admission, and duration and type of inpatient and outpatient antimicrobial therapy. Moreover, we identified which cardiac devices were re-
moved, replaced, or resulted in recurrent infection. Finally, we evaluated the patients’ overall 6-month survival outcome.

Definitions

CIED pocket infection was defined as having clinical signs and symptoms of local infection (including erythema, warmth, fluctuation, wound dehiscence, erosion, tenderness, and purulent drainage) plus microbiological confirmation based on results of cultures of intraoperatively collected fluid samples, explanted CIED, or purulent discharge from the pocket site. CIED-related endocarditis was diagnosed if both major Duke criteria were met, including microbiological evidence and echocardiographic evidence of right-sided infective endocarditis.6–10

A CIED-related infection was considered nosocomial if it occurred ≥48 hours after admission and was not incubating at the time of admission. Infection of CIED was regarded as health care associated if patients received intravenous therapy at home, attended an outpatient hemodialysis center in the previous 30 days, were hospitalized in an acute care hospital for 2 days in the 90 days before admission, or resided in a nursing home or long-term care facility. In contrast, CIED-related infection was recognized as community acquired if it did not fit the above definitions.11

Sepsis was defined as having a suspicion of infection plus systemic inflammatory response syndrome. Severe sepsis was de-
fined as sepsis associated with organ dysfunction, hypoperfusion, or hypotension. Septic shock was defined as severe sepsis-induced hypotension that persists despite adequate fluid resuscitation.12

The number of days of inappropriate antimicrobial coverage was calculated from the time of admission. Appropriate antimicrobial coverage was based strictly on a comparison of the antimicrobial susceptibility profile of the pathogenic organism(s) with the antimicrobials received by the patient. Recurrence of CIED infection was defined by having a subsequent CIED-related infection within 6 months after admission if the device was not removed or after the CIED was replaced. Additionally, if data were available, patient survival status was evaluated for 6 months after admission.

Statistical Analysis

Descriptive statistics are presented as mean±SD or median with 25th to 75th percentiles for continuous variables according to normal distribution and as numbers with percentages for categorical variables. All analyses were performed with STATA software (version 10, Stata Corp, College Station, Tex).

Results

Patient Characteristics

A total of 504 CIED-related infections were identified: 21% were culture-negative; 27% were due to coagulase-negative *Staphylococcus*; 12% were caused by methicillin-sensitive *S. aureus*; 22% were due to methicillin-resistant *S. aureus*; 2% were polymicrobial (*Staphylococcus* species plus a non-staphylococcal organism); and 16% (80 subjects, the focus of this study) presented with a non-staphylococcal CIED-related infection (the Figure).

Among the 80 patients with nonstaphylococcal CIED-related infection, the mean age was 62.5±1.8 years; 68% were male; and approximately two thirds were white. The main comorbid conditions included hypertension (88%), congestive heart failure (76%) with a mean ejection fraction of 32±2%, and coronary artery disease (59%). Additionally, 20% of patients had non–insulin-dependent diabetes mellitus, whereas 9% were diabetic and required insulin. The mean creatinine at baseline was 1.4±0.12 mg/dl, and only 5 subjects had end-stage renal disease, including 2 on perito-
neal dialysis and 3 on hemodialysis via arteriovenous graft or fistula. Furthermore, 44% were current tobacco users, 16% were current alcohol users, and 3% were current intravenous drug users. Four individuals were at high risk for bloodstream infection, including 2 who had a ventricular assist device and 2 with a peripherally inserted central catheter for the administration of milrinone. Seven individuals were chronically immunosuppressed: 1 patient had HIV infection and a CD4 count of 504 cells/μL; another patient received 3 mg/d prednisone for adrenal insufficiency; a third was treated with adalimumab and methotrexate for rheumatoid arthritis; and the remaining 4 patients were treated with radiation and chemotherapy for lung cancer (2 cases), rectal cancer (1 case), and Hodgkin lymphoma (1 case). Moreover, 48% were community-acquired infections and an equal number were health care–associated infections; only 3% were nosocomial acquired (Table 1).

### Characteristics of Cardiac Devices

Fifty-two percent of patients had an implantable cardioverter-defibrillator, and 48% had a permanent pacemaker. Half of the patients had 1 cardiac lead, and the other half had 2 cardiac leads. The generator was placed in the thoracic region in almost all of the patients (99%), and the leads were placed transvenously in 89% of the patients. The 3 main indications for CIED placement were history of ventricular tachycardia (27%), ejection fraction for CIED placement were history of ventricular tachycardia transvenously in 89% of the patients. The 3 main indications in almost all of the patients (99%), and the leads were placed cardiac leads. The generator was placed in the thoracic region the patients had 1 cardiac lead, and the other half had 2

