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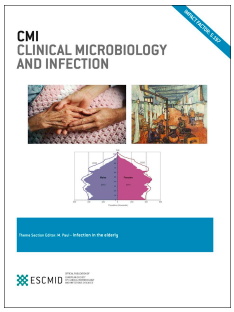

Which trial do we need? Long-acting glycopeptides versus oral antibiotics for infective endocarditis in patients with substance use disorder

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CMI Commentary: a RCT that has not been done and should be performed in order to answer a clinical question that matters to your patients.

Which trial do we need? Long-acting glycopeptides versus oral antibiotics for infective endocarditis in patients with substance use disorder

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The clinical question

A 45-year-old woman with both opioid and methamphetamine use disorders is hospitalized for tricuspid valve infective endocarditis (IE) due to methicillin-susceptible *Staphylococcus aureus*. Blood cultures cleared on hospital day 3. She has septic pulmonary emboli with two small pulmonary abscesses that do not require drainage. She had a two-year history of recovery while on methadone. One month prior to hospitalization, she started injecting fentanyl and methamphetamine after the death of a family member. On day 6 of hospitalization, she says she is fearful of losing her housing and job and desires early hospital discharge. The clinical team faced barriers in arranging outpatient parenteral antibiotic therapy (OPAT). She does not want to go to a facility to receive intravenous (IV) antibiotics. The clinical question is: What is the best option to treat IE, considering that the recommended IV antibiotic treatment duration for native valve IE due to *S. aureus* is 4–6 weeks [1, 2]?

Background

Injection drug-use-associated IE (IDU-IE) is a major cause of morbidity and mortality in people who inject drugs (PWID) [3, 4]. There is a complex array of individual, institutional, and societal barriers, including stigma against PWID that prevents optimal treatment of IDU-IE [5]. Multi-modal treatment of substance use disorder (SUD) is associated with decreased drug use, and better treatment outcomes of serious infectious diseases, including IDU-IE [6, 7].

OPAT decreases medical costs and allows patients to leave the hospital and continue care [8]. There is increasing evidence that OPAT can be safely and effectively delivered to PWID [9, 10]. There are IE cases in which OPAT is not an option due to lack of sufficient organizational time when patients are discharged before medically advised, lack of safe or stable housing, or (often unjustified) concerns that a peripherally inserted central catheter may be used for drugs other than antibiotics. When guideline-based IV antibiotics cannot be administered, oral formulation is currently considered as an option [1, 2]. There is growing

evidence that following initiations with IV antibiotics, switch to oral antibiotics is effective for (IDU-)IE treatment [11-14].

Long-acting lipoglycopeptides (LGPs) have been approved by the United States Food and Drug Administration and the European Medicines Agency for acute bacterial skin and soft-tissue infections in adults. LGPs and real-world data to manage off-label, clinically challenging situations, including IE, have been reviewed elsewhere [15-17]. With increasing time from the last administered dose, there is an escalating inter-individual variability in plasma levels of LGPs. This pharmacokinetic observation suggests that there is potential room for dosing flexibility without losing efficacy when a scheduled dose administration is missed by a few days. To date, there are no published clinical trials demonstrating that intermittent infusion of LGPs (e.g.; dalbavancin, oritavancin) is a treatment alternative in IE.

People with IDU-IE have higher rates of discharge before medically advised compared to those with IE due to non-SUD causes [18]. Discharges before medically advised can occur because of several issues, including but not limited to suboptimal treatment of pain, suboptimal management of mental illness including SUD, and patients' concerns about childcare, employment, and criminal-legal related responsibilities [19-22]. Discharges before medically advised are often chaotic experiences, and patients are not routinely offered treatment alternatives. Consequently, the risk of infection progression and readmission for severe and costly IE complications increases. Thus, a clinical trial comparing oral antibiotics versus LGPs in PWID with IE and desire discharge before medically advised is needed.

Study Design

In this proposed randomized, multi-national controlled trial, the safety and efficacy of LGPs will be compared with those of oral antibiotics for the treatment of native valve IE caused by methicillin-susceptible and methicillin-resistant *S. aureus* in PWID unable to complete IV treatment. Key inclusion criteria include SUD, probable or definite IE promulgated by American Heart Association (AHA) and European Society of Cardiology

guidelines with a *S. aureus* bloodstream isolate susceptible to the chosen LGP (MIC ≤0.125 mg/L [23]). Key exclusion criteria include possible IE, need for 'urgent' or 'emergent' heart valve surgery, cardiac implantable electronic device, and prior IE ≤6 months. Participants will be eligible for recruitment as soon as possible following an IE diagnosis, and no later than 14 days after initiation of active IV antibiotics (Supplementary figure 1A). In the LGP arm, the first dose will be given prior to discharge. Each dose accounts for 10 days of antibiotic therapy and is scheduled accordingly, with some flexibility for early and delayed shows of study participants (Supplementary figure 1B). In the oral treatment arm, antibiotic doses and frequency will be consistent with those listed in the American Heart Association Statement (Supplemental Table) [5], taking into account resistance patterns among blood culture isolates and drug interactions for each study participant. A total treatment duration of 6 weeks is targeted. For the study analysis, ≥4 weeks is defined as completion of therapy, whereas <4 weeks as incomplete therapy. The primary endpoint is a composite endpoint including death, unplanned cardiac valve surgery, *S. aureus* bacteremia within 6 months after randomization. Whole genome sequencing of *S. aureus* bloodstream isolates during both index admissions and subsequent presentations will be used to differentiate between microbiologic failure (i.e., relapse) and a de-novo infection with a new strain (i.e.; reinfection) [24, 25]. Secondary endpoints include IE-related death, IE-unrelated death, expenses and length of hospital admission, duration of antibiotic treatment, treatment costs, costs of subsequent treatment after failure (i.e. valve surgery), complications associated with the injection of LGPs, emergence of resistance towards LGPs in case of relapse and reinfection, adverse drug events, and interactions of prescribed drugs.

