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Injection Drug Use: A Minor Criterion with Major Implications for Patients with Infective Endocarditis

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Infective endocarditis (IE) in people who inject drugs (PWID) has dramatically escalated in the United States over the past decade as a consequence of the opioid epidemic. In response, numerous reports have highlighted the healthcare burden and profiled patient demographics, microbiology, diagnostic and management strategies, and outcomes for PWID who develop IE. This has unveiled several management conundrums including (but not limited to): the financial impact on healthcare systems, limited patient healthcare coverage, when to initiate drug addiction treatment, how to manage the frequent discharge against medical advice, the perceived limitations of cardiovascular surgery, particularly in PWID with ongoing high-risk behavior and/or history of recurrent IE, the need for an "endocarditis team" in individual patient management, and a desire to implement oral or long-acting parenteral antimicrobial therapy for treatment of IE as soon as feasible. The uniqueness of IE in PWID is further enhanced with the knowledge that except for underlying hepatitis C virus infection, which has been previously undiagnosed in many, the patient is otherwise young and healthy and not typically a heavy consumer of healthcare.

In contrast to the US experience, IE in PWID has received much less attention globally. Therefore, Pericas and his colleagues from the International Collaboration on Endocarditis (ICE) conducted a multinational investigation that included two prospective cohort studies with almost 600 PWID with IE and compared them to over 7,000 non-PWID IE patients (1). Patients with definite and possible IE were enrolled from two different time periods – the first between January 2000 and December 2006 and the second between September 2008 and December 2012. In the former group, 64 centers in 28 countries were involved; in the latter, 34 sites in 18 countries submitted cases. Of note, sites in Europe enrolled approximately 55% of cases, with other areas each enrolling considerably less. Overall, 8.4% of all patients enrolled were PWID.

The findings of the ICE investigation (1) are, on the one hand, expected, as the profile of IE in PWID included younger, healthier patients with underlying hepatitis C virus infection, right-sided native valve involvement due to *Staphylococcus aureus*, and lower mortality rates; patients were more likely to be treated without surgery as compared to IE patients without injection drug use (IDU). On the other hand, more than 40% of PWID-associated IE affected the left side of the heart. Moreover, pathogens other than *S. aureus* were more often identified, particularly oral viridans group streptococci (OVGS) and enterococci. Embolic events, including stroke, heart failure, and increased short-term mortality, were more often complications of left-sided IE in PWID and cardiac surgery was more likely to be done with left-sided valve involvement.

Results of a more contemporary prospective cohort that included all IE cases from 156 medical centers in 40 countries between January 2016 and March 2018 deserve comments (2). Patients from Europe accounted for three-fourths of cases and there was a similar prevalence (6.9%) of intravenous drug dependency as an associated IE risk factor, despite differences in medical center participation for the two investigations. Recognizing the inclusion of a more contemporary cohort (2), one might have anticipated more PWID. In one US survey of a national inpatient population, for example, IE in PWID increased from 4.8% to 15.1% ($P<0.001$) between 2003 and 2016 (3).

The pathogenesis of IE deserves to be addressed as we consider its applicability to PWID. Based on studies using animal models of experimental endocarditis (4), it is well-recognized that normal valvular endothelium is refractory to infection, as it is extremely rare for animals to develop IE even when relatively high concentrations of virulent organisms are administered intravenously, without prior damage to the heart valves.

Novel animal model work from Belgian investigators has provided exciting findings that may be applicable to IE in PWID (5). Through a series of sophisticated experiments, they came to the conclusion that there may be differences in IE pathogenesis. One platform may involve predisposing valve damage, which is a well-accepted theorem. A second postulate is based on inflammation of a valve surface that is caused by exogenous agents. It is tempting to speculate that recurrent bloodstream contamination during injection drug use could predispose to IE via an inflammatory-based mechanism that could affect the left and right sides of the heart. This could make PWID more susceptible to staphylococci introduced during drug use, but may also increase their susceptibility to other causes of bloodstream infections, particularly those containing OVGS or enterococci from the gut. It is well documented that PWID have significantly worse oral hygiene, periodontal disease and caries than the general population and this is compounded by drug-associated xerostomia and poor access to dental care (6). Together, these may explain the relatively high proportion of left-sided IE caused by OVGS in PWID.

Referral bias was probably involved in the ICE cohorts as medical centers participating in the investigation were sites where cardiovascular surgery was available (7). This could explain, in part, the high rates (39.3% and 47.5%, respectively) of surgical intervention in the PWID and non-PWID groups. It is certainly plausible that many cases of right-sided IE were medically treated in smaller primary care hospitals and were never transferred.

The ICE cohorts are unique as we consider the use of large databases to investigate the syndrome of IE, a low frequency condition. Cases included in the two temporally-defined cohorts were identified prospectively to ensure that they were appropriate for study inclusion with clinical data abstracted to meet IE definition criteria, in this case IDU as part of the modified Duke criteria (8). This is certainly not the case in many IE studies where large administrative databases are

used to identify cases with International Classification of Diseases (ICD) coding. Unfortunately, substantial limitations have been identified for detecting IE cases related to IDU; at this time, there are no specific ICD-10 codes for IDU or IDU-IE (9).

Although cited as necessary, the ICE investigators did not evaluate the impact of addiction medicine management. We know that this is critical as consultation for this management during the index hospitalization for IE can reduce the likelihood of readmission for serious infections and enhance completion of parenteral antimicrobial therapy (10). For institutions where resources have been available, a more traditional approach has included addiction medicine experts functioning as part of the endocarditis team, both in inpatient and ambulatory care settings. Another more recent option has included multispecialty care being provided in infectious diseases (ID) clinics with supportive staff to manage all aspects of addiction drug use (11). A call for addiction medicine expertise training of ID specialists represents another option with a more holistic approach (12). This option may gain traction as we think about the management of chronic infections due to HIV and hepatitis C currently being done in ID clinics. Based on the ICE data presented in this issue of *JACC*, IE in PWID is a global problem and will require complex strategies to control this epidemic. Life-long interventions will be needed to reduce IDU recidivism in PWID who have developed IE and survived because they remain at high risk for subsequent bouts of IE.

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