Staphylococcus aureus Bacteremia in Patients With Permanent Pacemakers or Implantable Cardioverter-Defibrillators

Anna Lisa Chamis, MD; Gail E. Peterson, MD; Christopher H. Cabell, MD; G. Ralph Corey, MD; Robert A. Sorrentino, MD; Ruth Ann Greenfield, MD; Thomas Ryan, MD; L. Barth Reller, MD; Vance G. Fowler, Jr, MD, MHS

Background—Although cardiac device infections (CDIs) are a devastating complication of permanent pacemakers or implantable cardioverter-defibrillators, the incidence of CDI in patients with bacteremia is not well defined. The objective of this study was to determine the incidence of CDI among patients with permanent pacemakers or implantable cardioverter-defibrillators who develop Staphylococcus aureus bacteremia (SAB).

Methods and Results—A cohort of all adult patients with SAB and permanent pacemakers or implantable cardioverter-defibrillators over a 6-year period was evaluated prospectively. The overall incidence of confirmed CDI was 15 of 33 (45.4%). Confirmed CDI occurred in 9 of the 12 patients (75%) with early SAB (<1 year after device placement). Fifteen of 21 patients (71.5%) with late SAB (≥1 year after device placement) had either confirmed (6 of 21, 28.5%) or possible (9 of 21, 43%) CDI. In 60% of the patients (9 of 15) with confirmed CDI, no local signs or symptoms suggesting generator pocket infection were noted.

Conclusions—The incidence of CDI among patients with SAB and cardiac devices is high. Neither physical examination nor echocardiography can exclude the possibility of CDI. In patients with early SAB, the device is usually involved, and ~40% of these patients have obvious clinical signs of cardiac device involvement. Conversely, in patients with late SAB, the cardiac device is rarely the initial source of bacteremia, and there is a paucity of local signs of device involvement. The cardiac device is involved, however, in ≥28% of these patients. (Circulation. 2001;104:1029-1033.)

Key Words: infection ■ pacemakers ■ echocardiography

Infection is a devastating complication of cardiac devices such as permanent pacemakers or implantable cardioverter-defibrillators. Morbidity and mortality associated with cardiac device infection (CDI) is high,1,2 and definitive management generally involves complete removal of the infected device.2–11 Thus, the accurate identification of CDI is essential to ensure that patients with infection involving a permanent pacemaker or implantable cardioverter-defibrillator are treated appropriately and that those patients with uninfected devices avoid unnecessary removal.

Although Staphylococcus aureus is an important cause of CDI,4,7,10,12–14 the risk of developing CDI after S aureus bacteremia (SAB) is inadequately defined. This uncertainty complicates patient management. Clinicians caring for patients with permanent pacemakers or implantable cardioverter-defibrillators who develop SAB often have difficulty in estimating the likelihood that the device is infected, leading to diagnostic and therapeutic delays. Thus, the objective of the present investigation is to determine the incidence of CDI in patients presenting with SAB. To achieve this objective, we prospectively evaluated 33 consecutive patients with cardiac devices who developed SAB.

Methods

Patient Selection

The research guidelines of Duke University were followed in the conduct of the clinical research of this report. From September 1994 until July 2000, daily reports were received by one of the authors (V.G.F.) from the Clinical Microbiology Laboratory identifying all patients at Duke University Medical Center with ≥1 blood culture positive for S aureus as previously described.19 One patient developed SAB in an outside hospital before being transferred to Duke University Medical Center; however, speciation was confirmed in the Duke University Clinical Microbiology Laboratory.

S aureus Bacteremia

An episode of SAB was defined as clinically significant if (1) ≥1 blood culture was positive for S aureus or (2) a single blood culture yielded S aureus in a patient with clinical evidence of infection. For the present study, only patients with clinically significant SAB and...
permanent pacemakers or implantable cardioverter-defibrillators were further analyzed. Episodes of SAB were classified as early (<1 year after device placement or the most recent surgical modification to the device) or late (≥1 year after device placement or the most recent surgical modification to the device) as previously described.20–22

Staphylococcal soft-tissue infection was considered to be the source of bacteremia if typical clinical signs of a local infection (e.g., cellulitis or abscess) antedated the bacteremia. An intravascular catheter was considered to be the source of bacteremia if (1) there was evidence of inflammation at the catheter insertion site and/or (2) a vascular catheter-tip culture was positive for \textit{S} aureus and (3) there was no clinical evidence of another source for the bacteremia.23 A permanent pacemaker or implantable cardioverter-defibrillator was considered to be the source of bacteremia if (1) it had been recently (<1 year) instrumented, (2) no other source of bacteremia was present, and either (3) \textit{S} aureus was cultured from the generator pocket or leads or (4) echocardiography demonstrated valvular or lead vegetations. The route of CDI was presumed to be via hematogenous seeding of the apparatus if the device had not been manipulated in ≥1 year.

