REVIEW

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Cardiovascular implantable electronic device infection: A stepwise approach to diagnosis and management

■ ABSTRACT

Infection related to cardiovascular implantable electronic devices is a serious complication, necessitating removal of the device and prolonged parenteral antibiotic therapy. Accurate diagnosis and optimal management of these infections are challenging. This review highlights the critical management decisions.

■ KEY POINTS

Although inflammatory signs at the generator pocket are the most common presentation of an infection occurring soon after the device is implanted, positive blood cultures may be the sole manifestation of a late-onset endovascular infection.

Staphylococci are the most common pathogens in both pocket infections and endovascular infections.

Two sets of blood cultures should be obtained in all patients suspected of having a cardiac device infection.

Transesophageal echocardiography should be ordered in all patients with suspected cardiac device infection who have positive blood cultures, as it can identify intracardiac complications of infection and assess for evidence of cardiac valve involvement.

THESE DAYS, an increasing number of people are receiving permanent pacemakers, implantable cardioverter-defibrillators, endovascular devices, and cardiac resynchronization therapy devices—collectively called *cardiovascular implantable electronic devices* (CIEDs). One reason for this upswing is that these devices have been approved for more indications, such as sick sinus syndrome, third-degree heart block, atrial fibrillation, life-threatening ventricular arrhythmias, survival of sudden cardiac death, and advanced congestive heart failure. Another reason is that the population is getting older, and therefore more people need these devices.

Although the use of a CIED is associated with a lower risk of death and a better quality of life, CIED-related infection can eclipse some of these benefits for their recipients. Historically reported rates of infections range from 0% to 19.9%.[1] However, recent data point to a disturbing trend: infection rates are rising faster than implantation rates.[2]

Besides causing morbidity and even death, infection is also associated with significant financial cost for patients and third-party payers. The estimated average cost of combined medical and surgical treatment of CIED-related infection ranges from $25,000 for permanent pacemakers to $50,000 for implantable cardioverter-defibrillators.[3,4]

Although cardiologists and cardiac surgeons are the ones who implant these devices, most patients receive their routine outpatient

care from a primary care physician, who can be a general internist, a family physician, or other specialist. Moreover, many patients with device infection are admitted to hospital internal medicine services for various diagnoses requiring inpatient care. Therefore, an internist, a family physician, or a hospitalist may be the first physician to respond to a suspected or confirmed device infection. Knowledge of the clinical manifestations and the initial steps in evaluation and management is essential for optimal care.

These complex infections pose challenges, which we will illustrate by presenting a case of CIED-related infection and reviewing key elements of diagnosis and management.

◼ AN ILLUSTRATIVE CASE

A 60-year-old man had a permanent pacemaker implanted 3 months ago because of third-degree heart block; he now presents to his primary care physician with increasing pain, swelling, and erythema at the site of his pacemaker pocket. He has a history of type 2 diabetes mellitus, stage 3 chronic kidney disease, and coronary artery disease.

The symptoms started 2 weeks ago and have slowly progressed, prompting him to seek medical care. He is quite anxious and wants to know if he needs to arrange an emergency consultation with his cardiologist.

◼ IMPORTANT CLINICAL QUESTIONS

This presentation raises several important questions:
- What should be the next step in his evaluation?
- Which laboratory tests should be done?
- Should he be admitted to the hospital, or can he be managed as an outpatient?
- Should he be started empirically on antibiotics? If so, which antibiotics? Or is it better to wait?
- When should an infectious disease specialist be consulted?
- Should the device be removed, and if so, all of it or which components?
- How long should antibiotics be given?

We will provide evidence-based answers to these questions in the discussions below.

Infection rates are rising faster than implantation rates

◼ PATHOGENESIS AND RISK FACTORS FOR DEVICE INFECTION

The first step in understanding the clinical manifestations of CIED-related infections is to grasp their pathogenesis. Risk factors for device infection have been evaluated in several studies.[1]

Several factors interact in the inception and evolution of these infections, some related to the care in the perioperative period, some to the device, some to the host, and some to the causative microorganism.[5] Although any one of these may play a predominant role in a given patient, most patients have a combination.

