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EDITORIAL COMMENT

Patients at High Risk for CIED Infection

Does Our Perception Mirror Reality?*

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With the increasing use of pacemakers and defibrillators, collectively referred to as cardiac implantable electronic devices (CIEDs), infection has become recognized as an important procedure-related complication. A prior scientific statement from the American Heart Association provided insights into the incidence and epidemiology of CIED infections, along with risk factors, the imposed financial burden for care, microbiology, diagnosis, and treatment (1). However, preventing infection remains the cornerstone of practice; to that end, combined with meticulous attention to sterility, prophylaxis with an intravenous antibiotic (most commonly cefazolin) that has in vitro activity against many *Staphylococcus* species carries a Class I recommendation (1,2). Despite these efforts, patients continue to experience infection and, therefore, are exposed to the morbidity and mortality associated with this complication. Thus, there is an important clinical need to identify patients at highest risk for infection and implement strategies to mitigate this risk.

Until recently, our understanding of CIED infections was based on studies with inherent limitations, including the lack of adequately powered, prospective, multi-center data; variability in definitions of CIED infection; and inadequate follow-up. Two studies published within the past year, PADIT (Prevention of Arrhythmia Device Infection Trial) and WRAP-IT (Worldwide Randomized Antibiotic Envelope Infection Prevention Trial), have greatly increased our understanding of the incidence of CIED infections, their risk factors, and the utility of various strategies to further reduce their risk (3–5).

PADIT was a cluster-randomized crossover trial performed in Canada. Centers used either a conventional (pre-procedural infusion of cefazolin) or incremental (pre-procedural cefazolin plus vancomycin, intraprocedural bacitracin pocket wash, and 2-day post-procedural oral cephalexin) periprocedural antibiotic strategy in 19,603 patients. The primary outcome, the 1-year rate of hospitalization for device infection, was observed in 99 (1.03%) patients in the conventional arm and 78 (0.78%) patients in the incremental arm; the 23% difference was not statistically significant (odds ratio: 0.77; 95% confidence interval: 0.56 to 1.05; $p = 0.010$) (3). In contrast, WRAP-IT enrolled 6,983 patients undergoing CIED pocket revision, generator replacement, or system upgrade or initial implantation of a cardiac resynchronization therapy defibrillator; patients were randomly assigned in a 1:1 manner to receive an absorbable, antibiotic-eluting envelope or not (4,5). The primary endpoint was infection resulting in system extraction or revision, long-term antibiotic therapy with infection recurrence, or death within 12 months after the CIED procedure. The primary endpoint occurred in 25 (0.7%) patients who received an envelope and 42 (1.2%) patients who did not receive an envelope; this represented a significant 40% reduction in the likelihood of infection (hazard ratio: 0.60; 95% confidence interval: 0.36 to 0.98; $p = 0.04$). These 2 prospective, large, randomized clinical trials effectively establish a benchmark of approximately 1% for the 12-month risk of a CIED infection. We now have to ask ourselves whether the "drive to zero" CIED infections is possible and, if so, at what cost?

In this issue of the *Journal*, Birnie et al. (6) sought to develop a risk score from the PADIT trial that could

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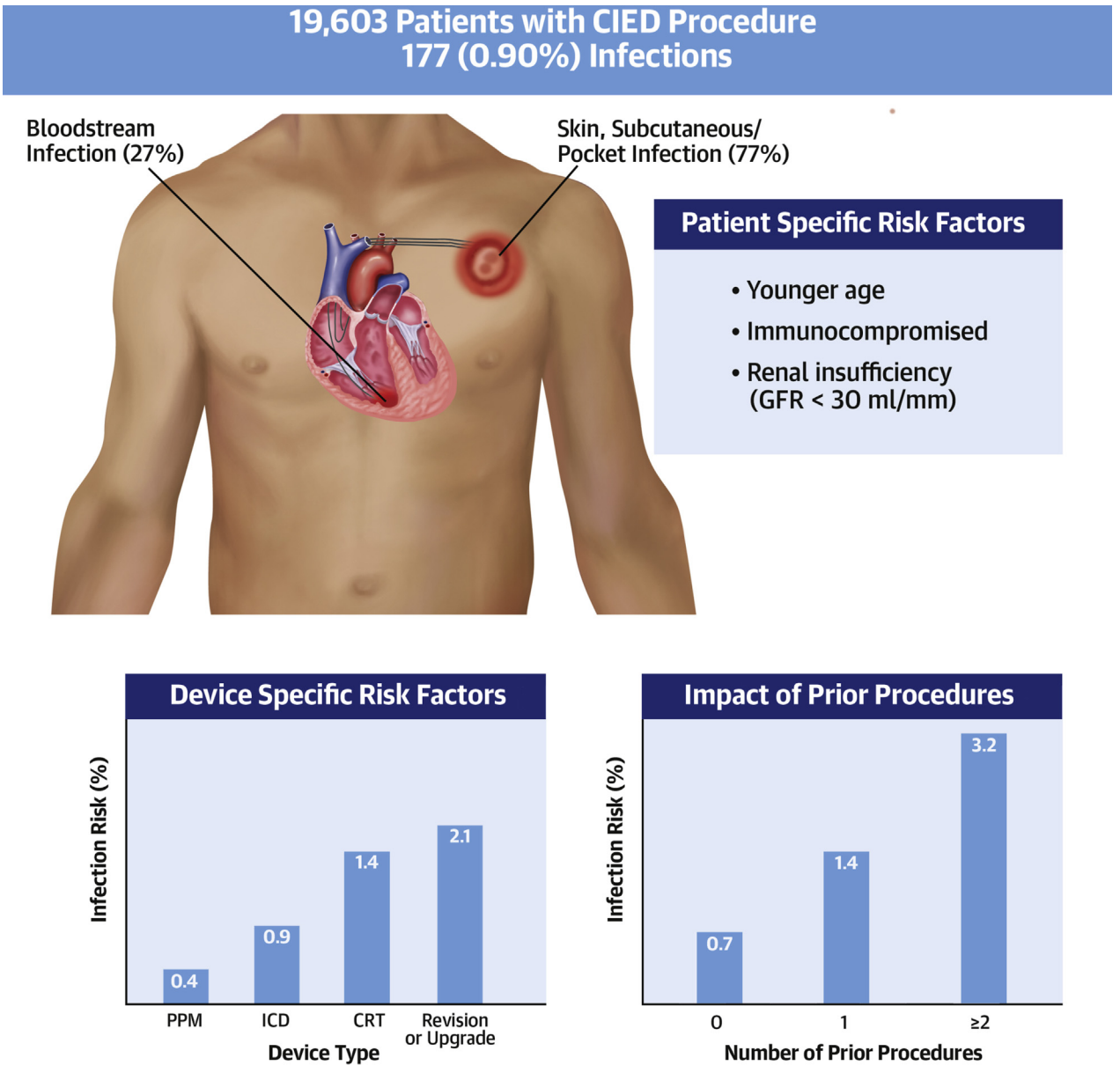
FIGURE 1 **Components of the PADIT Risk Score**