Cardiac Device Infections
Because permanent pacemakers and implantable cardioverter-defibrillators are structurally similar, patients were included in the present study if either device was present at the time of their SAB. Clinical evidence of CDI was defined as erythema, warmth, fluctuance, wound dehiscence, erosion, or tenderness at the generator site. CDI was defined as confirmed by either microbiological or clinical criteria. CDI was microbiologically confirmed if cultures from the generator pocket or electrode leads grew \textit{S} aureus. CDI was clinically confirmed if echocardiography demonstrated valvular or lead vegetations or the Duke criteria24 for infective endocarditis were met. CDI was rejected if (1) the patient had no evidence of CDI at the time of the initial blood culture, the cardiac device was not removed, and there was no evidence of recurrent infection 12 weeks after the onset of SAB and/or (2) no evidence of device infection was detected at autopsy. CDIs were defined as possible if death occurred before CDI was confirmed or rejected.

Patient Outcome
Patient outcome for a period of 12 weeks after the date of the first positive blood culture was established for all patients as previously described.19 Three clinical end points were defined: (1) cure: no evidence of recurrent staphylococcal infection within the 12-week follow-up period; (2) relapse: clinical resolution of the initial episode of SAB after the treatment course, but culture-confirmed recurrent \textit{S} aureus infection documented within the follow-up period; and (3) death: all-cause mortality within the 12-week follow-up period.

Echocardiography
Specific echocardiographic findings were analyzed as previously described.25 To reduce potential bias created by sequential readings, all transesophageal echocardiograms (TEE) were later reinterpreted in a blinded manner by one of the investigators (G.E.P.). The results of the clinical interpretation were used for all subsequent analyses.

Statistical Analysis
To preserve the independence of observations, only the initial episodes of SAB were included in the study. Descriptive statistics for continuous variables were summarized in terms of medians and interquartile ranges. Categorical variables were reported in terms of the number and percent of patients affected. Wilcoxon rank sum and Fisher’s exact tests were used to evaluate group differences for continuous and categorical variables, respectively. The $\kappa$ statistic was used to compare degrees of agreement between clinical and investigational interpretations of TEE studies. McNemar’s test was used to compare transesophageal echocardiography (TEE) and TEE in the detection of cardiac vegetations.

Results
During the 71-month study period, 786 adult, nonneutropenic inpatients had ≥1 blood culture positive for \textit{S} aureus. In 4 of these patients (0.5%), only 1 of multiple blood cultures yielded \textit{S} aureus, and the patients had no clinical evidence of infection. These 4 patients were excluded from the registry, leaving a study cohort of 782 patients. Twenty-nine patients with permanent transvenous pacemakers, 3 patients with transvenously implanted cardioverter-defibrillator devices, and 1 patient with both an epicardial pacemaker and an epicardial implanted cardioverter-defibrillator device developed SAB during the study period and were included in this report (4% of study cohort) (Table 1). A tissue infection was the most common presumed source of SAB, occurring in 51.5% of the 33 study patients. Ten of the 33 patients (30.3%) had an intravascular device source, whereas the primary source of bacteremia in 6 patients (18.2%) was the cardiac device. Patients with early SAB were significantly more likely to have a cardiac device source for their bacteremia, whereas patients with late SAB were significantly more likely to have a tissue source of their bacteremia.

The overall incidence of confirmed CDI was 15 of 33 (45.4%). No particular type of cardiac device was identified as being more likely to develop CDI. The incidence of confirmed CDI presumably acquired as a consequence of hematogenous seeding of the device from a distant (5 patients) or unknown (4 patients) primary site of infection was 9 of 33 patients (27.3%). CDI was microbiologically confirmed in 12 patients (generator pocket cultures only in 8 patients, cultures of both generator pocket and electrode leads in 3 patients, and electrode lead cultures only in 1 patient) and clinically confirmed in 3 patients. In 60% of the patients (9 of 15) with confirmed CDI, no local signs or symptoms suggesting generator pocket infection were noted, although generator pocket cultures ultimately yielded \textit{S} aureus in 5 of these 9 patients.

