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SUPPLEMENT PAPER

Epidemiology of cardiac implantable electronic device infections: incidence and risk factors

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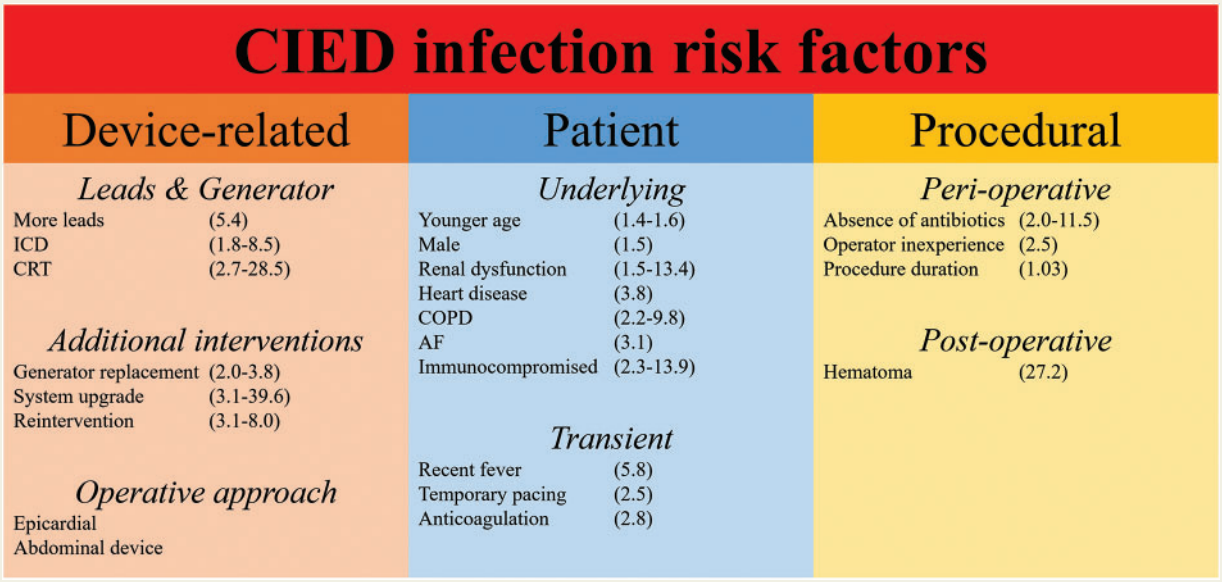
Abstract

Cardiac implantable electronic device (CIED) infection is a potentially devastating complication of CIED procedures, causing significant morbidity and mortality for patients. Of all CIED complications, infection has the greatest impact on mortality, requirement for re-intervention and additional hospital treatment days. Based on large prospective studies, the infection rate at 12-months after a CIED procedure is approximately 1%. The risk of CIED infection may be related to several factors which should be considered with regards to risk minimization. These include technical factors, patient factors, and periprocedural factors. Technical factors include the number of leads and size of generator, the absolute number of interventions which have been performed for the patient, and the operative approach. Patient factors include various non-modifiable underlying comorbidities and potentially modifiable transient conditions. Procedural factors include both peri-operative and post-operative factors. The contemporary PADIT score, derived from a large cohort of CIED patients, is useful for the prediction of infection risk. In this review, we summarize the key information regarding epidemiology, incidence and risk factors for CIED infection.

Graphical Abstract



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Keywords Cardiac implantable electronic device • Pacemaker • Defibrillator • Infection

Introduction

Cardiac implantable electronic device (CIED) infection is a potentially devastating cause of morbidity and mortality for patients,[1–3] resulting in significant strain on healthcare resources.[4,5] Despite heightened awareness and measures to reduce risk of infection,[6–8] the incidence remains high and the overall burden is increasing as the population receiving CIED continues to grow.[9–11] Various technical, patient, and procedural factors can influence the infection risk associated with CIED procedures.[12–14] In this review, we summarize the key information regarding epidemiology, incidence, and risk factors for CIED infection.

