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Are Oral Antibiotics Just as Good as Intravenous?

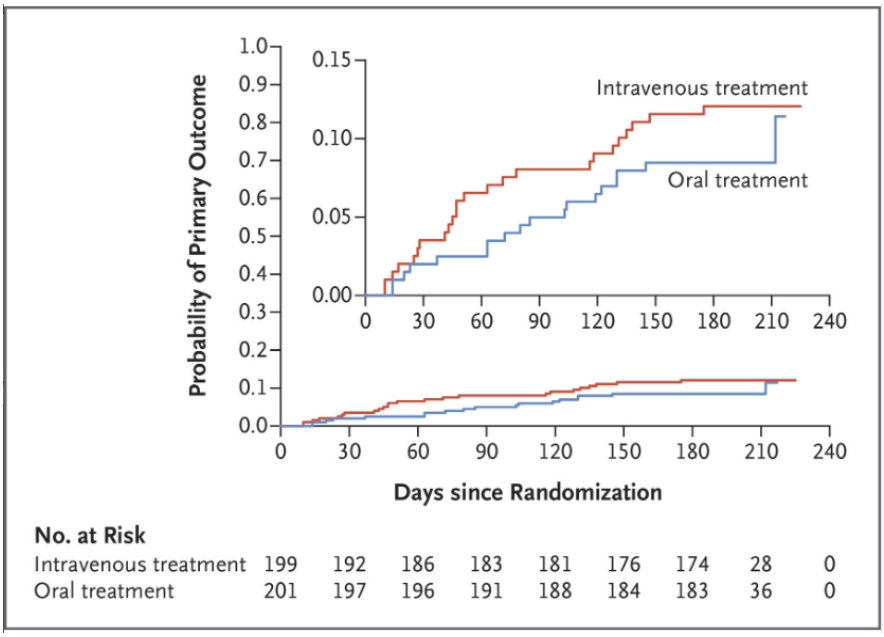
Policies that encourage conversions from intravenous (IV) to oral antibiotic therapy is standard for most antibiotic stewardship programs.[1] Treatment with oral antibiotics prevents adverse events related to IV access, such as IV infiltration, line-related infections, or thrombophlebitis, and is practical for anticipating transitions to outpatient therapy. However, some infections are inadequately treated by oral antibiotics for a variety of reasons, including insufficient antibiotic spectrum, high severity of illness, inadequate bioavailability for penetration into infected sites, or lack of clinical efficacy data. In this month's DASON newsletter, we review two recent New England Journal of Medicine (NEJM) articles that evaluated transition to or treatment with oral antibiotics for disease states that are traditionally treated with prolonged courses of IV antibiotics: endocarditis and osteomyelitis.

POET Trial

Recommended antibiotic management for native- and prosthetic-valve endocarditis has evolved over the past few decades, largely due to the development of antibiotic resistance. Current guidelines provide pathogen-specific recommendations for antibiotic choice. However, for almost all pathogens, guidelines recommend long, four- or six-week courses of intravenous therapy.[2,3] In a recent study published in the NEJM titled "Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis" (hereafter referred to as the POET trial), Iversen and colleagues challenged this dogma.[4]

The POET trial tested whether clinically stable patients with left-sided endocarditis randomized to complete treatment courses with oral antibiotics had similar outcomes compared to patients who received a full intravenous course. The primary outcome was a composite endpoint of all-cause mortality, unplanned cardiac surgery, embolic events, or relapsed bacteremia. Participants in the POET trial included 400 patients with left-sided endocarditis confirmed by Duke Criteria from Denmark. Patients received treatment with either IV therapy or oral antibiotics after at least 10 days of adequate IV therapy (7 if cardiac surgery performed for present endocarditis course). Causative organisms identified in study patients were largely *Streptococci* (~49%), but also included *Enterococcus faecalis* (~24%), methicillin-sensitive *S. aureus* (~21%), and coagulase-negative *Staphylococci* (~6%). Approximately 27% of patients had prosthetic valve endocarditis. Patients were randomized at a median of 17 days of treatment. Those randomized to IV therapy received a median of 19 additional days of antibiotics while those randomized to oral therapy received 17 days. The final results of the study met criteria for non-inferiority at a threshold of 10%. The primary outcome occurred in 9% of patients randomized to oral therapy and 12% of patients randomized to IV treatment (Figure 1). The authors interpreted the result to

Figure 1. POET Trial Kaplan-Meier Plot of the Probability of the Primary Composite Outcome.



indicate that transition to oral antibiotics added no additional risk of treatment failure, yet alleviated risks associated with IV therapy. However, undertreatment of endocarditis can lead to significant morbidity and mortality. Thus, we will outline specific details of the POET trial to highlight relevant caveats for providers practicing in US community hospitals.

