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The Characteristics and Outcome of Infective Endocarditis Involving Implantable Cardiac Devices

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Abstract Infection of implantable cardiac electronic devices in particular lead endocarditis (cardiac device infective endocarditis (CDIE)) is an emerging problem with significant morbidity, mortality and health care costs. The epidemiology is characterised with advanced age and health care association in cases presenting within 6 months of implantation. Risk factors include those of the patient, the procedure and the device. Staphylococcal species predominate as the causative organisms. Diagnosis is reliably made by blood cultures and transesophageal echocardiography. Complications include pulmonary and systemic emboli, persistent bacteremia and concomitant valvular involvement. Management includes complete device removal and prolonged antimicrobial therapy. With long-term follow-up to 1 year, the mortality of CDIE is as high as 23 %. It is associated with patient co-morbidities and concomitant valvular involvement and may be prevented by device removal during index admission.

Keywords Implantable electronic cardiac device · Infective endocarditis · Pacemaker infection · Lead endocarditis

Introduction

The twenty-first century has seen improved patient outcomes and increasing indications for implanted cardiac devices, such as permanent pacemakers (PM) and defibrillators (implantable cardioverter-defibrillators (ICDs)) [1–6]. This has resulted in a steady increase of implantation globally [7]. In the USA alone, over 4 million devices were implanted between 1993 and 2008 with an increase in all devices; ICDs in particular have increased by over 500 % [8••]. This coupled with an ageing population has resulted in an unprecedented increase in cardiac device uptake [7, 8••, 9].

Infection of cardiac devices is a major emerging problem. It may range from a superficial generator pocket space infection through to a blood stream infection and lead endocarditis (cardiac device infective endocarditis (CDIE)). The reported rates of infection are increasing worldwide and vary significantly from centre and country. Most cardiac device infections involve the subcutaneous generator pocket with about 10–20 % resulting in CDIE. The incidence of CDIE has been reported between 0.06 and 0.6 % per year [10] or 1.14 per 1000 device years [11]. Utilising ICD coding in US health care services, there has been a 200 % increase in cardiac device (CD) infection from 2004 (1.5 %) to 2008 (2.4 %) (see Fig. 1). With the establishment of cardiac device registries in several countries, it is expected that infection incidence rates will be monitored more closely [12, https://www.ncdr.com/webncdr/icd/, 13]. Infection has been associated with a 1 % increase in overall mortality per decade, hospitalisation stay of an average of 14 days and cost estimates of US$150,000 per episode of infection [8••].

Epidemiology

The pathogenesis of CDIE primarily involves skin contamination at the time of implantation or in late-onset cases from hematogenous seeding during bacteremia [14–16]. Specific risk factors for infection have been defined and include those of the patient, the procedure and the device. Patient factors

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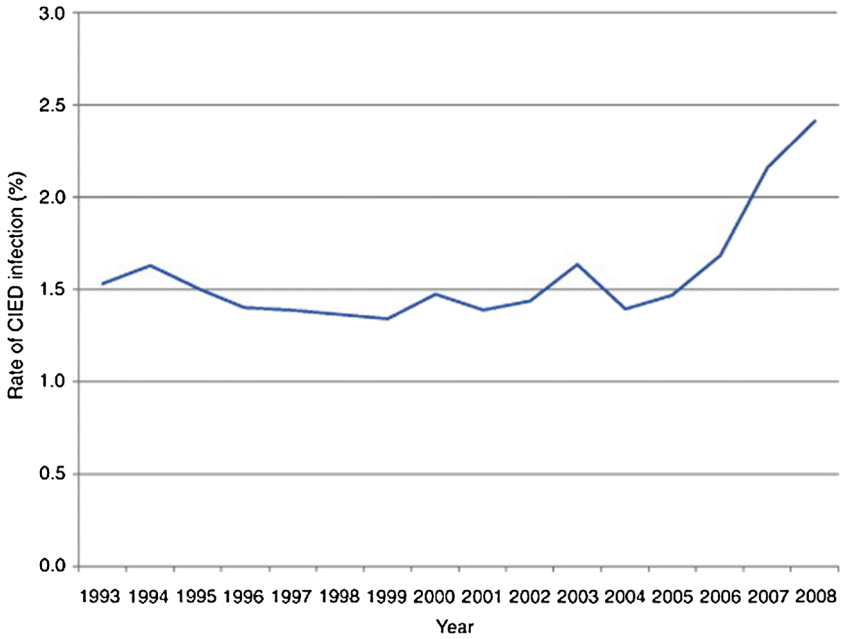

Fig. 1 Rise in CD infection rate from 1993 to 2008

include age (median 71 years), male gender (74 %), low BMI, diabetes mellitus, anticoagulation, immunosuppression, skin disorders, presence of another focus of infection including surgical site and catheter-related blood stream infection. Procedural factors include operators with low annual procedure volume, prolonged procedure time, presence of hematoma, the number of procedures such as generator replacement compared to the first implantation and compliance with antibiotic prophylaxis. In terms of device characteristics, larger ICDs carry a higher risk of infection compared to smaller pacemaker systems [11, 14, 15, 17, 18••, 19].