Early SAB
Twelve of the 33 patients (36.4%) were classified as having early SAB. Nine of these 12 patients (75%) with early SAB had microbiologically confirmed CDI (positive from the generator pocket cultures in 6 patients, positive generator pocket and pacemaker from the lead cultures in 3 patients), and 3 patients were rejected as having CDI. The permanent pacemaker or implantable cardioverter-defibrillator device was thought to be the primary source of infection in 6 of the 9 patients (67%) with early SAB and confirmed CDI. Three patients (33%) with early SAB and confirmed CDI developed hematogenous seeding of their device from a distant or unknown primary source of \textit{S} aureus infection (tunnelled hemodialysis catheter in 2 patients, no identifiable source in 1 patient).

Late SAB
Twenty-one of the 33 patients (63.6%) were classified as having late SAB. Six of the 21 patients (28.5%) with late SAB had confirmed CDI (3 microbiologically confirmed, 3 clinically confirmed) (Table 2). All 6 of these patients developed CDI as a consequence of hematogenous seeding of
their device from a distant or unknown primary source of \textit{S. aureus} infection. Nine of the 21 patients (43%) with late SAB died before final follow-up and were categorized as possibly having CDI. CDI was rejected in 6 patients (28.5%) with late SAB. Rates of confirmed CDI were significantly different between patients with early and late SAB ($P=0.01$). When rates of confirmed and possible CDI were combined, device infection rates were similar in patients with either early or late SAB (75% versus 71.4%).

Because a 1-year cutoff distinguishing early from late device infection is controversial, we also evaluated rates of confirmed CDI using a 12-week cutoff, with the following definitions: (1) early SAB: date of first episode of SAB within 12 weeks of cardiac device placement and (2) late SAB: date of first episode of SAB $>12$ weeks after placement of the cardiac device. Rates of confirmed CDI with the 12-week cutoff point and the 1-year cutoff point were similar: 80% (8 of 10) versus 75% (8 of 12) for early SAB and 30.4% (7 of 23) versus 28.5% (6 of 21) for late SAB.

**Echocardiography**

Twenty-eight of the 33 patients underwent some form of echocardiography (84.8%). Twenty-four patients underwent TTE, and 22 underwent TEE. Clinical and investigator interpretative agreement was excellent for all available TEEs ($k=0.89$). Of the 18 patients who underwent both TTE and TEE, vegetations were identified by both procedures in 2 patients (11.1%) and by TEE only in 6 patients (31.6%) (McNemar’s test: $P=0.12$). Of the 33 patients, 9 were diagnosed with definite infective endocarditis, and 6 were diagnosed with possible infective endocarditis. In 5 of the 28 patients undergoing echocardiography (17.9%), no vegetations were detectable, but \textit{S. aureus} was isolated from the generator pocket of the device.

**Treatment**

Cardiac devices were removed in 12 of the 33 patients with SAB (36.4%). Twenty-one patients (63.6%) received vancomycin, and 12 received nafcillin, cefazolin, or another antibiotic. The median duration of intravenous antibiotic therapy was 15 days among patients in whom the cardiac device was not removed and 35 days among patients who underwent device removal. Patients in whom the cardiac device was not removed were more likely to die (10 of 21 patients [47.6%] versus 2 of 12 patients [16.7%]: $P=0.13$, Fisher’s exact test) or fail therapy (death or development of recurrent SAB) than patients in whom the cardiac device was removed (11 of 21 patients [52.4%] versus 3 of 12 patients [25%]: $P=0.16$, Fisher’s exact test). Three patients with endocarditis and...
widespread metastatic staphylococcal infection not limited to their cardiac device failed therapy (2 deaths, 1 relapse) despite removal of the cardiac device.

**Clinical Outcomes**
Outcomes of patients with early and late SAB are presented in Table 2. The entire cardiac device was removed in 12 of the 15 patients with confirmed CDI. Nine of these 12 patients who underwent device removal were cured of their staphylococcal infection. The device was not removed in 3 patients with confirmed CDI (1 patient refused surgical intervention and demonstrated no evidence of recurrent infection at 12-week follow-up; 2 other patients requested withdrawal of care and died of sepsis). Patients infected with methicillin-resistant and methicillin-susceptible *S aureus* had similar mortality rates (8 of 18 versus 4 of 15; \( P=0.47 \), Fisher’s exact test).

