

# Treatment of Infected Cardiac Implantable Electronic Devices

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## Abstract

### Keywords

- cardiac implantable electronic devices
- left ventricular devices
- infection
- salvage therapy
- antibiotic beads

With their rising benefits, cardiac implantable electronic devices (CIEDs) such as pacemakers and left ventricular assist devices (LVADs) have witnessed a sharp rise in use over the past 50 years. As indications for use broaden, so too does their widespread employment with its attendant rise of CIED infections. Such large numbers of infections have inspired various algorithms mandating treatment. Early diagnosis of inciting organisms is crucial to tailoring appropriate antibiotic and or antifungal treatment. In addition, surgical debridement and explant of the device have been a longstanding modality of care. More novel therapies focus on salvage of the device by way of serial washouts and instilling drug-eluting antibiotic impregnated beads into the wound. The wound is then serially debrided until clean and closed. This technique is better suited to patients whose device cannot be removed, patients who are poor candidates for cardiac surgery, or patients who have failed conventional prior treatments.

Since their earliest application, cardiac implantable electronic devices (CIEDs), such as pacemakers, implantable defibrillators, and left ventricular assist devices (LVADs), have proven beneficial in the prevention of fatal cardiac-related disorders.<sup>1</sup> The past 50 years have seen a sharp rise in cardiac implantable device use with a resultant decline in deaths from ischemic, myocardial, and cardiac rhythm causes.<sup>2</sup> As the indications and guidelines governing CIED use broaden, so too does their widespread employment.<sup>3</sup> The rate of CIED infections has mirrored their increased use with some studies suggesting that the rate of device infections has overshadowed their implantation rate.<sup>4</sup> Infections pose a severe burden on patients, lead to significant health care costs and lengthy hospital stays, and may also lead to mortality.<sup>5</sup> When compared with noninfectious cardiac device complications, pacemaker infections result in an 8.4- to 11.6-fold increase in mortality rates along with a mean hospitalization cost ranging from \$31,149 to \$55,003.<sup>6</sup>

Although both pacemakers and LVADs are implantable cardiac devices, their infection profile and treatment differ significantly due to the size of the device and the need for an external power source for the LVAD. However, both demonstrate a wide range of infection rates, with the true incidence of infection remaining elusive.<sup>7</sup> Topkara et al report a pacemaker infection

rate of between 13% and 80%; however, others estimate it to be between 2% and 4% with rates rising 124% between years 1990 to 1999 and a 57% rise from 2004 to 2006, respectively.<sup>8,9</sup> Similarly, infection rates related to LVAD placement demonstrate a large range of between 13% and 80% among recipients.<sup>10</sup>

This wide variability in infection risk is in part due to different types of infections that have been included under the category of CIED-related infections. Various reports broadly included patients with surgical site infections, post-operative pneumonia, central venous catheter-related sepsis, and nosocomial urinary tract infections, in addition to infection of the CIED.<sup>10</sup> Various comorbidities may contribute to CIED infections. Patients of advanced age, with congestive heart failure, with a metastatic malignancy, on corticosteroid therapy, or with renal failure are more likely to develop CIED infections thereby increasing their mortality.<sup>9</sup>

## Device Infection Diagnosis

### Pacemakers

The diagnosis of pacemaker infections is often challenging. Pocket site infections are diagnosed clinically, often presenting with inflammatory skin changes including pain, swelling,



**Fig. 1** An 82-year-old man with an exposed pacemaker with necrotic skin.

and redness. There may be skin and soft tissue ulceration and drainage. The first sign of infection may be erosion through the skin at the site of the implant pocket, with external exposure of the device with or without local inflammatory changes (►Fig. 1).<sup>11</sup> Fever and other signs of systemic toxicity are frequently absent; however, infective endocarditis may be present. A diagnosis of pacemaker infective endocarditis is based on clinical parameters, blood cultures, and echocardiographic findings.<sup>12</sup> In cases of noninfective hematoma or seroma, device salvage may be undertaken (►Fig. 2).

