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MAJOR ARTICLE

# Predictors of Bloodstream Infection in Patients Presenting With Cardiovascular Implantable Electronic Device Pocket Infection

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***Background.*** Generator pocket infection is the most frequent presentation of cardiovascular implantable electronic device (CIED) infection. We aim to identify predictors of underlying bloodstream infection (BSI) in patients presenting with CIED pocket infection.

***Methods.*** We retrospectively reviewed all adults with CIED pocket infection cared for at our institution from January 2005 through January 2016. The CIED pocket infection cases were then subclassified as with or without associated BSI. Variables with *P* values <.05 at univariate analysis were included in a multivariable model to identify independent predictors of underlying BSI.

***Results.*** We screened 429 cases of CIED infection, and 95 met the inclusion criteria. Of these, 68 cases (71.6%) were categorized as non-BSI and 27 (28.4%) as BSI. There were no statistically significant differences in patient comorbid conditions or device characteristics between the 2 groups. In multivariable analysis, the presence of systemic inflammatory response syndrome criteria (tachycardia, tachypnea, fever or hypothermia, and leukocytosis or leukopenia) and hypotension were independent predictors of underlying BSI in patients presenting with CIED pocket infection. Overall, patients in the non-BSI group who did not receive pre-extraction antibiotics had a higher frequency of positive intraoperative pocket/device cultures than those with pre-extraction antibiotic exposure (79.4% vs 58.6%; $P = .06$).

***Conclusions.*** Patients with CIED pocket infection who meet systemic inflammatory response syndrome criteria and/or are hypotensive at admission are more likely to have underlying BSI and should be started on empiric antibiotics after blood cultures are obtained. If these features are absent, it may be reasonable to withhold empiric antibiotics to optimize yield of pocket/device cultures during extraction.

**Key words:** bloodstream infection; cardiovascular implantable electronic device infections; generator-pocket infection; predictors; treatment.

Cardiovascular implantable electronic device (CIED) infections have been recognized as a growing problem, with reported incidence of 1% for initial placement and up to 7% for device reintervention [1]. Pulse generator pocket infection, with or without associated bloodstream infection (BSI), is the most common clinical presentation, and the majority of patients present within 12 months of device placement or revision [2, 3]. Local manifestations of generator pocket infection include pain, erythema, swelling, drainage, dehiscence of the surgical incision, and generator or lead erosion [4, 5]. If undiagnosed or untreated, generator pocket infection may progress to involve intravascular or intracardiac portions of leads, which can present as systemic infection.

Although surgical site infections limited to superficial layers of skin, such as a stitch abscess can be managed with antibiotic therapy alone, the American Heart Association guidelines [4] recommend complete extraction of an infected device for deep incisional or pocket infection. Complete removal of infected system in combination with antibiotic therapy, guided by identification and susceptibilities of the causative pathogen, is essential for curing infection [4]. In clinical practice, providers frequently start empiric antimicrobial therapy at initial presentation, even in cases where infection is clinically limited to a generator pocket. Considering that majority of CIED infections are caused by staphylococci, and given the prevalence of oxacillin resistance among these organisms [6], vancomycin is often initiated empirically until culture results are available [7]. However, administration of antibiotics before device extraction frequently leads to negative intraoperative pocket and device cultures [8, 9], resulting in continuation of broad-spectrum

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antibiotic therapy after extraction. Unnecessary use of broad-spectrum antibiotics has been associated with emergence of antimicrobial resistance, one of the biggest medical challenges in modern times and a substantial threat to public health [10].

At present, there are no established criteria to differentiate patients with CIED pocket infection who may have underlying BSI, and therefore should immediately start empiric antibiotic therapy, from those in whom underlying BSI is unlikely and in whom it is therefore reasonable to withhold empiric antibiotic therapy, to optimize the yield of intraoperative cultures and avoid unnecessary antibiotic exposure. The aim of the current investigation was to identify independent predictors of BSI in patients presenting with device pocket infection.

## METHODS

We retrospectively reviewed all adults (aged >18 years) presenting with CIED infection at our institution from 1 January 2005 through 1 January 2016. Cases of device infection were identified using our institutional CIED registry and defined according to standardized criteria [11]. Cases were classified as CIED pocket infection if inflammatory changes were observed at the pocket site, including erythema, swelling, pain, warmth, drainage, purulence, erosion, and dehiscence [4]. Patients with lead or pocket erosion with no inflammatory changes at the pocket site were excluded. Patients with CIED pocket infection were then subclassified as either having or not having concomitant BSI based on blood culture results.

