Microbiology of cardiac implantable electronic device infections

Maria Grazia Bongiorni¹, Carlo Tascini², Enrico Tagliaferri²*, Andrea Di Cori¹, Ezio Soldati¹, Alessandro Leonildi², Giulio Zucchelli¹, Ilaria Ciullo², and Francesco Menichetti²

¹Second Division of Cardiovascular Diseases, Cardiac and Thoracic Department, New Santa Chiara Hospital, University Hospital of Pisa, Via paradisa 2, 56124 Pisa, Italy; and ²Infectious Diseases Unit, New Santa Chiara Hospital, University Hospital of Pisa, Via paradisa 2, 56124 Pisa, Italy

Received 16 September 2011; accepted after revision 11 February 2012; online publish-ahead-of-print 7 March 2012

Aims
The aim of the study was to describe the microbiological findings of cardiac implantable electronic devices (CIEDs) infection in the 2000–2011 period at the Cardiology Unit of New Santa Chiara Hospital in Pisa (Italy).

Methods and results
Removed CIED leads and pocket material were seeded on solid media and isolates tested for antimicrobial susceptibility with the Kirby Bauer method. Electrodes from 1204 patients were analysed and 854 (70.9%) tested positive. In 663 (77.6%) cases only one species was isolated, in 175 (20.5%) two species, and in 14 (1.8%) 3 species. In 116 cases material from the pocket was also cultured. The result was consistent with that from the electrodes in 69 (59%) cases. In 359 cases a blood sample was also obtained for culture. The result was consistent with that from the leads in 124 (35%) cases. A total of 1068 strains were isolated from electrodes. Gram-positive organisms were most frequently isolated (92.5% of isolates); particularly, coagulase-negative staphylococci (CoNS), mainly Staphylococcus epidermidis, in 69% of cases and Staphylococcus aureus in 13.8%, Gram-negative rods in 6.1%, yeasts in 1% and molds in 0.4%. Overall, Oxacillin resistance was 30%, in particular 33% among CoNS and 13% among S. aureus. Oxacillin resistance and quinolones resistance have increased in the period 2006–2011 with respect to the 5 years before. Seventeen percent of Enterobacteriaceae strains had a phenotype compatible with extended spectrum beta-lactamase expression.

Conclusions
Culture of the leads offers the possibility of an aetiological diagnosis in the majority of cases. When material from the pocket can be obtained, the microbiological result is often consistent with that from the electrodes, while species isolated from blood cultures are often different and more likely to be the result of contamination. Cardiac implantable electronic device infection is more often monomicrobial, CoNS are most frequently isolated and S. epidermidis is largely the main single agent. Very early infections were associated with S. aureus infection. The pattern of susceptibility to antimicrobials is in general that of community-acquired infections, although oxacillin resistance and quinolones resistance has increased in the last 5 years.

Keywords
Microbiology • Cardiovascular implantable electronic devices

Introduction
The field of cardiac pacing has grown rapidly since the first insertion of a pacemaker (PM) in the late 1950s: the rate of new implantation ranges from 200 per million population in the UK to 420 per million population in the USA.¹ A worldwide cardiac pacing and implantable cardioverter defibrillator (ICD) survey was conducted in 2009 and compared with a similar survey conducted in 2005.² Virtually all countries showed increases in implant numbers over the 4 years between surveys. High-degree atrioventricular block and sick sinus syndrome remain the major indications for implantation of a cardiac PM. Since their introduction early in the 1980s, ICDs have become a life-saving therapeutic tool for patients with ventricular arrhythmia. Virtually all countries surveyed showed a
significant rise in the use of ICDs with the largest implanter being the USA with 434 new implants per million population.

Despite improvements in cardiac device design, application of timely infection control practices, and administration of antibiotic prophylaxis at the time of device placement, infections continue to be observed. The infection rate is highly variable, ranging from 0.5 to 12%.3–5

Cardiac implantable electronic device (CIED) infection may be local, limited to the pulse generator pocket and/or the subcutaneous portion of the leads, or systemic, involving the transvenous intravascular electrode component, with or without endocarditis,6 which accounts for ~10% of PM infections.7,8

The pocket may become infected at the time of implantation, during subsequent surgical manipulation of the pocket, or if the generator or subcutaneous electrodes erode through the skin. Pocket infection may track along the intravascular portion of the electrode to involve the intracardiac portion of the PM or ICD. Alternatively, the pocket or intracardiac portion of the electrode may become infected as a result of haematogenous seeding during a bout of bacteraemia or fungaemia secondary to a distant infected focus.