One of the major challenges in diagnosis is the determination of the extent of the infection. On initial assessment, laboratory testing, blood, and exudate cultures as well as imaging modalities, including chest X-rays, transthoracic and transesophageal echocardiography, and computed tomography (CT) scanning are used to identify whether the infection is limited to the device pocket or stems from an endocardial or

peripheral source.<sup>13</sup> However, in addition to such studies, clinical experience helps to guide treatment decisions.

Identification of the causative agent requires cultures of the pacemaker pocket site and blood cultures (►Table 1). Tissue culture sensitivities are higher than swab cultures from the pocket site. However, up to 30% of patients with clinical signs of pacemaker infections have negative cultures.<sup>13</sup> Additional gram staining, anaerobic and aerobic bacterial cultures, along with fungal cultures and staining should be sought as well as mycobacteria cultures, if the initial gram stain is negative. Usually, bacterial seeding occurs at the time of implantation, revision, or replacement of the device. Lastly, the pacemaker may become hematogenously infected in the case of a bacteremia due to another infection.<sup>10</sup>

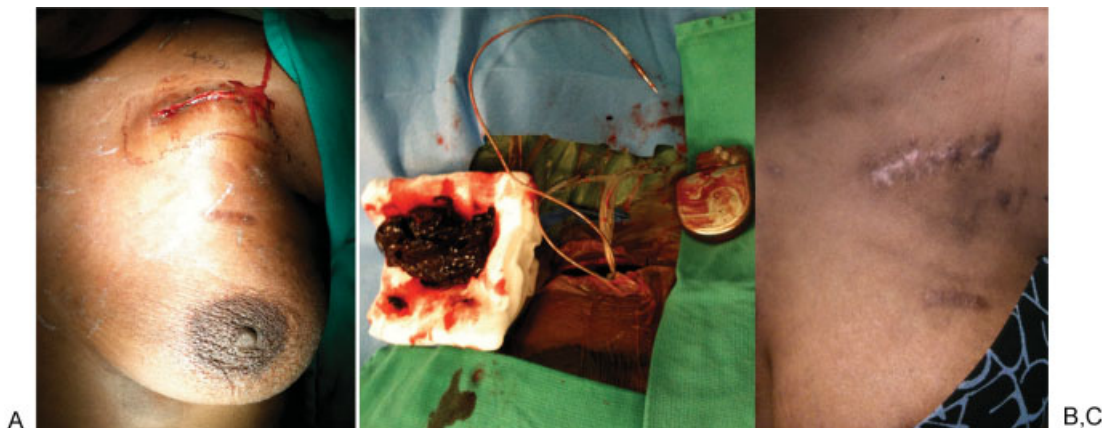
### Left Ventricular Assist Devices

Similar to pacemakers, determination of the extent of infection when faced with an LVAD infection is particularly difficult. Left ventricular assist device infections are classified into three categories: isolated driveline infections, pump pocket infections, and intravascular device infection or LVAD endocarditis. Patients present with an array of complaints including cellulitis, drainage from the LVAD driveline and possible exposure of the device. A CT scan is often employed to determine whether the infection is limited to the driveline or if it extends to the LVAD pocket, however, the true extent of infection can only be determined at the time of debridement. Fever, leukocytosis, and positive blood cultures can herald LVAD device endocarditis, which may ultimately respond only to device exchange.

## Microbiology of Device Infection

### Pacemakers

Cardiac device infections consist of a wide variety of organisms, with reports of polymicrobial infections between 7 to 15% of the time (see ►Fig. 3).<sup>14–16</sup> The most common organism found across multiple studies is the *Staphylococcus* species. Methicillin-resistant *Staphylococcus aureus*, methicillin-sensitive *S. aureus*, methicillin-resistant *S. epidermidis*, and methicillin-sensitive *S. epidermidis* contribute to more



**Fig. 2** (A) A 46-year-old woman with a hematoma. (B) Evacuation of hematoma and changing of generator. (C) Four months postoperative.

