

# Eligibility for and Use of Oral Antimicrobial Therapy among Veterans with Osteoarticular Infections: A Retrospective Study across Eight Medical Centers

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## INTRODUCTION

- There have been multiple randomized controlled trials that show no difference in outcomes when oral antimicrobials are used instead of parenteral therapy to treat osteoarticular infections.
- While the use of oral antimicrobials offers several advantages over parenteral therapy, it is unknown how often oral antimicrobials are being used to treat osteoarticular infections in routine clinical practice.
- The objective of this study was to investigate how often patients with osteoarticular infections qualified for oral antimicrobial step-down therapy and how often it was actually being prescribed across a geographically-diverse sample of Veterans Affairs (VA) medical centers.

## MATERIALS AND METHODS

### Selection of sites and participants:

- Two high-complexity (level 1) VA medical centers were randomly selected from each of the four US Census regions; this yielded eight total sites.
- Next, administrative data was used to retrospectively identify potentially eligible unique patients who were hospitalized with an osteoarticular infection during 1/1/2018-12/31/2020 at the eight centers. Criteria for defining eligibility are shown in Figure 1. The study timeframe was selected in order to include an observation period prior to and following the January 2019 publication of the OVIVA (Oral versus Intravenous Antibiotics for Bone and Joint Infection) trial.
- A manual chart review was then performed by a primary reviewer and then separately by a secondary reviewer in randomly-selected cases identified from the administrative data (Figure 1).

### Outcomes:

- The primary outcome was eligibility for oral antimicrobial therapy, based on the criteria of the OVIVA trial (Figure 1).
- The secondary outcome was how frequently oral antimicrobial step-down therapy was actually used. Oral antimicrobial step-down therapy was defined as transitioning to oral therapy within 2 weeks of antimicrobial initiation.
- An additional outcome was all-cause death or treatment failure within 12 months of the patient's hospital admission for the osteoarticular infection.

### Sample size:

- Assuming alpha=0.05, beta=0.2 and a baseline use of oral antimicrobial therapy equal to 10%, it was estimated that 144 total cases, or 48 per year, would need to be included to detect a  $\geq 20\%$  increase in the use of oral antimicrobials between 2018 (pre-OVIVA) and 2019-2020 (post-OVIVA). This estimation was based on a dichotomous outcome with two independent groups.

## RESULTS

- Table 1 summarizes the cohort.
- As shown in Table 2, there were 109 (75.2%) patients eligible for oral step-down, and 18 (16.5%) of these patients received it. There was no significant difference in the use of oral step-down therapy among eligible patients between 2018 (pre-OVIVA) and 2019-2020 (post-OVIVA): 12.8% vs. 18.6%,  $p=0.44$
- Of the 18 patients who received oral step-down therapy, 14 (77.8%) were from a single medical center. This center used oral step-down in 14 of its 15 (93.3%) eligible cases. Five out of the 8 facilities did not prescribe oral-step down therapy in any eligible patient reviewed.
- As shown in Table 3, there were no significant baseline differences in patients who received oral step-down and in those who were eligible but did not receive it.

Figure 1. Study flowchart to define patient eligibility for inclusion in the cohort and eligibility for oral step-down

**Step 1:** Using administrative data, potentially eligible cases were identified at the 8 VA medical centers (2018-2020) by meeting 3 criteria: discharge diagnosis of an osteoarticular infection based on International Classification of Diseases (ICD)-10 codes, received  $\geq 5$  days of inpatient antimicrobials, and had an inpatient Infectious Disease consult.

**Step 2:** The first reviewer (a clinical pharmacist) performed manual chart reviews to confirm the diagnosis of a qualifying osteoarticular infection and to verify that the infection was actively being treated with antimicrobials. At this stage, patients were excluded if they met any of the following criteria:  
a. No osteoarticular infection that was actively being treated  
b. Received less than 4 weeks of antimicrobials  
c. Already on chronic suppressive antimicrobial therapy prior to the index admission and this therapy was not further modified during the hospital stay  
d. An osteoarticular infection due to a mycobacterial, fungal, parasitic or viral etiology  
e. A non-qualifying type of osteoarticular infection. Eligible osteoarticular infections included peripheral osteomyelitis, vertebral osteomyelitis, prosthetic joint infection, septic arthritis of a native joint, and an orthopedic fixation-device infection. Osteomyelitis of the sacrum, skull and pelvis were not included.

**Step 3:** The second reviewer (an Infectious Disease physician) performed separate manual chart reviews to determine each patient's eligibility for oral antimicrobial therapy, as outlined below, and to assess for treatment failure. Patients were considered ineligible to receive oral step-down therapy if they met any of the following criteria:  
a. *Staphylococcus aureus* bacteremia or infective endocarditis on presentation or within the month prior to presentation  
b. Any other concomitant infection which warranted prolonged parenteral antimicrobial therapy  
c. Hemodynamic instability precluding use of oral antimicrobial therapy  
d. A dysfunctional gastrointestinal tract preventing reliable oral antimicrobial absorption  
e. No feasible oral antimicrobial options, based on available microbiologic cultures, pill burden, the possibility of drug toxicity and drug-drug interactions.