Several factors have been reported to be associated with a greater risk of CIED infection: (i) immunosuppression (e.g. renal dysfunction and corticosteroid use); (ii) oral anticoagulation use; (iii) patient coexisting illnesses; (iv) periprocedural factors, including the failure to administer perioperative antimicrobial prophylaxis; (v) device revision/replacement; (vi) the amount of indwelling hardware; (vii) operator experience; and (viii) the microbiology of bloodstream infection in patients with indwelling CIEDs, particularly Staphylococcus aureus bacteraemia.9

In addition to antimicrobial therapy, complete removal of all hardware is mandatory for CIED infections, considering that a conservative approach is often unsuccessful and associated with a high mortality rate.10–13 Transvenous extraction, allowing a high success rate with few complications, is considered the gold standard.14–16

The aim of the study was to describe the microbiological findings of the CIED infections observed during a 10-year period at the Cardiology Unit of Pisa (Italy), the national reference centre for transvenous removal of the infected CIED.6,17

Materials and methods

Population study

We evaluated all consecutive patients with infected PM or ICD who underwent transvenous removal at the Cardiology Unit of our centre between January 2000 and March 2011. Patient- and lead-related data were collected at baseline on each case and entered into a computerized database for retrospective analysis.

Time to infection was recorded and we divided CIED infections as very early among 1 month from the last procedure on CIED, early infections among 2 and 12 months from the last procedure, and late infection when it happened after 12 months from the last procedure.

Extraction procedure

As a general practice, cardiac leads were engaged in the following order: coronary sinus, right atrial, and right ventricular leads. The proximal of the lead end was clipped and a standard stylet introduced. Lead extraction was then attempted using gentle manual traction (MT). If MT was unsuccessful, a single-sheath mechanical dilatation (MD) technique with a superior approach was used (Cook Intravascular Inc., Leechburg, PA, USA). When the lead tip was detached from the coronary sinus by MT and/or MD but removal was impossible due to a related fibrous adherence, or when the lead was intravascular and free floating, we used a transfemoral vein approach with or without a transjugular approach, as previously described.17

Microbiology

The microbiology of the infection was documented culturing on solid media (Chocolate agar, McConkey agar, mannitol salt agar, and Sabouraud agar) the removed catheters leads and/or infected material from the pocket. The tip or other parts of the leads were rolled onto the solid media while the material drawn from the pocket was spread directly on the culture plate. Blood culture system used was BACTEC 9240 (Becton-Dickinson, Milano, Italy). For organism identification an automated system (API, Bio-Mérieux, Mercy L’Etoile, France) was used. Antimicrobial susceptibility was tested according to the Kirby Bauer method.18

Resistance phenotype was categorized according to the breakpoints indicated by the Clinical and Laboratory Standard Institute (formerly National Committee for Clinical Laboratory Standards) and the British Society for Antimicrobial Chemotherapy until 2009 and later on according to those indicated by the European Committee on Antimicrobial Susceptibility Testing.

Statistical analysis

Parametric tests for continuous variables are reported as mean and standard deviation (SD). Multiple group comparison was performed using analysis of variance. Differences between groups were evaluated using an unpaired two-tailed t-test. Non-parametric tests for continuous variables are reported as median and range. Differences between groups were evaluated using the Mann–Whitney U test. Categorical factors are summarized as percentages, and differences between groups were determined using Pearson’s χ² test. Statistical analyses were performed using SYSTAT 10.0 (Systat Software Inc., Chicago, IL, USA). Statistical significance was defined at P < 0.05.

Results

Epidemiology

Data from January 2000 to March 2011 were reviewed.