**Table 1** Causative agents behind pacemaker infections

Microorganism	% Infections
Coagulase-negative staph	42
<i>S. epidermidis</i>	
<i>S. saprophyticus</i>	
<i>S. schleiferi</i>	
<i>S. lugdunensis</i>	
<i>S. haemolyticus</i>	
Methicillin-sensitive <i>S. aureus</i>	25
Gram-negative bacilli	9
Enterobacteriaceae	
<i>Pseudomonas aeruginosa</i>	
Nonfermentative gram-negative bacilli	
Polymicrobial	7
Culture negative	7
Methicillin-resistant <i>S. aureus</i>	4
Gram-positive cocci	4
Fungi	2

than half the pacemaker infection cases reported. Other gram-positives include *Enterococcus faecalis*, *Enterobacter cloacae*, *Propionibacterium acnes*, and *Corynebacterium amycolatum*; they make up < 5% of infections. Gram-negative organisms comprise approximately 10% of infections and include *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Providencia stuartii*, *Serratia marcescens*, *Stenotrophomonas maltophilia*, *Enterobacter aerogenes*, *Escherichia coli*, *Citrobacter koseri*, and others. Fungal agents, although rare, include *Candida* species and *Aspergillus fumigatus* (see ►Fig. 3).<sup>14–16</sup>

Staphylococci and certain *Candida* infections are difficult to treat due to their ability to build biofilms on surfaces of foreign bodies such as CIEDs. Biofilms are a thick, multilayered film that mechanically traps bacteria, which when dormant, are highly resistant to bacteriocidal antibiotics via inhibition of cell wall biosynthesis, such as  $\beta$ -lactam antibiotics.<sup>17–19</sup>

### Left Ventricular Assist Devices

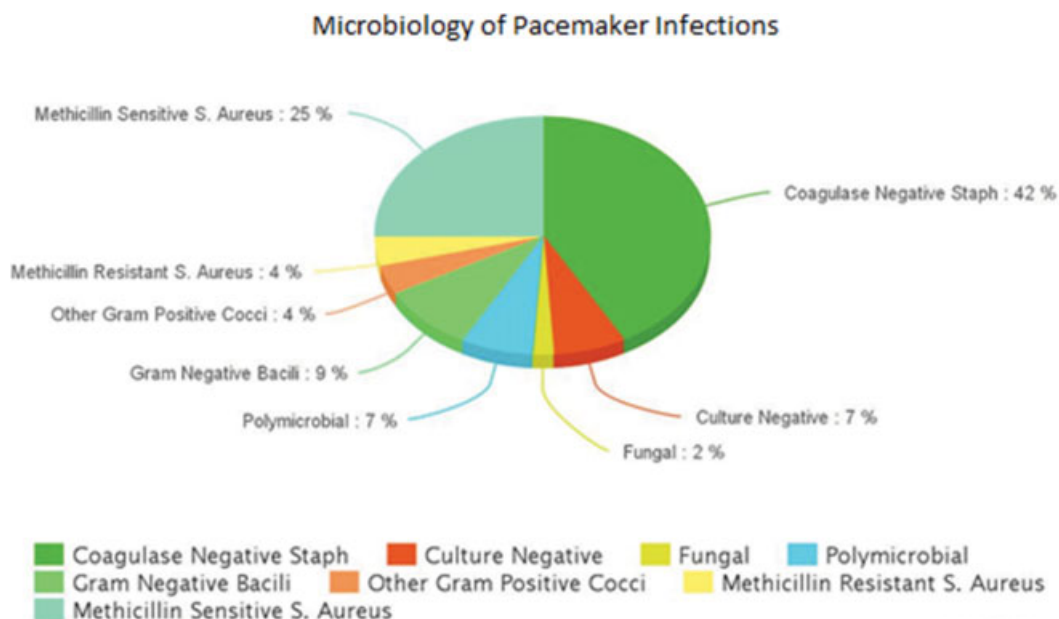
Similarly, LVAD infections may be attributed to various microorganisms. Driveline infections and pocket infections are mostly caused by gram-positive organisms, particularly the *Staphylococcus* and *Enterococcus* species. The most common gram-negative pathogen is *Pseudomonas*. *Candida* species may be attributed to driveline, pump-pocket, as well as LVAD-associated endocarditis in susceptible individuals. In addition, the majority of fungal pathogens may be drug resistant and be challenging to treat.<sup>5</sup>