1. Seventy-six patients were excluded for the following reasons: received less than 4 weeks of antimicrobial therapy (n=44), no osteo-articular infection (n=19), skull osteomyelitis (n=6), sacral osteomyelitis (n=4), pelvic osteomyelitis (n=1), and already on chronic antimicrobial suppression without further antimicrobial modification (n=2).

Table 2. Eligibility for and use of oral antimicrobial step-down in patients with osteoarticular infections treated at 8 VAs during 2018 (n=48) and 2019-2020 (n=97)

Eligibility for oral-step down therapy	Pre-OVIVA (2018), n (%)	Post-OVIVA (2019-2020), n (%)	Total, n (%)
<b>Eligible for oral step-down therapy</b>	39 (81.3)	70 (72.2)	109 (75.2)
Eligible and switched to step-down	5 (12.8)	13 (18.6)	18 (16.5)
Eligible but did not switch	34 (87.2)	57 (81.4)	91 (83.5)
<b>Not eligible for oral step-down therapy</b>	9 (18.8)	27 (27.8)	36 (24.8)
<b>Reasons for ineligibility:</b>			
Staphylococcus aureus bacteremia	5 (55.6)	14 (51.9)	19 (52.8)
No oral antimicrobial option	3 (33.3)	9 (33.3)	12 (33.3)
Other	1 (11.1)	2 (7.4)	3 (8.3)
Endocarditis	0	1 (3.7)	1 (2.8)
Another infection requiring IV therapy	0	1 (3.7)	1 (2.8)

## SUMMARY

- In this retrospective study across eight geographically-diverse VA medical centers, we found that, during the post-OVIVA period, only 1 in 5 patients with an osteoarticular infection eligible for oral antimicrobial treatment actually received oral step-down within 2 weeks of antimicrobial initiation.
- The vast majority of patients who transitioned to oral step-down therapy were from a single medical center, and most sites were not observed to use any oral step-down. This suggests that the use of oral antimicrobial therapy may be highly dependent on local practice patterns and institutional norms.
- Our findings indicate that there is an opportunity for local, hospital-based initiatives to implement the use of oral antimicrobials for osteoarticular infections.



Table 1. Characteristics of 145 patients with osteoarticular infections treated at 8 VA Medical Centers, 2018-2020

Characteristic	n (%)
<b>Age, median (IQR)</b>	65 years (60-71)
<b>Male gender</b>	142 (97.9)
<b>Comorbidities</b>	
Diabetes mellitus	90 (62.1)
Peripheral vascular disease	33 (22.8)
Renal disease	20 (13.8)
COPD	20 (13.8)
<b>Infection Type</b>	
Peripheral osteomyelitis	96 (66.2)
Septic arthritis	
Prosthetic joint	9 (6.2)
Native joint	12 (8.3)
Vertebral osteomyelitis	12 (8.3)
Orthopedic-fixation device infection	12 (8.3)
> 1 infection type	4 (2.8)
<b>Evidence of infection<sup>1</sup></b>	
Definitive	112 (77.2)
Probable/possible	33 (22.8)

1. Definitive and probable/possible were defined by criteria set forth by the OVIVA trial. Li HK, Rombach I, Zambellas R, et al. Oral versus Intravenous Antibiotics for Bone and Joint Infection. N Engl J Med 2019;380(5):425-436.

Table 3. Comparison of patients with osteo-articular infections who switched to oral antimicrobial step-down therapy and those who were eligible but did not switch to oral step-down across 8 VA medical centers, 2018-2020

Characteristic	Oral step-down (n=18)	Eligible for oral step-down but not given (n=91)	p-value
<b>Age, mean</b>	65.6 years	64.6 years	0.69
<b>Length of stay, mean (SD)</b>	8.1 days	9.3 days	0.37
<b>Peripheral osteomyelitis</b>	15 (83.3%)	59 (64.8%)	0.12
<b>Surgical debridement, n (%)</b>	13 (72.2%)	67 (73.6%)	1.00
<b>Time to surgical debridement, median (IQR)<sup>1</sup></b>	1 day (1-2)	2 days (1-4)	0.16
<b>Duration of IV therapy, mean</b>	6.0 days (4.8)	44.8 days (11.8)	<0.01
<b>Duration of total therapy, median</b>	49 days (44-79)	46 days (43-72)	0.38
<b>Therapeutic failure, n (%)</b>	8 (44.4%)	30 (33.0%)	0.35
<b>Death</b>	2 (11.1%)	4 (4.4%)	
<b>Treatment failure</b>	6 (33.3%)	26 (28.6%)	

## LIMITATIONS

- Factors that influenced decision-making about the route of antimicrobial administration may not have been well-documented in the medical record.
- The infrequent use of step-down therapy precluded a robust comparison of outcomes with oral versus IV
- Our findings may have limited generalizability due to the small number of sites included and our VA-focus.