

CLINICAL PRACTICE

Infections of Cardiovascular Implantable Electronic Devices

Larry M. Baddour, M.D., Yong-Mei Cha, M.D., and Walter R. Wilson, M.D.

This Journal feature begins with a case vignette highlighting a common clinical problem. Evidence supporting various strategies is then presented, followed by a review of formal guidelines, when they exist. The article ends with the authors' clinical recommendations.

A 75-year-old man presents with localized pain, redness, and swelling of 3 weeks' duration at the pocket site in the left upper shoulder, where an implantable cardioverter–defibrillator was placed 6 months earlier. He has no fever or other systemic symptoms. Physical examination reveals redness and induration at the site of the generator pocket on the left shoulder, with no stigmata of infective endocarditis. Results of blood cultures are negative. How should this case be managed?

THE CLINICAL PROBLEM

From the Department of Medicine, Divisions of Infectious Diseases (L.M.B., W.R.W.) and Cardiovascular Diseases (Y.-M.C.), Mayo Clinic College of Medicine, Mayo Clinic, Rochester, MN. Address reprint requests to Dr. Baddour at the Mayo Clinic, 200 First St. SW, Rochester, MN 55905, or at baddour.larry@mayo.edu.

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The use of cardiovascular implantable electronic devices (CIEDs) has increased in recent years, owing largely to the expansion of their functions and of indications for their use.¹ Despite the use of antibiotic prophylaxis at the time of device placement or revision,^{2,3} rates of device-related infection may have increased, according to reports from several national databases.⁴⁻⁷

For many years, infection rates were presumed to be similar for different types of CIEDs. However, results from some studies suggest that implantable cardioverter–defibrillators are associated with a greater risk of infection than are permanent pacemakers.^{5,8,9} The risk of infection associated with epicardial systems is similar to that associated with transvenous systems and is estimated to be approximately 2% at 5 years after implantation.¹⁰

Case–control and cohort studies have identified specific risk factors associated with CIED infections.¹¹⁻¹⁹ These include coexisting conditions, particularly renal failure; complications at the generator incision site, including hematoma formation; and implantation of devices with multiple leads, which are characteristic of the devices currently used.²⁰ Although many studies have also identified device revision or replacement as a risk factor for infection,^{11-14,16-19} findings from a large, prospective, multicenter investigation of complication rates with generator replacements or upgrades (REPLACE Registry) showed a low rate of major infection (0.8%).^{21,22} This low rate may be explained, in part, by scrupulous attention to preoperative skin antisepsis and systemic antibiotic prophylaxis in the study population, as well as the limited (6-month) follow-up, which would not have detected CIED infections of later onset.

The majority of CIED infections are caused by either *Staphylococcus aureus* or coagulase-negative staphylococci; both groups of organisms, and particularly coagulase-negative staphylococci, are often resistant to oxacillin. A variety of other bacteria and fungi are less commonly identified as causes of CIED infection.²³⁻²⁵

The interval between CIED placement or revision and the onset of infection varies widely, from days to years.²³⁻²⁵ In addition, the clinical presentation varies



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KEY CLINICAL POINTS

Infections Related to Cardiovascular Implantable Electronic Devices

- The rate at which cardiovascular implantable electronic devices (CIEDs) are being implanted has been increasing, with an associated increase in the number of CIED infections.
- Common risk factors for CIED infections include complications involving the generator pocket site (hematoma and poor wound healing), revision or replacement of the device, and renal failure.
- Staphylococcus species account for the majority of CIED infections.
- Complete removal of the device is required for cure, even when signs of infection are limited to the generator pocket site, and should be performed at a medical center with expertise in lead extraction.
- Antibiotic therapy is also given for up to 2 weeks (longer if there is evidence of endocarditis).
- Perioperative antibiotic prophylaxis is effective in reducing the risk of CIED infection.

with the site or sites of infection and with the virulence of the infecting organism. For example, infections due to coagulase-negative staphylococci usually have an indolent presentation, whereas *S. aureus* infections, particularly those complicated by bloodstream infection or CIED-related infective endocarditis, develop more rapidly, with more severe systemic manifestations.²⁶

