Dalbavancin as Secondary Therapy for Serious *Staphylococcus aureus* Infections in a Vulnerable Patient Population

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We retrospectively evaluated off-label use of dalbavancin as secondary therapy in 32 patients with serious *Staphylococcus aureus* infections (endocarditis, osteomyelitis, septic thrombophlebitis, epidural infection) who were also persons who use drugs. The majority of patients (56%) had a clinical response to treatment. Only 1 patient who completed the intended dalbavancin course experienced a treatment failure.

**Keywords.** dalbavancin; *Staphylococcus aureus*; substance use.

Serious staphylococcal infections often require prolonged courses of intravenous antibiotic therapy. Dalbavancin, a lipo-glycopeptide antibiotic with a long half-life, allows for weekly dosing, making it an appealing choice for patients requiring parenteral therapy, particularly in people who use drugs (PWUD). Retrospective case series are emerging regarding the efficacy and safety of dalbavancin in the treatment of deep-seated, Gram-positive infections [1, 2], though reports of its use in vulnerable patient populations such as PWUD remain scarce.

Outpatient parenteral antimicrobial therapy (OPAT) is widely used for the treatment of severe staphylococcal infections [3–5]. However, few studies have described enrolling PWUD, and more specifically persons who inject drugs (PWID), in standard OPAT programs [6–9].

Similar to programs developed at other institutions, we created a multidisciplinary inpatient team to provide a comprehensive care plan with coordinated medical treatment for PWUD, including consultation with nursing, psychiatrists, addiction medicine, acute pain management, and infectious disease (ID) specialists [10]. Despite these approaches, some patients are administratively discharged secondary to ongoing unsafe behaviors or leave against medical advice (AMA). These patients are at high risk of re-admission due to relapse of their incompletely treated infections or factors related to substance use. One study reported 43% of PWUD leaving AMA during hospitalizations between 2005 and 2011 [11], while another study documented significantly higher 30-day mortality in patients who were discharged AMA [12].

At our institution, PWUD who are discharged with parenteral antibiotics are offered close outpatient management including weekly ID clinic appointments, referral to an opioid replacement therapy clinic, and coordinated support; despite these measures, medication adherence remains a challenge. We described our clinical experience with the off-label use of intravenous (IV) dalbavancin for serious staphylococcal infections in this patient population.

**METHODS**

**Setting and Study Population**

This is a retrospective observational study conducted at a 413-bed university-affiliated urban teaching hospital, Harborview Medical Center (HMC), located in Seattle, Washington. It is a public safety net hospital for Seattle King County and a level 1 trauma and burn center for Washington, Wyoming, Alaska, Montana, and Idaho.

Dalbavancin was added to our institutional formulary in 2015 with restriction requiring approval from the ID team, antimicrobial stewardship, and the OPAT program. Clinical indications include bacteremia, complicated skin and soft tissue, or deep-seated infections for which conventional intravenous antimicrobial therapy is not recommended due to social circumstances. Situations that might warrant the use of dalbavancin include infections with organisms with no acceptable oral antibiotics and infections in patients who are discharged AMA or who are at high risk for administrative discharge because of behavioral issues and unsafe behaviors.

All patients ≥18 years old who were hospitalized between June 1, 2015, and September 30, 2017, for serious *Staphylococcus aureus* infections, who received initial conventional antibiotic treatment, and who were discharged on dalbavancin as secondary therapy were included. The initial dalbavancin dose was infused over 30 minutes on the day of hospital discharge, and duration of therapy was determined by the consulting ID physician. All patients were scheduled to return to the ID clinic for subsequent weekly infusions.
The institutional review board of the University of Washington approved the study and waived written informed consent.

Data Collection and Analysis
Data collection was performed using REDCap [13], a data-reporting quality improvement tool linked to the University of Washington's Clinical Data Repository. From the electronic medical record (EMR), we collected data on patient demographics, medical comorbidities, microbiology, and antibiotics. Outcomes were collected through our EMR at follow-up visits and via a linked EMR to other clinics and hospitals.