The device was removed from 1204 patients. Males were 939 (78%). Mean age was 64 ± 13 years (range 17–92 years). Among patients studied, 787 (65.4%) had local signs of infection, 417 (34.6%) systemic signs of infection. The time from implantation to extraction was on average 73 ± 69 months (range 4–420). Among the removed devices, PMs were 891 (74%) and ICDs were 313 (26%). In particular, single-chamber PMs were 325 (27%), dual-chamber PMs 554 (46%), three-chamber PMs 24 (2%), single-chamber ICD 96 (8%), dual-chamber ICD 120 (10%), and three-chamber ICD 84 (7%) (Table 1).

Microbiology

The analysis included all consecutive patients with CIED infection in the study period. They represented 79.5% of all patients who underwent extraction in the same period. The main reason for
extraction except for infection was malfunctioning. Out of the 1204 extracted CIEDs, 854 (70.9%) tested positive. In 663 (77.6%) cases, only one species was isolated, in 175 (20.5%) two species, and in 14 (1.8%) 2 species.

Cardiac leads
A total of 1068 strains were isolated from electrodes. Groups of microorganisms isolated are listed in Table 2. Gram positives were largely the most frequently isolated (92.5% of isolates); particularly, coagulase-negative staphylococci (CoNS) were isolated in 69% of cases and *S. aureus* in 13.8%. Gram-negative rods were isolated in 6.1% of cases (*Enterobacteriaceae* 3% and *Pseudomonas* spp. 1.5%), yeasts of *Candida* genus in 1%, and molds in 0.4%.

Among very early infections, we had more polymicrobial infection (30%) with respect to early and late infections (21 and 23%, respectively). In the very early period *S. aureus* infections accounted for 22% with respect to 15.3 and 14.8% in the other two periods (*P* < 0.05); conversely CoNS increased from 58.7% of very early period to 68.8 and 70.6%, respectively (*P* < 0.03). No differences among bacteremic patients and those with local infections were found. There were no other significant differences for infections due to overall Gram-positive, overall Gram-negative, or fungal infections. Erosion represented 7.2% of all CIED infections and it was not associated with any other specific type of CIED infection.

Different species of CoNS isolated are listed in Table 3. *Staphylococcus epidermidis* was the most frequently isolated single agent (67% of CoNS isolates), followed by *Staphylococcus capitis* (5.8%) and *Staphylococcus schleiferi* (5.3%).

*Corynebacterium* spp. and *Propionibacterium* spp. accounted for 5 and 2.5% of all isolates, respectively.

Pocket samples
In 116 cases material from the pocket was also cultured. The result was consistent with that from the electrodes in 69 (59%) cases, including 16 cases in which culture was negative from both samples. In 17 cases, culture was positive from the pocket and negative from the electrode (Table 4).

Blood samples
In 359 cases a blood sample was also obtained for culture. The result was consistent with that from the electrodes in 124 (35%) cases, including 70 cases in which culture was negative from both samples. In case *S. aureus* was isolated from the blood, the same microorganism was isolated from the electrodes in 55% of cases (10/18).

### Table 1 Patients characteristics and device features

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number of patients with CIED infection</td>
<td>1204</td>
</tr>
<tr>
<td>Males/females</td>
<td>939 (78%)/625 (22%)</td>
</tr>
<tr>
<td>Mean age</td>
<td>64 ± 13 years (range 17–92)</td>
</tr>
<tr>
<td>Signs of infection</td>
<td></td>
</tr>
<tr>
<td>Local</td>
<td>787 (65.4%)</td>
</tr>
<tr>
<td>Systemic</td>
<td>417 (34.6%)</td>
</tr>
<tr>
<td>Mean time from implantation to extraction</td>
<td>73 ± 69 months (range 4–420)</td>
</tr>
<tr>
<td>Device</td>
<td></td>
</tr>
<tr>
<td>Pacemaker (PM)/implantable cardioverter defibrillators (ICDs)</td>
<td>891 (74%)/313 (26%)</td>
</tr>
<tr>
<td>Single-chamber PM</td>
<td>325 (27%)</td>
</tr>
<tr>
<td>Dual-chamber PM</td>
<td>554 (46%)</td>
</tr>
<tr>
<td>Three-chamber PM</td>
<td>24 (2%)</td>
</tr>
<tr>
<td>Single-chamber ICD</td>
<td>96 (8%)</td>
</tr>
<tr>
<td>Dual-chamber ICD</td>
<td>120 (10%)</td>
</tr>
<tr>
<td>Three-chamber ICD</td>
<td>84 (7%)</td>
</tr>
</tbody>
</table>