STRATEGIES AND EVIDENCE

DIAGNOSIS AND EVALUATION

Although some cases of CIED infection present without obvious inflammatory changes of the skin, the diagnosis is most often (in about 70% of cases) based on findings at the generator pocket site, including local pain, swelling, redness, drainage, and skin and soft-tissue ulceration. The first sign of infection may be erosion through the skin at the site of the generator pocket, with external exposure of the generator, one or more leads, or both the generator and leads, with or without local inflammatory changes. Less often, there is persistent local pain without obvious swelling, or healing of the incision may be delayed, which can lead to erosion. It can be difficult to distinguish between early postoperative changes, such as noninfected hematomas and superficial cellulitis or infection of the surgical site, and CIED infection of early onset. Aspiration of the pocket site could result in infection and should therefore be avoided. Immediate evaluation by a physician with expertise in CIEDs is warranted. In cases of an indolent generator-site infection, surgical wound dehiscence often oc-

curs eventually. In patients who present with lead infection, fever and signs of systemic infection are usually evident. The lungs may also be involved, with emboli or infection.²⁷

Blood cultures are recommended in all suspected cases of CIED infection, regardless of whether the patient is febrile or has other signs or symptoms of systemic infection (Fig. 1). Blood samples should be drawn from different sites for at least two sets of cultures. However, blood cultures may be negative despite CIED infection, particularly in patients with pocket-site infection and in those given antibiotics shortly before blood samples are obtained for culture. Moreover, positive blood cultures may be due to a source other than an infected CIED. The likelihood that a CIED infection is present when blood cultures are positive varies according to the pathogen detected, the number and duration of positive blood cultures, and the presence of other findings that suggest device-related infections.²⁹⁻³⁴ CIED infection will ultimately be confirmed in 35% or more of patients with bacteremia due to staphylococcal species,^{29,31} whereas the likelihood of CIED infection is lower (20% or less) in patients with bacteremia caused by nonstaphylococcal gram-positive cocci or by gram-negative bacilli.³²⁻³⁴ A single blood culture that is positive for coagulase-negative staphylococci usually represents contamination rather than infection. In contrast, multiple blood cultures that are positive for coagulase-negative staphylococci should prompt consideration of a device-related infection even if there are no other suggestive symptoms or signs.

Transesophageal echocardiography (TEE) is

recommended for patients with bacteremia, especially if the bloodstream infection is due to staphylococcal species or if the source is not identified, and for patients with signs of systemic infection, regardless of blood-culture results.³⁵ The main purpose of TEE is to identify complications such as valvular vegetations or myocardial or perivalvular abscesses. In adults, TEE is more sensitive than transthoracic echocardiography for detecting evidence of an intracardiac infection.^{36,37} However, TEE is more costly than transthoracic echocardiography and is invasive. Complications of the procedure, including reactions to medications used for TEE, hemorrhage, bronchospasm, perforation of the upper respiratory or gastrointestinal tract, and cardiac arrhythmias, are uncommon (occurring in <1% of cases).³⁸ Vegetations on a lead are consistent with, but not diagnostic of, lead-related endocarditis; bland (uninfected) clots on leads have been found on echocardiographic examination in 5 to 10% of CIED recipients without infection,^{39,40} and these mass lesions usually cannot be distinguished from infected vegetations. Moreover, a negative result on TEE does not rule out the possibility of lead infection. The size of a lead vegetation identified on TEE correlates with the risk associated with percutaneous extraction (e.g., the risk of pulmonary emboli). Although most cases of pulmonary embolism associated with extraction are clinically insignificant, significant emboli are more common in patients with a larger lead vegetation (>2 to 3 cm in diameter); thus, this finding may identify patients for whom open cardiovascular surgery may be more suitable than percutaneous extraction for removal of the device.^{41,42}

CONFIRMATION OF THE DIAGNOSIS

Intraoperative findings with specimens obtained for culture are used to support the diagnosis of CIED infection. Findings at the pocket site that are suggestive of infection include purulence, inflammatory changes, gelatinous material, loss or thinning of subcutaneous tissue, and poor capsule formation. These findings may also be noted in patients without local signs or symptoms suggestive of generator-site infection.^{23,30} Deep-tissue specimens at the pocket site and lead tips should be obtained intraoperatively for culture and drug-susceptibility testing of isolates. Initially, anaerobic and aerobic bacterial cultures should be performed; if the results are negative, the remaining

Figure 1 (facing page). Algorithm for Management of an Infected Cardiovascular Implantable Electronic Device (CIED) in Adults.