The timing of CD procedures is significantly associated with either localised or systemic infection. Early infection occurring less than 6 months post-implantation is associated with percutaneous contamination at time of implantation. Early infection is often associated with localised generator pocket infection. Delayed-onset infection occurring greater than 6 months post-procedure is usually associated with systemic infection and lead endocarditis due to hematogenous seeding of leads in particular with *Staphylococcus aureus* in 38 % of cases [14, 20].

Health care association (HCA) is increasingly being recognised in all forms of infective endocarditis (IE) including CDIE [21, 22]. For CDIE, HCA is identified in about half of all cases [18••]. In CDIE, HCA is associated with a recent CD procedure, the presence of an intravascular device or hemodialysis. HCA CDIE is often caused by *S. aureus* (49 %), including MRSA (26 %), and is associated with persistent bacteremia. HCA is also independently associated with a poorer outcome in terms of both in-hospital (22 %) and 1-year mortality [18••].

Diagnosis

Clinical Features

The clinical features of CDIE are well characterised. Fever over 38.5 °C occurs in over 80 % of cases [18••, 23]. Localised generator site inflammation occurs in only 10–20 % of cases including erythema, swelling, fluctuance, tenderness, exudate and occasionally erosion or extrusion of the device.

Embolic episodes are documented frequently, in particular pulmonary, in between 10 and 27 % of cases given right heart involvement. Systemic emboli are reported in up to 14 % of cases [14, 16, 23]. Since in most published studies, embolic complications are not screened for routinely, by ventilation perfusion scan or CT pulmonary angiography (CTPA), it is likely that they are underdiagnosed.

Precordial signs including heart murmurs may be present in cases of concomitant valvular involvement resulting in regurgitation or heart failure.

Investigations

Cultures

When blood cultures are performed, they provide a very high yield with positive growth identified in over 84 % of cases [14, 16, 23]. There is a significant yield from other sites such as lead cultures following device removal with significant growth obtained from between 50 and 90 % of cases, but

contamination rates can be high [15]. When specimens are obtained from the generator site pocket, cultures are positive in up to 38 to 70 % in some studies [15, 19].

Echocardiography

The presence of vegetations on cardiac device leads is noted in most cases. Transthoracic echocardiography has a very poor sensitivity, as low as 23 % in identifying lead vegetations. Factors such as lead artefact and poor visualisation greatly limit its utility. Transesophageal echocardiography has sensitivity greater than 95 % with vegetations seen on the lead in over 76 % of cases of CDIE [14, 18••, 23, 24]. Echocardiography also has an important role in identifying concomitant valvular involvement or complications such as myocardial abscess and valvular regurgitation. A recent study comparing the use of intra-cardiac with transesophageal echocardiography in confirmed cases of CDIE reported excellent sensitivity for the detection of lead vegetations in CDIE [25].

Other Imaging

Ultrasound of generator pocket to delineate or guide drainage of an infected collection may also be of value. A recent pilot study of 21 cases of CD infection utilising positron-emission tomography (PET) CT found good sensitivity and specificity for generator pocket site infection but poor diagnostic utility for lead endocarditis [26].

Microbiology

In all studies of CDIE, staphylococcal species predominate as the pathogenic organism making up over 70 % of cases [14, 18••, 23, 24]. These consist of mainly *S. aureus* (35 %) and coagulase-negative staphylococci (CNS) species in about 32 % of cases. A significant proportion may also be methicillin resistant. The microbiology correlates with health care association, particularly in early CDIE. There are also reports of less common but virulent strains of coagulase-negative staphylococci such as *Staphylococcus lugdunensis* causing CDIE [27, 28]. Importantly, many of these organisms are known to produce biofilm, thus evading immune defences and making antimicrobial treatment less effective.

The remaining culture-confirmed cases of CDIE are made up of *Enterococci, Viridans streptococci* and some gram-negative bacteria. As diagnostic systems and culture methods continue to improve, there are increasing reports of emerging infections caused by *Propionibacteria acnes*, *Candida* species and other rare microorganisms [29–32].

Complications

CDIE may be complicated by embolic episodes. These are documented frequently, in particular septic pulmonary emboli, between 10 and 27 % cases given the right heart chamber involvement, and systemic emboli occur in up to 14 % of cases. Since in most published studies, embolic complications are not screened for routinely, by ventilation perfusion scan or CTPA, it is likely that they are under reported.

Persistent bacteremia is an important complication in any type of infective endocarditis. It is defined as bacteremia for greater than 72 hours despite appropriate antimicrobial therapy [18••, 33]. It is reported in over 15 % cases and is significantly associated with an increased in-hospital mortality (odds ratio (OR) 5.0).

Concomitant valvular involvement has been reported in a significant number of cases of CDIE and should be actively investigated. The tricuspid valve is most frequently involved in up to 37 % of CDIE cases. The presence of concomitant valvular involvement is associated with a poorer outcome and an increased In-hospital mortality with OR 3.3 [18••].