Blood culture contamination was defined by criteria proposed by Bekeris et al [12]. Accordingly, a blood culture was considered contaminated if ≥1 of the following was identified in only 1 bottle of a series of blood culture specimens: coagulase-negative *Staphylococcus* species (CoNS), *Propionibacterium* (now *Cutibacterium*) *acnes*, *Micrococcus* species, viridans-group streptococci, *Corynebacterium* species, or *Bacillus* species. A blood culture series was defined as ≥1 specimen collected serially within a 24-hour period to detect an episode of BSI. Patients with contaminated blood culture specimens were not included in our microbiologic analysis.

To ensure accuracy and consistency of clinical and laboratory data collected from initial evaluation, we included only patients who were evaluated at our institution . To avoid false-negative blood culture data, we also excluded from analysis patients who received antibiotic therapy before blood cultures were obtained, as well as those who had abnormal white blood cell (WBC) count owing to medication effects or secondary to well-defined noninfectious comorbid conditions.

Demographic, clinical, laboratory, imaging and microbiologic data were extracted from each chart. Systemic inflammatory response (SIRS) was defined as the presence of ≥1 of the following clinical parameters: temperature ≥38.3°C or ≤36°C, pulse rate >90/min, respirations >20/min, and WBC count >12 000/μL or <4000/μL. Hypotension was defined as systolic blood pressure <90 mm Hg or a ≥40 mm Hg from baseline.

Significant microbial growth from operative cultures was defined as isolation of ≥20 colony-forming units from 10 mL of sonicate fluid, colony growth reported in ≥2 quadrants of the culture plate from a single specimen, or microbial growth of the same organism reported from ≥2 operative samples [8]. Device removal and associated complications were documented. The study was approved by the Mayo Clinic Institutional Review Board.

### Statistical Analysis

We used $\chi^2$ tests for categorical variables and Wilcoxon rank sum tests to associate continuous variables with 2-level categorical data. We assessed the predictors of BSI using univariate and multivariable logistic regression models. Odds ratios, 95% confidence intervals, and likelihood ratio $P$ values were reported for the logistic models. Statistical tests were 2 sided, with differences considered statistically significant at $P < .05$. Analyses were performed using JMP 13.0 software (SAS Institute).

## RESULTS

### Demographic, Clinical, and Device Data

Overall, 429 cases of CIED infection were seen during the study period (Figure 1). Among those, 248 of 429 (57.8%) had inflammatory changes at the pocket site, and 95 of them met study criteria. The excluded cases are outlined in Figure 1. Of these 95 study subjects, 68 (71.6%) were classified as non-BSI and 27 (28.4%) as BSI. Demographic data and underlying comorbid conditions for both groups are summarized with statistical analysis in Table 1. There was no significant difference in the median age at presentation for the non-BSI and BSI groups. There was no difference in the prevalence of medical comorbid conditions or device characteristics between groups.

### Symptoms Reported at Initial Evaluation

Concomitant lead or generator erosion was reported in 25 of 68 patients (36.7%) in the non-BSI group and 3 of 27 (11.1%) in the BSI group ($P = .01$). In the BSI group, pocket infection was complicated with CIED valvular endocarditis in 2 of 27 cases (both due to *Staphylococcus aureus*) and with CIED lead endocarditis in 5 of 27 (1 due to *S. aureus,* 2 due to *Enterococcus faecalis,* and 2 due to CoNS). There were 2 cases of CIED lead and tricuspid valve endocarditis related to *S. aureus*. A majority of patients in the non-BSI group reported symptoms at the pocket site >14 days in duration (60.2% vs 33.3%; $P = .02$). General malaise was reported more frequently in the BSI (92.8%) than in the non-BSI (2.9%) cohort ($P < .001$).

