Review Article ISSN 2639-944X

Journal of Medical - Clinical Research & Reviews

Cardiac Implantable Electronic Device-Related Infection

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Received: 22 December 2018; Accepted: 08 January 2019

Citation: John D Rozich, Ryan C Garbalosa. Cardiac Implantable Electronic Device-Related Infection. J Med - Clin Res & Rev. 2019; 3(1): 1-5.

Keywords
CIED infections, Cardiologists, TEE, Patient.

Introduction

Cardiac implantable electronic devices (CIEDs) have become an essential therapeutic tool for patients with life threatening cardiac illnesses. A common request made of cardiologists is to perform a transesophageal echocardiogram (TEE) in patients with CIEDs who have documented bacteremia. These patients may be complex and may not have obvious pocket-related CIED infections. The basic premise for a TEE in this setting is often to determine optimal management of the patient as clinical strategies can vary considerably. The focus of the present limited review is to examine what can be expected and offered from performing TEEs in the setting of bacteremia in a patient with a CIED.

Perspective

Over the last three decades, devices implanted under expanding guideline-validated indications have increased dramatically. Between 1997 and 2004 pacemakers (PPM) and implantable cardioverter-defibrillators (ICD) increased by 19% and 60% respectively [1]. The vast majority of these patients, nearly 70%, were 65 years of age or greater and had at least one or more existing co-existent illness [1]. Mayo Clinic data further supports this finding with Olmsted County, Minnesota patients undergoing PPM implant between 1975 and 2004 having progressively increasing numbers of chronic illnesses [2,3]. Paralleling this increase in implant rates has been a foreseeable rise in CIED-related infections resulting in increased morbidity, death and cost to an already overburdened health system [4]. Precise cost-estimates associated with CIED infections vary significantly and thus are imprecise, but 2008 data suggests that each CIED infection is associated with expenditures of approximately $146,000 [5]. Rates of PPM infections have also varied significantly, with literature showing values between 0.13% and 19.9% [6,7]. While the majority of CIED infections are pocket infections, 10% of PPM-related infections have already progressed to endocarditis when diagnosed [8].

CIED infection also carries a high risk of death, with an estimated 30-day mortality between 5% and 6% [9]. The 1-year mortality rate is also increased for CIED extractions, reaching between 8-17%, despite effective removal and appropriate antibiotic therapy [10-12]. In a CMS (Medicare) data repository, older patients had double the risk of death at 1 year compared to patients without infection [13]. Thus, while prevention is optimal, often the imaging specialist is asked to assist those caring for a patient experiencing bacteremia in the setting of previous CIED implant.

Real World Expectations, Requests and Requirements

A frequent concern of cardiologists asked to perform a TEE on patients with CIEDs and bacteriemia is the utility found in its performance. The basic issue is whether TEE imaging adds determinative information to the therapeutic strategy. More specifically, when does this form of imaging provide information that will alter or refine therapy? These aforementioned considerations underscore concerns that even though TEE is a relatively innocuous imaging procedure in terms of risk, it nonetheless has some finite risk and incremental cost. Thus, the imaging specialist has an obligation in all clinical settings to address when and under what circumstances a TEE is additive to therapy. In the setting of bacteremia with CIEDs, seemingly superficial incisional infection or inflammation may actually represent more serious systemic involvement.

Understanding What a TEE Offers

Abundant literature documents that TEE offers a higher sensitivity for detecting vegetations and myocardial structural injury compared with transthoracic echocardiography (TTE) [14]. However, the relevant issues are when and how such information contributes to a reasonable strategy to address therapy for potentially infected CIEDs [15]. A fundamental decision point begins with whether

there is a "pocket infection" after insertion of a CIED [15]. Implanting a CIED traditionally has meant that there is a skin incision opening to an area or pocket that is prepared during surgery for the generator subcutaneously. Thoracic subcutaneous pocket infections are most readily identified by their discoloration, warmth and tenderness. Frank erosion or draining may also ensue after implant. This is often obvious and it is tempting to argue that TEE offers little incremental value since present HMS guidelines support prompt removal of the device. But this approach may limit the gathering of essential data to optimize care of CIED infections and does not address the possibility of involvement of other cardiac structures. Even in the earliest stages of infection TEE, may provide valuable additional information and several observations support its early use [15].

