Background: Cardiovascular implantable electronic device (CIED) therapy can reduce morbidity and mortality, but this benefit can be diminished by CIED infection. Currently, there are limited published data on the mortality and cost associated with CIED infection.

Methods: We analyzed the risk-adjusted total and incremental admission mortality, long-term mortality, admission length of stay (LOS), and admission cost associated with infection in a retrospective cohort of 200,219 Medicare fee-for-service patients admitted for CIED generator implantation, replacement, or revision between January 1, 2007, and December 31, 2007.

Results: There were a total of 5817 admissions with infection. Infection was associated with significant increases in adjusted admission mortality (rate ratios, 4.8-7.7; standardized rates, 4.6%-11.3%) and long-term mortality (rate ratios, 1.6-2.1; standardized rates, 26.5%-35.1%), depending on CIED type. Importantly, approximately half of the incremental long-term mortality occurred after discharge. The adjusted LOS was significantly longer with infection (length of stay mean ratios, 2.5-4.0; standardized length of stay, 15.5-24.3 days), depending on CIED type. The standardized adjusted incremental and total admission costs with infection were $14,360 to $16,498 and $28,676 to $53,349, respectively, depending on CIED type. The largest incremental cost with infection was intensive care, which accounted for more than 40% of the difference. Adjusted long-term mortality rate and cost ratios with infection were significantly greater for pacemakers than for implantable cardioverter/defibrillators or cardiac resynchronization therapy/defibrillator devices.

Conclusions: Infection associated with CIED procedures resulted in substantial incremental admission mortality and long-term mortality that varied with the CIED type and occurred, in part, after discharge. Almost half of the incremental admission cost was for intensive care.


See Invited Commentary at end of article

In the present analysis, we sought to define the CIED type–specific risk-adjusted mortality and cost and the cost allocation associated with hospital admissions for CIED generator implantation, replacement, or revision with infection.

CARDIOVASCULAR IMPLANTABLE electronic device (CIED) therapy reduces morbidity and mortality in appropriately selected patients, but this benefit is thought to be mitigated by complications, including infection. Although it is well recognized that the rate of CIED infection is increasing faster than the rate of CIED implantation, there are limited published data on the risk-adjusted mortality and cost associated with CIED infection or the relationship of these outcomes to different CIED types.

METHODS

DATA

The study cohort was derived from the 100% Medicare Standard Analytic File Limited Data Set version for inpatient admissions for the 2007 calendar year and consisted of all admissions that included a procedure for CIED generator implantation, replacement, or revision identified using the corresponding International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) procedure codes for pacemakers (PMs) (37.80, 37.81, 37.82, 37.83, 37.85, 37.86, and 37.87), implantable cardioverter/defibrillators (ICDs) (37.94, 37.96, and 37.98), cardiac resynchronization therapy devices with defibrillator (CRT-D) (00.51 and 00.54), or cardiac resynchronization therapy devices without defibrillator (CRT-P) (00.50 and 00.53). Admissions that included only electrode implantation, replacement, or revision were not included because most CIED infections are treated with complete system explantation. Admissions including other major cardiac procedures (eTable 1; http://www.archinternmed.com) were excluded to avoid
The unit of analysis for all 4 outcomes was the individual discharge. Both admission mortality and long-term mortality were adjusted for age, sex, race, and a set of 28 comorbidity measures originally derived by Elixhauser et al and validated for risk adjustment of administrative data. The patient status for this set of comorbidities was collected from the administrative data using the comorbidity software (versions 3.2-3.3) from the Agency for Healthcare Research and Quality (AHROQ) that specifies ICD-9-CM codes corresponding to each comorbidity. Peptic ulcer disease was omitted because it was rare in the study cohort. The primary condition screens, including for cardiac conditions, were not used because this study was narrowly defined to patients receiving CIED therapy.

Our analysis had 4 primary outcomes: admission mortality, long-term mortality (during admission quarter or subsequent 4 quarters), admission length of hospital stay (LOS), and admission cost. The unit of analysis for all 4 outcomes was the individual discharge.