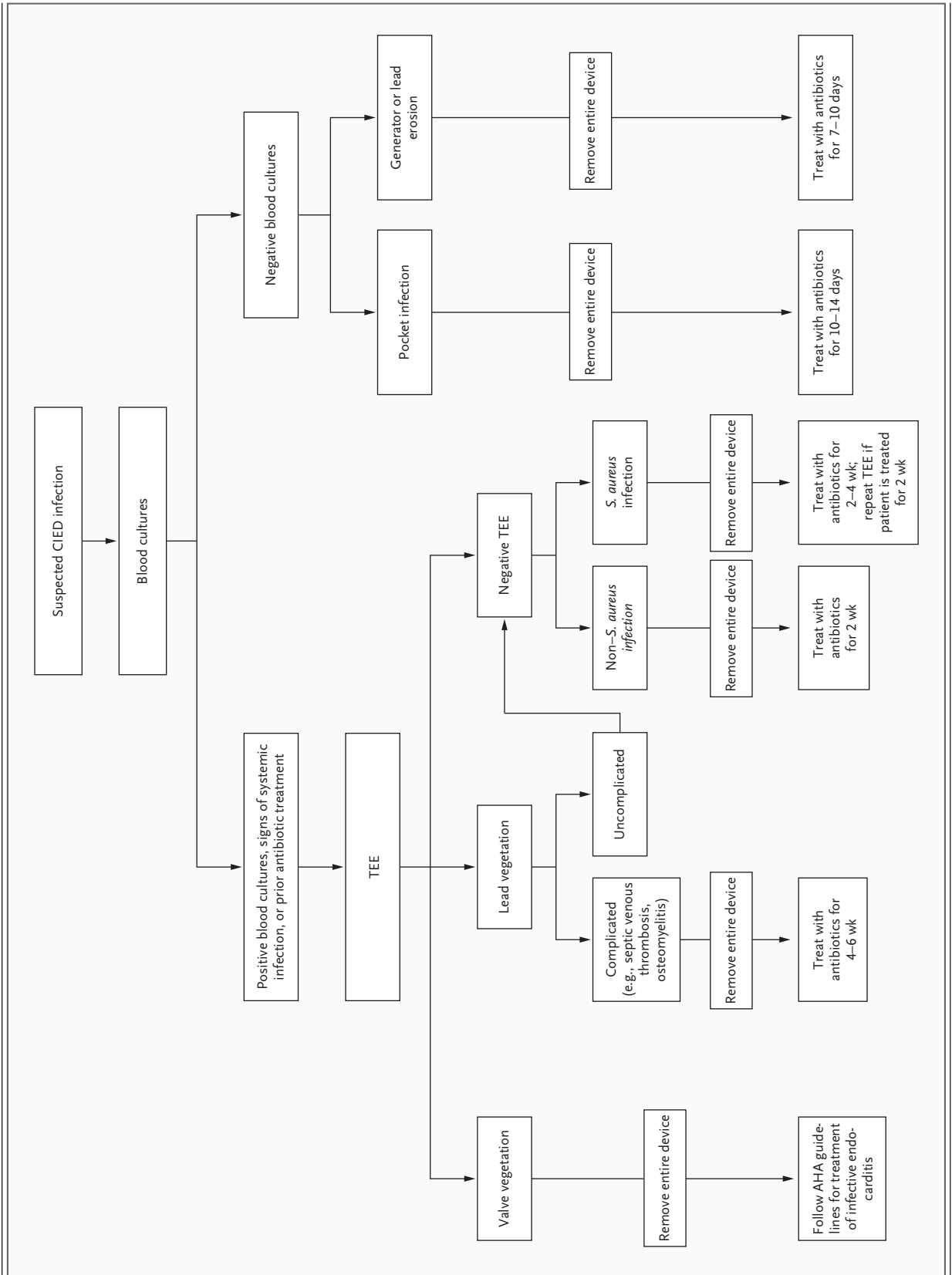
Before the device is removed, a standard assessment should be carried out, including a history taking and physical examination, appropriate imaging procedures, and interrogation of the device. Antibiotic therapy, counted from the day of explantation, can be extended to 4 weeks or longer if there are complications or if bacteremia persists. AHA denotes American Heart Association, and TEE transesophageal echocardiography. Adapted from Baddour et al.²⁸

tissue specimens should be submitted for fungal and mycobacterial smears and cultures, particularly if the patient did not receive antibiotic therapy before the device was extracted. Positive tissue cultures are more sensitive for confirming infection than are positive swab cultures.⁴³ The high frequency of positive cultures of leads extracted through the femoral vein (to avoid contamination of the pocket site) in patients with findings limited to the pocket site (72% in one series⁴⁴) underscores the contention that the spread of infection from the pocket site is common and that complete removal of the device is warranted to prevent relapse.