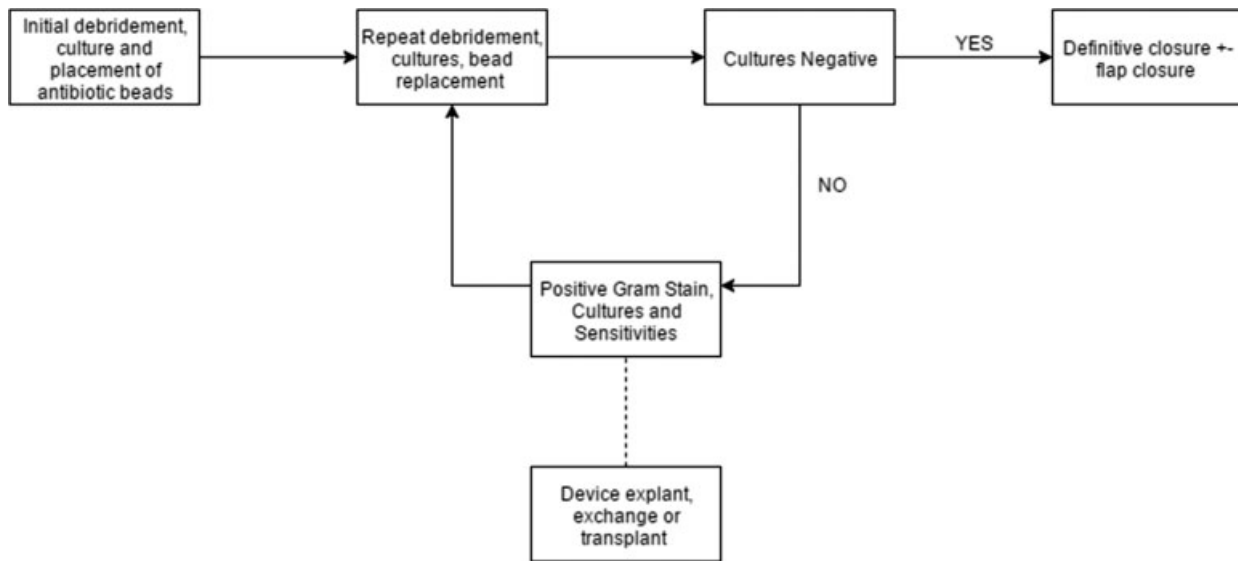
### Treatment of Device Infections

Cardiac implantable electronic device explantation along with culture-driven intravenous (IV) antibiotics, remain the standard treatment modality in addressing device infections.<sup>14</sup> Device salvage, as discussed below, is reserved for patients that are LVAD dependent and unable to tolerate explantation.

