Cardiovascular implantable device infections

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Conflict Of Interests

- Lecture fees from MSD, Pfizer, Novartis, Astellas, Angelini, Zambon, Gilead, Johnson & Johnson; and consulting fees for Advisory Boards from MSD, Pfizer, 3M, The Medicines Company, Achaogen, Astellas.

Background

- **Cardiac implantable electronic devices (CIEDs) have extended survival and improved quality of life of many patients with cardiac diseases.**

- **However, despite the great advancement in technology, complications continue to occur, and infection is one of the most feared because it can lead to serious consequences that could be catastrophic.**

- **Management of CIED infection involves a long hospital stay, prolonged antibiotic courses, in addition to the need for device and lead removal**

- **As more people are living longer with more significant cardiac disease, permanent pacemakers (PPMs), implantable cardioverter-defibrillators (ICDs), and cardiac resynchronization therapy (CRT) devices are being inserted more frequently.**

- **Beginning early in the 21st century, there has also been an expansion in the indications for cardiac implantable electronic devices (CIEDs, a term which includes PPMs, ICDs, and CRT devices, as well as other devices such as insertable cardiac monitors [also sometimes referred to as implantable cardiac monitors or implantable loop recorders] and left ventricular assist devices), and device therapy has become more commonplace.**

- **Recent estimates suggest that 1.2–1.4 million CIEDs are implanted annually worldwide**

(MedMarket Diligence LLC Report C500)

Epidemiology

In a large cohort of patients from 44 centers who underwent the CIED implantation, the incidence rate and risk factors of CIED infection was assessed prospectively.

Of 6,319 procedures, 4,465 were first implants and the other 1,854 were a replacement or revision;

- **42 patients (0.68%) developed CIED infection by 12 months after the procedure,**
- **and the incidence of infection in replacement or revision cases was nearly twice the rate found in first implants.**

Klug D et al. Circulation 2007; 116:1349–1355.

PATHOGENESIS

- **A CIED can become infected at the time of implantation or pocket revision.**
- **The infection can then track along the endovascular portion of the leads resulting in endovascular infection and possibly endocarditis.**
- **A CIED can also become infected as a result of the hematogenous seeding of the leads or pocket during an episode of bacteremia.**

Table 3 Risk factors for cardiovascular implantable electronic device infection[154–166]

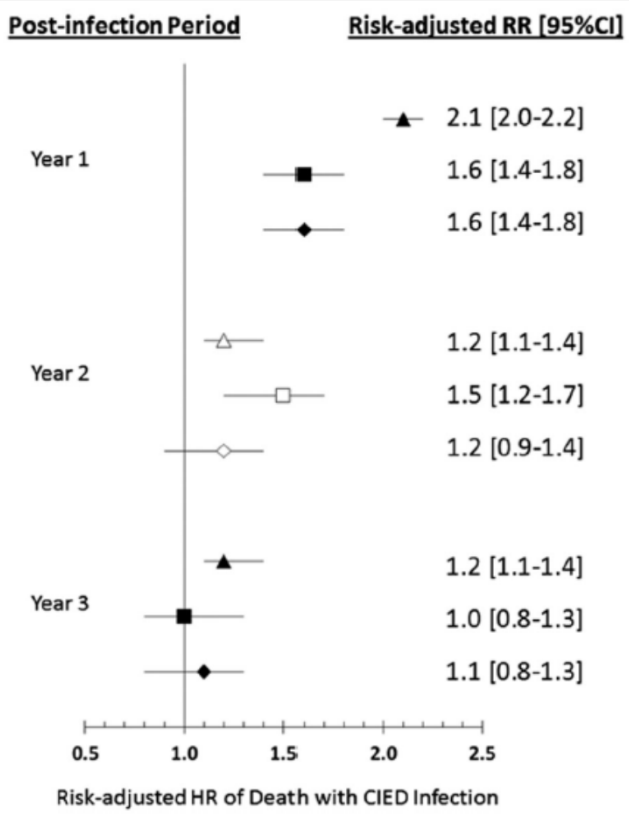
Patient-related factors	Procedure-related factors	Microbe-related factors
Age	Pocket reintervention (generator change, upgrade, lead or pocket revision)	Highly virulent microbes (eg, staphylococci)
Chronic kidney disease	Pocket hematoma	
Hemodialysis	Longer procedure duration	
Diabetes mellitus	Inexperienced operator	
Heart failure	ICD (compared with PM)	
Chronic obstructive pulmonary disease	Lack of use of prophylactic antibiotics	
Preprocedure fever		
Malignancy		
Skin disorder		
Immunosuppressive drug		
Prior CIED infection		
Anticoagulation		

CIED = cardiovascular implantable electronic device; ICD = implantable cardioverter defibrillator; PM = pacemaker.

