Implantable Cardioverter Defibrillator Infections and Community-Associated MRSA: Diseases of Progress

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Infections attributable to cardiovascular implantable electronic devices are one of the most challenging complications in modern medicine. For the past few decades the rate of implantation of cardiovascular devices has been rising. Continuous increasing indications for implanting various types of cardiovascular devices, such as permanent pacemakers, cardiac resynchronization therapy devices, and implantable cardioverter defibrillators [1], have been observed.

CIEDs are used not only for controlling and treating life-threatening arrhythmias, but also for advanced heart failure, thus resulting in a dramatic reduction of patient morbidity and improved survival [1]. However, infection has been a major and sometimes devastating complication of CIED implantation. Moreover, the rate of infections of CIEDs is increasing, out of proportion to implantation rates [2,3].

Cabell et al. [2] reported an alarming 125% increase in the rate of CIED infections during the decade 1990–1999, while the implantation rate of CIEDs during the same study period increased by only 42%.

Similar results were reported by Voigt and co-authors [3], who observed a 2.8-fold increase for permanent pacemakers and sixfold increase for ICD in hospital admissions secondary to CIED infections, while the rate of CIED implantation during the same study period was 50%. The increasing age of CIED recipients with several comorbidities and frequent contact with the health care system may partially explain this infection rate upsurge.

Contamination of CIED pocket tissue, electrode leads or generator at the time of implantation by skin colonizers, mainly staphylococci, is the most common mechanism of CIED infection. Hematogenous seeding of the CIED electrodes in the context of bacteremia of staphylococci or, rarely, Gram-negative organisms seems to be a possible but much less frequent mechanism of infection [4].

Staphylococcus aureus and coagulase-negative staphylococci are the most commonly implicated organisms in these infections, accounting for 60% to 80% of cases [5]. Staphylococci are frequent colonizers of human skin. Their ability to adhere to foreign bodies and produce biofilm on device surfaces facilitates creation of these infections. Once the pocket or generator is colonized, the bacteria are moved along the electrode leads and manifest as tunnel infection, bacteremia or vegetations on the electrode leads or cardiac valves [5].

In this issue of *IMAJ*, Gottesman et al. [6] present a patient with community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA) bacteremia related to an ICD. Using traditional definitions, the authors defined, with justification, the isolated strains of MRSA as CA-MRSA on the basis of its phenotypic, genotypic and epidemiologic characteristics. In addition to the epidemiologic and clinical criteria for defining "community-associated MRSA," the isolate was susceptible to clindamycin and other non-beta-lactam anti-staphylococcal antibiotics and carried a SCC*mec* type IVa. However, it lacked the Panton-Valentine leukocidin (*PVL*) gene.

In addition, the patient had had multiple comorbidities and obviously had been in contact with the health care system. A cardioverter defibrillator had been implanted 8 months prior to his admission. Eventually, the patient's wife was found to be a carrier of MRSA in her nares. The isolates of both the wife and the patient were phenotypically and genotypically identical; therefore, the patient was probably a carrier of the CA-MRSA in his nares prior to the development of the bacteremic episode [6]. Hence, whether MRSA isolates in this case should be defined as community-acquired or hospital- or health care-associated MRSA with community onset is complicated. One possibility is that the bacteremia developed in the community as a result of some kind of skin and/or nasal mucosa break. On the other hand, it is possible that the pathogen, as a skin colonizer, had contaminated the electrode leads or the generator at the time of the ICD implantation. However, the absence of vegetation on the electrode leads in trans-esophageal echocardiography, and the negative culture results of the removed electrode tips argue against this possibility but do not exclude it.

CIED = cardiovascular implantable electronic device

ICD = implantable cardioverter defibrillator

CA-MRSA = community-associated methicillin-resistant *Staphylococcus aureus*

Microbiology and epidemiology of CA-MRSA have evolved over the past few years. Traditional definitions have been redefined. According to the U.S. Centers for Disease Control criteria of CA-MRSA, MRSA must be identified in the outpatient setting or less than 48 hours after hospital admission in an individual with no medical history of MRSA infection or colonization, admission to a health care facility, dialysis, surgery or insertion of indwelling devices during the previous year [7]. The CDC states that the inclusion of an assessment of previous health care contact means that the MRSA was linked to hospitalization but presented in the community or at a hospital re-admission, are to be classified as hospital-acquired MRSA (HA-MRSA).

Indeed, several studies have found that most MRSA bacteremias diagnosed on hospital admission and therefore designated by some as community-acquired infections are caused by nosocomial strains of MRSA (HA-MRSA) from a previous health care contact [8,9].

Some authors recommend the use of SCCmec typing alone in order to understand the MRSA genetic background. However, this is ineffective in determining the MRSA lineage because isolates with a non-typable SCCmec cassette may be missed, and SCCmec IV-carrying HA-MRSA lineages may be misclassified as CA-MRSA [10,11].