Definition

Various classifications exist for CIED infection. These can include conditions not necessarily requiring intervention, such as post-operative wound inflammation or simple stitch abscess. In contrast, conditions, which require intervention, include isolated pocket/generator infection, device pocket pre-erosion, pocket erosion with generator or lead externalization, isolated bacteraemia, pocket infection with systemic involvement, and device-related infective endocarditis (*Figure 1*).[15–18]

Incidence

Multiple factors influence the overall incidence of CIED infection including the type of CIED procedure and follow-up duration (*Table 1*). Of note, these studies have focused on CIED infections which require intervention. Based on two recent prospective multicentre trials, the overall 12-month CIED infection rate is ~1%.[7,8]

De novo CIED implants are associated with lower infection risk when compared with generator procedures or lead revisions and upgrades.[5,14,24,28,29] Pacemaker (PM) procedures are associated with lower infection risk compared to implantable cardioverter-defibrillator (ICD) and cardiac resynchronization therapy (CRT) procedures.[5,14,24,29,30] In a retrospective study of 78 267 French patients having a CIED procedure, the 36-month infection rate for *de novo* device implant was 0.5–1.6% [0.5% for PM, 1.6% for ICD, 1.0% for CRT-pacemaker (CRT-P) and 1.6% for CRT-defibrillator (CRT-D)] compared to an infection rate of 1.3–3.9% for generator change procedures (1.4% for PM, 2.9% for ICD, 1.3% for CRT-P, and 3.9% for

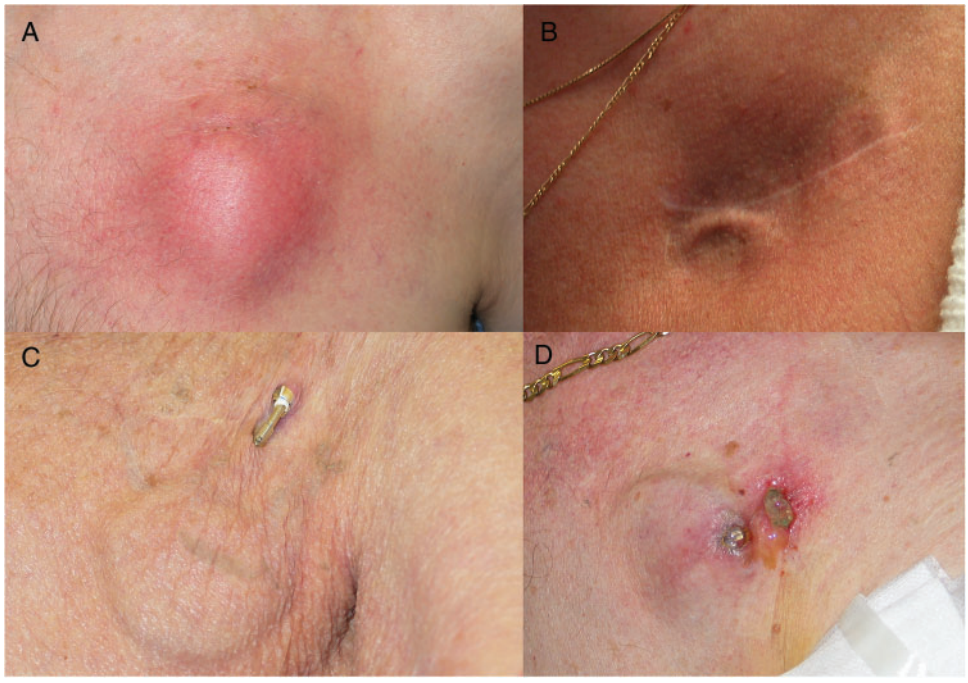

Figure 1 Examples of CIED infections. (*A*) Localized pocket infection; (*B*) device tethering consistent with pre-erosion; (*C*) device erosion without site inflammation; and (*D*) localized inflammation and erosion. CIED, cardiac implantable electronic device.