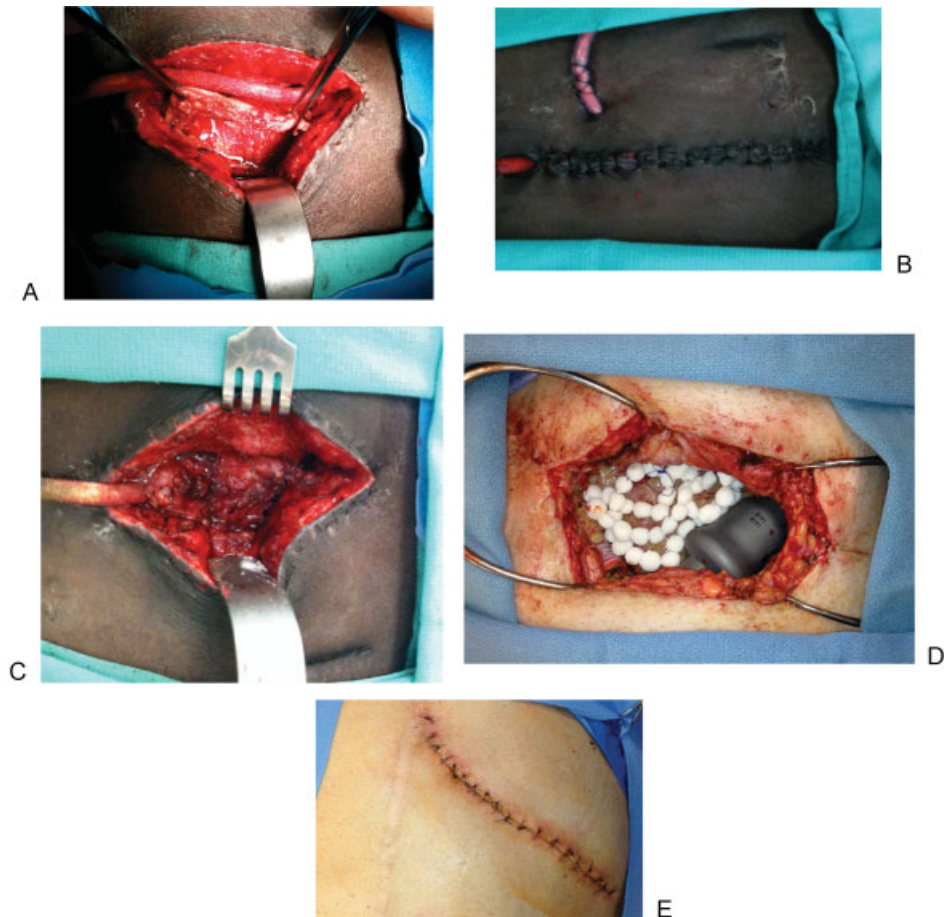
### Pacemakers

The treatment of pacemaker infection consists of complete removal of the infected hardware and a capsulectomy followed by individualized antimicrobial therapy.<sup>15,20–25</sup> If patients are pacemaker dependent, a temporary pacer is placed at or before the time of exchange.<sup>15,23</sup> Reimplantation of devices, if necessary, depends on the location of the infection. Preferably, the pacemaker should be placed on

**Fig. 3** The microbiology of pacemaker infections.



**Fig. 4** Algorithm used for treatment of all patients. Repeated débridement and bead exchange were typically performed every 1 to 2 weeks until results of surgical-site cultures were negative or until other definitive endpoints were reached (i.e., device removal, transplantation, or death).<sup>5</sup>



**Fig. 5** (A–C) Patient undergoing coverage of salvaged left ventricular assist devices (LVAD) drive line using the anterior rectus sheath. (D, E) Placement of antibiotic beads for salvage of LVAD.

the contralateral side to the infection, after cellulitis has resolved and cultures are negative. Another strategy involves the placement of the device in a novel plane, often subpectoral. This ensures the device is covered by healthy vascularized muscle. It is particularly useful in emaciated or

thin patients with poor overlying tissues and thin skin. This process is usually undertaken in a mean of 7 days. When infective endocarditis is present, timing is guided by negative blood cultures, a clinical assessment of the patient, and improved vegetation burden.<sup>15</sup>



Time to reimplantation using the traditional approach averages between 7 and 15 days, depending on the location of the infection and the presence/absence of cardiac device-related infective endocarditis (CDIE). Patients with CDIE have the longest time to reimplantation. The reported mortality rates in this population ranges from 13% to 21%.<sup>14,15,26</sup> Complications that may arise when following the traditional method of device explantation include cardiac arrest, sepsis, operative cardiac tear, pulmonary embolism, hematoma of the device pocket site, pericardial effusions, pericarditis, venous or arterial thrombosis, and pneumothorax. Rodriguez et al reported fatal complications from extraction procedures in 2 of 506 patients. Tarakji et al reported fatal complications from device extraction in 2 of 412 patients, and a 1-year mortality rate of 17%; 2.6% of patients who underwent reimplantation had relapsing infection.<sup>16</sup>