Admission costs were calculated with the method used by the Centers for Medicare & Medicaid Services (CMS) to calculate costs for establishing payment rates under the Inpatient Prospective Payment System. Specifically, charges were standardized using factors to reflect the admitting hospital's geographic location, teaching status, and indigent care load. The standardized charges were summarized for 15 cost centers (ie, routine care, intensive care, pharmacy, supplies, therapy, laboratory, operating room, cardiology, radiology, emergency, blood, delivery, inhalation therapy, anesthesia, other), and then charges for each cost center were multiplied by a nationally calculated cost-to-charge ratio to estimate costs.

**STATISTICAL ANALYSIS**

Unadjusted admission mortality rates were compared using a 2-tailed z statistic test for proportions. Unadjusted LOS and admission cost were compared using a 2-tailed t test. Long-term mortality functions were estimated using Kaplan-Meier survival analysis and compared using a log-rank test. A χ² test was used to evaluate unadjusted admission and long-term mortality ratios, and an approximate z statistic test was used to evaluate unadjusted LOS and cost ratios. A significance level of .05 was used for all tests. Statistical tests were performed using SAS version 9.1.3 (2004) (SAS Institute Inc, Cary, North Carolina).

For each admission, the probability of each outcome was adjusted for age, sex, race, and a set of 28 comorbidity measures.
RESULTS

STUDY COHORT

The final study cohort of 200,219 admissions consisted of 131,342 PM (65.6%), 37,642 ICD (18.8%), 27,261 CRT-D (13.6%), and 3,974 CRT-P (2.0%) procedures (Table 1). There were a total of 5817 (2.9%) admissions with infection. More than 90% of infections were identified with ICD-9-CM codes corresponding to infection with a cardiac (33%) or vascular (2%) device, sepsisemia (37%), endocarditis (8%), bacteremia (7%), and shock (3%) (eTable 2).

ADMISSION AND LONG-TERM MORTALITY

After adjustment for demographics and comorbidities, the admission mortality ratio (with infection/without infection) remained significantly greater than unity for all CIED types (4.8- to 7.7-fold; all P < .001) (Table 2 and eTable 3). The standardized adjusted total and incremental admission mortality with infection were 4.6% to 11.3% and 3.9% to 9.6%, respectively, depending on the CIED type (Table 2). Survival analyses revealed that unadjusted long-term mortality (death during the admission quarter or subsequent 4 quarters) with infection was significantly greater than without infection for PM, ICD, and CRT-D (Table 2 and Figure 1). There were insufficient data for a survival analysis of CRT-P. The adjusted long-term mortality rate ratio (with infection/without infection) remained significantly greater than unity for PM, ICD, and CRT-D (1.6- to 2.1-fold; all P < .001), but was significantly greater for PM than for ICD or CRT-D (2.1- to 2.2-fold). The standardized adjusted total and incremental long-term mortality with infection were 11.8% to 16.0% and 5.2% to 10.5%, respectively (Table 2).
for all CIED types (2.5- to 4.0-fold; all P < .001) but was significantly smaller for PM compared with ICD and CRT-D (Table 3 and eTable 5). The standardized adjusted total and incremental LOS with infection were 15.5 to 24.3 days and 9.4 to 18.2 days, respectively (Table 3).

ADMISSION COST AND COST ALLOCATION

The adjusted cost ratio (with infection/without infection) remained significantly greater than unity for all CIED types (1.4- to 1.8-fold; all P < .001) but was significantly greater for PM than ICD or CRT-D (Table 4 and eTable 6). The standardized adjusted total and incremental costs with infection were $28 676 to $53 349 and $14 360 to $16 498, respectively (Table 4).

The study cohort admission costs were allocated to 15 cost centers. Seven of these cost centers accounted for more than 90% of the mean admission cost without infection, regardless of the CIED type: supplies, operating, intensive care, routine care, cardiology, pharmacy, and laboratory (Figure 2). Together, intensive care and pharmacy accounted for more than half of the total incremental cost with infection for all CIED types (Table 5). The single largest incremental cost with infection was for intensive care, which accounted for 41% to 50% of the difference (Table 5). Supplies (including the cost of the CIED) was the most expensive cost center, with or without infection, but accounted for only approximately 10% or less of the incremental cost with infection (Table 5).