Uslan DZ et al. Am Heart J 2008;155:896–903.
Lin G et al. J Interv Card Electrophysiol 2008;22:65–70.
Epstein AE et al. Heart Rhythm 2009;6:1136–1143.
Uslan DZ et al. Pacing Clin Electrophysiology 2012;35:81–87.
Polyzos KA et al. Europace 2015;17:767–777.
Sohail MR et al. Am J Cardiol 2013;112:1403–1409.
Chu XM et al. Biomed Res Int 2014;2014:725163.
Asif A et al. Semin Dial 2013; 26:111–113.
Tompkins C et al. J Cardiovasc Electrophysiol 2011;22:1099–1104
Guha A et al. Heart Rhythm 2015;12:2395–2401.
Tayebjee MH et al. J Med Microbiol 2013;62:1215–1219.
Uslan DZ et al. Pacing Clin Electrophysiology 2010;33:407–413.
Mulpuru SK et al. Circulation 2013;128:1031–1038.

Increased Long-Term Mortality in Patients with Cardiovascular Implantable Electronic Device Infections

Retrospective study design to analyze 3-year mortality in 200,219 Medicare fee-forservice patients admitted for CIED generator implantation, replacement, or revision between January 1, 2007 and December 31, 2007.



CIED recipients who develop device infection have increased, device-dependent, longterm mortality even after successful treatment of infection.

Rizwan Soahil M et al. *PACE 2015; 38:231–239*

Trends of Cardiovascular Implantable Electronic Device Infection in 3 Decades

A Population-Based Study

TABLE 2 Microbiologic Distribution of CIED Infections

Organism	Infections
Staphylococcus aureus	27 (43.5)
Coagulase-negative *staphylococcus*	16 (25.8)
Enterococcus faecalis	8 (12.9)
Cutibacterium/Propionibacterium acnes	4 (6.5)
Others*	4 (6.5)

Values are n (%), *Includes *Escherichia coli*, *Stenotrophomonas maltophilia*, *Viridans* group of streptococci, and *Cutibacterium/Propionibacterium avidum*.

Dai M et al. J Am Coll Cardiol EP 2019; 5: 1071–80

Microbiology of Cardiac Implantable Electronic Device Infections

Study population: 816 consecutive patients with confirmed CIED infections who underwent transvenous lead extraction at the Cleveland Clinic between 2000 and 2011. Blood cultures were obtained in addition of pocket swabs, pocket capsule, and leads.

FIGURE 1 Microbiology and Pathogens in 816 Consecutive Patients Who Underwent Lead Extraction or Removal for Device Infection at the Cleveland Clinic Between 2000 and 2011