Perioperative factors that may contribute to a higher risk of infection include device revision; use of temporary pacing leads before placement of the permanent device; lack of antibiotic prophylaxis before implantation; longer operative time; operative inexperience; development of postoperative pocket hematoma; and factors such as diabetes mellitus and long-term use of corticosteroids and other immunosuppressive drugs that impair wound healing at the generator pocket.[6–11]

Device factors. Abdominal generator placement, use of epicardial leads, and complexity of the device play a significant role.[6,12,13] In general, implantable cardioverter-defibrillators and cardiac resynchronization therapy devices have higher rates of infection than permanent pacemakers.[2,14]

Host factors. Diseases and conditions that predispose to bloodstream infection may result in hematogenous seeding of the device and its leads and are associated with a higher risk of late-onset infection. These include an implanted central venous catheter (for hemodialysis or other long-term access), a distant focus of primary infection (such as pneumonia and skin and soft-tissue infections), and invasive procedures unrelated to the CIED.[10,15]

In general, contamination at the time of surgery leads to early-onset infection (ie, within weeks to months of implantation), whereas hematogenous seeding is a predominant factor in most patients with late-onset infection.[16]

STAPHYLOCOCCI ARE THE MOST COMMON CAUSE

A key to making an accurate diagnosis and determining the appropriate empiric antibiotic therapy is to understand the microbiology of device infections.

Regardless of the clinical presentation, staphylococci are the predominant organisms responsible for both early- and late-onset infections.[17,18] These include *Staphylococcus aureus* and coagulase-negative staphylococci. Depending on where the implanting hospital is located and where the organism was acquired (in the community or in the hospital), up to 50% of these staphylococci may be methicillin-resistant,[17,18] a fact that necessitates using vancomycin for empiric coverage until the pathogen is identified and its susceptibility is known.

Gram-negative or polymicrobial CIED infections are infrequent. However, empiric gram-negative coverage should be considered for patients who present with systemic signs of infection, in whom delaying adequate coverage could jeopardize the successful outcome of infection treatment.

Fungal and mycobacterial infections of cardiac devices are exceedingly uncommon, mainly occurring in immunocompromised patients.

CLINICAL MANIFESTATIONS OF CARDIOVASCULAR DEVICE INFECTION

The clinical presentations of CIED-related infection can be broadly categorized into two groups: generator pocket infection and endovascular infection with an intact pocket.[17,18]

Generator pocket infection

Most patients with a pocket infection present with inflammatory changes at the device generator site. Usual signs and symptoms include pain, erythema, swelling, and serosanguinous or purulent drainage from the pocket.

Occasionally, a pocket infection may present with the generator or leads eroding through the skin (FIGURE 1). It is arguable whether this device erosion is a manifestation of an underlying occult infection or a manifestation of a secondary cause of skin breakdown such

FIGURE 1. Cardiovascular implantable electronic device (CIED) generator and lead erosion.

as poor wound healing due to prior radiation, skin fragility due to chronic steroid use, or chronic skin disease. However, once exposed to the environment, the generator and leads invariably become contaminated with skin organisms and must be treated as pocket infections for all practical purposes.

Patients with a pocket infection generally present within weeks to months of implantation, as the predominant mechanism of pocket infection is contamination of the generator or leads during implantation. However, occasionally, pocket infection caused by indolent organisms such as *Propionibacterium*, *Corynebacterium*, and certain species of coagulase-negative staphylococci can present more than 1 year after implantation. Hematogenous seeding of the device pocket, as a result of bacteremia from a distant primary focus, is infrequent except in cases of *S aureus* bloodstream infection.[19]

Endovascular infection with an intact pocket

A subset of patients with CIED-related infections, mostly late-onset infections, present only with systemic signs and symptoms without inflammatory changes at the generator