**Discussion**
To the best of our knowledge, this study is the largest prospective evaluation to date of patients with SAB and permanent pacemakers or implantable cardioverter-defibrillators. Previous studies have shown that CDI occurs in 0.13% to 19.9% of permanent pacemakers and 0.8% to 1.3% of transvenous non–thoracotomy implantable cardioverter-defibrillators. The most relevant clinical question, however, is not the overall incidence of CDI among patients with these devices but rather the incidence of CDI in patients who present with SAB. The present study answers this question with several key observations.

First, the probability of CDI in patients with SAB and intracardiac devices is high. Approximately 70% of the patients in this study with SAB and a permanent cardiac device had confirmed or possible CDI. Our results are similar to those of Camus and colleagues, who found that sustained *S aureus* or *S epidermidis* bacteremia was due to an infected cardiac pacing system in 67% of 21 retrospectively identified patients. In the present study, the incidence of confirmed CDI acquired via hematogenous spread was also high (27.3%). This estimate of hematogenous seeding of cardiac devices after SAB is consistent with previous observations. Taken together, these findings emphasize the high risk of bacteremic seeding of prosthetic material among patients with SAB.

Our data also underscore the difficulty of identifying CDI among patients with SAB, particularly if the infection involves the generator pocket. Sixty percent of the patients with confirmed CDI had no clinically detectable local signs of generator pocket infection. In agreement with previous reports, we found that TEE was more sensitive than TTE in detecting vegetations on the lead wires of the device, although our small sample size obscured the statistical significance of this observation. Neither form of echocardiography, however, could exclude infections of the generator component of the device. In 17% of the patients in this study who underwent echocardiography, no lead wire or valvular vegetations were detected, but *S aureus* was isolated from the generator pocket of the device. These results suggest that clinicians caring for patients with permanent cardiac devices who develop SAB should have a high index of suspicion that the implant is infected, even if local signs of generator pocket infection are absent and no generator wire or valvular vegetations are detected by TEE.

The results of this investigation support the systematic extraction of cardiac devices among most patients who develop SAB, both with and without clear device involvement, as long as skilled transvenous extraction is available to the patient. A recent report by Chua and colleagues confirmed that definitive management of CDI requires prompt extraction of the device and leads, followed by a course of intravenous antibiotics and device reimplantation at another site during a separate surgical procedure. Such management provided almost universal cure without substantial risk for operative mortality or recurrent infection. Thus, given the high rate of CDI in the present study, cardiac devices and leads should be removed from patients with SAB if (1) clinical or echocardiographic evidence of CDI is present, (2) clinical or echocardiographic evidence of CDI is absent but no clear source of SAB can be identified, or (3) the patient develops recurrent SAB. Cardiac devices may sometimes be retained in patients with an identifiable source of *S aureus* infection (eg, infected intravascular catheter) and no clear involvement of the leads or device by TEE or physical examination. Such patients, however, require careful follow-up to detect relapsing infection, which will generally occur within 12 weeks after antibiotic therapy is stopped if the prosthetic device was seeded at the time of the initial episode of SAB. Patients found to have relapsing infection should undergo complete device extraction.

The present study has several limitations. First, it was undertaken at a tertiary referral center and was subject to referral bias. Second, mortality in subjects with possible CDI prevented confirmation of infection status. Thus, our rate of confirmed CDI (45.4%) probably underestimates the true rate of device infection. Third, this investigation focused on rates of CDI involving *S aureus* because of this pathogen’s frequency, virulence, and tendency to adhere to implanted foreign material. Thus, these findings cannot be extrapolated to CDIs involving other organisms. Fourth, the risk of any particular patient’s developing CDI probably hinges on a variety of factors related to the host (eg, susceptibility factors), the pathogen (eg, virulence factors), and the implanted device (eg, types of biomaterials) that were not considered in this article. Finally, the small number of patients with SAB but no CDI limited our ability to identify clinical characteristics distinguishing these patients from patients with infected cardiac devices.

The results of this investigation demonstrate that patients with a permanent pacemaker or implantable cardioverter-defibrillator who develop SAB have a high rate of device infection. CDI should be considered among all patients with permanent cardiac devices who develop SAB, especially within the first year after implantation. Additional studies are needed to identify patient-specific characteristics that can help distinguish bacteremic patients with infected and uninfected cardiac devices, as well as pathogen-specific characteristics that may promote hematogenous seeding of cardiac devices.
Acknowledgment
This study was supported by grant AI-01647 (to Dr Fowler) from the National Institutes of Health and by a SmithKline Beecham Junior Faculty Award (to Dr Fowler).

References
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/104/9/1029

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/