Therefore, it is proposed that combining a genotyping method (such as multilocus sequence typing or pulsed-field gel electrophoresis) with SCCmec analysis of the MRSA is currently the best way to define CA-MRSA strains. These isolates may be *PVL* positive or *PVL* negative, may have diverse clinical presentations, may have different antimicrobial susceptibility patterns, and may be classified as either health care or community associated using epidemiologic criteria. CA-MRSA can be acquired in either the community (common) or health care (uncommon but increasing) settings.

Despite substantial progress in the understanding of the pathogenesis, risk factors and management of CIED infections in the past decade, several important questions remain to be answered. Some of these questions are related to the article by Gottesman et al. in this *IMAJ* issue [6].

- What is the appropriate approach to patients with *S. aureus* bacteremia but with no clinical or echocardiographic evidence of ICD infection? This is one of the most challenging issues we frequently face in our practice. On one hand, routine removal of ICDs in all cases of *S. aureus* bacteremia would result in a significant number of unnecessary removals and would be associated with patient morbidity and financial cost. On the other hand, delayed removal of an infected device would be associated with higher in-hospital mortality, metastatic complications and risk of relapse. Based on limited available evidence in their updated scientific statement on CIED infections and their management, the American Heart Association [5] recommended complete device and lead removal for patients with occult staphylococcal bacteremia (level of evidence B, i.e., limited populations evaluated and data derived from a single randomized trial or non-randomized studies) [5]. Further research is needed to distinguish patients with *S. aureus* bacteremia and no echocardiographic evidence of device infection who prove to have an ICD infection from those who do not, so that unnecessary device removal can be avoided.
- When should the device be replaced? There are no prospective trial data on the exact timing of replacing the old device for a new one and the risk of relapsing infection. However, it is imperative to wait until the blood cultures are negative before a new device is implanted.
- How long should the physician wait from the first negative blood culture to device replacement? The AHA recommends re-implanting the device if repeated blood cultures are negative for at least 72 hours (level of evidence C) [5]. It is unclear why it must be 72 hours and not 48 or 96.
- What is the impact of *S. aureus* nasal carriage in patients with implanted ICDs? Is screening for the *S. aureus* carriage before ICD implantation, followed by short-term eradication therapy among identified carriers, associated with a decreased rate of staphylococcal device infections? Will treating all patients without previous screening result in preventing more infections?

In a multicenter double-blind placebo-controlled trial, preoperative screening for the nasal *S. aureus* carriage, followed by *S. aureus* eradication treatment of identified carriers with nasal mupirocin ointment and chlorhexidine gluconate soap, all within one week before surgery, was associated with 79% and 55% reductions in deep-seated and superficial *S. aureus* infections, respectively [12].

It should be emphasized that before adopting a policy of universal mupirocin treatment for *S. aureus* eradication, further research will be needed to prove that the benefits of preventing device infection are balanced against the risks of mupirocin resistance.

Most studies examining the management of CIED infections are small and non-randomized. Large-scale, multicenter, prospective studies are needed to address the confusing and unsettled issues regarding optimal management of CIED infections.

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CDC = Centers for Disease Control
HA-MRSA = hospital-acquired MSRA
PVL = Panton-Valentine leukocidin
AHA = American Heart Association

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Capsule

Black mamba venom peptides target acid-sensing ion channels to abolish pain

Polypeptide toxins have played a central part in the understanding of physiological and physiopathological functions of ion channels. In the field of pain, they led to important advances in basic research and even to clinical applications. Acid-sensing ion channels (ASICs) are generally considered principal players in the pain pathway, including in humans. A snake toxin activating peripheral ASICs in nociceptive neurons was recently shown to evoke pain. Diochot et al. show that a new class of three-finger peptides from another snake, the black mamba, is able to abolish pain through inhibition of ASICs expressed either in central or peripheral neurons. These peptides, called mambalgins, are not toxic in mice but show a potent analgesic effect upon central and peripheral injection that can be as strong as morphine. This effect is, however, resistant to naloxone, and mambalgins cause much less tolerance than morphine and no respiratory distress. Pharmacological inhibition by mambalgins combined with the use of knockdown and knockout animals indicates that blockade of heteromeric channels made of ASIC1a and ASIC2a subunits in central neurons and of ASIC1b-containing channels in nociceptors is involved in the analgesic effect of mambalgins. These findings identify new potential therapeutic targets for pain and introduce natural peptides that block them to produce a potent analgesia.