Definitions
Active substance use was defined as the use of cocaine, heroin, or methamphetamine in any form within the last 30 days; information regarding use of other opiates was unavailable. A clinical response was defined as any patient who had a follow-up visit within 1 year at HMC or a neighboring hospital, linked through a common EMR, without evidence for an ongoing or relapsed infection, regardless of whether they completed the intended course of therapy. Loss to follow-up was defined as any patient not having a subsequent encounter to evaluate their infection at either the HMC ID clinic or another institution, linked via the EMR, within 1 year. Successful completion of total antibiotic course was defined as completion of total prespecified antimicrobial course, including dalbavancin and other subsequent oral antibiotics. All-cause readmission was defined as a hospital admission within 30 days from the previous hospital discharge in our shared EMR.

RESULTS
We identified 32 PWUD treated with dalbavancin for serious Staphylococcus aureus infections. The average age (interquartile range [IQR]) was 38 (25–50) years, 23 (72%) were male, 28 (88%) were Caucasian, 2 (6%) were Hispanic, and 2 (6%) were Native American. The majority of patients, 28 (88%), were PWID; 15 (47%) had hepatitis C, 15 (47%) were homeless, 1 had a history of diabetes, and 1 was HIV infected. The mean Charlson comorbidity index (IQR) was 0.8 ± 1.3 (0–2). The indications for antibiotic treatment are listed in Table 1. The majority of infections, 28 (88%), were due to methicillin-resistant Staphylococcus aureus, and 26 (81%) of the isolates were fluoroquinolone resistant.

Patients received an average of 13 days of antibiotic therapy before receiving dalbavancin; vancomycin was the most commonly prescribed antibiotic (84%). Peripherally inserted central catheter (PICC) placement was avoided in 15/32 (47%) patients. Twenty-two patients received a single dose, 7 received 2 weekly doses, 2 received 3 weekly doses, and 1 received 5 weekly doses of dalbavancin. The average hospital length of stay (LOS) was 12.2 ± 8.5 days. Overall, 17 (53%) patients completed the intended course of therapy. A clinical response was documented in 18 (56%) of patients, and 4 (13%) patients experienced a clinical failure. The remaining 10 (31%) patients were lost to follow-up and unevaluable. Six patients (19%) were re-admitted to the hospital within 30 days of discharge—none for adverse effects related to dalbavancin, 2 (6%) for treatment failures reported above, and 4 (13%) for reasons unrelated to their initial treatment.

Nine patients were treated for endocarditis (2 with methicillin-sensitive Staphylococcus aureus and 7 with methicillin-resistant Staphylococcus aureus), all involving the native tricuspid valve. Of these patients, 6 received a single dose of dalbavancin, and 3 received 2 doses. The average duration of in-patient therapy was 17 days. All patients had negative follow-up blood cultures before transition to dalbavancin. None of the patients with endocarditis were known to have failed treatment with dalbavancin, although 4 were lost to follow-up, and 5 were judged to have had a clinical response to treatment.

DISCUSSION
To our knowledge, this is the first study evaluating the secondary use of dalbavancin for treating complicated staphylococcal infections among PWUD in the OPAT setting. Our findings support the off-label use of dalbavancin as an option for the completion of antibiotic therapy for complicated Staphylococcus aureus infections among PWUD, following an initial period of conventional antibiotic treatment, including patients with infective endocarditis. Although PICC placement was often required for antibiotics during hospitalization, PICC placement was avoided in almost 50%, reducing the likelihood of catheter-associated complications such as secondary bacteremia, a recognized complication in the homeless PWID population [8]. We previously reported that medical respite can be an alternative treatment venue for homeless PWUD suffering from serious infections who require parenteral therapy [4]. However, OPAT is generally not an option for housed PWUD, and this then leads to prolonged hospitalizations solely for completion of parenteral antibiotic therapy.