### Table 2 Isolates from electrodes of cardiac implantable electronic devices (Pisa, 2000–2011)

<table>
<thead>
<tr>
<th>Species</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total infected leads</td>
<td>1204</td>
<td></td>
</tr>
<tr>
<td>Total isolates</td>
<td>1068</td>
<td>100.0</td>
</tr>
<tr>
<td>Gram positive</td>
<td>988</td>
<td>92.5</td>
</tr>
<tr>
<td>CoNS</td>
<td>737</td>
<td>69.0</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em></td>
<td>147</td>
<td>13.8</td>
</tr>
<tr>
<td><em>Corynebacterium</em> spp.</td>
<td>53</td>
<td>5.0</td>
</tr>
<tr>
<td><em>Propionibacterium</em> spp.</td>
<td>27</td>
<td>2.5</td>
</tr>
<tr>
<td>Gram negative</td>
<td>65</td>
<td>6.1</td>
</tr>
<tr>
<td><em>Enterobacteriaceae</em></td>
<td>32</td>
<td>3.0</td>
</tr>
<tr>
<td><em>Pseudomonas</em> spp.</td>
<td>16</td>
<td>1.5</td>
</tr>
<tr>
<td><em>Candida</em> spp.</td>
<td>11</td>
<td>1.0</td>
</tr>
<tr>
<td><em>Candida albicans</em></td>
<td>4</td>
<td>0.4</td>
</tr>
<tr>
<td>Molds</td>
<td>4</td>
<td>0.4</td>
</tr>
</tbody>
</table>

### Table 3 Coagulase-negative staphylococci isolated from electrodes of cardiac implantable electronic devices (Pisa, 2000–2011)

<table>
<thead>
<tr>
<th>Species</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CoNS</td>
<td>737</td>
<td>100</td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
<td>494</td>
<td>67.0</td>
</tr>
<tr>
<td><em>Staphylococcus capitis</em></td>
<td>43</td>
<td>5.8</td>
</tr>
<tr>
<td><em>Staphylococcus schleiferi</em></td>
<td>39</td>
<td>5.3</td>
</tr>
<tr>
<td><em>Staphylococcus hominis</em></td>
<td>24</td>
<td>3.3</td>
</tr>
<tr>
<td><em>Staphylococcus lugdunensis</em></td>
<td>17</td>
<td>2.3</td>
</tr>
<tr>
<td><em>Staphylococcus haemolyticus</em></td>
<td>16</td>
<td>2.2</td>
</tr>
<tr>
<td><em>Staphylococcus cohnii</em></td>
<td>8</td>
<td>1.1</td>
</tr>
<tr>
<td><em>Staphylococcus xylosus</em></td>
<td>8</td>
<td>1.1</td>
</tr>
<tr>
<td><em>Staphylococcus sciuiri</em></td>
<td>7</td>
<td>0.9</td>
</tr>
<tr>
<td><em>Staphylococcus warneri</em></td>
<td>5</td>
<td>0.7</td>
</tr>
<tr>
<td><em>Staphylococcus saprophyticus</em></td>
<td>4</td>
<td>0.5</td>
</tr>
<tr>
<td><em>Staphylococcus simulans</em></td>
<td>2</td>
<td>0.3</td>
</tr>
<tr>
<td>Other CoNS</td>
<td>70</td>
<td>9.5</td>
</tr>
</tbody>
</table>
Antimicrobial susceptibility

Antimicrobial susceptibility of CoNS and S. aureus is reported in Figure 1. Netilmicin was the most active aminoglycoside against CoNS and S. aureus (99 and 98% of isolates susceptible) and moxifloxacin was the most active quinolone (88% in both cases); 33% (99 and 98% of isolates susceptible) and moxifloxacin decreased from 91 to 74% (P < 0.01) and levofloxacin susceptibility decreased from 91 to 74% (P < 0.01) for S. aureus and from 78 to 59% for CoNS (P 0.01).