Staphylococci are responsible for most infections, both early- and late-onset

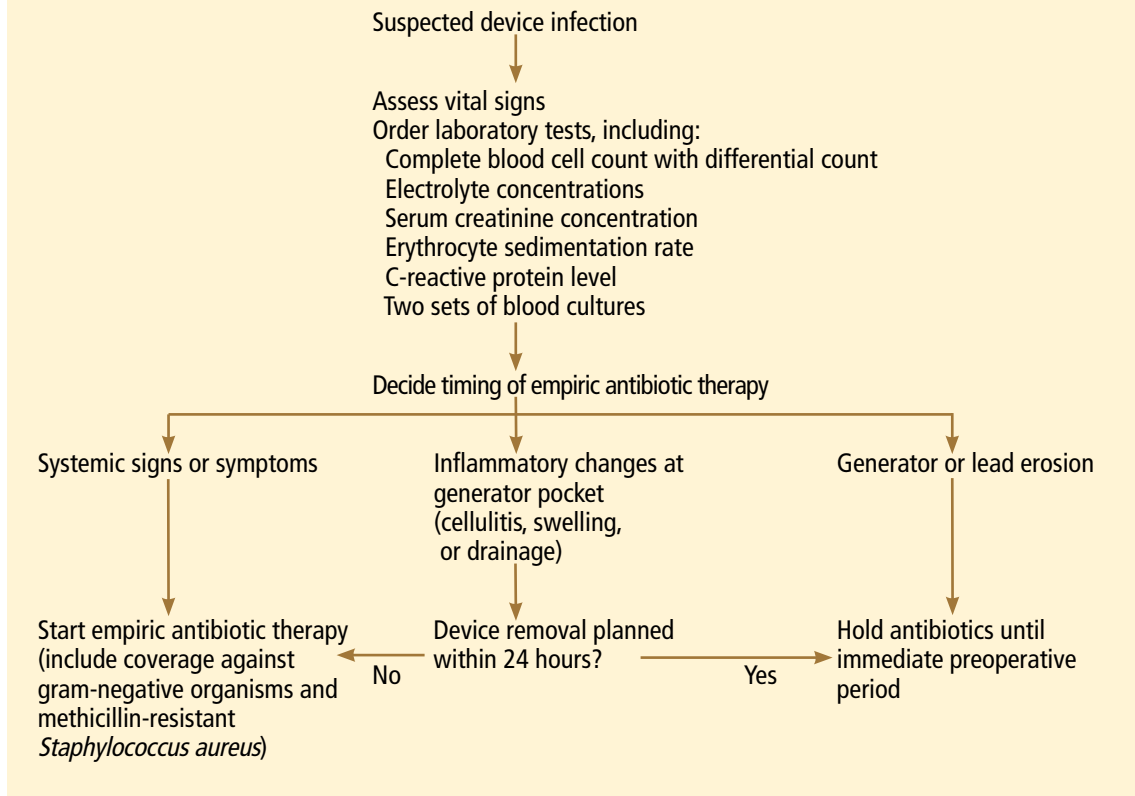## Initial evaluation and empiric antibiotic therapy for cardiovascular implantable electronic device infection

Suspected device infection

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Assess vital signs
Order laboratory tests, including:
   Complete blood cell count with differential count
   Electrolyte concentrations
   Serum creatinine concentration
   Erythrocyte sedimentation rate
   C-reactive protein level
   Two sets of blood cultures

↓

Decide timing of empiric antibiotic therapy

| Systemic signs or symptoms | Inflammatory changes at generator pocket (cellulitis, swelling, or drainage) | Generator or lead erosion |

Start empiric antibiotic therapy (include coverage against gram-negative organisms and methicillin-resistant *Staphylococcus aureus*)

← No — Device removal planned within 24 hours? — Yes →

Hold antibiotics until immediate preoperative period

FIGURE 2

Blood cultures may be falsely negative if antibiotics are started empirically

pocket.[16–18] Most of these patients have multiple comorbid conditions and likely acquire the infection via hematogenous seeding of transvenous device leads from a distant focus of primary infection, such as a skin or soft-tissue infection, pneumonia, bacteremia arising from an implanted long-term central venous catheter, or bloodstream infection secondary to an invasive procedure unrelated to the CIED.