### Left Ventricular Assist Device Salvage

Patients presenting with LVAD infections with recovering cardiac tissue are best treated with removal of the device. This can occur in the setting of cardiac recovery or in cases where a transplant heart becomes available. However, these procedures are not without inherent morbidity and mortality. Various techniques have been described to salvage infected LVADs, including IV antibiotics, wet to dry dressing changes around the device, and negative pressure wound therapy. Recently, a novel approach for device salvage of infected LVADs was developed for high-risk patients where the LVAD could not be removed, patients who were poor candidates for major cardiac surgery, or patients who had failed previous treatments. Salvage procedures involve surgical incision, drainage and aggressive debridement, and placement of antibiotic impregnated beads or slurry (►Fig. 4).

Using the algorithm above, Kretlow et al successfully cleared infections in 17 of 26 patients with left ventricular assist devices. Cleared infections led to a dramatic decline in mortality rates. For patients whose infection persisted, mortality rates were 67% (6 of 9 patients) over the course of the study, whereas that of the cleared population was 29% (5 of 17 patients). The cause of mortality in all those with persisting infections was sepsis, whereas the cause in those with cleared infections included cerebrovascular accident, right heart failure, left ventricular assist device-related gastrointestinal perforation, and graft rejection.<sup>5</sup>

Antibiotic-impregnated beads have been successfully used in the treatment of prosthetic-related infections by orthopedic and vascular surgeons with reported clearance rates ranging from 60% to 100% with recurrence rates ranging from 0 to 20%.<sup>22,27-31</sup> The beads are capable of delivering high concentrations of necessary antibiotics directly to a site of infection, thereby reducing the systemic side effects. Beads are available in resorbable and nonresorbable materials. Nonresorbable beads require bead exchange or removal, unlike their resorbable counterparts.

Polymethylmethacrylate is a nonresorbable medium that is used across many subspecialties to deliver high concentrations of antibiotics locally. Its high cure temperature of 93°C requires the use of heat-stable antibiotics such as vancomycin, tobramycin,

and gentamicin, which sometimes limits its use.<sup>31</sup> However, if resistance to these antimicrobials is encountered, fibrin sealant or calcium sulfate impregnated with the susceptible heat-labile antibiotic of choice may be used. Kretlow et al encountered difficulty with this alternative regimen. Two of three patients treated with fibrin sealant or calcium sulfate-based beads had difficulty clearing infections. This was possibly due to the decreased efficacy of the fibrin sealant and calcium sulfate compared with polymethylmethacrylate; however, this may also have been due to the challenge of treating multidrug-resistant organisms.<sup>5</sup>

Repeated debridement and bead exchange typically performed every 1 to 2 weeks until surgical site cultures were negative or until other definitive endpoints had been reached (device removal, transplant, or if the patient expired). Subsequently, the device was permanently covered with a vascularized flap using a myocutaneous, fasciocutaneous, and/or ommental flap.

The location of the infection ultimately played a role in treatment. Once cultures were negative, patients with infection at the driveline underwent repositioning of the driveline underneath the anterior rectus sheath (►Fig. 5A–C). Infection of the device pocket (►Fig. 5D, E) required local tissue coverage and rectus abdominis muscle flaps where soft tissue coverage was warranted.<sup>5</sup>

### Conclusion

Although tremendous gains have been made in our understanding of the pathogenesis, risk factors, and management of CIED infections over the last decade, the burden on patients and the health care system represents a significant challenge. For these patients, early diagnosis can make a great difference in terms of survival. Intravenous antibiotics and nonsurgical approaches may not provide definitive treatment in some of these conditions, with many recommending extraction and device removal, although that is not without its attendant risks. Patients who are LVAD dependent and are unable to undergo major cardiac surgery may benefit from antibiotic bead placement and device salvage with outcomes comparable with those of the currently recommended treatments above.

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