Table 1 CIED infection rates

Study	Year	N[a]	Design	Follow-up	Infection rate (%, *de novo* implant unless specified)
Klug *et al.*[19]	2007	6319	Prospective, cohort	12 months	1.2% overall
Poole *et al.*[20]	2010	1744	Prospective, cohort	6 months	1.4% generator; 1.1% lead procedure
Romeyer-Bouchard *et al.*[21]	2010	303	Retrospective	31 months (mean)	1.6% CRT-P; 8.6% CRT-D; 1.5% CRT upgrade
Johansen *et al.*[22]	2011	56 657	Retrospective	12 months	0.5% PM; 1.2% PM generator within 12 months
				Device years[b]	0.1% PM; 0.3% PM generator after the first 12 months
Krahn *et al.*[22]	2011	1081	Prospective, cohort	45 days	2.1% ICD generator
Lyman *et al.*[23]	2011	38 992	Retrospective	90 days	1.2% ICD
Palmisano *et al.*[24]	2013	2671	Retrospective	Device years	0.9% overall; 0.2%, 0%, 2.1% for PM, ICD CRT respectively; 1.2% generator; 3.0% lead procedure
Schuchert *et al.*[25]	2013	402	Retrospective	12 months	1.2% CRT-P; 1.3% CRT-D
Peterson *et al.*[26]	2013	32 034	Retrospective	90 days	0.7% ICD
Prutkin *et al.*[27]	2014	200 909	Retrospective	6 months	1.7% ICD procedures; 2.0% CRT-D; 1.9% ICD generator
Kirkfeldt *et al.*[28]	2014	5918	Retrospective	6 months	0.8% overall; 0.6% implant; 1.5% generator; 1.9% lead procedure
Clémenty *et al.*[5]	2018	78 267	Retrospective	36 months	0.5%, 1.6%, 1.0%, 1.6% for PM, ICD, CRT-P, CRT-D respectively; 1.4%, 2.9%, 1.3%, 3.9% for PM, ICD, CRT-P, CRT-D generators respectively
Yang *et al.*[29]	2019	16 908	Retrospective	Device years	2.0% overall; 1.4%, 1.5%, 1.5% for PM, ICD, CRT, respectively; 3.5%, 6.5%, 6.8% for PM, ICD, CRT generators, respectively
Tarakji *et al.*[8]	2019	6983	Prospective, randomized	12 months	1.0% overall CRT-D or repeat procedure
Birnie *et al.*[14]	2019	19 599	Prospective, randomized	12 months	0.9% overall; 0.3%, 0.9%, 0.6%, 1.1% for PM, ICD, CRT-P, CRT-D, respectively; 0.5%, 1.0%, 2.5% for PM, ICD, CRT generators, respectively; 2.1% lead procedures

CIED, cardiac implantable electronic device; CRT, cardiac resynchronization therapy; CRT-D, CRT-defibrillation; CRT-P, CRT-pacemaker; ICD, implantable cardioverter-defibrillator; PM, permanent pacemaker.
[a]Number of procedures (where available), otherwise number of patients.
[b]After 12 months.

CRT-D).[5] Similarly, in a prospective, multicentre study of 19 599 patients having a CIED procedure, the 12-month infection rate for *de novo* device implant was 0.3–1.1% (0.3% for PM, 0.9% for ICD, 0.6% for CRT-P, and 1.1% for CRT-D) compared to an infection rate of 0.5–2.5% for generator procedures (0.5% for PM, 1.0% for ICD, and 2.5% for CRT) and an infection rate of 2.1% for lead revision or upgrade procedures.[14]

The infection rate is greatest in the initial period after CIED procedure.[21,27,31] In a retrospective study of 200 909 ICD procedures, the infection rates at 30, 60, and 90 days were 0.8%, 1.2%, and 1.4%, respectively.[27] In another retrospective study of 56 657 PM procedures (46 299 patients) with 236 888 device-years of follow-up, the annual infection rate within the initial 12 months was 0.5% for *de novo* implants and 1.2% for generator change procedures. However, there remained a residual risk of late infections, with an annual infection rate of 0.1% for *de novo* implants and 0.3% for generator change procedures after the initial 12-month period.[31] This late risk likely stems from the high prevalence of subclinical pocket colonization which may lie dormant for many years. In patients undergoing elective CIED generator replacement, ~25% have evidence of asymptomatic bacterial colonization of the pocket.[32,33]

Temporal trends up until 2012 indicated that the rate of CIED infections was increasing, with concurrent growth in device procedures performed.[11,34,35] Using national registry data from the USA, CIED infection rates increased from 1.5% in 1993 to 2.4% in 2008 and 3.4% in 2012.[11,35] This is explained, in part, by an increase in complex and thus higher risk device procedures, whereby ICDs accounted for 12% of total implants in 1993, but 35% of total implants in 2008.[35] Global trends have also shown an increase in the number of CRT devices implanted as a proportion of total CIED procedures.[9,10] While differences in CIED case mix may be partially responsible for this increase, infection rates for individual subsets of CIED procedures also appeared to be rising.[11] This finding is likely due to an increased incidence of comorbidities including renal failure, diabetes mellitus, heart failure, and chronic respiratory disease in patients receiving CIED.[35] The subsequent prospective PADIT and

Table 2 Cost of CIED infections

Country	Estimated cost
France[5]	€22 000—mean over 24 months
UK[4,41]	£15 000—median per episode
Germany[42]	€32 000—mean over 36 months
USA[43]	$51 000 (USD)—mean admission
Canada[44]	$30 000 (CAD)—mean per episode
Australia[45]	$17 000 (AUD)—mean admission
Korea[29]	$17 000 (USD)—mean admission

CIED, cardiac implantable electronic device.