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**Table 3. Cardiovascular Implantable Electronic Device (CIED) Procedure Admission Length of Stay, With and Without Infection**

<table>
<thead>
<tr>
<th>Admission LOS</th>
<th>PM</th>
<th>ICD</th>
<th>CRT-D</th>
<th>CRT-P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Without Infection</td>
<td>With Infection</td>
<td>P Value</td>
<td>Without Infection</td>
</tr>
<tr>
<td>Unadjusted</td>
<td>Mean (SD), d</td>
<td>4.8 (5.2)</td>
<td>14.4 (13.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td></td>
<td>Minimum, d</td>
<td>0</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td></td>
<td>Maximum, d</td>
<td>274</td>
<td>205</td>
<td>278</td>
</tr>
<tr>
<td>Increment, d</td>
<td>9.6</td>
<td>11.7</td>
<td>10.7</td>
<td>10.7</td>
</tr>
<tr>
<td>LOS mean ratio with infection, (95% CI)</td>
<td>3.0 (2.9-3.1)</td>
<td>&lt;.001</td>
<td>3.6 (3.4-3.8)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Adjusteda</td>
<td>Mean (SD), d</td>
<td>6.1</td>
<td>15.5</td>
<td>6.1</td>
</tr>
<tr>
<td></td>
<td>Increment, d</td>
<td>9.4</td>
<td>12.7</td>
<td>11.8</td>
</tr>
</tbody>
</table>

Abbreviations: CRT-D, cardiac resynchronization therapy device with defibrillator; CRT-P, cardiac resynchronization therapy device without defibrillator; ICD, implantable cardioverter/defibrillator; LOS, length of stay; PM, pacemaker.

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The adjusted model accounts for age, sex, race, and 28 Elixhauser comorbidity measures. The adjusted mean LOS and LOS increment were calculated using infected patients as the standard population.
To our knowledge, our study provides the first risk-adjusted, device type–specific estimates of mortality, LOS, and cost associated with CIED infection in the current era of CIED use. This information is critical because it permits clinicians, patients, and payers to more accurately estimate the morbidity and mortality associated with specific CIED types. Importantly, the incremental effects of CIED infection were not uniform across CIED types. Specifically, the adjusted long-term mortality rate and cost ratios were significantly higher and the adjusted LOS mean ratio was significantly lower for PM procedures with infection compared with ICD or CRT-D procedures with infection (Tables 2-5).

A key strength of our analysis is the use of a contemporary cohort of CIED recipients. This is important because significant advances have been made in device manufacturing and implantation techniques over time, and guidelines for CIED infection management have also evolved.5,6

Admission mortality rates associated with CIED infection have been reported to be 3.7% to 8.1%.3,6,14-16 A retrospective cohort study of National Hospital Discharge Survey data for CIED procedures from 1996 through 2003 derived a partially risk-adjusted odds ratio for admission death with infection of 2.41.17 However, the generalizability of these data to current practice may be limited because they were derived from older, single-institution, referral center, or ICD/CRT-only cohorts, and are not adequately risk-adjusted.

Prior investigations suggest that sepsis and its sequelae are major contributors to incremental admission mortality associated with CIED infection. In 2 retrospective, single-center series enrolling a total of 451 CIED-infected patients treated since 2000, 12 of 19 (63%)16 and 3 of 3 (100%)15 admission deaths were attributed to sepsis or end-organ failure. Another retrospective single-center series enrolling 210 patients with CIED infection treated from 1995 through 2006, reported 13 of 17 (77%) of deaths were attributed to sepsis14 and that other risk factors for mortality included complications due to the explantation procedure, congestive heart failure, cardiac arrest, and renal failure.14

Comparison of the risk-adjusted incremental admission and long-term mortality associated with each type of CIED therapy in our analysis indicates that approxi-
mately half of the incremental long-term mortality occurs after discharge. The etiology of the incremental mortality after hospital discharge is not clear because the cause of death could not be accurately determined from the administrative data used in our study. A retrospective study of 210 CIED infections treated between 1995 and 2006 reported a 6-month mortality of 17.6%, which was independently associated with septic embolization, renal insufficiency, abnormal right ventricular function, and moderate or severe tricuspid regurgitation. Another retrospective study of 412 CIED infections treated between 2002 and 2007 reported 12-month mortality of 17.2%. In both series, mortality after discharge exceeded admission mortality, but the absence of a control group without infection prevented an accurate assessment of how much of this mortality after discharge is associated with infection. Most patients with CIED infections in the present study were discharged to settings other than home or self-care (PM, 70%; ICD, 59%; CRT-D, 55%; and CRT-P, 59%), indicating that increased awareness of the mortality risk following discharge may improve patient outcomes.