Most patients with an endovascular device infection have positive blood cultures at presentation. However, occasionally, blood cultures may be negative. The main reason for negative blood cultures in this setting is the use of empiric antibiotic therapy before blood cultures are drawn.
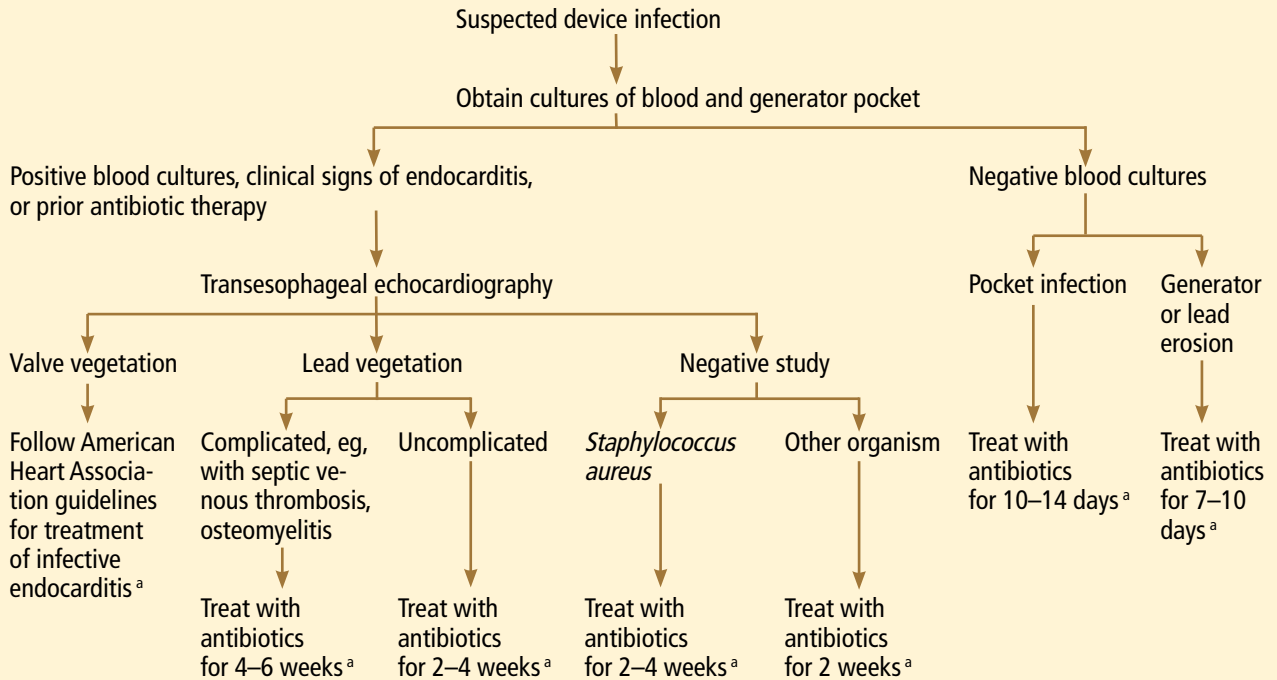
Endovascular device infections are further complicated by the formation of infected vegetations on the leads or cardiac valves in up to one-fourth of cases.[16–18,20,21] This complication poses additional challenges in manage-

ment, such as choosing the appropriate lead extraction technique, the waiting time before implanting a replacement device, and the optimal length of parenteral antimicrobial therapy. Many of these decisions are beyond the realm of internal medicine practice and are best managed by consultation with an infectious disease specialist and a cardiologist.

