Increased late complex device infections are determined by cardiac resynchronization therapy-defibrillator infection

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Aims
The incidence of cardiac device infection (CDI) more than 12 months following complex device implant (late infection) has not been extensively reported. Our objective was to compare both early (within 12 months) and late infection rates following complex device implantation.

Methods and results
Patients who received either a cardiac resynchronization therapy (CRT) device with or without a defibrillator (CRT-D or CRT-P), or a defibrillator alone [implantable cardioverter-defibrillator (ICD)], between March 2005 and December 2011 were studied retrospectively. The study endpoint was device removal due to CDI. A total of 496 patients underwent complex device implantation. There were 1883 patient years of follow-up. Mean age was 73 ± 8 years. Seventy per cent were male. Overall, 24 infections (4.8%) were identified; 6 infections were within 12 months (1.2%) and 18 (3.7%) infections at least 12 months following implant (P < 0.025). The mean intervals between implant and infection were 6 months (± 3.7) and 30 months (± 14.4) in the early and late groups, respectively. Early infection rates (%) for ICD, CRT-P, and CRT-D devices were 1.5, 1.6, and 0.6, respectively. Corresponding late infection rates were 2.2, 2.1, and 6.4. The increased late infection rate was driven by increased CRT-D infection (P < 0.01; compared with early CRT-D infection).

Conclusion
Early CDI rates are consistent with published data. Compared with early infection, late CDI rates are significantly increased and are due to CRT-D infection. These findings are consistent with emerging reports. Late CRT-D infection threatens to undermine the long-term costs and overall health gain from these devices.

Keywords
Infection • Cardiac resynchronization • Defibrillator

Introduction
Implantation rates for both cardiac resynchronization therapy (CRT) and implantable cardioverter-defibrillator (ICD) have increased exponentially during the previous decade. Proportionate infection rates have also increased, and threaten to undermine the long-term costs and overall health gain from these devices.¹ ²

Until recently, most reports of infection following complex intra-cardiac devices (CIDs) implantation have been limited to the first 12 months following implant. Recent prospective studies would suggest, however, that the impact of late CID infection (i.e. more than 12 months following implant) is considerable.³ ⁴⁻⁷

We report the incidence of both early and late infection (with extended follow-up) following implantation of ICD and CRT devices.
Increased late complex device infections

What’s new?
• The incidence of complex cardiac device infection increases with duration of follow-up.
• The majority of these infections presents more than 12 months following implant; 9 of 24 infections presented more than 2 years following implant.
• Cardiac resynchronization therapy-defibrillator device infection accounts for the majority late infection.

6 and 3 months, respectively. Patients not seen during the study period, including the deceased, had their electronic records reviewed. Given the systematic and comprehensive methods of data collection, we are confident that all patients who developed complex device infection, and subsequent extraction during the study period, were identified.

Infection was defined as the presence of local warmth, tenderness, fluctuation, and erythema at the generator site. Wound dehiscence and frank erosion (with or without purulent discharge) were also considered manifestations of infection.4 Since our study was retrospective, infection was reasonably presumed by the need for device extraction.

Device-related bacteraemia and endocarditis were established by blood cultures, echocardiography and scrutiny of both case and pathology records.

Infections occurring within 12 months of device implant were classified as ‘early infection’, and infections identified more than 12 months following implant thereafter as ‘late infection’.

Statistics
Absolute numbers, percentages, means, and standard deviations were calculated as appropriate. Fisher’s exact test was used for comparison of categorical variables and continuous variables were assessed using Student’s t-test or Mann–Whitney. Statistical tests were one- or two-sided, as appropriate. A P-value of <0.05 was considered to be statistically significant. Statistical analyses were performed using the Stats Direct software package (Statsdirect Ltd).

Results
Between March 2005 and December 2011, 498 patients underwent complex device implantation at our institution. The mean age of the cohort was 73 ± 8 years. Seventy per cent were male. The number of patients who received ICD, CRT-P, and CRT-D implants were 134, 193, and 171, respectively. The corresponding ages were 69 ± 9, 73 ± 9, and 72 ± 10 years. Overall, there were 1883 patient years of follow-up (range 14–95 months).

Twenty-four infections (4.8%) were identified; 6 infections within 12 months (1.2%) and 18 (3.7%) infections more than 12 months following implant; 9 infections presented more than 24 months following implant. Pocket haematoma was recorded in 2 of the 24 infections; in both instances exploration was not required.

The intervals between implantation and infection ranged from 2 to 60 months; the mean intervals between implant and infection were 6 (± 3.7) months and 30 (± 14.4) months in the early and late groups, respectively. Compared with infection within 12 months of implant, late device infections were increased (P < 0.025) and almost entirely due to CRT-D infection (P < 0.01; compared with early CRT-D infection). Early and late infection rates stratified to device type are shown in Figure 1.