### Vital Signs at Initial Evaluation

Patients with pocket infection and BSI had a higher median maximum temperature than the non-BSI group (38.1°C

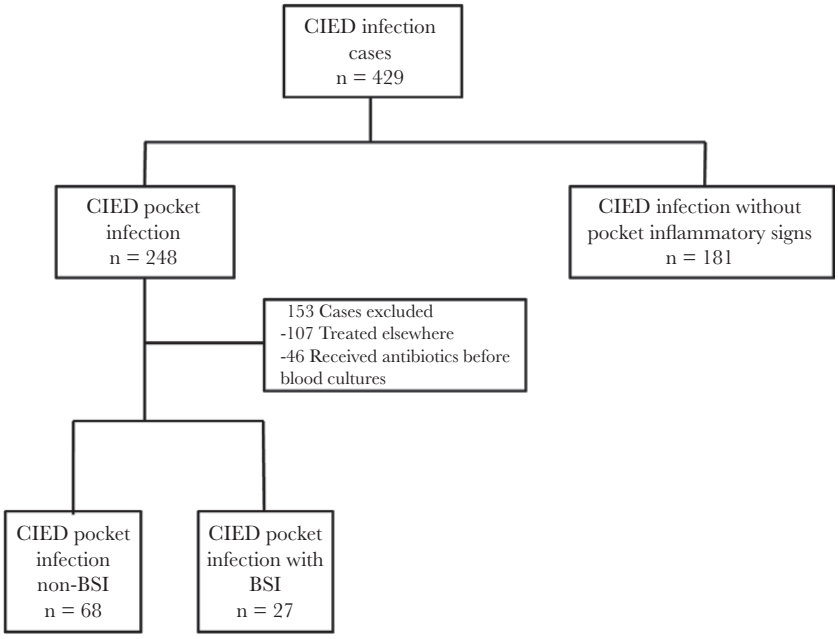


**Figure 1.** Screening and classification of study groups. Abbreviations: BSI, bloodstream infection; CIED, cardiovascular implantable electronic device.

[interquartile range (IQR)], 36.5°C –38.8°C] vs 36.6°C [36.5°C –36.8°C]; $P < .001$) and more frequently documented fever or hypothermia at presentation (40.7% vs 1.4%, respectively; $P < .001$). Patients with BSI were also more likely to present with hypotension (40.7% vs 4.4%, respectively; $P < .001$), pulse rate >90/min (37% vs 4.4%; $P < .001$), respirations >20/min (38.4% vs 16.4; $P = .02$), septic shock (21.4% vs 0%; $P < .001$), and organ failure (42.3% vs 1.4%; $P < .001$), primarily acute kidney injury (63% [7 of 11]).

**Table 1. Demographic, Clinical, and Device Characteristics of 95 Patients With CIED Pocket Infection**

| Variable | Patients, No. (%)[a] | | |
|---|---|---|---|
| | Non-BSI Group (n = 68) | BSI Group (n = 27) | *P* Value |
| Demographics | | | |
| Age, median (IQR), y | 67 (53–81) | 69 (58.8–77.7) | .77 |
| Male sex | 48 (70.5) | 18 (66.6) | .71 |
| Comorbid conditions | | | |
| Type 2 diabetes mellitus | 15 (22.0) | 4 (14.8) | .89 |
| Chronic kidney disease | 13 (19.1) | 4 (14.8) | .62 |
| Chronic heart failure | 40 (58.8) | 20 (74) | .16 |
| COPD | 7 (10.2) | 2 (7.1) | .66 |
| Immunosuppression | 5 (7.3) | 2 (7.4) | .99 |
| Prosthetic valve | 11 (16.4) | 7 (25.9) | .27 |
| Previous CIED infection | 4 (5.8) | 3 (11.1) | .38 |
| Device | | | |
| Initial placement | 18 (26.4) | 9 (33.3) | .50 |
| Device revision | 48 (70.5) | 18 (66.6) | .71 |
| ICD<br>Permanent pacemaker<br>CRT | 27 (39.7)<br>26 (38.2)<br>15 (22) | 12 (44.4)<br>9 (33.3)<br>6 (22.2) | .89 |
| Time from implantation/revision to development of symptoms, median (IQR), d | 140 (35–623) | 106.5 (22.2–756.7) | .35 |

Abbreviations: BSI, bloodstream infection; CIED, cardiovascular implantable electronic device; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; IQR, interquartile range.

[a]Data represent No. (%) of patients, unless otherwise specified.

### Laboratory Data at Initial Presentation

The BSI group had a higher median WBC count at admission than the non-BSI group ($12.4 \times 10^9$/L [IQR, 8.7–16.1 $\times 10^9$/L] vs $7.2 \times 10^9$/L [5.6–9.1 $\times 10^9$/L], respectively; $P < .001$), with leukocytosis or leukopenia present in 59.2% vs 2.9%, respectively ($P < .001$). The BSI cohort also had higher median serum creatinine (1.1 [IQR, 0.9–1.65] vs 1 [0.8–1.3] mg/dL; $P = .04$) and aspartate aminotransferase (29 U/L [25–47) vs 22 [20–27] U/L; $P = .02$) values. There were no statistically significant differences in platelet count, blood lactate level, erythrocyte sedimentation rate, or C-reactive protein level.