Evidence supporting dalbavancin use outside of its currently approved indication for acute bacterial skin and skin structure infections (ABSSSIs) is limited despite its off-label use in clinical practice. An initial phase II study of dalbavancin compared with vancomycin for staphylococcal catheter-related bloodstream infections demonstrated higher efficacy of dalbavancin (87% vs 50%), although only 56% of vancomycin-treated patients had their catheter removed at baseline, compared with 93% of dalbavancin-treated patients [14]. A more recent retrospective multicenter study in Spain described the use of dalbavancin in 69 patients with prosthetic joint infection, osteomyelitis, catheter-related bacteremia, and ABSSSIs and reported a clinical efficacy of 84%, with reductions in hospital LOS and cost [1]. Other published clinical experience also documented a 93%
Barriers to dalbavancin use include the cost of the drug and the need for IV access for administration. The majority of the patients in this study received their first dalbavancin dose at the end of their inpatient hospitalization, incurring a substantial cost to our institution, though this may be offset by earlier hospital discharge and a shorter hospital LOS. Subsequent surgical debridement needed on day of first dalbavancin dose due to development of vertebral osteomyelitis - 8 months later.

Abbreviation: TMP-SMX, trimethoprim/sulfamethoxazole.

Table 1. Duration, Indication, Prior Treatment, and Outcomes of Patients Receiving Dalbavancin

| Duration of Dalbavancin Therapy, wk | Weekly Dalbavancin Doses, mg | Successful Completion of Total Course Type of Infection | Inpatient Antibiotics Used | No. of Days of Prior Antibiotic Response | Clinical Reason | Reason for Dalbavancin Failure |
|------------------------------------|-------------------------------|---------------------------------------------------------|---------------------------|-----------------------------------------|----------------|-------------------------------|
| Planned                            | Actual                        |                                                          |                           |                                         |                |                               |
| 5                                  | 5                             | 1500, 1000, 500, 500, 500                                 | Yes                       | Osteomyelitis, extremity               | Vancomycin,   | 10                             | Yes                          |
|                                    |                               |                                                          |                           |                                         | TMP-SMX        |                               |
| 3                                  | 3                             | 1500, 1000, 1000                                         | Yes                       | Bacteremia with infected thrombophlebitis | Vancomycin   | 6                              | Yes                          |
| 2                                  | 2                             | 1000, 500                                               | Yes                       | Osteomyelitis, extremity               | Vancomycin   | 1                              | Yes                          |
| 3                                  | 2                             | 1000, 500                                               | No                        | Endocarditis                           | Cefazolin     | 4                              | Yes                          |
| 2                                  | 2                             | 1000, 500                                               | No                        | Osteomyelitis, extremity               | Vancomycin, doxycycline | 17                         | Yes                          |
| 2                                  | 2                             | 1000, 500                                               | No                        | Endocarditis                           | Vancomycin    | 8                              | Yes                          |
| 1                                  | 1                             | 1000                                                    | No                        | Bacteremia, flexor tenosynovitis       | Vancomycin    | 10                             | Yes                          |
| 1                                  | 1                             | 1000                                                    | Yes                       | Septic arthritis                      | Vancomycin    | 8                              | Yes                          |
| 1                                  | 1                             | 1000                                                    | No                        | Endocarditis                           | Ceftazolin    | 24                             | Yes                          |
| 1                                  | 1                             | 1000                                                    | No                        | Osteomyelitis, spine                   | Vancomycin    | 3                              | Yes                          |
| 1                                  | 1                             | 1000                                                    | Yes                       | Bacteremia                             | Vancomycin    | 3                              | Yes                          |
| 1                                  | 1                             | 1000                                                    | Yes                       | Endocarditis                           | Vancomycin    | 32                             | Yes                          |
| 1                                  | 1                             | 1000                                                    | Yes                       | Bacteremia                             | Vancomycin    | 8                              | Yes                          |