Of the late infections (n = 18), Staphylococcus aureus and mixed coliforms were isolated from two and one patients, respectively. None of the infections were associated with renal replacement therapy or an indwelling vascular catheter.

All patients with infection underwent successful system extraction. Following extraction, there was one death due to sepsicaemia and multi-organ failure. The remaining cases (n = 23) underwent device re-implantation following systemic antibiotic therapy (median duration 14 days; range 7–28 days).

The specific clinical syndromes which prompted device explant, and microbiology where positive, are shown in Table 1.

Discussion
Cardiac resynchronization therapy infection rates
Early infection rates following complex device implantation (both CRT and ICD) were consistent with previous reports.3,5,8 However, late infection rates (beyond 12 months following implant) were increased (1.2 and 3.7%, respectively, P < 0.025). The increased late infection rate was driven primarily by CRT-D infection (Figure 1).

Late infection following bradycardia pacemaker implantation is acknowledged. From an extensive prospective database, Johansen et al.4 reported early and late infection rates of 0.43 and 0.34%, respectively. In a retrospective case-controlled study, Lekkerkerker et al.10 identified 75 infections from 3410 pacemaker and device implants (2.2%); 28 of these infections presented more than 12 months after implantation, and a further 18 presented more than 2 years later.

In a recently published report, de Bie et al.5 followed 2476 patients following ICD and CRT implantation for a median 30 months. The overall infection rate was 2.6%, reflecting a 0.9% per year incidence of infection. Early and late infection rates stratified to device type are shown in Figure 1.

Figure 1 Early and late infection rates (%) according to device types and time from implant. Early infection, within 12 months of implant; late infection, beyond 12 months following implant; ICD, implantable cardioverter-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; CRT-D, cardiac resynchronization therapy-defibrillator.
throughout three consecutive years of follow-up. Infection rates of ICD and CRT implants were not separately reported.

In a retrospective study of early complex device infection, Mittal et al.\textsuperscript{11} reported a 6-month CRT-D infection rate of 4.23%. The corresponding infection rates for CRT-P and ICD were 0.0 and 1.33%. In a prospective study of CRT implants with longer follow-up, Romeyer-Bouchard et al.\textsuperscript{4} reported an overall infection rate of 4.3%. Late infections were dominated by a 9.5% infection rate following CRT-D implantation; all infections presented within 12 months of implant, and no additional cases were reported during extended follow-up (mean 31 ± 19 months); these findings contrast with our study in which the majority of infections presented more than 12 months following implant.\textsuperscript{4} Possible explanations for this are discussed below.

Published studies reporting CRT device infections since 2000 are presented in Table 2.

### Increased cardiac resynchronization therapy-defibrillator infection

The increased infection rate with CRT-D devices (when compared with ICD, CRT-P devices) may be explained by device, patient, and procedure-specific issues.

Successful implantation of CRT devices may involve prolonged manipulation of the LV lead with associated minor venous damage. Secondary inflammation and thrombosis would then predispose to bacterial colonization and infection.\textsuperscript{15} In addition, there appears to be a ‘dose–response’ relationship between the number of implanted leads and infection risk, reflecting both increased procedural time and complexity; thus, the time required for LV lead implantation may promote bacterial colonization and infection.\textsuperscript{4}

In addition, compared with CRT-P generators, CRT-D generators are significantly larger and with an increased surface area, which may contribute to the overall risk of infection.\textsuperscript{4,16}

Finally, there may be significant demographic and morbidity variances between ICD and CRT P/D recipients; heart failure, diabetes, and associated co-morbidity are more prevalent in the latter and are associated with reduced host defence and resistance to infection.\textsuperscript{1,15}

### Mechanism of late infection

There is emerging evidence that late device infection reflects bacterial contamination at the time of primary intervention.\textsuperscript{17} The timing and clinical manifestations of any subsequent infection are then determined by the equilibrium between host defence and the virulence of the infecting organism, which may be influenced by a number of factors.\textsuperscript{18,19} Should the equilibrium swing in favour of

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**Table 1** Clinical manifestations of infection stratified by device type

<table>
<thead>
<tr>
<th>Device type (number of infections)</th>
<th>Pocket infection only</th>
<th>Pocket infection with bacteraemia</th>
<th>Lead-related endocarditis and bacteraemia</th>
<th>Organism</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICD (5)</td>
<td>4</td>
<td>1</td>
<td>0</td>
<td>S. aureus</td>
</tr>
<tr>
<td>CRT-P (7)</td>
<td>4</td>
<td>2</td>
<td>1</td>
<td>S. aureus (2) MRSA</td>
</tr>
<tr>
<td>CRT-D (12)</td>
<td>10</td>
<td>2</td>
<td>0</td>
<td>S. aureus coliforms</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>5</td>
<td>1</td>
<td></td>
</tr>
</tbody>
</table>

ICD, implantable cardioverter-defibrillator; CRT-P, cardiac resynchronization therapy-pacemaker; CRT-D, cardiac resynchronization therapy-defibrillator; MRSA, methicillin-resistant S. aureus.