Pocket Infection: With and Without Blood Culture Positivity

A CIED pocket infection is generally a clinical diagnosis, however, TEE may be indispensable to assess for subtle or concealed evidence that the infection has become endovascular. In most cases, patients diagnosed with a CIED pocket infection will almost exclusively have their device removed unless the risk of removal is prohibitive. However, if in this setting, a TEE demonstrates classic vegetations or evidence of endocarditis, both the duration of antimicrobial therapy and prognosis for uneventful recovery changes. Figure 1 demonstrates a large vegetation adherent to the anterior leaflet of the tricuspid valve measuring 2.4 x 1.2cm. These large vegetations raise concern over embolic risk in addition to possible damage to other myocardial structures. Thus, discovery of infection involving endovascular or myocardial elements fundamentally alters duration of therapy and requisite monitoring for subsequent adverse vascular outcomes.

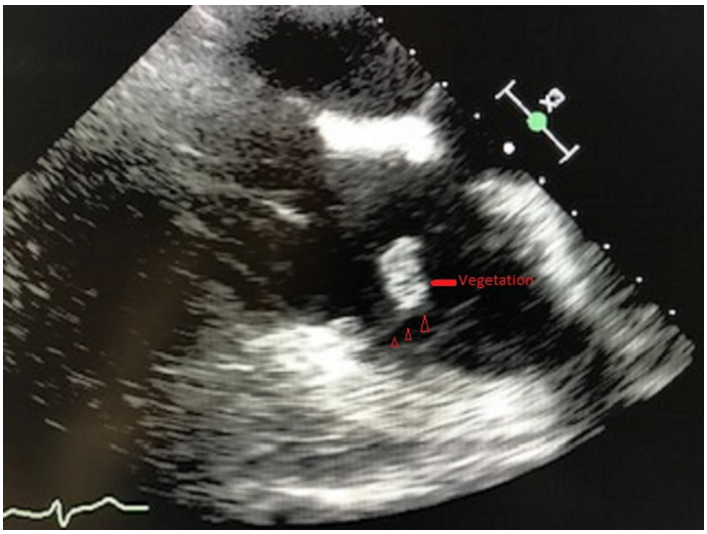

Figure 1: View obtained from TEE demonstrating large vegetation (arrow) on tricuspid anterior leaflet (arrow heads). The patient had a CIED placed 2 years before these images were obtained and developed recurrent bacteremia that did not clear despite completion of two (2) separate guideline-directed antibiotic courses. Eventual removal of the device was necessary.

Terms: TE-transesophageal echocardiography, CIED-cardiac implanted electronic devices).

Should every pocket infection after CIED implant be screened with TEE? Pocket bacteria from CIED infection can spread down implanted leads into the soft tissue or into the intravascular and endovascular structures. Classically progression of the infection is linked to systemic symptoms such as fever, chills, and frank rigors [16]. A positive blood culture demands a TEE per the HRS guidelines, however in the absence of bacteremia this imaging is recommended only when there is concern over systemic infection [15]. But these symptoms are variable in their occurrence and have been correlated to a confluence of host and bacterial factors. Older patients, those with certain co-morbidities or on certain drug regimens in addition to the actual pathogen may lack prototypical evidence of infection. It is thus understandable that inconstant symptoms create clinical challenges as to the early or prompt recognition of infection. Staphylococcos aureus accounts for 60-80% of CIED infections and is a particularly virulent organism representing 25% of the systemic occurrences [17-19]. But other species of staphylococcus, such as coagulase-negative species are generally less virulent and may foreseeably have fewer systemic symptoms [18,19]. In one study, intravascular lead involvement was present in 88% of patients presenting with pocket infection despite lack of symptoms of systemic infection [20]. Given that symptoms can be unreliable predictors as to the extent of infection, a reasonable approach may therefore be to perform a TEE on all patients to ensure that endovascular involvement is absent and that the duration of antimicorbial therapy can be appropriately administered. This may be especially true when finding that the offending organism is staphylococcos aureus even without obvious systemic symptoms being present.