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Eitan Israeli

Capsule

Generation of functional thyroid from embryonic stem cells

The primary function of the thyroid gland is to metabolize iodide by synthesizing thyroid hormones, which are critical regulators of growth, development and metabolism in almost all tissues. So far, research on thyroid morphogenesis has been missing an efficient stem cell model system that allows for the in vitro recapitulation of the molecular and morphogenic events regulating thyroid follicular cell differentiation and subsequent assembly into functional thyroid follicles. Antonica et al. report that a transient overexpression of the transcription factors NKX2-1 and PAX8 is sufficient to direct mouse embryonic stem cell differentiation into thyroid follicular cells that organize into three-dimensional follicular structures when treated with thyrotropin. These in vitro-derived follicles showed appreciable iodide organification activity. Importantly, when grafted in vivo into athyroid mice, these follicles rescued thyroid hormone plasma levels and promoted subsequent symptomatic recovery. Thus, mouse embryonic stem cells can be induced to differentiate into thyroid follicular cells in vitro and generate functional thyroid tissue.

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Eitan Israeli

"The trees that are slow to grow bear the best fruit"

Moliere (1622-1673), French actor and playwright considered one of the greatest masters of comedy in Western literature

Ankylosing Spondylitis: Field in Progress

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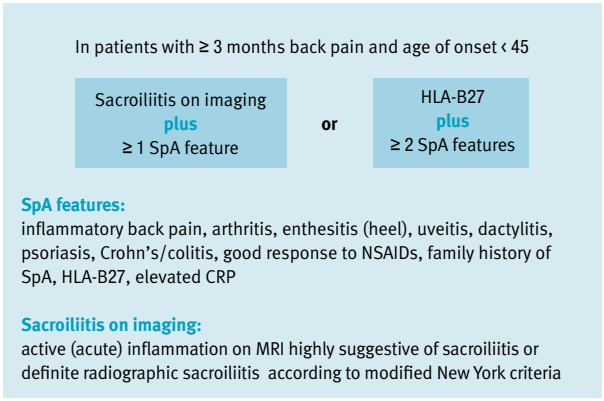
Ankylosing spondylitis, the prototype disease in the spectrum of spondyloarthritides, is a chronic disabling inflammatory disorder strongly associated with HLA-B27. Sacroiliitis, spinal inflammation and enthesitis are the hallmarks of AS, but the disease may involve also peripheral joints, eye, gut and aorta. The study of AS has made significant progress in the last decade. New knowledge in the genetics and pathophysiology of this disorder as well as better understanding of the dynamics of disease development led to the new diagnostic approach and efficient treatment for the majority of AS patients and opened new horizons for both basic and clinical research in this field. In this review we summarize and discuss these new achievements in the study of AS, emphasizing the most problematic issues in both the understanding of the disease mechanisms and the real-life management of AS patients.

THE CONTINUUM OF AS: THE AXIAL SPONDYLOARTHRITIS APPROACH

One of the major clinical problems is, and always has been, the search for proof of sacroiliitis in patients who present with the typical clinical picture of AS and normal X-ray films of sacroiliac joints. These patients might be classified for years as having undifferentiated SpA or diagnosed with an alternative rheumatic disorder or even a non-rheumatic condition, such as mechanical back pain. In view of the new effective therapies that have become available, the long delay in diagnosing patients with AS is unacceptable. The need for a new diagnostic approach thus emerged. The observation that many patients with inflammatory back pain but without sacroiliitis on X-ray films represent the earliest phase of AS and will develop radiographic changes diagnostic for AS within a period of time, usually measured in years, has created a platform for the development of the new disease concept [1]. It has been demonstrated that the presence of HLA-B27 and/or magnetic resonance imaging findings of active SIJ inflammation in these patients could, with a significant degree of accuracy, help to predict which patients will subsequently develop the classical picture of AS [2]. This led to the development of the concept of pre-radiographic AS, which, together with classical AS, formed the basis for the new entity of axial SpA (AxSpA). Other SpA with predominant spinal involvement, such as related to psoriasis or inflammatory bowel disease, and sharing many clinical and imaging features with AS can also be classified in the group of AxSpA by recently suggested criteria [3] [Figure 1]. Thus, the umbrella of AxSpA not only unifies patients with a similar disease pattern, permitting advanced research, but also provides the opportunity for earlier diagnosis and better management of patients with pre-radiographic AS and AS-like psoriatic and inflammatory bowel disease-related arthritis. Studies, however, still have to show whether implementation of this new approach will shorten the diagnostic delay in AS patients.

Figure 1. ASAS classification criteria for axial spondyloarthritis



EPIDEMIOLOGY AND SIGNIFICANCE

PREVALENCE

The prevalence of AS is recognized as 0.5% of the general population. However, the prevalence of AxSpA, which comprises also patients with pre-radiographic AS as well as other

AS = ankylosing spondylitis
SpA = spondyloarthritis

SIJ = sacroiliac joint