Can implantable cardiac electronic device infections be defined as ‘early’ or ‘late’ based on the cause of infection?

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Implantable cardiac electronic device (ICED) infections are a major cause of morbidity and mortality. Understanding the pathogenesis of these infections is important in their prevention and management. We hypothesized that ICED infections could be classified as ‘early’ or ‘late’, based on differences in microbiological cause within or beyond 1 year of implantation, respectively. A comprehensive review of the literature was undertaken to test this hypothesis. Prosthetic valve endocarditis cases were included for comparison. Articles were included if the time from device implantation to infection, definite evidence of infection (pocket/bacteraemia/endocarditis) and a positive microbiological diagnosis were included. There were no statistically significant differences in microbiology to support a 1 year cut-off between early and late ICED infection. Staphylococcus aureus and coagulase-negative staphylococci were the predominant causes of ICED infection both within and beyond 1 year of ICED implantation. To further assess the microbiological causes of ICEDs and their implications for pathogenesis a large-scale multicentre study is required.

INTRODUCTION

The clinical indications for implantable cardiac electronic devices (ICEDs) are increasing (Zhan et al., 2008). This has led to a rapid rise in the number of implants especially in patients with multiple comorbidities. Despite improvements in technology, infection remains an important complication of ICEDs with a reported incidence of 4.82/1000 pacemaker years (Voigt et al., 2010). Infection of ICEDs may involve the generator pocket or the leads or both. Systemic sepsis and endocarditis are potentially grave complications. Any intervention to reduce the occurrence of ICED infection would have important clinical as well as financial consequences. Staphylococci (both Staphylococcus aureus and coagulase-negative staphylococci (CoNS)) are the predominant causes of ICED infection, which may result from infection introduced at the time of implantation or as a result of haematogenous spread from a source of infection elsewhere (Habib et al., 2009). Occasionally the leads or box erode through the skin allowing direct contamination of the device sometime after insertion.

The low pathogenicity of CoNS means that infections caused by these bacteria are often low grade, insidious in onset and present clinically many months after a procedure. Largely based on the incidence of infections caused by CoNS, early prosthetic valve endocarditis (EPVE) has been defined as valve infection occurring within 1 year of surgery (López et al., 2007). Details of the causative organisms of EPVE can be used to inform antimicrobial prophylaxis regimens at the time of surgery. Infection of ICEDs can occur at any time after implantation and, to date, no distinction between ‘early’ or ‘late’ ICED infections has been agreed. Greater insight into the micro-organisms that are most commonly introduced at the time of ICED implantation would inform measures to prevent infection, including antimicrobial prophylaxis, and perhaps also empirical treatment regimens.

We hypothesized that ICED infections could be classified as ‘early’ or ‘late’ based on differences in microbiological cause within or beyond 1 year of implantation, respectively. We therefore reviewed the published literature to test this hypothesis. Because this approach has been used to define EPVE, we included prosthetic valve endocarditis (PVE) cases for comparison.

METHODS

A comprehensive literature search was undertaken to identify cases of ICED infection that included both the microbial cause and time of
onset after implantation/manipulation using Pubmed. Inclusion criteria were all articles from 1980 to the end of 2011. The keywords used to extract the articles were pacemaker, implantable defibrillator, review, cardiac resynchronization, implantable, infection, pocket, endocarditis, lead and sepsis. Of these articles, only those that were relevant to infection and ICED or prosthetic valves were included. These articles were reviewed and further analysed if they included the following details: time from device implantation to infection and definite evidence of infection (pocket/bacteraemia/endocarditis) and a positive microbiological diagnosis. In cases where an article included more than one patient or a number of micro-organisms, data from each case were included. The causative organisms were grouped for analysis as ‘staphylococci’ (also subdivided into S. aureus and CoNS), ‘streptococci’, ‘enterococci’, ‘fungus’, ‘culture negative’ and ‘other’. ‘Early’ and ‘late’ ICED infections were defined as those occurring <1 year before and ≥1 year after implantation or manipulation of the device or valve, respectively. A second, truncated, literature search was undertaken to identify cases of PVE cases that included both the microbial cause and time of onset after implantation/manipulation by using Lopez et al. (2007) as a reference article and the ‘related citations’ feature on Pubmed.

Statistical analysis. For ICED infection, we tested the null hypothesis that there was no difference in the percentage of cases caused by the different pathogen groups in early and late infections. This was repeated for PVE. Chi-squared analysis was used to assess differences in the incidence of infection separately in ICED and prosthetic valve for each pathogen group using Minitab 13 (Minitab Inc.). Analysis was not performed if numbers were small, i.e. incidence of infection <5%.