Heart failure is reported in 15 % of CDIE cases. It is likely related to concomitant valvular involvement and is significantly associated with reduced in-hospital survival OR 3.1 [18••] .

Management

Surgery

There is general agreement that CDIE is optimally managed by complete removal or explantation of the electronic system. In most cases, this can be performed safely and effectively by percutaneous extraction using laser or other sheath traction devices. Complications of extraction are very uncommon but include pulmonary emboli and cardiac rupture. In cases of very large vegetations greater than 2 cm, open cardiotomy may be required; however, percutaneous methods may still be considered [34].

If replacement of the CD is essential, i.e., the patient is pacemaker dependent, this should be deferred until antimicrobial therapy is completed with temporary pacing if needed. This should be followed by placement at a new anatomical location including consideration for epicardial placement. When possible, we recommend a period of no antimicrobial therapy to assess the patient's clinical cure before any device replacement. In cases of very frail patients, device removal may not be performed but is associated with high rates of relapse [14, 19, 23]. Cardiac device removal is associated with a significant survival benefit at 1-year follow-up (hazard ratio (HR) 0.42) (see Fig. 2) [18••, 23].

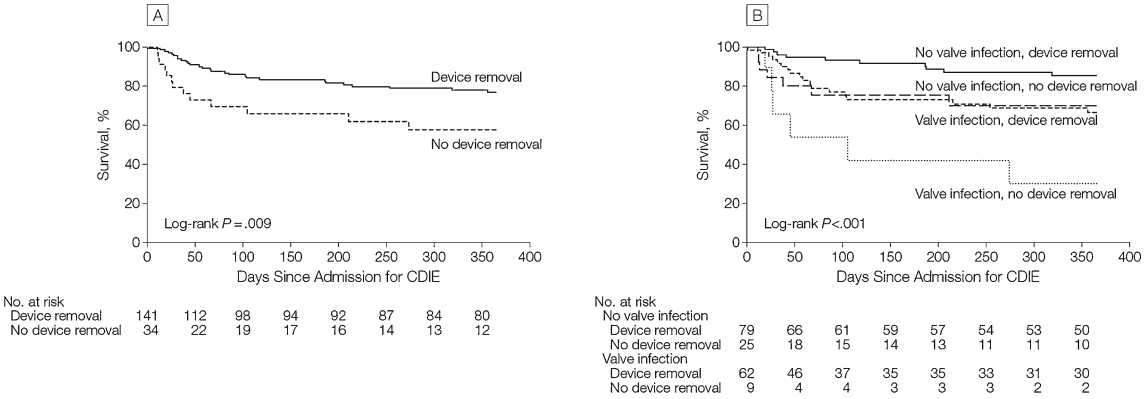

Fig. 2 One year survival with device removal alone and One year survival with device removal and co-existing valvular involvement

Antimicrobial Therapy

Following device removal, all cases should be treated with at least 14 days parenteral bactericidal antibiotics when the organism identification and susceptibilities are known. For most methicillin-susceptible strains, this includes flucloxacillin, nafcillin or a first-generation cephalosporin. For methicillin-resistant strains, glycopeptides including vancomycin or teicoplanin are recommended. Daptomycin, a synthetic cyclic lipopeptide approved for use in right-sided endocarditis, has also been used successfully in the treatment of CDIE [35] .

In cases of CDIE with concomitant valvular involvement, antimicrobial therapy should be modified as for native or prosthetic valve endocarditis with consideration for surgical management if indicated.

If the cardiac device is not removed, a prolonged course of combination therapy for 4 to 6 weeks including a biofilm active antibiotic such as rifampicin or ciprofloxacin is recommended and long-term suppression may be required.

Outcomes

Early in-hospital mortality ranges from as low as 7 % [17] or as high as 15 %. It is significantly associated with the presence of persistent bacteremia, heart failure, *S. aureus*, concomitant valvular involvement (OR 3.3) and health care association [18••, 23, 24, 36•] .

In long-term follow-up to 1 year, the mortality of CDIE is as high as 23 %. It is associated with patient co-morbidities and concomitant valvular involvement and may be prevented by device removal during index admission (HR 0.42) (see Fig. 2) [18••, 23, 36•].

Conclusion

The twenty-first century has seen an unprecedented increase in the uptake of implantable electronic cardiac devices globally. Unfortunately, this has been followed by an increasing rate of infection. The most serious form is lead endocarditis (CDIE). The epidemiology is characterised by advanced age and health care association and caused predominantly by staphylococcal species. The diagnosis is usually confirmed by blood culture and transesophageal echocardiography. The management is complex and involves appropriate antimicrobial therapy and complete removal of the system. Complications are common and include concomitant valvular involvement. Early in-hospital and 1-year mortality is high and improved by early device removal.

Compliance with Ethics Guidelines

Conflict of Interest Eugene Athan has no conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by the author.

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