The HRS algorithm offers a bifurcated therapeutic approach when assessing early "superficial site infection" for suspected CIED pocket infection [15]. The recommendations suggest that for minor erythema or a stitch abscess localized to the superficial aspect of the wound within 30 days of implant, a course of oral antibiotics may be appropriate as initial therapy [15]. If completely resolving within an appropriate duration then no further action is required. While nearly every physician performing implants has encountered this scenario there are several caveats that all would agree upon, namely the requisite need to place these recommendations in the proper context. First is the setting or simply the particular host that is receiving the implant. There is a striking potential difference between an immuno-compromised elderly patient who is undergoing hemodialysis, suffers from systemic lupus erythematosis and diabetes and that of an otherwise healthy older individual. Even evidence of what appears to be a minor superficial infection in the former may result in more aggressive assessment especially if the organism cultured from minimal drainage is staphylococcos aureus.

This leads to an important second consideration involving the type of organism identified. While initial adherence of the organism to endothelial tissue is thought to be a critical event in establishing an infection, it is also believed that injured endothelial tissue is most vulnerable [21]. This explains why, at least in part, that streptococci become relevant agents immediately post implant.

Adherence of bacteria to the endothelial tissues mechanistically involves interaction between host adhesive extracellular matrix molecules and bacterial surface molecular structures [21]. These host-bacterial surface structures interact and form what is believed the first step in the infection process [21,22]. But importantly, while many bacterial species require or are facilitated by the injured endothelial surface exposing the extracellular matrix molecules, other species such as S. aureus have no such requirement [22,23]. And while portions of this proposed vulnerability to infection remain theoretical, based on existing data, clinical outcomes with S. Aureus demonstrate its enhanced virulence and destructive potential. S. aureus was the predominant species recovered and accounted for both early, defined as within 1 year of implant or pocket intervention, and late endovascular infections [18]. Its presence may suggest deeper or a systemic infection involving the endovasculature [18,22]. This is especially true when this organism is found in an immuno-compromised patient where its presence must register heightened concern. Noted in Table 1 is a modified published summary of early versus late CIED pocket and endovascular infections demonstrating the different species of organisms encountered in each [18]. Finally, and most importantly is the "totality" of the clinical presentation using all information to render a comprehensive assessment of CIED infection and its attendant risk.

Pocket Infections		Early Infection (%)	Late Infection (%)	P Value
Bacterial Type				<0.001
Staphylococcus aureus		30.2	16.3	
Coagulase-negative Staphylococcus		40.0	53.6	
Staphylococcal resistance				0.04
Methicillin resistant		29.8	34.4	
Methicillin sensitive		40.5	35.4	
Endovascular Infections	Bacterial Type			0.6
	Staphylococcus aureus	51.7	44.5	
	Coagulase-negative Staphylococcus	27.6	26.1	
	Staphylococcal resistance			0.6
	Methicillin resistant	42.5	39.8	
	Methicillin sensitive	36.8	30.8	

Table 1: Modified Summary of Microbiology of Early versus Late CIED Pocket or Endovascular Infections Modified from (Hussein et al.) [18]. Terms: CIED-cardiac implantable electronic devices.

The amount of drainage, the timing of its appearance, the changing tissue color, warmth, or appearance all must be taken into consideration as elements that call for greater or more aggressive assessment. Additionally, firm decision-endpoints should be predetermined to avoid unnecessary delays and thus progression resulting in more serious complications. A single round of antibiotics, or even a short extension in their use, should be foreseeably linked to a firm endpoint of device removal if drainage or suspected infection persists. Every variable of both wound appearance and host characteristics must be continually assessed with appropriate adjustments in therapeutic strategies provided. Even then, mistakes may be made as hidden pockets of infection provide challenges to even the most experienced implanter. Thus, it is our practice, that even in limited pocket infections, TEE may offer incremental beneficial data in excluding unrecognized systemic or vascular involvement.