### Predictors of BSI

We performed univariate and multivariable analysis of clinical predictors associated with BSI in patients presenting with CIED pocket infection. In the univariate analysis (Table 2), patients with BSI were more likely to meet SIRS criteria, have hypotension, and have ≥2 abnormal laboratory values (C-reactive protein, erythrocyte sedimentation rate, aspartate aminotransferase, and blood urea nitrogen). Symptom duration >14 days before presentation was correlated with a lower risk of BSI. Given the small sample size, only variables from the univariate analysis with *P* values <.05 were included in multivariable

analysis (Table 3). Independent variables associated with BSI in multivariable analysis included the presence of SIRS criteria and hypotension.

#### Antimicrobial Management and Operative Culture Yield

Management, operative culture yield and outcomes in all 95 patients with CIED pocket infection are summarized in Table 4. At admission, providers elected to withhold antimicrobials until device removal in slightly more than half of patients in the non-BSI group (57.3%) and in 1 of 25 in the BSI group. In this particular patient, no SIRS criteria were recorded at admission or laboratory abnormalities at presentation. Antibiotic therapy was started in this patient once blood culture results returned positive.

The median time off antibiotic therapy until device removal in the non-BSI group was 2 (IQR, 1–7) days. None of the patients in the non-BSI group showed clinical progression or deterioration while off antibiotic therapy. The device was removed in all patients in the non-BSI group and 25 of 27 (92.5%) in the BSI group. Of the 2 patients whose device was retained, 1 died of infection complications before the scheduled procedure and the other declined surgical intervention and was kept on life-long antibiotic suppression. Both received antimicrobials at the time of initial presentation.

Of the patients undergoing device removal, complications were reported in 1 patient in the non-BSI group, who had superior vena cava rupture, and in 1 in the BSI group, who experienced cardiac arrhythmia and subsequently died. However, none of the patients in whom antibiotic therapy was initially withheld had infection-related complications. No infection relapse or recurrence, after reimplantation of a new device, was reported in patients in whom initial antibiotic therapy was withheld until extraction of the infected device.

**Table 2. Clinical Presentation in 95 Patients With CIED Pocket Infection**

| Variable | Patients, No. (%)[a] | | *P* Value |
|---|---|---|---|
| | Non-BSI Group (n = 68) | BSI Group (n = 27) | |
| Symptoms | | | |
| Reported symptoms for >14 d | 41 (60.2) | 9 (33.3) | .02 |
| Chills | 4 (5.8 | 24 (85.7) | <.001[b] |
| General malaise | 2 (2.9) | 26 (92.8) | <.001[b] |
| Altered mental status | 0 | 4 (14.8) | <.001[b] |
| Signs at physical examination | | | |
| Erythema | 46 (67.6) | 18 (66.6) | .93 |
| Tenderness | 31 (45.5) | 17 (62.9) | .13 |
| Swelling | 21 (30.8) | 12 (44.4) | .21 |
| Warmth | 4 (5.8) | 3 (11.1) | .38 |
| Purulent drainage | 6 (22.2) | 18 (26.4) | .67 |
| Fluctuance | 3 (4.4) | 4 (14.8) | .08 |
| Surgical incision dehiscence | 9 (13.2) | 2 (7.4) | .42 |
| Lead or generator erosion | 25 (36.7) | 3 (11.1) | .01[b] |
| Vital signs at initial evaluation | | | |
| Maximum temperature, median (IQR), °C | 36.6 (36.5–36.8) | 38.1 (36.52–38.8) | <.001[b] |
| Maximum temperature >38.3°C or <36°C | 1 (1.4) | 11 (40.7) | <.001[b] |
| Pulse rate, median (IQR), beats/min | 70 (62–80) | 75 (65–100) | .08 |
| Pulse rate, >90 beats/min | 3 (4.4) | 10 (37) | <.001[b] |
| Respirations, median (IQR), respirations/min | 18 (16–19) | 18 (17.5–22.5) | .04[b] |
| Respirations >20/min | 11 (16.4) | 10 (38.4) | .02[b] |
| SBP, median (IQR), mm Hg | 120 (108–131.5) | 112 (85–125) | .02[b] |
| SBP <90 mm Hg or ≥40–mm Hg drop from baseline | 3 (4.4) | 11 (40.7) | <.001[b] |
| Septic shock | 0 | 6 (21.4) | <.001[b] |
| Organ failure | 1 (1.4) | 11 (42.3) | <.001[b] |
| Laboratory data at initial presentation | | | |
| WBC count, median (IQR), $\times 10^9$/L | 7.2 (5.6–9.1) | 12.4 (8.7–16.1) | <.001[b] |
| WBC count >12 × $10^9$/L or <4 × $10^9$/L | 2 (2.9) | 16 (59.2) | <.001[b] |
| Serum creatinine, median (IQR), mg/dL | 1 (0.8–1.3) | 1.1 (0.9–1.7) | .04[b] |
| BUN, median (IQR), mg/dL | 20 (14–28) | 1.2 25 (17.7–37) | .06 |
| AST, median (IQR), U/L | 22 (20–27) | 29 (25–47) | .02[b] |