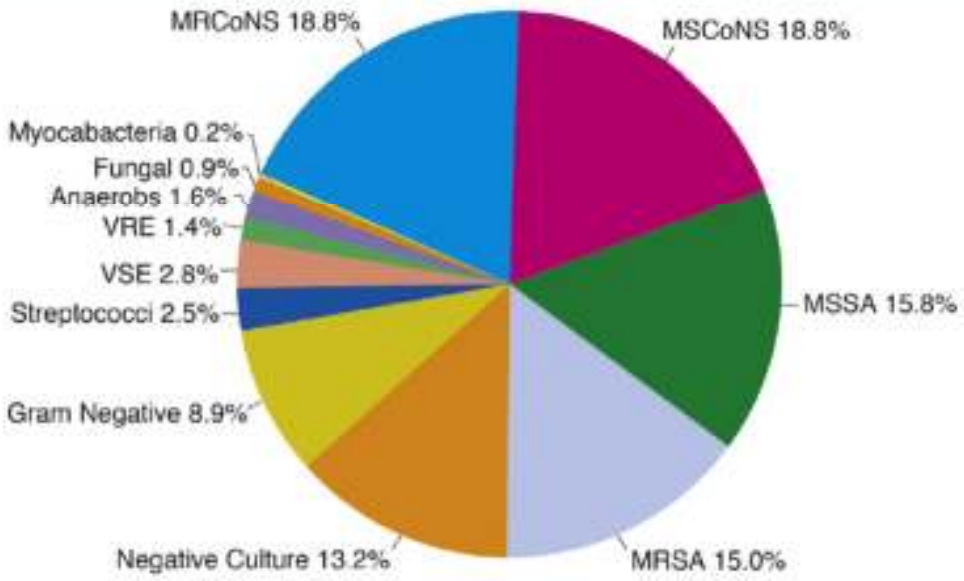


TABLE 2 Microbiology of Early Versus Late Cardiac Implantable Electronic Device Pocket or Endovascular Infections

	Early Infection (%)	Late Infection (%)	p Value
Pocket infections, n	217	213	
Bacterial type			<0.001
Staphylococcus aureus	30.2	16.3	
Coagulase-negative *Staphylococcus*	40.0	53.6	
Enterococcus	0.5	0.0	
Negative cultures	16.7	23.9	
Others	12.6	6.2	
Staphylococcal resistance			0.04
Methicillin resistant	29.8	34.4	
Methicillin sensitive	40.5	35.4	
Endovascular infections, n	115	213	
Bacterial type			0.6
Staphylococcus aureus	51.7	44.5	
Coagulase-negative *Staphylococcus*	27.6	26.1	
Enterococcus	5.7	8.1	
Negative cultures	3.4	7.1	
Others	11.5	14.2	
Staphylococcal resistance			0.6
Methicillin resistant	42.5	39.8	
Methicillin sensitive	36.8	30.8	

Hussein AA et al. Am Coll Cardiol EP 2016;2:498–505

2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction

Heart Rhythm 2017;14:e503–e551

I	B-NR	Preprocedural transesophageal echocardiography (TEE) is recommended for patients with suspected systemic CIED infection to evaluate the absence or size, character, and potential embolic risk of identified vegetations.

- **TEE is a useful imaging modality for establishing the diagnosis of CIED-related endocarditis and/or lead infection.**
- **The sensitivity of TEE for endocarditis and perivalvular extension of infection is superior to that of transthoracic echocardiography (TTE).**
- **The sensitivity of TTE for detecting endocarditis was only 32%, and the specificity was 100% when compared with TEE.**
- **TEE benefits include the confirmation of native or prosthetic valve endocarditis and identifying the presence and the size of vegetation(s) on the valve or lead(s), valvular malfunction, and perivalvular abscess.**

Greenspon AJ et al. JACC Cardiovasc Imaging 2014; 7: 541–549.

2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction

Heart Rhythm 2017;14:e503–e551

I	C-EO	Evaluation by physicians with specific expertise in CIED infection and lead extraction is recommended for patients with documented CIED infection.

- **When the diagnosis of CIED infection is documented, consulting physicians who have the expertise in CIED infection (including infectious disease specialists, cardiologists, and surgeons who specialize in managing device-related infection and/or performing lead extraction) is beneficial.**

- **Delayed, inappropriate, or incomplete therapy can result in significant morbidity and mortality for patients with CIED infection.**

2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction

Heart Rhythm 2017;14:e503–e551

IIb	C-LD	Additional imaging may be considered to facilitate the diagnosis of CIED pocket or lead infection when it cannot be confirmed by other methods.

- **PET/CT scanning might provide helpful evidence when diagnosis of CIED pocket or lead infection is doubtful.**
- **One study showed that PET/CT had a high sensitivity of 87% and a specificity of 100% for device pocket infection but a low sensitivity of 31% and a specificity of 62% for endocarditis.**
- **In another single-center, prospective, controlled study of 86 patients, patients with suspected generator pocket infection requiring CIED extraction had significantly higher 18F-FDG activity (4.80 [3.18–7.05]) compared with those who did not have the infection (1.40 [0.88–1.73]) and compared with controls (1.10 [0.98–1.40]).**
- **The diagnostic performance of 99mTc-hexamethypropylene amine oxime–labeled autologous white blood cell (99mTc-HMPAO-WBC) scintigraphy had a sensitivity of 94% for both detection and localization of CIED-associated infection.**

Cautela J et al. Europace 2013;15:252–257 – Ahmed FZ et al. Eur Heart J Cardiovasc Imaging 2015;16:521–530 – Erba PA et al. JACC Cardiovasc Imaging 2013;6:1075–1086.