#### Table 5. Types of Infection, Treatment Modalities, and Patient Outcome

<table>
<thead>
<tr>
<th>Condition</th>
<th>CIED Infected Cases, n</th>
<th>Hospitalization (25th–75th Percentile), d</th>
<th>ICU Care, n (%)</th>
<th>Device Completely Removed, n (%)</th>
<th>Only Generator Removed, n</th>
<th>No Device Components Removed, n</th>
<th>Suppressive Antibiotics Administered, n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pocket infection with negative blood cultures‡</td>
<td>65</td>
<td>10 (6–12)</td>
<td>2 (3)</td>
<td>61 (94)</td>
<td>1</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Pocket infection with positive blood cultures‡</td>
<td>6</td>
<td>17 (5–23)</td>
<td>2 (33)</td>
<td>5 (83)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Endocarditis‡</td>
<td>13</td>
<td>13 (10–15)</td>
<td>3 (23)</td>
<td>11 (92)</td>
<td>0</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Total</td>
<td>80</td>
<td>12 (6–14)</td>
<td>6 (8)</td>
<td>73 (91)</td>
<td>2</td>
<td>5</td>
<td>2</td>
</tr>
</tbody>
</table>

ICU indicates intensive care unit. Values are medians except for inappropriate antimicrobial coverage, for which mean values were used, or as noted.

* Those subjects who received suppressive antibiotics did not have any component of their CIED removed.

† The denominator excluded patients who retained the infected cardiac generator, died, or were lost to follow-up during the 6-month study period.

‡ Four patients were classified as having both a CIED pocket infection and CIED endocarditis.

and drainage of the pocket site (1%), following which infection resulting from *P. aeruginosa* recurred within 4 weeks (Table 2).

#### Signs and Symptoms

The duration of clinical symptoms before admission was also relatively prolonged at a mean of 48±12.8 days. The principal local findings at the pocket site included, in decreasing frequency, intraoperative purulence (80%), external purulent discharge (73%), erythema (70%), pain (51%), and warmth (36%). Four fifths of patients (81%) presented with no fever, and only a few had systemic manifestation, with sepsis occurring in 15%, severe sepsis in 3%, and septic shock in 1% (Table 3).

#### Laboratory Data

The mean peripheral white blood cell count on admission was 8400±3800/μL, with only 16% presenting with leukocytosis (>10,000 cells/μL). Only 11 patients had erythrocyte sedimentation rate measured, with 64% having a value >30 mm/h (Table 3). Normal measurements of temperature, white blood cell count, and erythrocyte sedimentation rate (triple combination) at admission had a negative predictive value of 100% in ruling out endocarditis for nonstaphylococcal infections of CIED. However, if ±1 values were elevated, the positive predictive value for having endocarditis was only 57%.

#### Echocardiograph and Imaging Findings

Nineteen percent of patients did not undergo echocardiographic examination, 60% had a transthoracic echocardiogram, and 21% had a transesophageal echocardiogram. Cardiac vegetations were present in 13 patients (16%), with 69% located within the right atrium and 69% having vegetation >10 mm. Additionally, there was only 1 documented case of CIED endocarditis with metastatic embolization to the lungs caused by *Enterococcus faecalis*.

#### Microbiology

Three subjects who had a positive blood culture within the past year were subsequently diagnosed with CIED-related endocarditis (2 with *P. aeruginosa* and 1 with *C. tropicalis*).
with the only potential source being a peripherally inserted central catheter line and a vascular catheter for total parenteral nutrition, respectively. Furthermore, there were numerous cases of secondary seeding of the CIED from a recent infection occurring within a mean of 3.7 ± 1.1 weeks before the CIED infection. The sources of infection were peritoneal dialysis catheter (C. tropicalis and Acinetobacter baumannii) in 2 patients, pyelonephritis (coinfection by P. aeruginosa and Klebsiella pneumonia) in 1, a vascular Percath (diphtheroids) in 1, a vascular port for chemotherapy (Acinetobacter baumannii) in 1, a superficial infection of percutaneous esophagogastronomy tube (P. aeruginosa) in 1, and an infected abdominal mesh (Enterococcus faecalis) in 1. Only 16% had a positive blood culture at the time of admission (Table 3). All positive blood cultures had matched the pocket or hardware device cultures on extraction, which yielded growth of P. aeruginosa (4 cases), Enterococcus faecalis (3 cases), Streptococcus viridans (2 cases), C. tropicalis (2 cases), diphtheroids (1 case), and S. marcescens (1 case). The most common organisms obtained from the explanted cardiac devices were P. aeruginosa, S. marcescens, Enterobacter cloacae, and Enterococcus faecalis. Additionally 10 fungal cases were encountered, including C. albicans, tropicalis, parapsilosis, glabrata, and Aspergillus niger. There was also 1 case of infection caused by Nocardia species and another by Mycobacterium fortuitum. Furthermore, stratification of these microorganisms by primary CIED or manipulation of the device showed that they appear to be rather evenly distributed (Table 4).