Patients receiving a PM had a significantly higher adjusted long-term mortality rate ratio with infection (rate ratio, 2.1; 95% CI, 2.0-2.2), compared with ICD (1.6; 95% CI, 1.4-1.8) or CRT-D (1.6; 95% CI, 1.4-1.8). This may be owing to differences in the severity of infection (eg, rate of sepsis), management (eg, LOS or follow-up at chronic care facilities), or other factors. Incomplete risk adjustment (eg, attendant illness) could be another contributing factor to apparently higher mortality rate ratio in this group. The clinical information available in this administrative database is limited and does not permit an adequate examination of the etiology.

There are few published data on the current cost of managing CIED infection. Moreover, these analyses do not reflect the current patient population receiving CIED therapy. For example, recent cost-effectiveness analyses of ICD therapy are based on data from randomized trials that limited enrollment of patients older than 75 years. We believe Medicare beneficiary administrative data are a more appropriate tool to study the financial cost of CIED infections because the majority of CIED are implanted in older individuals. In our study, the risk-adjusted long-term mortality rate ratios for ICD (1.33-2.42; P < .001) and CRT-D (1.22-1.73; P < .001) procedures indicate that age 75 or older is associated with a significant effect on long-term mortality (eTable 4).

An earlier single-center investigation of 18 patients with CIED infection (17 PM and 1 ICD) treated from 1989 through 1994 reported the mean (SD) incremental admission cost for a PM infection was $24,459 ($14,585). The standardized adjusted incremental admission cost

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### Table 5. Cardiovascular Implantable Electronic Device (CIED) Procedure Cost Allocation, With and Without Infection

<table>
<thead>
<tr>
<th>Incremental Cost Allocation</th>
<th>PM</th>
<th>ICD</th>
<th>CRT-D</th>
<th>CRT-P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intensive care</td>
<td>6865 (41)</td>
<td>8267 (42)</td>
<td>8724 (44)</td>
<td>12,748 (50)</td>
</tr>
<tr>
<td>Pharmacy</td>
<td>1943 (12)</td>
<td>2307 (12)</td>
<td>2151 (11)</td>
<td>2342 (9)</td>
</tr>
<tr>
<td>Routine care</td>
<td>2545 (15)</td>
<td>2562 (13)</td>
<td>2289 (12)</td>
<td>1394 (3)</td>
</tr>
<tr>
<td>Laboratory</td>
<td>1150 (7)</td>
<td>1393 (7)</td>
<td>1446 (7)</td>
<td>1706 (7)</td>
</tr>
<tr>
<td>Supplies</td>
<td>973 (6)</td>
<td>1208 (6)</td>
<td>775 (4)</td>
<td>2729 (11)</td>
</tr>
<tr>
<td>Operating</td>
<td>748 (4)</td>
<td>946 (5)</td>
<td>1247 (4)</td>
<td>1048 (4)</td>
</tr>
<tr>
<td>Cardiology</td>
<td>141 (1)</td>
<td>80 (0)</td>
<td>319 (2)</td>
<td>−44 (0)</td>
</tr>
<tr>
<td>All other cost centers</td>
<td>2486 (15)</td>
<td>2985 (15)</td>
<td>2657 (16)</td>
<td>3658 (14)</td>
</tr>
</tbody>
</table>

Abbreviations: CRT-D, cardiac resynchronization therapy device with defibrillator; CRT-P, cardiac resynchronization therapy device without defibrillator; ICD, implanta

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Figure 2. Cost allocation for 200,219 Medicare beneficiary admissions for CIED procedures, with and without infection. Allocation of costs to the 7 most expensive cost centers for 200,219 admissions for CIED generator implantation, replacement, or revision procedures, without (A) and with (B) infection, in Medicare beneficiaries during the 2007 calendar year. CIED indicates cardiovascular implantable electronic device; CRT-D, cardiac resynchronization therapy device with defibrillator; CRT-P, cardiac resynchronization therapy device without defibrillator; ICD, implantable cardioverter/defibrillator; and PM, pacemaker.
for a PM with infection was approximately 30% less in our study ($16,208), which may, in part, be due to a shorter incremental LOS (9.4 days vs 15.9 days) with current practice. An analysis of more contemporary study data, the Medicare Provider Analysis and Review (MedPAR) file for the fiscal year 2003, estimated the risk-adjusted incremental admission cost and LOS for ICD/CRT-D infection were $18,477 and 9.6 days. In contrast, the standardized adjusted incremental cost in our study was approximately 10% less, despite a 20% to 30% longer mean risk-adjusted LOS. This cost difference could be, in part, due to methodological differences. Moreover, increasingly cost-effective admissions may also affect comparisons of cost estimates between earlier and more recent CIED infection cases.