MANAGEMENT

Data from randomized, controlled trials to guide the management of CIED infections are lacking. Recommendations for complete extraction of the device, the route of administration and the duration of antimicrobial therapy, and the timing for placement of a new device are largely based on observational data, clinical experience, or both. Observations from several medical centers universally support complete removal of the device to cure infection and reduce morbidity and mortality.⁴⁴⁻⁴⁶ Removal of the generator without lead extraction should be avoided.

A variety of percutaneous lead-removal techniques are available, and only a small minority of patients require open cardiovascular surgery for complete device removal. The choice of percutaneous or open surgical removal should take into account not only the size of a vegetation, as visualized on echocardiography, but also several other factors, including the patient's age, how long the device has been in place, the type of device, the number of retained leads from previous devices, the presence or absence of a history of difficult or complicated percutaneous extractions,



and status with respect to coexisting conditions. Complications, including death, may occur with either percutaneous or surgical removal of the device.^{41,47} Major complications are reported in less than 2% of patients who undergo percutaneous removal,⁴¹ but the rate may be higher with surgical removal, which is generally performed after unsuccessful or complicated percutaneous extraction. After complete removal of the infected CIED and before implantation of a new device, the patient should be evaluated to determine whether the device is still needed. A new CIED should be placed in a remote anatomical location, usually the shoulder contralateral to the site of the infected device. Although the most appropriate timing for placement of a new device remains undefined, it should not be done until blood-culture results are negative in those with previously positive culture results and until infection at the pocket site has been controlled.

In addition to removal of the device, antimicrobial therapy is needed. Owing to the predominance of staphylococcal species as pathogens and the frequency of oxacillin resistance among these isolates, intravenous vancomycin is recommended as the initial empirical therapy pending culture results and when cultures are negative. If vancomycin has unacceptable side effects, consultation with an infectious diseases expert is recommended.

The duration of antibiotic coverage recommended by expert consensus guidelines²⁸ varies depending on the clinical setting (Fig. 1). For patients with negative blood cultures, the recommended duration of antibiotic therapy is 7 to 10 days for patients with generator or lead erosion (or both) and 10 to 14 days for infection of the generator pocket. For patients with bloodstream infection, signs of systemic infection, or prior antibiotic treatment, TEE should be performed. In these cases, at least 2 weeks of therapy is recommended. If a bloodstream infection is caused by *S. aureus*, antimicrobial therapy should be administered for at least 14 days after extraction of the device and from the date of negative blood cultures. In cases complicated by endocarditis (i.e., with valve vegetation), septic venous thrombosis, or osteomyelitis, more prolonged treatment (4 to 6 weeks) is recommended.

PREVENTION

The increasing rate of CIED infection has prompted a reevaluation of the usual insertion practices

and an examination of novel interventions (discussed below). A meta-analysis of seven randomized trials suggested that antibiotic prophylaxis given at the time of permanent pacemaker insertion significantly reduced the infection rate (pooled odds ratio, 0.26; 95% confidence interval, 0.10 to 0.66); however, the individual trials were underpowered, included a variety of penicillin and cephalosporin regimens, and yielded inconsistent results.² Still, the overall finding that systemic perioperative antibiotic prophylaxis was beneficial is consistent with the results of two case-control studies,^{9,16} a large, prospective registry,¹⁰ and a retrospective population-based study.¹⁷ Cefazolin prophylaxis was used predominantly in one of the case-control studies⁹; unidentified beta-lactam antibiotics were used in the other case-control study¹⁴ and for most of the patients included in the large, prospective registry.¹⁰