In PADIT, 177 (0.90%) of 19,603 patients developed an infection within the first year of the procedure. Infections were nearly 3 times more likely to present as a subcutaneous or pocket infection than as a bloodstream infection. Patient- and device-specific risk factors and the number of prior procedures contributed to the overall risk of infection. CIED = cardiac implantable electronic device; CRT = cardiac resynchronization therapy; GFR = glomerular filtration rate; ICD = implantable cardioverter-defibrillator; PADIT = Prevention of Arrhythmia Device Infection Trial; PPM = permanent pacemaker.

identify patients at highest risk for CIED infection. The final model identified 5 independent PADIT risk factors for CIED infection: a prior procedure (P), younger age (A), depressed renal function (estimated glomerular filtration rate: <30 ml/min) (D), immunocompromised (I), and procedure type (T). With respect to procedure type, an implantable cardioverter-defibrillator, cardiac resynchronization therapy, and revision/upgrade procedure were associated with a 2-fold, 3-fold, and 4-fold increased risk of infection, respectively, compared with a pacemaker. These risk factors were used to generate a

PADIT risk score that ranged from 0 to 15; patients with scores of 0 to 4 (71.3% of the overall cohort) had an infection rate of 0.51%, those with scores of 5 or 6 (21.4% of the overall cohort) had an infection rate of 1.42%, and those with scores of ≥7 (7.3% of the overall cohort) had an infection rate of 3.41%. Although these variables can be readily ascertained in patients undergoing a CIED procedure, can they really inform clinical practice? We need to acknowledge that none of these independent risk factors is modifiable and that the "high-risk" cohort accounted for only 27% of all infections observed in the study. Thus, in absolute terms, most of the CIED infections occur in patients with an intermediate or low risk of infection.

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The PADIT study showed that the risk of infection could not be lowered by using an incremental antibiotic strategy in any of the 3 risk groups as defined by the PADIT score (5). Should our attention turn toward the antibacterial envelope, which is the only intervention shown to reduce the risk of CIED infection beyond the routine pre-procedure use of a prophylactic intravenous antibiotic? Although a formal risk factor score has not yet been developed from the WRAP-IT cohort, the following variables could not identify patients most likely to benefit from the envelope: age, sex, body mass index, presence or absence of cardiomyopathy, coronary artery disease, prior myocardial infarction, chronic obstructive pulmonary disease, diabetes, renal dysfunction, use of an anticoagulant or oral antidiabetic drug, and CIED type (low- vs. high-power device) (5). The biggest barrier to routine use of the antibacterial envelope is likely to be cost, given that the number needed to treat with an envelope to prevent 1 major CIED infection is 200 patients; a formal cost-effectiveness analysis is eagerly awaited.

As 2019 comes to a close, what have PADIT and WRAP-IT taught us about CIED infections? First, the perception that the rate of CIED infections is high (>2%) does not appear to be true, at least in the context of clinical trials (7). Both of these contemporary studies have reported a 12-month infection rate of <1%. It remains to be seen what effect, if any, the wider use of leadless pacemaker systems and subcutaneous implantable cardioverter defibrillators will have on these infection rates; perhaps they may trend even lower. Second, assuming that the PADIT score can be validated in an independent cohort, there appear to be clear patient-, device-, and procedure-specific risk factors for infection (**Figure 1**). Understanding these risk factors can help clinicians convey to individual patients their particular risk factor profiles for infection, and the risk factors may inform decisions regarding the type of procedure and timing of device upgrades. Third, procedural use of an antibacterial envelope appears to mitigate this risk, in contrast to a strategy of using incremental antibiotics. Although we wait for a formal cost-effectiveness analysis of the value of the envelope, the identification of patients at low risk may be the most valuable lesson of PADIT. Patients with pacemakers (n = 9,572) accounted for nearly half of the total cohort but had a major infection rate of only 0.4% (40 events). For the remaining patients, the good news is that the perception of infection risk has not matched the observed reality; the bad news is that it then becomes that much harder to budge the needle to a more favorable status for our patients with CIEDs.

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