Corynebacterium spp. and Propionibacterium spp. isolates showed generally low levels of antimicrobial resistance, except in an isolate of Corynebacterium spp. resistant to glycopeptides but still susceptible to beta-lactams.

Seventeen percent of Enterobacteriaceae strains had a phenotype compatible with extended spectrum beta-lactamase (ESBL) expression; none was resistant to carbapenems. Thirteen strains of Pseudomonas aeruginosa were isolated and none was resistant to carbapenems. Two Achromobacter baumannii strains were isolated and one was susceptible only to polymyxins.

Discussion

In our knowledge, this is the widest case series of CIED infection. Although our data might reflect the Italian epidemiology, we believe they could be of interest for the general debate about CIED infection and provide useful information for the lab and clinical staff involved in CIED infection management.

Epidemiology

Cardiac implantable electronic device infection more often occurs with local signs of infection and this is also consistent with the fact that a bloodstream infection was contemporarily demonstrated in a small minority of patients. The fact that most of the patients had only local signs of infection but the culture of the electrode resulted positive in the majority of them confirms the indication for hardware removal in all cases of suspected CIED infection.

Demographic characteristics of patients and type of device reflect those of the general population of CIED carriers. The fact that dual-chamber and three-chamber devices were more represented in our case series might also be due to the fact that the total amount of hardware is also recognized as a risk factor for CIED infection.

In our knowledge, this is the widest case series of CIED infection. Infections generally occurred a long time after implantation and might therefore be assumed to be community-acquired infections.

Microbiology

Culture of the removed electrodes offers the possibility of an aetiological diagnosis of the CIED infection in the great majority of cases. This means that microbiological analysis is mandatory in the case of suspected CIED infection. Sterile manipulation after removal, fast submission to the microbiology laboratory, and seeding of the removed hardware are essential to optimize the management of CIED infection. The proportion of positive samples we found is consistent with what reported in other works.

When material from the pocket is cultured, the microbiological result is often consistent with that from the electrodes. Therefore, the possibility of obtaining a sample from the pocket, by swab in the case of skin erosion or by aspiration in the case of deep abscess, should always be pursued. The fact that in 17 cases the culture of the electrode was negative while that from the pocket was positive, might suggest that contamination does not necessarily occur when the electrode is removed through an infected pocket, as some authors have speculated.
Species isolated from blood cultures are often different and therefore more likely to be the result of contamination. In other words, one single blood culture positive for CoNS is insufficient evidence for a therapeutic strategy. Instead, a blood culture positive for S. aureus has a greater diagnostic value, both in our study and in the existing literature. In fact, in a cohort of 33 patients with implanted devices and subsequent S. aureus bacteraemia, nearly one-half (45.4%) had confirmed CIED infection, and only a minority had local signs or symptoms that suggested generator–pocket infection. Similarly, in a cohort study from Olmsted County, MN, USA, 55% of 22 patients with cardiac devices and subsequent S. aureus bacteraemia had definite or possible CIED infection.

Cardiac implantable electronic device infection is monomicrobial in the great majority of cases, consistently with the existing literature and with the pathogenesis, mainly due to contamination at the moment of implantation or subsequent bacteraemia. The dominant role of staphylococci is in line with what has been reported previously: staphylococcal species account for 60 to 80% of cases in most reported series.

Coagulase-negative staphylococci are most frequently isolated and S. epidermidis is largely the main single agent in our work as in the existing literature. Isolation of CoNS usually represents a challenge for the clinician since it might be the result of contamination, given the generally low pathogenicity of CoNS, with the exception of S. lugdunensis which tends to cause infections with a more severe course, resembling that of S. aureus.

The development and persistence of CoNS infections are often associated with foreign materials. The attachment is thought to be first due to non-specific physicochemical forces and then due to the specific interaction of bacterial surface adhesins with the uncoated device, directly and with host proteins that coat the device. Coagulase-negative staphylococci may adhere directly to plastic polymers of the device via fimbria-like surface protein structures and/or a capsular polysaccharide adhesive. Bacteria may also adhere to host matrix proteins, such as fibrinogen, fibronectin, and collagen that coat the surface of an implanted device. The layers of bacteria on the surface of an implanted device are encased in an extracellular slime made of a polysaccharide intercellular adhesive and constitute a biofilm. Microbes in a biofilm are protected by this dense extracellular matrix and are more resistant to antibiotics and host defences.