■ **DIAGNOSIS OF INFECTION AND ASSOCIATED COMPLICATIONS**

The clinical diagnosis of pocket infection is usually quite straightforward. However, occasionally, an early postoperative pocket hematoma can mimic pocket infection, and distinguishing these two may be difficult. Close collaboration between an internist, cardiologist, and infectious-disease specialist and careful observation of the patient may help to avoid a premature and incorrect diagnosis of pocket infection and unnecessary removal of the device in this scenario.

How to determine the duration of therapy for cardiovascular implantable electronic device infection

Suspected device infection

↓

Obtain cultures of blood and generator pocket

Positive blood cultures, clinical signs of endocarditis, or prior antibiotic therapy

Negative blood cultures

Positive side:

Transesophageal echocardiography

- **Valve vegetation** → Follow American Heart Association guidelines for treatment of infective endocarditis [a]
- **Lead vegetation**
  - Complicated, eg, with septic venous thrombosis, osteomyelitis → Treat with antibiotics for 4–6 weeks [a]
  - Uncomplicated → Treat with antibiotics for 2–4 weeks [a]
- **Negative study**
  - *Staphylococcus aureus* → Treat with antibiotics for 2–4 weeks [a]
  - Other organism → Treat with antibiotics for 2 weeks [a]

Negative blood cultures side:

- Pocket infection → Treat with antibiotics for 10–14 days [a]
- Generator or lead erosion → Treat with antibiotics for 7–10 days [a]

[a] Duration of antibiotics should be counted from the day of device explantation.

ADAPTED FROM SOHAIL MR, USLAN DZ, KHAN AH, ET AL. MANAGEMENT AND OUTCOME OF PERMANENT PACEMAKER AND IMPLANTABLE CARDIOVERTER-DEFIBRILLATOR INFECTIONS. J AM COLL CARDIOL 2007; 49:1851–1859, WITH PERMISSION FROM ELSEVIER. WWW.SCIENCEDIRECT.COM/SCIENCE/JOURNAL/07351097.

FIGURE 3

While diagnosing a pocket infection may be simple, an accurate and timely diagnosis of endovascular infection with an intact pocket can be challenging, especially if echocardiography shows no conclusive evidence of involvement of the device leads. Even when the infection is limited to the generator pocket, attempts to isolate causative pathogens may be hampered if empiric antibiotic therapy is started before culture samples are obtained from the pocket and from the blood.

We suggest the following tests if a CIED-related infection is suspected (**FIGURE 2**):

Complete blood count with differential cell count.

Electrolyte and serum creatinine concentrations.

Inflammatory markers, including erythrocyte sedimentation rate and C-reactive protein concentration.

Swabs for bacterial cultures should be sent if there is purulent drainage from the generator pocket. This can be done in the office before referral to the emergency department or a tertiary care center for inpatient admission. If the pocket appears swollen or fluctuant, needle aspiration should be avoided, as it can introduce organisms and cause contamination.[5]

Two sets of peripheral blood cultures should be obtained. If the patient has an implanted central venous catheter, blood cultures via each catheter port should also be obtained, as they may help to pinpoint the source of bloodstream infection in cases in which blood culture results are positive.

Transesophageal echocardiography (TEE) should be ordered if the blood cultures are positive, to look for infected vegetations on the device leads or cardiac valves (**FIGURE 3**).[17] Transthoracic echocardiography (TTE) has

lower sensitivity in detecting vegetations on leads and prosthetic valves and is not adequate to rule out a complicated device infection.[5,12,20]

TEE should also be performed in patients with systemic signs and symptoms (such as fever, chills, malaise, dyspnea, hypotension, or peripheral stigmata of endocarditis) or abnormal test results (leukocytosis, elevated inflammatory markers, or evidence of pulmonary emboli on imaging), even if blood cultures are negative. Similarly, TEE should also be considered in patients in whom blood cultures may be negative as a result of previous antimicrobial therapy.