Abbreviations: AST, aspartate aminotransferase; BSI, bloodstream infection; CIED, cardiovascular implantable electronic device; IQR, interquartile range; SBP, systolic blood pressure; BUN, blood urea nitrogen; WBC, white blood cell.

[a]Data represent No. (%) of patients, unless otherwise specified.

[b]Significant at $P < .05$.

**Table 3. Univariate and Multivariable Analysis of Predictors Associated With Bloodstream Infection in the 95 Patients With CIED Pocket Infection**

| Risk Factor | Univariate OR (95% CI) | *P* Value | Multivariable OR (95% CI) | *P* Value |
|---|---|---|---|---|
| Age >65 y | 1.2 (.5–3.1) | .58 | … | … |
| ≥2 Medical comorbid conditions[a] | 1.0 (.4–2.6) | .87 | … | … |
| SIRS criteria[b] | 29.5 (8.8–98.1) | <.001[c] | 28.9 (7.6–144) | <.001[c] |
| SBP <90 mm Hg or >40–mm Hg drop from baseline | 14.8 (3.7–59.7) | <.001[c] | 12.8 (1.9–101) | <.001[c] |
| ≥2 Abnormal laboratory values[d] | 3.0 (1.1–7.7) | .02[c] | 2.7 (.5–13.0) | .19 |
| Reported symptoms for >14 d | 0.3 (.1–.8) | .02[c] | 0.29 (.06–1.1) | .58 |

Abbreviations: CI, confidence interval; CIED, cardiovascular implantable electronic device; OR, odds ratio; SBP, systolic blood pressure; SIRS, systemic inflammatory response syndrome.

[a]Medical comorbid conditions included the following: diabetes mellitus, chronic kidney disease, heart failure, liver disease, chronic pulmonary obstructive disease, prosthetic valve replacement, hematologic cancer, and immunosuppression.

[b]SIRS is defined as ≥ of the following: temperature ≥38.3°C or ≤36°C, pulse rate >90/min, respirations >20/min, and white blood cell count >12 000/μL or <4000/μL.

[c]Significant at $P < .05$.

[d]Abnormal laboratory values included the following: creatinine >1.2 mg/dL, erythrocyte sedimentation rate >22 mm/h, C-reactive protein >3.0 mg/L, blood urea nitrogen >20 mg/dL, and aspartate aminotransferase >40 U/L.

Overall, in the non-BSI group, positive intraoperative device/tissue cultures were more common in patients in whom antibiotics were initially withheld until device extraction (79.4% vs 58.6% in their antibiotic-treated counterparts), however, this difference was not statistically significant ($P = .061$).

### Microbiology

Organisms isolated in blood and operative cultures from the 95 cases of CIED pocket and BSI are shown in Table 5. The median time to blood culture positivity was 16 (IQR, 11.5–35.5) hours, and the median duration of BSI was 2.5 (1–4.25) days. In patients with positive blood and intraoperative cultures, concordance was reported in 80% (20 of 25) of cases. Of the remaining 5 cases, 2 had discrepant results between blood and intraoperative cultures; and 3 had negative intraoperative culture results. All 5 of these cases received antibiotics at the time of presentation.

