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Invited Commentary | Infectious Diseases

High-Risk Infective Endocarditis in People Who Inject Drugs
Are New Bloodstream Infections a Complication and Marker?

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In *JAMA Network Open*, Tan and colleagues[1] performed a retrospective cohort study to describe the occurrence of and risk factors associated with new bloodstream infections (BSIs) and mortality among people who inject drugs (PWIDs) with infective endocarditis. They included 420 consecutive episodes of infective endocarditis occurring in 309 patients from April 1, 2007, to March 31, 2018, in 3 tertiary hospitals in London, Ontario, Canada. Participants were young (mean [SD] age, 35.7 [9.7] years), with a predominance of *Staphylococcus aureus* endocarditis (326 [77.6%]) involving the tricuspid valve (296 [70.5%]). Opiates were the most frequently injected substance (365 [86.9%]), but polysubstance use was common (321 [76.4%]), as was homelessness (72 [17.1%]). The investigators found that new BSIs during treatment were common (138 episodes, 68 of which were polymicrobial) but were not significantly associated with mortality.

This study was performed in the context of an increasingly well-described epidemic of complex invasive bacterial injection-related infections among PWID. For example, hospitalizations for treatment of drug use–associated infective endocarditis in North Carolina increased 10-fold from 0.10 to 1.38 per 100 000 persons during the same decade that the present study was conducted, and in 2017, 2 in every 5 patients undergoing valve surgery for treatment of endocarditis had injected drugs.[2] Indeed, it is notable that among the 688 episodes of endocarditis screened for inclusion in this study (identified using *International Classification of Diseases, Ninth Revision, Clinical Modification*, or *International Statistical Classification of Diseases, Tenth Revision, Clinical Modification* codes for infectious endocarditis), 420 (61.0%) involved patients with a documented history of injecting drug use within the previous 3 months.[1] Clearly the morbidity and mortality resulting from injection-related infections among PWID are associated with a substantial cost, and this cost is likely to be increased by the tendency to avoid outpatient parenteral antimicrobial therapy (OPAT).[3]

Importantly, Tan and colleagues[1] found that outpatient treatment was not associated with an increase in frequency of new BSIs compared with inpatient treatment, challenging dogmatic concerns around the safety of OPAT for PWID. Rather, patients who had been predominantly treated in an inpatient setting (compared with an OPAT setting) experienced both a higher rate of new BSIs (hazard ratio [HR], 4.49; 95% CI, 2.30-8.76) and higher 90-day mortality (HR, 3.39; 95% CI, 1.53-7.53). These findings should be viewed in the context that patients would have been carefully selected for OPAT and thus are systematically different from those receiving treatment in the inpatient setting. Therefore, although OPAT appears to be safe for some patients, it should not be concluded that this is safe for all patients.

The surprisingly high frequency of new BSIs complicating 82 episodes of infectious endocarditis (19.5%) is a novel observation. Importantly, the causative organisms and their antimicrobial susceptibility profile for new BSI were quite different from those causing the index episode. New BSIs were characterized by a predominance of gram-negative organisms (especially nonfermenters, such as *Pseudomonas*, *Acinetobacter*, and *Stenotrophomonas* species) and *Candida* species, and often resulted in treatment with additional broad-spectrum antibiotics and/or antifungals (mostly fluconazole). The possibility of new BSIs and the spectrum of organisms should clearly be considered in the differential diagnosis for patients who develop new fever or sepsis while being actively treated for infectious endocarditis.

Interestingly, new BSIs were not associated with increased 90-day mortality. Although 143 total gram-negative isolates were recovered (of 266 total isolates) from 138 individual episodes of new BSI, in only 45 episodes was antibiotic treatment directed at gram-negative isolates reported. It is unclear whether new BSI episodes were not always considered clinically significant. Could some episodes represent transient bacteremia after injection of drugs? If inpatients were more likely to have regular physical observations, including temperature, and thus be investigated with blood cultures, it may partly explain the increased rate of new BSI in inpatients compared with outpatients. It would be helpful to know whether the new BSIs were associated with persistent bacteremia or other markers of morbidity such as increased length of stay or health care–related costs. Longer-term follow-up would also be of value given that despite a younger age, PWID with infectious endocarditis have been reported to have similar short-term morbidity and mortality as patients with noninjecting drug use–related infectious endocarditis, but poorer long-term outcomes.[4] The occurrence of new BSIs is likely to be a marker of ongoing injecting drug use and thus associated with increased long-term morbidity. Although inpatient addiction services were associated with a reduced rate of new BSIs, perhaps the occurrence of new BSIs should also highlight patients at highest risk of poor long-term outcomes and greatest need for inpatient and outpatient addiction services.

The rising health-economic burden of endocarditis and other injecting drug–related infections highlights the need for robust evidence about the model(s) of care that optimize outcomes. One of the most common questions arising is where treatment should occur. There has traditionally been hesitation to manage PWID with OPAT because of perceived risk to both staff and patients themselves, and among the most prominent of these is the possibility of a new BSI resulting from ongoing drug use. To some extent, this belief has origins in the mutual mistrust that has characterized hospital care of PWID.[5] A review of OPAT among PWID has previously suggested that OPAT may be both effective and safe,[3] but the study from Tan and colleagues[1] provides new evidence regarding the safety for carefully selected patients and the health benefits of OPAT for them. These findings align with previous evidence suggesting that from the patient perspective, rather than being the safe alternative, the "social and structural conditions [in hospitals] produce discharges against medical advice and, in turn, more complicated and protracted medical treatment."[6(p64)]

There are several additional management issues for PWID with infectious endocarditis, including the role of surgery for right-sided infectious endocarditis, the appropriate duration and route of antibiotics, and the place for long-acting glycopeptide antibiotics. Perhaps most important is the need to prioritize referral and access to addictions and harm reduction services. Tan and colleagues[1] found that receipt of inpatient addiction treatment services was associated with reduced risk of new BSIs, and other studies have similarly demonstrated associations between receipt of such services and improved clinical outcomes.[7] Even at hospitals with research groups that have been exploring the epidemiology of PWID with infectious endocarditis for many years, the proportion of patients who receive appropriate evidence-based addiction treatment services continues to be suboptimal.[8] For example, Tan and colleagues[1] report patients in their cohort received a consultation for inpatient addiction treatment for only 156 infectious endocarditis episodes (37.1%) and referral to outpatient addiction treatment for only 151 (36.0%). It is clearly time to move beyond descriptions and to either implement the delivery of such services for as many PWID with infectious endocarditis as possible or, if resources are limited, to consider randomizing patients to such services.[9]

ARTICLE INFORMATION

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