| 1                                  | 1                             | 500                                                     | Yes                       | Bacteremia                             | Vancomycin    | 7                              | Yes                          |
| 1                                  | 1                             | 1000                                                    | Yes                       | Osteomyelitis, spine                   | Vancomycin, ceftriaxone | 18                         | Yes                          |
| 1                                  | 1                             | 1000                                                    | No                        | Endocarditis, empyema                  | Vancomycin    | 24                             | Yes                          |
| 2                                  | 1                             | 1000                                                    | No                        | Bacteremia                             | Vancomycin    | 16                             | Yes                          |
| 1                                  | 1                             | 1000                                                    | Yes                       | Bacteremia                             | Vancomycin    | 9                              | Yes                          |
| NA                                 | 3                             | 1000, 500                                               | Yes                       | Septic arthritis, bacteremia           | Vancomycin    | 20                             | No                           | Subsequent surgical debridement needed - 4 months later |
| 2                                  | 2                             | 1000, 500                                               | No                        | Bacteremia with subdural & epidural abscess | Nafcillin          | 12                             | No                           | Development of vertebral osteomyelitis - 8 months later |
| 3                                  | 1                             | 1000                                                    | No                        | Osteomyelitis, spine                   | Vancomycin    | 29                             | No                           | Worsening back pain and bacteremia - 2 months later |
| 2                                  | 1                             | 1000                                                    | No                        | Osteomyelitis, extremity               | Vancomycin    | 10                             | No                           | Subsequent surgical debridement needed - 4 months later |
| 2                                  | 2                             | 1500, 500                                               | Yes                       | Endocarditis, infected thrombophlebitis | Vancomycin    | 20                             | Unknown                     |
| 2                                  | 2                             | 1000, 500                                               | Yes                       | Septic arthritis                      | Vancomycin    | 14                             | Unknown                     |
| 1                                  | 1                             | 1000                                                    | Yes                       | Bacteremia with epidural phlegmon      | Vancomycin    | 8                              | Unknown                     |
| 1                                  | 1                             | 1000                                                    | Yes                       | Bacteremia                             | Vancomycin    | 7                              | Unknown                     |
| 2                                  | 1                             | 1000                                                    | No                        | Bacteremia with epidural abscess       | Vancomycin    | 13                             | Unknown                     |
| 1                                  | 1                             | 1000                                                    | Yes                       | Bacteremia                             | Daptomycin    | 13                             | Unknown                     |
| 2                                  | 1                             | 1000                                                    | No                        | Endocarditis                           | Cefazolin     | 13                             | Unknown                     |
| 2                                  | 1                             | 1000                                                    | Yes                       | Endocarditis, empyema                  | Vancomycin    | 17                             | Unknown                     |
| 2                                  | 1                             | 1000                                                    | No                        | Bacteremia with infected thrombophlebitis | Vancomycin, TMP-SMX | 11                         | Unknown                     |
| 2                                  | 1                             | 1000                                                    | No                        | Endocarditis                           | Vancomycin    | 13                             | Unknown                     |
dalbavancin doses were administered in the outpatient clinic; the majority of this cost was covered by individual patient insurance plans. Obtaining IV access in the outpatient setting for PWID may also be difficult, though of the patients reviewed here, none required clinic PICC placement or delay in treatment due to difficulty obtaining a peripheral IV.