Table 3 Microbiology of CIED infections

Organism	Infections rate[a]
Staphylococci	
S. aureus	29–44%
Methicillin sensitive	12–25%
Methicillin resistant	4–22%
Coagulase negative	26–42%
Methicillin sensitive	~19%
Methicillin resistant	~19%
Streptococci	0.6–2.5%
Enterococci	4–13%
Anaerobes	1.6–6.5%
Gram negative	5–9%
Fungi	1–2%
Mycobacteria	0.2%
Polymicrobial	2–14%
Culture negative	7–21%

CIED, cardiac implantable electronic device.
[a]Infection rates summarized from Refs.[37,47–51]

WRAP-IT trials conducted after 2012 reported a lower rate of infection in the order of 0.5–1.5% between risk groups in the control arm.[7,8,14] Both studies involved a broad range of centre types and intentionally involved high-risk patients. While increasingly complex CIED procedures and patients should provide impetus for physicians to evaluate approaches for minimization of risk, a target infection rate of 1% is clearly achievable.

Healthcare consequences

Cardiac implantable electronic device infections are associated with significant consequences for the patient and the healthcare system. In-hospital mortality is estimated to be ~5–10%,[35–37] while 1-year all-cause mortality ranges between 16% and 36%,[36–39] although both appear to be reducing over time.[11,39,40] Hospitalization for CIED infection typically lasts 1–3 weeks,[11,29,35,36,40,41] with an associated reduction in quality of life.[39]

The resultant healthcare costs are therefore substantial (*Table 2*), although this varies according to geographic region, type of CIED, and associated management decision.[4,5,11,29,41,43–46] Costs related to medical care include hospitalization, procedural (both extraction and reimplantation of replacement device), physician service, outpatient care, and associated investigations and medications.[5,41,42,44] In addition, the provision of sick pay contributes to the societal burden of CIED infections.[42] Of all CIED complications, infection has the greatest impact on mortality, requirement for re-intervention, and additional hospital treatment days.[24]

Microbiology

Staphylococcal species, both *Staphylococcus aureus* and coagulase negative staphylococci, account for ~60–70% of CIED infections (*Table 3*).[47] Of note, a significant proportion of these organisms display methicillin resistance, varying by local risk of exposure to resistant organisms.[48,49] Other organisms identified include enterococci, streptococci, gram-negative bacteria, anaerobes, fungi, mycobacteria, and polymicrobial.[37,48–51] In addition, up to 21% of CIED infections may be culture negative.[48] Those with CIED infection due to *Staphylococcus aureus* have consequently longer treatment duration requirements compared to those with coagulase negative staphylococci or those which are culture negative,[47] along with having a higher 12-month mortality.[37] The impact of antimicrobial-resistant organisms on the treatment and outcomes of CIED infections requires further clarification.

Temporally, infections occurring within 12 months are more likely to be caused by *Staphylococcus aureus* which is methicillin sensitive, while infections after 12 months are more likely to be caused by coagulase negative staphylococci or be microbial negative, using traditional culture methods.[49] The implementation of sonification techniques may increase the microbiological diagnostic yield in these circumstances.[33,52]

Cardiac implantable electronic device infection risk factors

Cardiac implantable electronic device infection may be related to several factors, which should be considered with regards to risk minimization and appropriate pre-procedural planning. These include device-related factors, patient factors that may or may not be modifiable, and procedural factors.