**Clinical Outcome and Therapeutic Modality**

Only 8% required intensive care unit admission. The median duration of hospitalization was 12 days (25th to 75th percentiles, 6 to 14 days; Table 5). Antimicrobial coverage was deemed inappropriate in ≈50% of the time with a mean period of 2.1 days (Table 5). The total days of hospitalization and antibiotic use are stratified by condition in Table 5. More than 91% of the cardiac devices were completely removed, and only 2 devices were partially removed. One subject died before having the CIED removed, and 4 devices were not removed (including 2 that required suppressive antibiotics for P. aeruginosa CIED pocket infection) because of high surgical risk. However, no patients had a recurrence of infection of the CIED after 6 months of follow-up. Moreover, even though 7 subjects were lost to follow-up, only 61% required a CIED replacement, with no recurrence of infection of the newly placed CIED after 6 months of follow-up. All replaced devices were placed on the contralateral site. Unfortunately, there were 3 deaths during hospitalization (1 with a pocket infection by K. pneumonae and Nocardia species each, and 1 with a pocket infection and endocarditis due to diphtheroids; Table 5).

**Discussion**

To the best of our knowledge, this study represents the largest evaluation so far of patients with a nonstaphylococcal infection of the CIED. The overall patient characteristics and microbiological causes of CIED infections in our study are rather similar to those in other studies.10–13 However, our study illustrates a number of previously unrecognized key points. First, the microbiological diversity of nonstaphylococcal infections of CIED is rather extensive, including other Gram-positive bacteria like streptococci and enterococci, Gram-negative bacteria, atypical bacteria like Nocardia species, fungi like Candida and Aspergillus species, and mycobacterial organisms.

Second, nonstaphylococcal infection occurred rather late, ≈2 years after placement of CIED. In contrast, the majority of CIED infections reportedly occur early (within the first 6 to 12 weeks after CIED insertion).6 Reasons for the higher rate of infection during the early period after CIED implantation include perioperative contamination and the lack of ensheathment of the leads in fibrocollagenous tissue until a few months after placement, thereby making them more prone to microbiological attachment.14

Compared with staphylococci, nonstaphylococcal organisms appear to be less virulent, result in more protracted clinical manifestations of CIED infection before hospital admission, and are less lethal with a low infection-related mortality of 4% compared with 9% for S. aureus.10 Seven individuals in our study did not have their CIED completely removed because of high surgical risk and had to be treated with partial removal of the infected device or antibiotic

---

**Table 5. Continued**

<table>
<thead>
<tr>
<th>Inpatient (25th–75th Percentile)</th>
<th>Outpatient (25th–75th Percentile)</th>
<th>Total (25th–75th Percentile)</th>
<th>Inappropriate Antimicrobial Coverage (25th–75th Percentile), d</th>
<th>Device Replaced, n (%)†</th>
<th>Reinfection, n</th>
<th>Death, n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10 (6–12)</td>
<td>12 (8–14)</td>
<td>20 (14–25)</td>
<td>2 (0–4)</td>
<td>36/57 (63)</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>17 (5–18)</td>
<td>25 (11–40)</td>
<td>38 (29–45)</td>
<td>2.3 (0–4)</td>
<td>5/6 (83)</td>
<td>0</td>
<td>0 (0)</td>
</tr>
<tr>
<td>13.5 (10–15)</td>
<td>21.7 (14–28)</td>
<td>32 (26–41)</td>
<td>3 (0–4)</td>
<td>4/10 (40)</td>
<td>0</td>
<td>1 (8)</td>
</tr>
<tr>
<td>11 (6–14)</td>
<td>16 (10–14)</td>
<td>24 (15–29)</td>
<td>2.1 (0–4)</td>
<td>43/70 (61)</td>
<td>0</td>
<td>3 (4)</td>
</tr>
</tbody>
</table>
therapy alone without recurrence of infection within 6 months of follow-up (Table 5). However, 6 subjects who had a previous CIED infection that was managed with antibiotic therapy without complete removal of the infected device developed recurrent infection that qualified them for inclusion in our series (Table 2). Therefore, we do not recommend retaining any component of the infected CIED because it has reportedly been associated with a high rate of recurrent infection, probably because of the inability to completely eradicate biofilm-embedded organisms.\textsuperscript{13}

Many studies have previously reported that the probability of CIED infection due to secondary seeding of the cardiac device in patients with Staphylococcus bacteremia is approximately \(40\%\).\textsuperscript{15,16} However, Gram-negative bacteremia was thought not to cause secondary seeding of the device.\textsuperscript{17} In contrast, we identified in our study 3 patients with a history of Gram-negative bacteremia (2 resulting from infection of a peripherally inserted central catheter line and 1 from a vascular port for chemotherapy) that was responsible for causing secondary seeding of the CIED and 2 others with infections that had occurred at a distant site (infection of peritoneal dialysis catheter and pyelonephritis in 1 case each) most probably secondarily seeded the CIED via hematogenous spread. Additionally, our series included 2 cases of CIED infections caused by \textit{C. tropicalis} that had previously caused infection of a vascular catheter for total parenteral nutrition and a peritoneal dialysis catheter. Therefore, regardless of the nature of the microorganism, one must always remain cautious of the potential for secondary seeding of the CIED in any patient with bacteremia or a distant bodily site infection.