## DISCUSSION

Our study findings suggest that patients with CIED pocket infection who present with SIRS criteria (fever or hypothermia, tachycardia, tachypnea, and leukocytosis or leukopenia) and/or hypotension (systolic blood pressure <90 mm Hg or a >40–mm Hg drop from baseline) are more likely to have underlying BSI. Consequently, patients presenting with these features should be started on empiric antimicrobial therapy once blood cultures have been obtained. On the contrary, the absence of these features suggests that underlying BSI is less likely, and it may be reasonable to withhold starting empiric antimicrobial therapy. In our cohort, none of the patients who were deemed clinically stable (absence of SIRS criteria or hypotension) and in whom empiric antibiotics were withheld (for a median of 2 days) experienced clinical progression or hemodynamic deterioration while awaiting device extraction. Furthermore, in the non-BSI group, the percentage of cases with significant microbial growth

**Table 4. Management, operative culture yield and outcomes of the 95 patients with CIED pocket infection**

| | Patients, No. (%)[a] | | |
|---|---|---|---|
| Treatment and Complications | Non-BSI Group (n = 68) | BSI Group (n = 27) | *P* Value |
| CIED removal | 68 (100) | 25 (92.5) | .02 |
| Antibiotics withheld until device removal | 38 (55.8) | 1/25 (4)[b] | <.001[c] |
| Duration off antibiotic therapy until device removal, median (IQR), d | 2 (1–7) | 0 (0–2.7) | <.001[c] |
| Clinical deterioration while hospitalized and off antibiotic therapy | 0 | 0 | … |
| Complications at time of removal[d] | 1 (1.4)[d] | 1/25 (4)[d] | .56 |
| CIED infection relapse or recurrence[e] | 2/66 (3.0) | 3/25 (12) | .10 |
| Culture yield from CIED devices | | | |
| Positive Gram stain | 12 (31.5) | 7 (23.3) | .50 |
| Significant microbial growth from intraoperative cultures | 48 (70.5) | 22/25 (80) | .08 |
| Antibiotics withheld before CIED removal (n = 39) | 31 (79.4)[f] | … | … |
| Antibiotics received before CIED removal (n = 29) | 17 (58.6)[f] | … | … |

Abbreviations: BSI, bloodstream infection; CIED, cardiovascular implantable electronic device; IQR, interquartile range.

[a]Data represent No. (%) of patients, unless otherwise specified.

[b]Only 25 patients in the BSI group underwent device removal.

[c]Significant at $P < .01$.

[d]One patient in the non-BSI had a mechanical complication and the other in the BSI had complications related to infection.

[e]A total of 66 patients in the non-BSI and 25 in the BSI group underwent device reimplantation after treatment of the index episode.

[f]$P = .06$ for comparison between these 2 non-BSI subgroups.

**Table 5. Microbiology of the 95 Cases of CIED Pocket Infection**

| Organism | Positive Cultures, No. | | |
|---|---|---|---|
| | Non-BSI Group: Intraoperative Cultures (n = 48) | BSI Group | |
| | | Blood Cultures (n = 27) | Intraoperative Cultures[a] (n = 20) |
| CoNS | 20 | 7 | 5 |
| *Staphylococcus aureus* | 12 | 16 | 13 |
| *Corynebacterium* sp. | 1 | 1 | 1 |
| *Enterococcus faecalis* | 0 | 3 | 0 |
| *Cutibacterium acnes* | 9 | 0 | 0 |
| *Pseudoclavibacter* sp. | 1 | 0 | 0 |
| Gram-negative bacteria | 2 | 0 | 1 |
| ≥2 Organisms | 3 | 0 | 0 |

Abbreviations: BSI, bloodstream infection; CIED, cardiovascular implantable electronic device; CoNS, coagulase- negative *Staphylococcus* species

[a]Intraoperative cultures obtained in the 25 patients with BSI who underwent device removal.

reported from intraoperative cultures was higher in patients in whom antibiotic therapy was withheld until device removal (79.4% vs 58.6% among those in whom it was not withheld; $P = .06$). The statistical non-significance of this comparison is likely due to the small sample size.

Similar observations have been reported for hip and knee prosthetic joint infections, in which discontinuation of antibiotic therapy for ≥14 days before surgery led to higher culture sensitivity in patients with planned resection arthroplasty [13]. Based on these observations, withholding antibiotic therapy for suspected prosthetic joint infections, in patients who do not have BSI, is now a standard clinical practice at our institution and others. We believe a similar case can be made for patients with CIED pocket infections, without BSI, in whom device extraction is planned in the next 2–3 days.