Pocket Appears Normal but Bacteremia is Detected

Another common clinical scenario is the occurrence of confirmed bacteremia in the setting of prior CIED implant with no evidence of pocket infection. TEE is often requested and here the echocardiographer must understand both the benefits and limitations of imaging under these circumstances. Imaging is very useful in confirming the diagnosis of CIED-related endovascular infection or lead infection. Compared with TTE, which demonstrated a sensitivity of only 32% and specificity of 100%, TEE resulted in a specificity of 99% with a single false positive result [24]. It has also been suggested that serial imaging studies maybe useful, temporally separating examination of lead and endovascular structures. The change in sensitivity and specificity is not well quantified, but confusing bacteremia results or persistent leukocytosis in the setting of negative blood cultures and an "unremarkable" first TEE may warrant a "second look". Here the focus is on re-examining endovascular appearance and leads hunting for subtle time-related change. It is also prudent to again note that staphylococcos aureus must be more aggressively addressed since the rate of lead-associated endovascular involvement with this species is increased [18]. Most agree that TEE in the setting of bacteremia with a CIED provides important data assisting in management [15].

The foremost benefit of TEE, in the setting of bacteremia is confirmation of systemic bacterial infection [4,15,19]. Here the demonstration of vegetation(s) on a valve or lead(s) and/or previously unrecognized valvular dysfunction is critical. Additionally, injury such as a perivalvular abscess or cardiac fistula, is a less common but potentially life-threatening finding. Meticulous review of images may also support early changes in "anatomic proportionality", meaning that subtle changes in the smooth contours of annular structural surfaces and/or tissue thickness may hint at edema signifying early infective changes in myocardial histopathology. Analysis of TEE images within the context of the specific organism (if known) further enhances utility for decisions regarding CIED re-implantation, duration of antibiotic therapy and even surgical myocardial repair. Decisions predicated on TEE images may also address specific location(s) and the morphology of vegetations allowing alternative strategies for repair or replacement to be carefully assessed by an integrated medical team.

Influence of Implant Duration on Lead Infection Susceptibility

There is some debate over the theoretical protection against seeding or infection of CIED leads that are in place for longer durations. This narrative suggests that prolonged duration of lead implant

enables endothelial covering of lead surface structures and thus prevents bacterial adherence. Thus the clinical outcome is thought to be a lower risk of lead and thus CIED-related infection(s). However, the genesis of this hypothesis originated in cardiac valve replacement literature and even here it remains unproven. Cardiac valve data revealed that 71% of prosthetic valve endocarditis occurred within the first year after implant [25]. It is believed this is secondary to absent endothelialization of the mechanical valves, which usually requires about 1 year to occur [25]. During the year prior to conclusive endothelial layering of the prosthetic valve, its prosthetic material is exposed to pathogens in the bloodstream, and appears prone to seeding or colonization by various bacterial species. Again these are observational data and unproven even for cardiac valves and may not be directly applicable to the multiple types of leads and generators. Thus endothelial surface coating impacting inherent infective susceptibility for CIED-leads and generators is unknown, and there is no data to suggest that the duration of lead implantation should affect the determination for further imaging with TEE.

Conclusion

TEE offers an important tool to assist in CIED generator and lead infection. When pocket infections are present TEE may demonstrate involvement of the endovascular structures thus mandating longer durations of antimicrobial therapy or even the need for endovascular structural repair or replacement. When pocket infections are not visibly present, immuno-compromised patients must be assessed on a case-by-case basis. TEE may be critical when the initial clinical impression is that only a small superficial suture abscess or insignificant incisional infection is present, only to discover with TEE that involvement of the endovascular structures suggest a far more serious process is present. In the absence of a pocket infection, TEE can provide incremental value in the setting of bacteremia with a CIED, assessing for lead or valve involvement and potentially altering treatment.

CIED implants have increased dramatically reflecting their value as a lifesaving tool for patients with severe cardiac illnesses [15]. This appropriate growth has also foreseeably paralleled an increase in CIED-related infections resulting in higher morbidity, death, and burdensome costs [4,15,18]. Clinicians asked to contribute to the care of these patients must be aware of the complexities involved in treating CIED-related infections. This includes but is not limited to patient-specific risk factors for endocarditis, relevant literature, and the outcomes associated with different treatments. Furthermore, physicians are asked to perform TEEs to supplement guideline-directed recommendations for CIED-related infections, and knowledge of TEE strengths and limitations linked to prudent clinical judgment is essential.

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