Device-related factors

Leads and generator

Procedures involving ICD or CRT-D generators result in more infections than procedures involving PM or CRT-P generators, respectively [adjusted odds ratio (aOR) 1.8–8.5].[14,53] Furthermore, CRT devices confer a higher infection risk than non-CRT devices (both PM and ICD) (aOR 2.7–28.5).[14,21,24,54] The presence of additional leads (abandoned intravascular leads and not necessarily CRT) may also influence CIED infection risk. Procedures on patients with >2 CIED leads are independently associated with more infections compared to devices involving two implanted leads (aOR 5.4).[55] It is

Table 4 Risk prediction scores for CIED infection

	Infections/Patients		Factors	Points	Score	Infection risk (%)
PADIT[14]	177/19 603	Device related	Procedure type		0	0.36
			ICD	2	1	0.32
			CRT	4	2	0.39
			Revision/upgrade	4	3	0.65
			Number of previous procedures		4	0.81
			1	1	5	1.06
			≥2	3	6	1.64
		Patient	Age		≥7	2.91
			<60	2		
			60–69	1		
			Renal dysfunction (eGFR<30)	1		
			Immunocompromise	3		
Mittal *et al.*[12]	33/2891	Device related	Reintervention	11	0–7	1
			Upgrade	2	8–14	3.4
		Patient	Male gender	6	15–25	11.1
			Diabetes	3		
			Heart failure	1		
			Hypertension	1		
			Renal dysfunction (eGFR<60)	1		
Shariff *et al.*[13]	19/1111	Device related	Generator change/upgrade	1	<3	1
			Epicardial lead	1	≥3	2.4
			>2 leads	1		
		Patient	Diabetes	1		
			Heart failure	1		
			Oral anticoagulation	1		
			Corticosteroid	1		
			Renal dysfunction (Cr>1.5mg/dL)	1		
			Prior CIED infection	1		
			Temporary pacing	1		

CIED, cardiac implantable electronic device; Cr, serum creatinine; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter-defibrillator.

postulated that a greater burden of hardware—either more intravascular leads or larger generator battery—poses additional technical challenges and provides increased foreign body surface area for microbial adherence,[56] thereby potentiating infection risk.

Additional interventions

Any intervention to an existing CIED system carries additional infection risk when compared with a *de novo* implant. This includes generator changes (aOR 2.0–3.8),[19,57–59] device system upgrades (aOR 3.1–39.6),[14,24,60] and other lead or pocket re-interventions (aOR 3.1–8.0).[14,21,57,60] Alternatively, it can be considered that each additional CIED procedure after the initial implant carries incremental risk for device infection where 2, 3, 4, and 5 (or more) procedures are associated with an infection risk of 1.5–2.7, 3.4–3.8, 5.5, and 8.7, respectively (all aOR when compared with an initial implant).[14,31] Factors that contribute to this include the presence of an existing relatively avascular pocket with impaired immunity and increasing procedural complexity associated with reinterventions.[20,57]

Operative approach

Cardiac implantable electronic device infections are also more common using epicardial and extrathoracic approaches compared to a transvenous approach with infraclavicular device placement. This includes the placement of epicardial leads, placement of epicardial or extrapericardial defibrillator patch electrodes, or use of a tunnelling approach (aOR 5.0–9.7).[61–65] While transvenous devices are now considered standard of care, alternate surgically implanted devices remain important in certain subsets of patients including young children or those with limiting transvenous anatomy.[66,67]

Patient factors

Underlying factors

Contemporary studies indicate that younger age is associated with a greater risk of infection.[14,31,54] In a retrospective Danish cohort of 46 299 patients and 56 637 device procedures, younger age was independently associated with CIED infection.[31] Similarly, a prospective multi-centre study from Canada and Europe involving 19 603 patients found incremental CIED infection risk with

younger age (aOR 1.4–1.6).[7,14] While the reasons for this are unclear, it is postulated that younger individuals have firmer subcutaneous tissue resulting in more traumatic pocket creation.

While some studies have suggested that male gender (aOR 1.5) is associated with an increased risk of CIED infection,[12,31] this was not demonstrated in two recent multi-centre prospective studies.[8,14] The potential reasons for this are unclear, although the presence of firmer prepectoral subcutaneous tissue in males may provide a similar pathophysiological explanation.

Certain comorbid conditions independently predict CIED infections. Foremost, patients who have had a previous CIED infection are unsurprisingly at greater risk of subsequent infections.[68] Other comorbidities include chronic kidney disease with (aOR 13.4) or without (aOR 1.5–4.6) dialysis,[12,14,21,57] heart disease (including hypertrophic cardiomyopathy, valvular disease, or congestive cardiac failure, aOR 3.1),[12,69] chronic obstructive pulmonary disease (aOR 2.2–9.8),[59,65] atrial fibrillation (aOR 3.1),[60] and immune suppression (aOR 2.3–13.9).[14,55] In general, the presence of these conditions indicates an underlying vulnerability resulting from medical comorbidities.