Patients with a longer duration of symptoms at initial presentation were more likely to have infection limited to the generator pocket on univariate analysis. However, this association was not significant in multivariable analysis, probably owing to small sample size. The paucity of systemic symptoms and the absence of BSI in patients presenting with longer duration of symptoms may be, in part, due to infection with more indolent organisms, as demonstrated by higher prevalence of CoNS in this group of patients. Interestingly, compared with the non-BSI group, patients with BSI were more likely to have pocket infections due to *S. aureus*, suggesting that infection with this particular organism might lead to higher risk of endovascular infection. Although an association between *S. aureus* BSI from a remote site of infection and hematogenous seeding of CIED leads has been observed earlier [14], this particular association between pocket infection with *S. aureus* and higher risk of associated BSI is novel and not reported earlier.

Predictors of BSI in patients presenting with CIED pocket infection have not been specifically evaluated in prior publications. Le et al [15] analyzed risk factors for CIED-related infective endocarditis (CIED-IE) in an earlier investigation and reported that use of immunomodulator therapy and hemodialysis were associated with a higher risk of CIED-IE. These patients were more likely to present with leukocytosis, fever, or malaise compared to non CIED-IE cases. Interestingly, patients with CIED-IE were less likely to present with infection at the generator pocket site, suggesting that the predominant mechanism of IE in these cases was hematogenous seeding of device leads or heart valves from distant sources of bacteremia.

Distinguishing patients with CIED pocket infection who may have underlying BSI from those who do not, before availability of blood culture results, is crucial, because patients with BSI have poorer outcomes, and delays in starting empiric antibiotics and device extraction can have detrimental effects [16].

In current practice, empiric antimicrobial therapy before device removal is based on personal discretion of the treating physician without much evidence to guide the decision-making process. This approach is concerning from a stewardship perspective, as routine administration of empiric antibiotics in stable patients, with no risk factors for underlying BSI, can negatively impact the yield of blood and operative specimen cultures. Consequently, pathogen-specific therapy is not an option in patients with negative cultures, who are often treated with broad-spectrum antimicrobial therapy [9]. Such approach opposes current efforts to minimize antibiotic overuse in an attempt to reduce antimicrobial resistance.

Based on our study findings and review of the published literature, we recommend obtaining 2 sets of blood cultures in all patients regardless of clinical presentation. Patients with ≥1 predictor of underlying BSI should be started on empiric antibiotic therapy directed against staphylococci. Whether or not addition of aerobic gram-negative coverage is necessary should be determined on a case-by-case basis. For patients without any positive predictors of underlying BSI, antibiotic therapy may be withheld to optimize the intraoperative culture yield. All patients with confirmed CIED infection, regardless of clinical presentation, should be evaluated as soon as possible for complete device extraction [16].

Our study is retrospective, and its design has inherent limitations. Considering the large tertiary academic nature of our practice, there is also a possibility of referral bias. It is certainly possible that patients referred to our medical center were sicker and more likely to have received prior courses of antimicrobial therapy and prior management, such as partial removal of cardiac device. This might skew our data compared with overall cases of CIED infection, which might affect subsequent interpretation of results. Owing to the small sample size, we were

unable to develop a robust scoring system to predict underlying BSI in patients presenting with CIED pocket infection.

In conclusion, our study findings suggest that patients with CIED pocket infection who are afebrile, hemodynamically stable, and have normal leukocyte counts at admission are unlikely to have underlying BSI. Therefore, it may be reasonable to withhold antimicrobial therapy in these patients to optimize the intraoperative culture yield, provided that device extraction is planned in the next 2–3 days.

## Notes

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***Potential conflicts of interest.*** P. A. F. reports honoraria/consultant fees from Medtronic, Guidant, and Astra Zeneca; research grant from Medtronic, Astra Zeneca via Beth Israel, Guidant, St Jude, Bard; and intellectual property rights with Bard EP, Hewlett Packard, and Medical Positioning. L. M. B. reports royalty payments (authorship) from UpToDate (<$20 000) and consultant payments from Boston Scientific; <20,000. M. R. S. reports receiving funds from Medtronic for prior research unrelated to this study and honoraria/consulting fees from Medtronic, Spectranetics, Boston Scientific, and Aziyo Biologics (all <$20 000). All other authors report no conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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