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**Table 2** Reported infection rates for CRT-P and CRT-D devices since 2000

<table>
<thead>
<tr>
<th>References</th>
<th>Device (n)</th>
<th>Follow-up (months)</th>
<th>Infection rate (%)</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alonso et al.\textsuperscript{12}</td>
<td>CRT-P 102</td>
<td>15 ± 13</td>
<td>3.0</td>
<td>All infections within 3 months from implant.</td>
</tr>
<tr>
<td>Daoud et al.\textsuperscript{13}</td>
<td>CRT-D 66</td>
<td>11 ± 9</td>
<td>3.0</td>
<td>Thoracotomy CRT devices not included. Both infections detected within 30 days of implant.</td>
</tr>
<tr>
<td>Knight et al.\textsuperscript{3}</td>
<td>CRT-D 443</td>
<td>30 ± 13</td>
<td>1</td>
<td>Infections reported 329 ± 180 days following implant.</td>
</tr>
<tr>
<td>Kautzner et al.\textsuperscript{14}</td>
<td>CRT-P 92</td>
<td>2.2</td>
<td></td>
<td>Duration of follow-up not stated.</td>
</tr>
<tr>
<td>Leon et al.\textsuperscript{8}</td>
<td>Both CRT-P and CRT-D 1903</td>
<td>6</td>
<td>1.1</td>
<td>Includes ppm upgrades.</td>
</tr>
<tr>
<td>Romeyer-Bouchard et al.\textsuperscript{4}</td>
<td>CRT-P 123</td>
<td>31 ± 19</td>
<td>1.6</td>
<td>All infections presented within 12 months from implant.</td>
</tr>
<tr>
<td></td>
<td>CRT-D 116</td>
<td></td>
<td>9.5</td>
<td></td>
</tr>
<tr>
<td></td>
<td>PPM 1740</td>
<td>6</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICD 667</td>
<td></td>
<td>1.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRT-P 48</td>
<td></td>
<td>0.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>CRT-D 426</td>
<td></td>
<td>4.2</td>
<td></td>
</tr>
</tbody>
</table>

Includes only those studies which reported device-specific infection rates.
the infecting organism, infection may ensue. Should the equilibrium swing in favour of host defence, the contamination is obliterated.20

In our patients, the routine use of both intravenous and intra-pocket antimicrobials (standard operative procedure during the study period) is likely to have suppressed peri-operative bacterial colonization and thus explain subsequent delayed infection. The later advent of clinical infection would perhaps reflect some disturbance of the hitherto stable relationship between microbe and host, for instance by local trauma.20

Finally, haematogenous seeding from a distant source of infection (skin sepsis, indwelling catheter, etc.) may account for late infection in some instances but is probably less common.

**Clinical implications**

The infection rates observed following CRT-D implant (specifically) mandates careful review of infection control measures. These include assuring that there is no evidence of concurrent infection before implant, pre-operative antibiotics have been administered at the appropriate time and are specific for commonly encountered pathogens, and implant conditions are of an appropriate standard. Our usual antibiotic regime is Teicoplanin 400 mg IV 30 min before the procedure and Gentamicin 80 mg administrated directly into the pocket at the end of the procedure.

Because of the complexity and potential complications, complex device implanters must be suitably experienced; there is a recognized association between device infection and operator experience. Beyond experience, reduced implant times (and infection risk) await technical developments including improved LV implant kit and smaller CRT-D devices. Pocket haematoma remains prevalent and is a significant risk factor for infection. Care should be taken to reduce the likelihood of haematoma, with intervention only when necessary on the grounds of wound viability. Antimicrobial pouches offer the potential for reduced infection,21 especially in high-risk patients and follow-up studies are awaited. Finally, the increased risk of late infection following implantation of CRT-D devices should be discussed with patients when planning therapy.

**Conclusions**

We studied early and late infection following implantation of CIDs. The incidence of infection within 12 months of implant was 1.2% and consistent with previous published series. However, infection beyond 12 months of infection was higher at 3.6% and was driven by increased late CRT-D device infection. These observations are consistent with a limited number of previous studies of late infection. We also discuss potential explanations for these observations and clinical implications.

**Acknowledgement**

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**Conflict of interest:** none declared.

**References**