If a decision is made to remove the device (see below), **intraoperative pocket tissue and lead-tip cultures** should be sent for Gram staining and bacterial culture. Fungal and mycobacterial cultures may be necessary in immunocompromised hosts, or if Gram staining and bacterial cultures from pocket tissue samples are negative. Caution must be exercised when interpreting the results of lead-tip cultures, as lead tips may become contaminated while being pulled through an infected pocket during removal.[20,22]

This approach should lead to an accurate diagnosis of CIED-related infection and associated complications in most patients. However, the diagnosis may remain elusive if results of blood cultures are positive but the pocket is intact and there is no echocardiographic evidence of lead or valve involvement. This is especially true in cases of S aureus bacteremia, in which positive blood cultures may be the sole manifestation of underlying device infection.[19,23] Factors associated with higher odds of underlying device infection in this scenario include bacteremia lasting more than 24 hours, prosthetic valves, bacteremia within 3 months of device implantation, and no alternative focus of bacteremia.[12]

Evidence is emerging that underlying device infection should also be considered in patients with bloodstream infection with coagulase-negative staphylococci in the setting of an implanted device.[24] On the other hand, seeding of device leads with gram-negative organisms is infrequent, and routine imaging of intracardiac leads is not necessary in cases of gram-negative bacteremia.[25]

In our opinion, cases of bacteremia in

which underlying occult device infection is a concern are best managed by consultation with an infectious disease specialist.

■ A STEPWISE APPROACH TO MANAGING DEVICE INFECTION

Should antibiotics be started empirically?
The first step in managing CIED-related infection is to decide whether empiric antibiotic therapy should be started immediately once infection is suspected or if it is prudent to wait until the culture results are available.

In our opinion, if the infection is limited to the generator pocket, it is reasonable to wait until immediately before surgery to maximize the culture yield from pocket tissue samples. An exception to this rule is when systemic signs or symptoms are present, in which case delaying antibiotic therapy could jeopardize the outcome (**FIGURE 2**). In such cases, empiric antibiotic therapy can be started once two sets of peripheral blood samples for cultures have been obtained.

Which antibiotics should be given empirically?
Because gram-positive organisms, namely coagulase-negative staphylococci and S aureus, are the causative pathogens in most cases of CIED-related infection, empiric antibiotic therapy should provide adequate coverage for these organisms. Because methicillin resistance is quite prevalent in staphylococci, we routinely use vancomycin (Vancocin) for empiric coverage. In patients who are allergic to vancomycin or cannot tolerate it, daptomycin (Cubicin) is an alternative.

Empiric gram-negative coverage is generally reserved for patients who present with systemic signs and symptoms, in whom delaying adequate coverage could have untoward consequences. We routinely use cefepime (Maxipime) for empiric gram-negative coverage in our institution. Other beta-lactam agents that provide coverage for gram-negative bacilli, especially *Pseudomonas*, are also appropriate in this setting.

Should the device be removed?
Superficial infection of the wound or incision site (eg, stitch abscess) early after implantation can be managed by conservative antibiot-

Because methicillin resistance is common in staphylococci, we use vancomycin for empiric coverage

ic therapy without removing the device. However, complete removal of the device system, including intracardiac leads, is necessary in all other presentations of device infection, even if the infection appears limited to the generator pocket.[5,12] Leaving the device in place or removing parts of the device is associated with persistent or relapsed infection and is not advisable.[17,26]

Leaving the device in place may be necessary in extenuating circumstances, eg, if surgery would be too risky for the patient or if the patient refuses device removal or has a short life expectancy. In these cases, lifelong suppressive antibiotic therapy should be prescribed after an initial course of parenteral antibiotics.[27] Antibiotic choices for long-term suppressive therapy should be guided by antimicrobial susceptibility testing and consultation with an infectious disease specialist.

How should the leads be removed?