There are several limitations to our study. First, various dalbavancin dosing regimens were used as there are no current standardized dose regimens for dalbavancin use in the treatment of non-ABSSSI [1, 2]. A single randomized controlled trial demonstrates that 1500 mg of dalbavancin on day 1 and day 8 is effective for the treatment of debrided osteomyelitis [15]. Second, it is difficult to separate the effectiveness of the initial course of antibiotic therapy from any added benefit due to dalbavancin as all patients received both treatments. However, most patients included in this study had deep-seated *Staphylococcus aureus* infections that required prolonged courses of antibiotics, longer than the duration of their initial conventional treatment, suggesting that dalbavancin did contribute to their treatment outcomes. Third, our small sample size and single center limit generalization to other clinical settings. Finally, the low rate of treatment completion, high rate of loss to follow-up, and ability to track patients only in settings linked to our EHR hinder our ability to confidently assess the clinical effectiveness of dalbavancin. Unfortunately, this low rate of engagement in care and follow-up is common among PWUD [7, 16] and highlights the challenges in caring for this population. Among 101 housed and homeless PWID receiving OPAT without dalbavancin from our institution, we note a similar rate of clinical cure (49%) and a high rate of unknown outcome (47%) due to loss to follow-up [17].

In spite of these limitations, our study supports the use of weekly dalbavancin as a reasonable secondary therapeutic alternative to prolonged daily intravenous therapy for the treatment of serious staphylococcal infections among poorly resourced patients who are homeless or use drugs, for whom creating a safe and effective treatment plan can be challenging. Additional studies that employ innovative strategies to keep these hard-to-engage patients in care long enough to complete dalbavancin or alternative treatments are needed to validate this treatment strategy.

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**References**

1. Bouza E, Valerio M, Sotorno A, et al; DALBUSE Study Group (Dalbavancina: Estudio de su Uso Clínico en España). Dalbavancin in the treatment of different gram-positive infections: a real-life experience. Int J Antimicrob Agents 2018; 51:571–7.

2. Tobudic S, Forstner C, Burgmann H, et al. Dalbavancin as primary and sequential treatment for Gram-positive infective endocarditis: 2-year experience at the General Hospital of Vienna. Clin Infect Dis. 2018; cyz279.

3. Tice AD, Rehm SJ, Dalovisio JR, et al; IDSA. Practice guidelines for outpatient parenteral antimicrobial therapy. IDSA guidelines. Clin Infect Dis 2004; 38:1651–72.

4. Beieier AM, Dellit TH, Chan JD, et al. Successful implementation of outpatient parenteral antimicrobial therapy at a medical respite facility for homeless patients. J Hosp Med 2016; 11:531–5.

5. Hernandez W, Price C, Knepper B, et al. Oral parenteral antimicrobial therapy administration in a homeless population. J Influs Nurs 2016; 39:81–5.

6. Ho J, Archeleta S, Sulaiman Z, Fisher D. Safe and successful treatment of intravenous drug users with a peripherally inserted central catheter in an outpatient parenteral antibiotic treatment service. J Antimicrob Chemother 2010; 65:2641–4.

7. Buehrle DJ, Shields RK, Shah N, et al. Risk factors associated with outpatient parenteral antibiotic therapy program failure among intravenous drug users. Open Forum Infect Dis 2017; 4(X):XXX–XX.

8. Zhou Y, Beieier A, Dhanireddy S. Outpatient antibiotic treatment outcomes in vulnerable populations: homeless and current injection drug users. Open Forum Infect Dis 2016; 3(suppl_1):XXX–XX.

9. D’Couto HT, Robbins GK, Ard KL, et al. Outcomes according to discharge location for persons who inject drugs receiving outpatient parenteral antimicrobial therapy. Open Forum Infect Dis 2018; 5(X):XXX–XX.

10. Rolfe RJ, Mathews RE, Rodriguez JM, et al. Implementation of a standardized protocol for hospitalized patients who inject drugs and require long-term antibiotics reduces length of stay without increasing 30-day readmissions. Open Forum Infect Dis 2017; 4(suppl_1):S340–1.

11. Ti L, Milloy M-J, Buxton J, et al. Factors associated with leaving hospital against medical advice among people who use illicit drugs in Vancouver, Canada. PLoS One 2015; 10:e0141594.

12. Glasgow JM, Vaughan-Sarrazin M, Kaboli PJ. Leaving against medical advice (AMA): risk of 30-day mortality and hospital readmission. J Gen Intern Med 2010; 25:926–9.

13. Harris PA, Taylor R, Thielke R, et al. Research electronic data capture (REDCap): a metadata-driven methodology and workflow process for providing translational research informatics support. J Biomed Inform 2009; 42:377–81.

14. Raad I, Darouiche R, Vazquez J, et al. Efficacy and safety of weekly dalbavancin therapy for catheter-related bloodstream infection caused by gram-positive pathogens. Clin Infect Dis 2005; 40:374–80.

15. Rappo U, Pattagunta S, Shevchenko V, et al. Dalbavancin for the treatment of osteomyelitis in adult patients: A randomized clinical trial of efficacy and safety. Open Forum Infect Dis 2018; 5:ofy331.

16. Lall A, Hu A, Allison G. Follow-up appointment adherence of outpatient parenteral antimicrobial therapy (OPAT) patients. Open Forum Infect Dis 2017; 4(suppl_1):S332–3.

17. Beieier A, Magaret A, Zhou Y, et al. Outpatient parenteral antimicrobial therapy in vulnerable populations - people who inject drugs and the homeless. J Hosp Med 2019; 14:105–109.