2017 HRS expert consensus statement on cardiovascular implantable electronic device lead management and extraction

Heart Rhythm 2017;14:e503–e551

COR	LOE	Recommendations
I	C-LD	If antibiotics are going to be prescribed, drawing at least two sets of blood cultures before starting antibiotic therapy is recommended for all patients with suspected CIED infection to improve the precision and minimize the duration of antibiotic therapy.

- **Microbial growth can be suppressed by antibiotics and can mislead or mask CIED-related bloodstream infection.**
- **Early identification of the pathogen will guide appropriate selection and duration of antimicrobial therapy.**
- **Blood culture should include two sets of aerobic and anaerobic bacterial cultures.**
- **Multiple positive blood cultures might be needed to distinguish bloodstream infection vs contamination in cases of infection due to skin flora, in particular, coagulase-negative staphylococci**

Tarakji KG et al. Arrhythm Electrophysiol Rev 2016;5:65–67

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Heart Rhythm 2017;14:e503–e551

I	C-LD	Gram stain and culture of generator pocket tissue and the explanted lead(s) are recommended at the time of CIED removal to improve the precision and minimize the duration of antibiotic therapy.

- **Collecting device pocket tissue for Gram stain and culture at the time of device removal is useful for identifying the causative organism.**
- **The sensitivity of tissue culture (69%) is higher than that of the swab culture (31%) of the pocket.**
- **The entire explanted leads or lead tips should also be sent for culture, although lead contamination can occur when leads are extracted through the generator pocket.**
- **Pathogen guided therapy enhances antimicrobial drug selection by targeting the causal microbe, guiding appropriate treatment duration to minimize recurrent infection, and identifying potential drug resistance.**

Dy Chua J et al. Pacing Clin Electrophysiol 2005; 28: 1276–1281.