Leads are extracted percutaneously in most cases. Percutaneous extraction is generally considered safe even in cases in which infection is complicated by lead vegetations, which raises concern about pulmonary embolization of detached vegetation fragments during extraction.[5,20]

Thoracotomy is generally reserved for patients who have cardiac complications (such as a cardiac abscess or the need to replace cardiac valves) or in whom attempts to extract the leads percutaneously are unsuccessful.

Details of the removal procedure and choice of extraction technique are beyond the scope of this paper and are best left to the discretion of the treating cardiologist or cardiac surgeon. Because of the potential for complications during percutaneous device removal, such as laceration of the superior vena cava or cardiac tamponade, the patient should be referred to a high-volume center where cardiothoracic intervention can be provided on an emergency basis if needed.

How long should antibiotic therapy go on?

An algorithm for deciding the duration of antibiotic therapy is shown in **FIGURE 3**. These guidelines, first published in 2007,[17] were adopted by the American Heart Association in its updated statement on the management of CIED-related infections.[5] However, it should be noted that these guidelines are not based on randomized clinical trials; rather, they represent expert opinion based on published series of patients with CIED-related infections.

In general, cases of device erosion or pocket infection can be treated with 1 to 2 weeks of appropriate antibiotic therapy based on antimicrobial susceptibility testing. However, cases of bloodstream infection require 2 to 4 weeks of antibiotic therapy—or sometimes even longer if associated complications are present, such as septic thrombosis, endocarditis, or osteomyelitis.

We favor parenteral antibiotics for the entire course of treatment. However, patients can be discharged from the hospital once the bloodstream infection has cleared, and the antibiotic course can be completed on an outpatient basis.

Outpatient antimicrobial monitoring

We recommend adherence to the Infectious Diseases Society of America's guidelines for monitoring outpatient parenteral antimicrobial therapy.[28]

At discharge from the hospital, patients should be instructed to promptly call their primary care physician if they have a fever or notice inflammatory changes at the pocket site. If the patient reports such symptoms, repeat blood cultures should be ordered, and the patient should be monitored closely for signs of a relapse of infection.

A routine follow-up visit should be arranged at 2 weeks and at the end of parenteral antibiotic therapy (for patients receiving therapy for 4 weeks or longer) to make sure the infection has resolved.
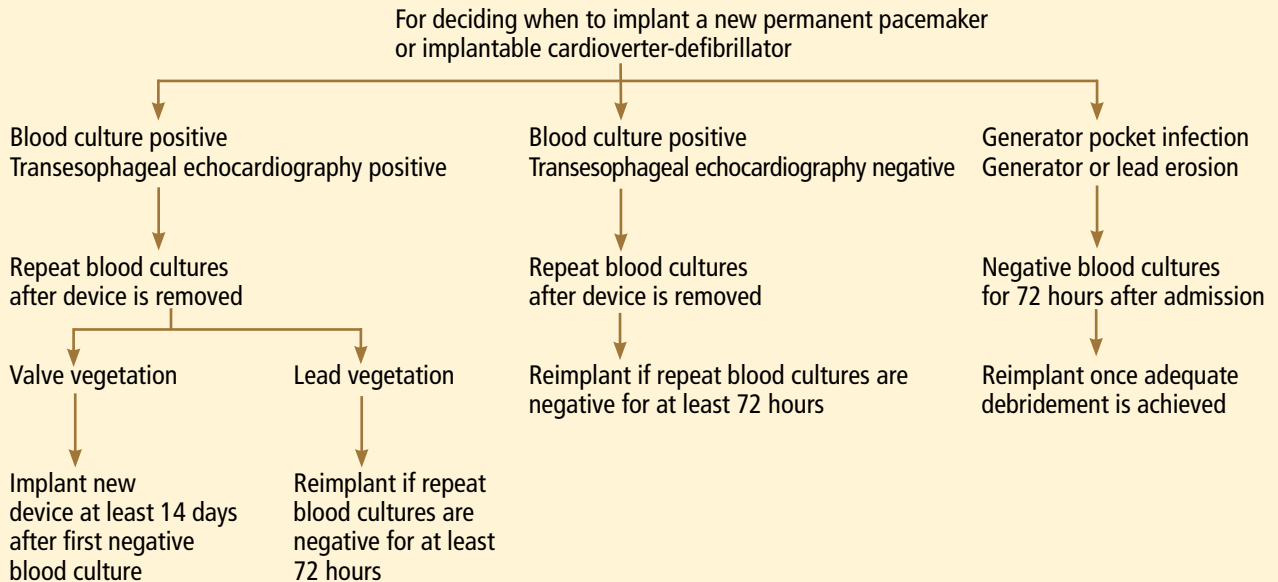
When should a new device be implanted?