Not unexpectedly, because the majority of all CIED infections are caused by staphylococcal organisms, the majority of our patients were started empirically on antibiotics that provide Gram-positive coverage. However, antimicrobial coverage was deemed inappropriate \(\approx 50\%\) of the time with a mean period of 2.1 days. Because there were only 3 deaths in our study, we could not sufficiently evaluate whether the practice of providing only empirical antibiotic coverage against Gram-positive bacteria was associated with a higher mortality rate. Nonetheless, it is probably reasonable to recommend empirical coverage against both Gram-positive and Gram-negative bacteria until the infecting pathogen is identified because nonstaphylococcal organisms may be the culprit in \(10\%\) to \(30\%\) of cases of CIED infection.\textsuperscript{6,7}

Our study has several limitations, the first of which is the retrospective study design. Second, all 4 included hospitals were tertiary care centers with potential referral bias. Third, 7 patients (8\%) returned to their hospital of origin after discharge, and their 6-month outcome was unknown. However, our case series is the largest study of nonstaphylococcal CIED-related infections. The overall microbiological proportion of CIED-related infections was similar to that in prior large studies.\textsuperscript{10–13} For example, fungi accounted for 15\% of nonstaphylococcal infections in our series, which is in agreement with the previously reported prevalence of fungal infections (2\%) among all causes of CIED infection.\textsuperscript{10} Moreover, the 4 hospitals that were included in our study had a very diverse population of patients and practices, thereby enhancing the external validity of our results.

Conclusions

Nonstaphylococcal CIED-related infections are quite diverse with relatively more benign courses and lower mortality rates than staphylococcal infections. Additionally, many nonstaphylococcal organisms, including Gram-negative bacteria and fungi, appear to be capable of secondarily seeding the CIED. A high suspicion for CIED-related infection is therefore warranted in patients with bacteremia and a CIED. Furthermore, adequate Gram-positive and Gram-negative antibacterial coverage should be administered until the microbiological cause is identified.

Acknowledgments

We are thankful for the support provided by the Michael E. DeBakey Veterans Affairs Medical Center, St Luke’s Episcopal Hospital, the Methodist Hospital, and the Memorial Hermann Hospital, Houston, Tex.

Source of Funding

This study was supported in part by funds from Baylor College of Medicine, Houston, Tex.

Disclosures

None.

References


CLINICAL PERSPECTIVE

The number of infections of cardiac implantable electronic devices (CIEDs) continues to increase disproportionately to the increase in implantation rates. The average cost of combined medical-surgical treatment may surpass tens of thousands of dollars. Staphylococcal organisms account for 70% to 90% of all CIED infections. However, little is known about nonstaphylococcal organisms, which have been described only in case reports, in small case series, or combined in larger studies with staphylococcal CIED infections, thereby diluting the impact of nonstaphylococcal infections. Our study identified 504 patients with infection of a CIED, 80 (16%) of whom had a nonstaphylococcal infection. Although the demographics and comorbidities of subjects were comparable to those in other reports, our study illustrates many key points. First, the microbiological diversity of nonstaphylococcal infections was rather extensive because it included other Gram-positive bacteria like streptococci and enterococci, a variety of Gram-negative bacteria, atypical bacteria like Nocardia and Mycobacteria, and fungi like Candida and Aspergillus. Second, the duration of CIED insertion before nonstaphylococcal infection was relatively prolonged (mean, 109 ± 27 weeks). Third, nonstaphylococcal organisms appear to be less virulent, cause prolonged clinical symptoms before admission (mean, 48 ± 12.8 days), and are associated with lower mortality (4%). Fourth, contrary to prior reports, Gram-negative bloodstream infections could cause secondary seeding of the CIED. Finally, inappropriate antimicrobial coverage was provided in ~50% of nonstaphylococcal infections for a mean period of 2.1 days. These findings should enhance our appreciation of the unique attributes of nonstaphylococcal infections of CIEDs.
Nonstaphylococcal Infections of Cardiac Implantable Electronic Devices
George M. Viola, Leah L. Awan and Rabih O. Darouiche

Circulation. published online May 3, 2010;
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/early/2010/05/03/CIRCULATIONAHA.110.936708.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/