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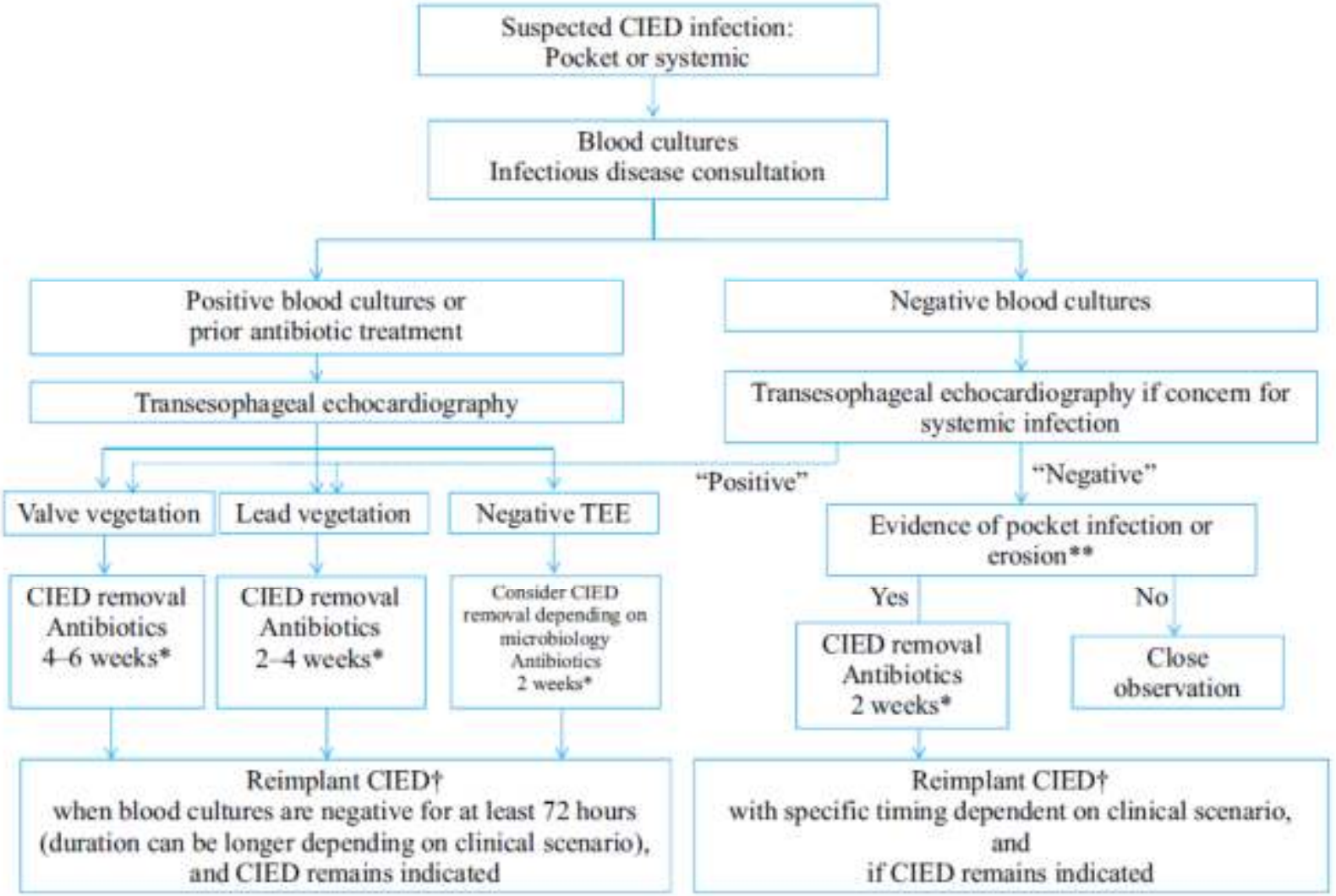
Heart Rhythm 2017;14:e503–e551