Before deciding *when* a new device should be implanted, one should carefully assess *whether* the patient still needs one. Studies indicate that up to 30% of patients may no longer require a cardiac device.[17,18]

If the cardiologist deems that a new device is necessary, it is reasonable to proceed once repeat blood cultures (obtained after device removal) have been negative for at least 72 hours and adequate pocket debridement has been achieved (**FIGURE 4**).

However, we believe that removal of drains

In most cases, the complete device must be removed to eradicate the infection

Guidelines for reimplantation of new device in patients with pacemaker or ICD infection

For deciding when to implant a new permanent pacemaker or implantable cardioverter-defibrillator

Blood culture positive
Transesophageal echocardiography positive
→ Repeat blood cultures after device is removed
→ Valve vegetation → Implant new device at least 14 days after first negative blood culture
→ Lead vegetation → Reimplant if repeat blood cultures are negative for at least 72 hours

Blood culture positive
Transesophageal echocardiography negative
→ Repeat blood cultures after device is removed
→ Reimplant if repeat blood cultures are negative for at least 72 hours

Generator pocket infection
Generator or lead erosion
→ Negative blood cultures for 72 hours after admission
→ Reimplant once adequate debridement is achieved

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FIGURE 4

All patients should receive antibiotic prophylaxis before implantation

and closure of the old pocket are not necessary before implanting a new device in a different location (usually the contralateral pectoral area). Exceptions to this general principle are cases of valvular endocarditis, in which a minimum of 2 weeks is recommended between removal of an infected device (plus clearance of bloodstream infection) and implantation of a new device.

■ OUTCOMES OF INFECTION

Despite improvements in our understanding of how to manage CIED-related infection, the rates of morbidity and death remain significant.

The outcome, in part, depends on the clinical presentation and the patient's comorbid conditions. In general, the death rate in patients with a pocket infection is less than 5%. However, in patients with endovascular infection, it may be as high as 20%.[16–18] Other factors that affect the outcome include complications such as septic thrombosis, valvular endocarditis, or osteomyelitis; complications during device extraction; the need for open heart surgery; and the overall health of the patient.

Complete removal of the device system is a requisite for successful outcome, and the risk of death tends to be higher if only part of the infected CIED system is extracted.[26]

■ STRATEGIES TO PREVENT DEVICE INFECTION

Preventive efforts should focus on strategies to minimize the chances of contamination of the generator, leads, and pocket during implantation.[29] Patients who are known to be colonized with methicillin-resistant S aureus may benefit from decolonization programs, which should include nasal application of mupirocin (Bactroban) ointment preoperatively.[30] In addition, use of chlorhexidine for surgical-site antisepsis has been shown to reduce the risk of surgical site infection.[31]

Moreover, all patients should receive antibiotic prophylaxis before implantation of a CIED.[32,33] Most institutions use a first-generation cephalosporin, such as cefazolin (Ancef), for this purpose.[34] However, the increasing rate of methicillin resistance in staphylococci has led to the routine use of vancomycin for preoperative prophylaxis at some centers.[18]

Regardless of the antibiotic chosen for prophylaxis, protocols that ensure that all patients receive an appropriate antibiotic at the appropriate time are a key determinant in the success of these infection-control programs. ■

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