A large, randomized, double-blind, placebo-controlled trial of cefazolin for prophylaxis was stopped early (after enrollment of 649 patients, with a planned total enrollment of 1000 patients) because an interim data analysis showed substantial benefit.³ The incidence of device-related infection was significantly lower in the cefazolin group than in the placebo group (0.63% vs. 3.28%). On multivariable analysis, hematoma formation at the pocket site and the lack of perioperative cefazolin use were independent predictors of device-related infection.³

The presence of a CIED is not considered an indication for systemic antibiotic prophylaxis for invasive procedures.²⁸ Evidence to suggest that transient bacteremia associated with dental, gastrointestinal, or genitourinary procedures can result in CIED infections is lacking. Moreover, staphylococci, which are the most common microbiologic causes of CIED infections, are infrequently associated with the transient bacteremia related to these procedures.

Patients receiving more complex devices for an expanding list of indications are usually ill with multiple coexisting conditions that affect various organ systems.^{6,7,20,22,48} Therefore, extensive training in surgical techniques, including pocket formation and wound management to diminish the risk of complications, is an important component of electrophysiology fellowship programs. In addition, the implementation of a comprehensive infection prevention and control program would be expected to reduce the rate of CIED infection.⁴⁹

AREAS OF UNCERTAINTY

As noted above, data from randomized trials are lacking to provide guidance regarding major components of the management of CIED infection, including the duration of antibiotic therapy and the timing of reimplantation after a device has been removed. Studies are needed to identify the clinical predictors of device-related infection among patients with positive blood cultures but with no other clinical or echocardiographic findings suggestive of infection or endocarditis. Several investigations have included calculations of device-related infection in which the number of patients who have positive cultures is compared with the number of patients presumed to have device-related infection on the basis of clinical or echocardiographic findings.²⁹⁻³⁴ Without the consideration of other factors, these studies may have underestimated or overestimated the true rate of infection associated with a device. The specific microorganism recovered from blood cultures and the number and duration of positive blood cultures, together with clinical and echocardiographic findings, are better indicators of device-related infection than simply a positive result on blood culture.²⁹⁻³⁴ The most effective management in the case of a patient who has a positive blood culture in the absence of local or echocardiographic findings suggestive of a device-related infection or infective endocarditis is unclear. Documentation of a positive result on blood culture should not automatically lead to removal of the device. One option when there is no other evidence of a device-related infection is to retain the device and administer a course of antimicrobial therapy. After completion of therapy, it is essential to obtain follow-up blood cultures if systemic signs of infection develop; if *S. aureus* bacteremia recurs, the device should be removed.

GUIDELINES

In 2010, the American Heart Association (AHA) published guidelines that addressed the diagnosis, treatment, and prevention of CIED infections²⁸; these guidelines are endorsed by the Heart Rhythm Society (HRS) and the Infectious Diseases Society of America. In addition, guidelines updated in 2009 by the HRS,⁴¹ and endorsed by the AHA, provided recommendations for lead extraction; these guidelines are pertinent because infection is one of the

most common reasons for lead extraction. In contrast to earlier HRS guidelines,⁵⁰ the current HRS⁴¹ and AHA²⁸ guidelines consider complete device and lead removal to be mandatory in all cases of CIED infection. The recommendations described below are concordant with these guidelines.

CONCLUSIONS
AND RECOMMENDATIONS

The patient described in the vignette has evidence of an infected generator pocket site — the most common presentation of CIED infection. For all patients with pocket-site infection, blood cultures should be obtained, regardless of whether the patient has a fever or other systemic evidence of an infection. Adults with positive cultures or other signs of systemic infection should undergo TEE to detect any evidence of a valve infection. The presence of such an infection would influence the duration of antibiotic therapy and could prompt a cardiovascular surgical intervention if there were complications, such as perivalvular abscess formation or severe valvular insufficiency. Complete removal of the device, including all leads and the generator, is required for cure of CIED infection. Although data from randomized trials to define the appropriate timing for placement of a new device are lacking, we would implant a new device at least 72 hours after the infected device has been removed and would place the new device in the contralateral side of the chest. In patients with no evidence of infective endocarditis, antibiotic therapy should be administered for up to 14 days, starting with intravenous vancomycin and then adjusting the choice of therapy on the basis of tissue-culture and drug-susceptibility results. Patients with CIED infection should be cared for in medical centers with multidisciplinary expertise in the management of such infections, including electrophysiologists with experience in lead extraction.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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