Management of Suspected CIED Infection



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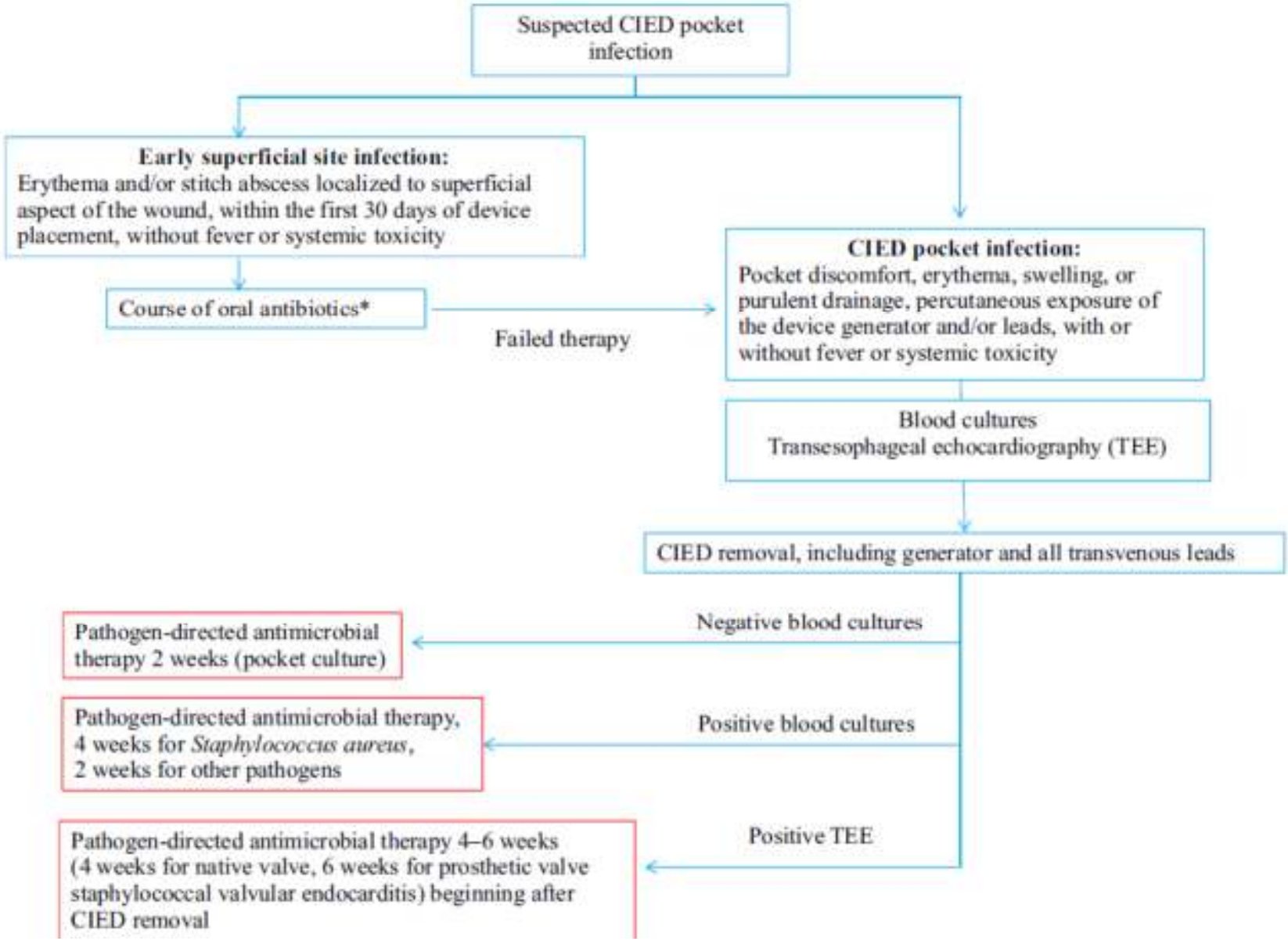