Corynebacterium spp. and Propionibacterium spp. are normally considered as contaminants. Nevertheless, our data suggest that they can play a significant role in CIED infection. Most likely, bacteria scarcely pathogenic in normal conditions can be responsible of invasive infections in presence of prosthetic devices and other permanent foreign bodies.

The fact that CoNS and other bacteria, usually part of the skin flora, were most frequently isolated and the generally low levels of antimicrobial resistance of the isolates in our study support the endogenous, non-healthcare-associated acquisition of the infection. Consistently, an association has been noted between the presence of preaxillary skin flora and the pathogens isolated from PM infection. In particular, S. schleiferi, which is reported to be a member of the preaxillary skin flora, accounted for 5.3% of all CoNS in our case series and it has already been described as a cause of PM infection. On this basis, isolation of S. schleiferi from CIED infection should be evaluated cautiously rather than easily dismissed as contamination.

The pattern of susceptibility to antimicrobials, in this study, is in general that of community-acquired infections. In particular, oxacillin resistance in our case series was similar to that reported by other recent study studies, though a worrisome trend towards resistance over time was observed and was statistically significant for CoNS. Resistance to oxacillin indicates resistance to all beta-lactams antibiotics, including cephalosporins and carbapenems. In our opinion the choice of a prophylactic drug different from a betalactam antibiotic should be probably reconsidered in the case of a resistance rate over 30% (that is our current epidemiology).

**Implications for antimicrobial prevention and therapy**

Given the financial and clinical burden of CIED infection, we believe that these levels of resistance already justify an initial aggressive approach in empirical treatment, for instance, with glycopeptides. For the same reason, we believe that an antimicrobial prophylaxis before implantation with an agent active against oxacillin-resistant staphylococci should be considered instead of the most commonly used cephazolin.

The fact that moxifloxacin showed an advantage compared with the other fluoroquinolones towards staphylococci is not surprising since it is in line with the existing literature. In the last period we have observed a decreased activity of the two quinolone molecules with more activity against Gram-positive microorganism. This trend should be considered in the case of empiric antibiotic therapy for CIED infections. The good activity of oral molecules such as doxycyclin, possibly in association with rifampicin, suggests the possibility of a shorter hospital length of stay and can be a resource for a long-term suppressive treatment in those cases where extraction is not feasible.

As far as resistance among Gram-negative organisms is concerned, at this moment ESBL production among Enterobacteriaceae is significant, but not yet epidemiologically relevant, given the minor role of Gram-negative bacteria in CIED infection. A phenotype consistent with carbapenemase production was revealed only for an A. baumannii strain.

The good activity of oral molecules such as doxycyclin, possibly in association with rifampicin, suggests the possibility of a shorter hospital length of stay and can be a resource for a long-term suppressive treatment in those cases where extraction is not feasible.

As far as resistance among Gram-negative organisms is concerned, at this moment ESBL production among Enterobacteriaceae is significant, but not yet epidemiologically relevant, given the minor role of Gram-negative bacteria in CIED infection. A phenotype consistent with carbapenemase production was revealed only for an A. baumannii strain.

The good activity of oral molecules such as doxycyclin, possibly in association with rifampicin, suggests the possibility of a shorter hospital length of stay and can be a resource for a long-term suppressive treatment in those cases where extraction is not feasible.

As far as resistance among Gram-negative organisms is concerned, at this moment ESBL production among Enterobacteriaceae is significant, but not yet epidemiologically relevant, given the minor role of Gram-negative bacteria in CIED infection. A phenotype consistent with carbapenemase production was revealed only for an A. baumannii strain.

The good activity of oral molecules such as doxycyclin, possibly in association with rifampicin, suggests the possibility of a shorter hospital length of stay and can be a resource for a long-term suppressive treatment in those cases where extraction is not feasible.
References