Following discharge, participants will be followed for clinical and laboratory assessments, including antibiotic plasma levels and pill counts. All patients will be given cell phones to facilitate reminder texts about medications, study visits, and facilitate quick replacement prescriptions if medications are lost. Directly observed treatment will be offered and coordinated with medications for SUD when possible. Visits will be once weekly following discharge until the 6th week of treatment, then at three and six months after the date

of IE diagnosis. Blood cultures will be obtained at all visits after completion of antibiotics treatment. Echocardiography prior to discharge or at first follow-up visit and within one week of therapy completion should be performed to evaluate treatment response.

Analytic plan and sample size calculations

The hypothesis is that LGPs are non-inferior to oral antibiotics in the treatment of IE. For the sample size calculations, the following parameters are estimated: a non-inferiority margin 10%, level of significance (alpha value) 5%, power (1-beta) 80%, 20% event rate of the primary endpoint [24]. The required sample size per group is 198, 396 in total. Because a drop-out proportion of 25% over the 6-month follow-up is estimated, we will target 540 study participants. Twenty centers over a study period of three years will participate, leading to an average recruitment target of 9 study participants per center and year. We plan to only include tertiary sites that have multi-disciplinary services for PWID. Interim analysis will be conducted when 50, 100, and 200 patients have been included to assess the frequency of the event rate and inclusion rate to adjust the intended size of the study population. Intention-to-treat and per-protocol analysis will be performed, using multivariate regression analysis for variables associated with the primary outcome. Subgroup analysis will include infection site (left versus right), number of valves involved, time to randomization (1–7 days versus 8–14 days), and antibiotic treatment regimens. Statistical modelling will aid to answer questions on time-dependent co-variables.

Practice and Ethical Considerations

A steering committee of experts to assist in the details of recruitment, consent, and retention will be convened to address ethical and practical protocol development and operationalization. The committee will include people with lived experience with SUD, addiction-trained professionals, infectious diseases clinicians, pharmacists, cardiologists, cardiothoracic surgeons, ethics experts, representatives of local services for people with SUD (e.g., clean syringe access services, mobile health units, shelters). All participating

institutions will be supported by experts who have skills in performing phlebotomy in PWID. High-tech vein-mapping tools will be available for all venipuncture and initiation of IV access for infusion of antibiotics if venous access is challenging. Partnership with the community-based sites where people with SUD access services is a crucial aspect to the success of this protocol. We will have several options available to participants for follow up study visit locations. One option will be the hospital, but other options will include medical respites. Funding will be provided through governmental resources.

Limitations

The potential imbalance of infection sites (i.e., right-sided>left-sided or bilateral IE) as well as the predictable heterogeneity of different antimicrobial compounds, even within the same treatment course, will be limitations in interpretation of results. Another limitation is that the trial does not include a guideline-based 'standard of care' option. However, there have been no clinical trials that support the superiority of IV-only therapy and the evidence for effective treatment of oral antibiotics in IE is steadily increasing [26].

The time point of randomization may be unpredictable in individuals being discharged before medically advised because these patient-driven decisions typically occur within a short notice of time. Therefore, the treatment duration of conventional IV antibiotics prior to switch in either of the study arms will likely vary. The approach chosen in this study is pragmatic and reflects "real-life" clinical practice. Finally, the drop-out rate may be unpredictable. However, the estimated proportion of 25% is reasonable and supported by others [27]. By defining ≥4 weeks of antibiotic therapy as complete treatment, study participants with drop-outs in the 5th or 6th week of treatment will be included in the per protocol analysis.

Summary of Clinical Trial Importance

There are several stakeholders who may benefit from this proposed clinical trial. There is tremendous financial burden associated with keeping people in the hospital for

extended periods of time for IV antibiotics, and alternatives are not only cost-saving for the institution but also often support the financial status of the patient [28]. Trial results have the potential to shift the treatment paradigm in not only IDU-IE, but also non-IDU IE patients. Moreover, people with IDU-IE are often excluded from clinical trials and we seek to address this imbalance while we recognize the multitude of patient and societal complexities in doing so.

Transparency Declarations

There is no conflict of interest. LB reports authorship duties from UpToDate®, Inc., and consulting fees for Boston Scientific; Roivant Sciences; Botanix Pharmaceuticals.

Authors contribution

AW wrote the first draft of the manuscript and performed the literature review. PS was responsible for the study idea, study design and revision of the drafts. LB contributed to the study idea and revised the manuscript drafts. LM and DdS contributed to the study idea, performed literature research and revised the manuscript drafts. All authors reviewed and approved the final version.

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