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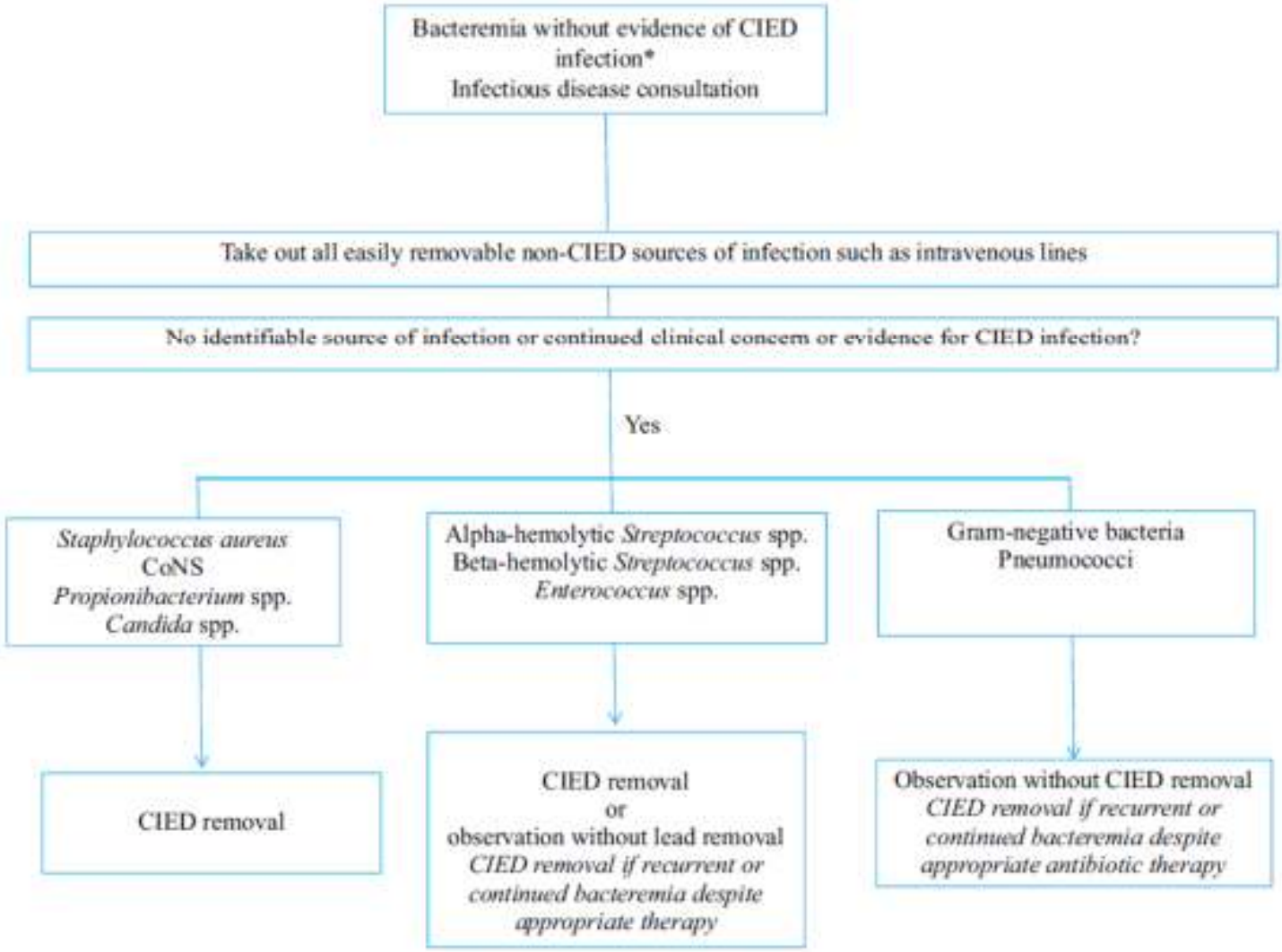