The CMS provides supplementary payments for admissions with costs that exceed the basic prospective payments by a fixed-loss cost threshold. The proportion of admissions with infection that qualified for these outlier payments was 3.3- to 8.5-fold the proportion without infection, depending on the therapy (PM, 17% vs 2%; ICD, 32% vs 6%; CRT-D, 42% vs 12%; and CRT-P, 40% vs 11%; all P < .001) (Table 4).

Another important observation in our study was that nearly half of the current incremental cost associated with management of CIED infections was for intensive care. Strategies to shorten the time to explantation, including expeditious diagnosis, could reduce intensive care expenses. Also, patients should be carefully assessed for the requirement of external electrical support following explantation of the infected device, since up to 30% of patients may not require implantation of a new device. These simple but important measures can limit the duration of intensive care and substantially reduce cost. In our analysis, the standardized adjusted incremental LOS with infection was 9.4 to 18.2 days. Earlier transition to outpatient parenteral antibiotic therapy, when indicated, may also reduce hospital LOS and treatment costs for CIED infection.

Although it is important to reduce admission costs associated with CIED infection, preventing infections or reducing the severity of infections through early detection would have a significant impact on both mortality and cost associated with these infections.

Our analysis has several important limitations. First, infections identified using ICD-9-CM codes for cardiac or vascular device infection, endocarditis, or cardinal manifestations of infection, in the setting of a CIED implantation, were presumed to be CIED infections. However, some of these infections may not have been related to the CIED. There are no ICD-9-CM codes specific for CIED infection; previous analyses have used a variety of ICD-9-CM code-based strategies to identify CIED infections in administrative databases. We took an approach similar to Voigt et al that incorporates multiple distinct code-based criteria to increase the sensitivity of the search. Approximately 55% of the infections were identified for admissions with a CIED generator implantation and a concurrent cardiac manifestation of infection (septicemia, bacteremia, shock, cellulitis, and fever). It is likely that most of these represent CIED infections because it is unusual to implant a CIED during an admission that includes infection of another organ system, unless the infection of that organ system was due to a CIED infection or leads to a CIED infection. Nonetheless, it is conceivable that some of the cases included in our study were infections due to other causes, and this could affect the accuracy of the mortality analysis, length of stay, and cost estimates. Second, this study does not capture CIED infections for which reimplantation was not performed or performed during another encounter. Because CIED infections are usually treated on an inpatient basis, while implantations are often done on an outpatient basis, and because infections treated with reimplantation at a subsequent encounter were not captured, the proportion of patients with infection in this cohort is not a true reflection of actual incidence of infection following CIED implantation. Third, because inpatient physicians’ fees and required outpatient care are not captured, it may underestimate the cost associated with treatment of CIED infections. Fourth, the group of CIED admissions without infection may be enriched for patients with more complications than the typical CIED implantation, which are often performed on an outpatient basis. Therefore, this study may underestimate the incremental admission mortality and cost with infection. Fifth, these data were collected from the Medicare Inpatient Standard Analytic File, which is a claims-based database and therefore may be less accurate than a clinical database for evaluating some aspects of these admissions. Finally, cost data are based on calculations made from charges and cost-to-charge ratios, rather than direct cost data. Despite these limitations, we believe these data provide useful insights into mortality and cost associated with infection of CIED as they are being used in current practice.

Our work demonstrates that Medicare beneficiary admissions for CIED procedures with infection are associated with significant, device-dependent, incremental increases in admission mortality and long-term mortality, LOS, and cost compared with those without infection. Intensive care and pharmacy services accounted for more than half of the incremental cost with infection and could be targeted to reduce costs associated with management of CIED infection. The etiology of excess mortality in patients with CIED infection after hospital discharge remains unclear and merits further investigation.

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Additional Contributions: David J. Wright, PhD (Wes tat, Rockville, Maryland), performed a statistical review of the data.

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