Transient factors

Transient and potentially modifiable patient factors such as fever in the 24-h prior to device procedure (aOR 5.8),[19] presence of temporary pacing wire (aOR 2.5),[19] and anti-coagulation therapy (aOR 2.8)[57] are also independent predictors of CIED infections. Judicious management of anti-coagulation is critical for minimization of infectious complications. In a multicentre randomized controlled trial, BRUISE CONTROL assigned 681 patients on warfarin at high risk for thromboembolic complications to warfarin continuation vs. warfarin cessation with bridging heparin.[70] The trial was stopped early due to significantly more pocket haematoma in the warfarin cessation group,[71] which in turn resulted in significantly more CIED infections at 12-month follow-up.[72] Additionally, careful consideration of procedural timing and necessity of temporary pacing may further minimize CIED infection rates.

Procedural factors

Peri-operative factors

Administration of peri-procedural antibiotics is now considered standard care in CIED procedures. The absence of antibiotics is consistently shown to be an independent predictor of CIED infections (aOR 2.0–11.5),[19,31,55,58] while randomized trials demonstrate that intravenous antibiotics reduce infection risk.[73,74] In a single-centre, randomized, double-blind, placebo-controlled trial comparing peri-procedural administration of 1 g IV cefazolin vs. placebo, the trial was stopped early (649 out of an intended 1000 patients enrolled) due to significantly lower CIED infection rates in those receiving antibiotic therapy.[74] The infection rate in the antibiotic arm was 2 of 314 (0.6%) compared to 11 of 335 (3.3%) in the placebo arm.

Additional antibiotic therapies may offer risk modification in certain cases. The results of the PADIT and WRAP-IT trials are discussed in detail later in this Supplement, but consideration of incremental systemic antibiotics or use of the TYRX antibiotic eluting absorbable envelope may be considered in certain circumstances.[7,8,14,75,76]

In addition, operator proficiency affects the CIED infection risk. Both lower volume implanter status (aOR 2.5),[77] and increasing procedure time have been found to be independent predictors of CIED infections.[21] Thus, a robust training curriculum for device implanters is critical for infection minimization.[78]

Post-operative factors

Post-operative complications are associated with increased risk of CIED infections. Wound complications, predominantly haematoma, independently predict CIED infections (aOR 27.2).[65,72,74] This is can be largely mitigated by careful perioperative anti-coagulation and anti-platelet management.[79] Lead dislodgement is also associated with infection,[21] although this is likely due to the repeat intervention rather than as a direct cause.

Cardiac implantable electronic device infection risk prediction

Several risk scores have been developed for the pre-operative assessment of CIED infection risk, combining both device related and patient factors (*Table 4*).[12–14] The PADIT score was developed from a contemporary prospective study involving 19 603 patients with infection outcomes defined at 12 months.[7,14] Risk score points are assigned for individual variables of age (<60 or 60–69), procedure type (ICD, CRT or revision/upgrade), renal insufficiency (eGFR <30 mL/min), immunocompromise, and number of previous procedures (1 or ≥2). Based on this cohort, a total score of 0–4, 5–6, and ≥7 confers a CIED infection risk of <1%, 1–2%, and 2.9%, respectively. A convenient web-based calculator is available for point of care use when considering extent of prevention measures (https://padit-calculator.ca), including the administration of additional antibiotics and/or use of an antibiotic envelope in high-risk patients. Two additional risk scores have been proposed by Mittal *et al.* and Shariff *et al.*,[12,13] although these were developed from smaller cohorts of retrospectively studied patients.

Conclusion

Cardiac implantable electronic device infections can have potentially devastating consequences, resulting in significant burdens to healthcare systems. Various device related, patient and procedural factors may potentiate risk of CIED infection. Strategies to minimize risk include identifying higher risk individuals using risk score systems, avoidance of haematoma including careful management of anticoagulants, and the use of additional antimicrobial measures in selected high-risk groups. With the advancement of risk recognition and mitigation strategies, an overall CIED infection rate of 1% is achievable.

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Data availability

Source data for this review article have been cited and are available from web-based medical libraries.

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