Figure 4 Management of bacteremia without evidence of CIED infection. *Important to distinguish between blood stream infection and contamination in bacteremia involving skin flora.

Prevention of Arrhythmia Device Infection Trial

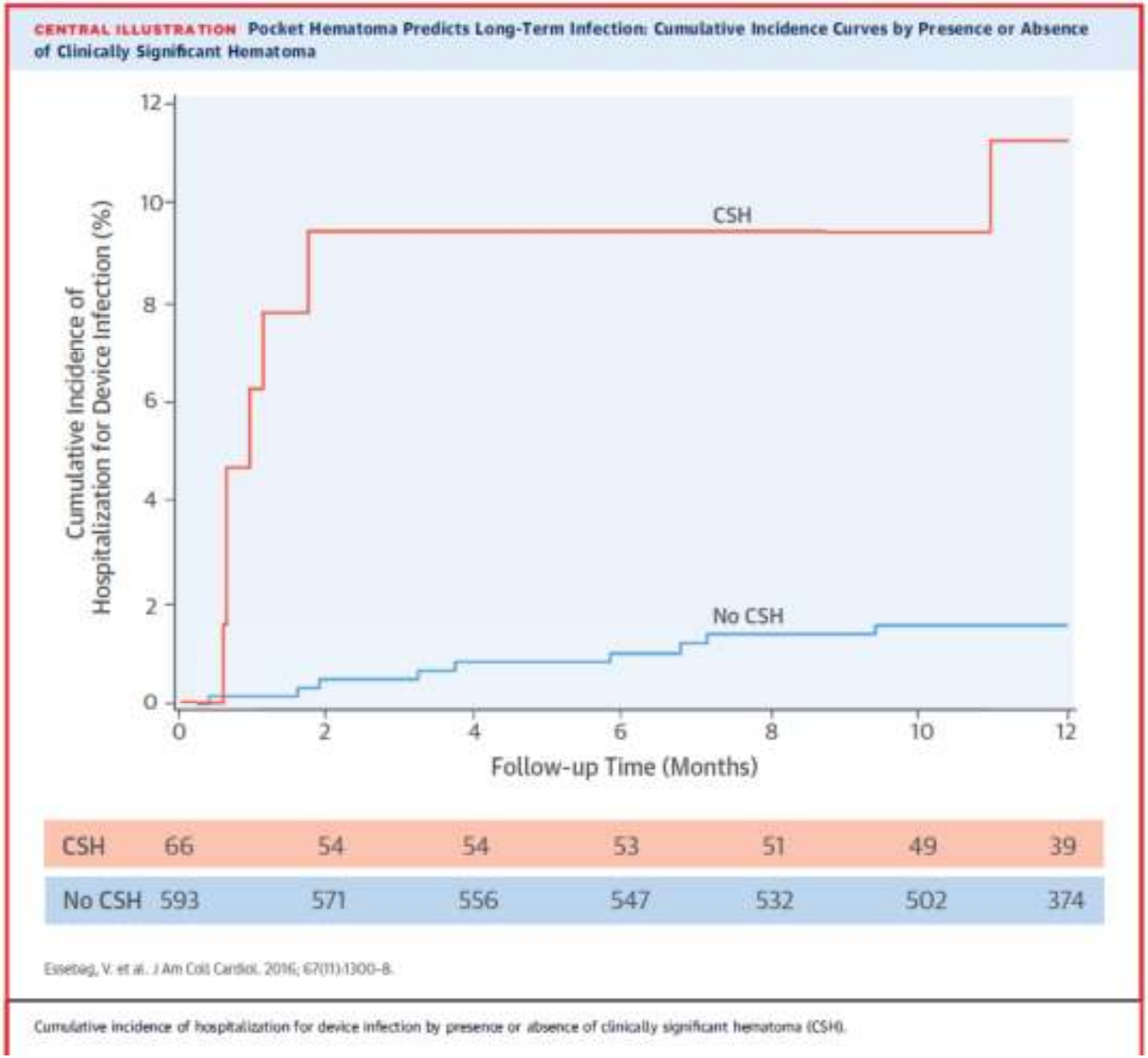
The PADIT Trial

Krahn AD et al. J Am Coll Cardiol 2018;72:3098–109

cluster randomized crossover trial with 4 randomly assigned 6-month periods: pre cefazolin, pre cefazolin+vancomycin, bacitracin pocket wash, 2-day post-procedural oral cephalexin.

- The cluster crossover design efficiently tested clinical effectiveness of incremental antibiotics to reduce device infection.
- Device infection rates were low.
- The observed difference in infection rates was not statistically significant.

Clinically Significant Pocket Hematoma Increases Long-Term Risk of Device Infection
BRUISE CONTROL INFECTION Study



Hessebag V et al. J Am Coll Cardiol 2016; 67:1300–8

Antibacterial Envelope to Prevent Cardiac Implantable Device Infection

randomized, controlled clinical trial to assess the safety and efficacy of an absorbable, antibiotic-eluting envelope in reducing the incidence of infection associated with CIED implantations

A total of 6983 patients underwent randomization: 3495 to the envelope group and 3488 to the control group.

The primary end point (infection resulting in system extraction or revision, long-term antibiotic therapy with infection recurrence, or death) occurred in 25 patients in the envelope group and 42 patients in the control group (12-month Kaplan–Meier estimated event rate, 0.7% and 1.2%, respectively; hazard ratio, 0.60; 95% confidence interval [CI], 0.36 to 0.98; P = 0.04).

Tarakiji KG et al. NEJM 2019; 380: 1895-905

WRAP-IT WRAP-UP

WRAP-IT: Largest global cardiac device trial to date

6,983 patients | 181 centers | 25 countries

Patients undergoing cardiac implantable electronic device (CIED) procedures randomized 1:1 to:

Standard-of-care infection prevention	Standard of care + TYRX™ antibiotic-eluting envelope to surround CIED

After 12 months…

- 40% relative reduction in major CIED infections in envelope group
- Comparable rates of complications in envelope and no-envelope groups

BOTTOM LINE | With >1 million people worldwide receiving CIEDs annually, the antibiotic envelope is an effective strategy for reducing risk of devastating CIED infections.

Cleveland Clinic

SOURCE Tarakji KG, et al. *N Engl J Med.* 2019 Mar 17 [Epub ahead of print].

Take home messages

- **Management of CIED infection involves a long hospital stay, prolonged antibiotic courses, in addition to the need for device and lead removal.**

- **TEE is a useful imaging modality for establishing the diagnosis of CIED-related endocarditis and/or lead infection.**

- **Consulting physicians who have the expertise in CIED infection is beneficial.**

- **Early identification of the pathogen will guide appropriate selection and duration of antimicrobial therapy.**