RESULTS

Two hundred and forty articles fulfilled the initial inclusion criteria for ICED infections. Out of these 55 were included. These provided 240 cases, with the majority of articles being case reports. The related citations feature for Lopez et al. (2007) produced 224 articles; of these, 20 fulfilled the inclusion criteria, but the full texts of four were not in English, and seven had used different definitions of early and late infections and were therefore excluded. The remaining nine articles provided 498 cases. The data are shown in Table 1. The majority (71%) of all ICED infections were attributable to staphylococci (both S. aureus and CoNS). This was followed by Gram-negative bacteria. Analysis of the prosthetic valve endocarditis data demonstrated a statistically significant reduction in the number of early infections caused by CoNS compared to late PVE (P=0.001) and an increase in streptococcal late PVE (P=0.002) (Table 1). There were no significant differences between the number of ICED infections caused by S. aureus and CoNS in the defined ‘early’ and ‘late’ periods (Table 1).

**Table 1. Late and early infection in prosthetic valve and ICED infection**

CoNS, coagulase-negative staphylococci. The table was compiled using data from articles listed in References.

<table>
<thead>
<tr>
<th>Organism</th>
<th>PVE Early, n (%)</th>
<th>Late, n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>47 (19%)</td>
<td>41 (17%)</td>
<td>0.814</td>
</tr>
<tr>
<td>CoNS</td>
<td>103 (41%)</td>
<td>78 (32%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Streptococci</td>
<td>15 (6%)</td>
<td>24 (10%)</td>
<td>0.476</td>
</tr>
<tr>
<td>Enterococci</td>
<td>16 (6%)</td>
<td>3 (1%)</td>
<td>0.106</td>
</tr>
<tr>
<td>Fungus</td>
<td>18 (7%)</td>
<td>72 (30%)</td>
<td>0.682</td>
</tr>
<tr>
<td>Culture negative</td>
<td>12 (5%)</td>
<td>18 (7%)</td>
<td>0.369</td>
</tr>
<tr>
<td>Other</td>
<td>41 (16%)</td>
<td>59 (24%)</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>252 (100%)</td>
<td>246 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Organism</th>
<th>ICED infections Early, n (%)</th>
<th>Late, n (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>S. aureus</td>
<td>63 (44%)</td>
<td>25 (26%)</td>
<td>0.125</td>
</tr>
<tr>
<td>CoNS</td>
<td>42 (29%)</td>
<td>40 (24%)</td>
<td>0.275</td>
</tr>
<tr>
<td>Streptococci</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>*</td>
</tr>
<tr>
<td>Enterococci</td>
<td>2 (1%)</td>
<td>2 (2%)</td>
<td>*</td>
</tr>
<tr>
<td>Fungus</td>
<td>5 (3%)</td>
<td>6 (6%)</td>
<td>0.463</td>
</tr>
<tr>
<td>Culture negative</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>*</td>
</tr>
<tr>
<td>Other</td>
<td>32 (22%)</td>
<td>22 (23%)</td>
<td>0.916</td>
</tr>
<tr>
<td>Total</td>
<td>144 (100%)</td>
<td>96 (100%)</td>
<td></td>
</tr>
</tbody>
</table>

*Statistical analyses were not carried out as numbers were too small.

**DISCUSSION**

A 1 year cut-off to define ‘early’ and ‘late’ ICED infections is not supported by this analysis. S. aureus and CoNS were the most commonly reported causes of ICED infection in both the early and late time periods. The number of S. aureus ICED infections fell after 1 year while the number of CoNS infections rose, but the difference was not statistically significant. The finding of significantly greater EPVE cases caused by CoNS and significantly more late PVE cases caused by streptococci is consistent with the previous analysis (Lopez et al., 2007).

It is assumed that EPVE usually results from valve infection at the time of the operation or during the early perioperative period. It seems reasonable to assume that the microbiology of early ICED infection might be similar to that of EPVE, but this is not consistent with our observations. Late PVE has been mainly attributed to community-acquired organisms similar to native valve endocarditis, with streptococci responsible for 32%; however, ‘late’ ICED infections continue to be mainly caused by staphylococci, in particular CoNS (42%). It is plausible that the incubation period is longer in ICED infections compared with EPVE because the bacterial inoculum is likely to be smaller during ICED implantation,
the procedural times are generally shorter and the procedure is less invasive. Moreover, in the case of generator pocket infections, the device is not in direct contact with the bloodstream but is surrounded by a relatively avascular fibrous pocket. Indeed, it is well known that ICED infections occur more commonly after reintervention, for example after a box change (Voigt et al., 2010).

There are limitations to this kind of literature review. Denominator data (i.e. the number of devices implanted during the study period, or number of ICED days) are often lacking, so only crude percentages can be discussed. Only studies that fulfilled the inclusion criteria could be analysed, resulting in a large proportion of papers with information on microbiology being rejected. There is likely to be bias towards the more unusual causes of infection. Despite this, it is important to point out that the perceived more-common organisms still accounted for the majority of the infections. As infections may take a long time to develop and present with very non-specific symptoms, patients may not necessarily be managed for infection at their first presentation, a detail that is hard to extract from the literature and may skew the time estimates. Finally, patients may be treated with antibiotics before cultures are taken or the infection may be ‘culture negative’.

In conclusion, S. aureus and CoNS are the predominant reported causes of ICED infections identified both within and beyond 1 year of implantation. This has implications for the prophylaxis and treatment of ICED infection. A large-scale multi-centre study is required to support these findings.

REFERENCES