First, unlike the structure of the current clinical practice guidelines, this study was not powered to evaluate pathogen-specific antibiotic regimens or outcomes and no subgroup analyses were performed. For example, *S. aureus* is generally considered a more virulent organism than other Gram-positive bacteria, and it is a common pathogen in US hospitals.[5] Complicated *S. aureus* bacteremia *without* endocarditis requires four weeks of IV therapy, while other Gram-positive bloodstream infections may be adequately treated in two.[6] Treatment of endocarditis caused by different pathogens under one universal algorithm is not consistent with current clinical practice or knowledge of pathogen virulence. Importantly, POET included zero patients with methicillin-resistant *S. aureus*, which is a critical pathogen to consider in US-based practice.

Multiple different antibiotic regimens were used in the POET trial. The protocol allowed up to four different oral regimens for each specific pathogen from which clinicians could choose. All regimens included two-agent combination therapy and many included agents rarely used in the United States (i.e., fusidic acid, rifampicin). For patients with streptococcal endocarditis, the most common oral regimens used were amoxicillin plus moxifloxacin (47%) or amoxicillin plus linezolid (25%). The agents had a wide variety of oral bioavailability (i.e., linezolid vs. amoxicillin) and high doses which may impact tolerability. Finally, the oral treatment arm had intensive clinic follow up schedules to monitor and maintain medication adherence. All patients underwent serum drug concentration monitoring with dose adjustment when needed to ensure adequate drug exposure. This may not be practical for US-based practice. Thus, meaningfully translating this study into practice for clinicians within the DASON network is difficult.

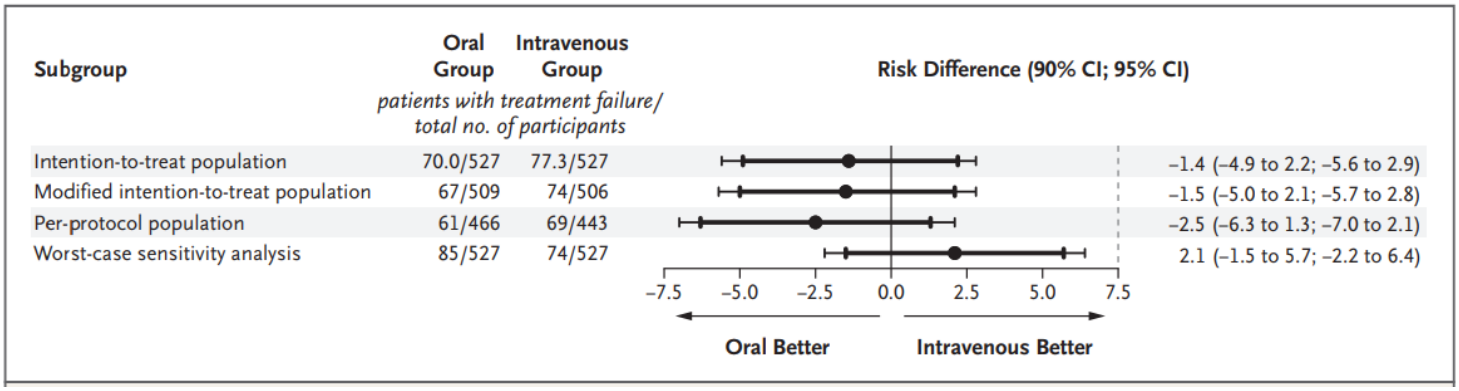
Despite these important limitations, this study design was rigorous and the results suggested that conversion to oral therapy is reasonable in at least a subset of highly adherent patients with left-sided, Streptococcal endocarditis. We recommend that any potential transition to oral therapy for endocarditis is done in consultation with infectious disease experts. Further, for these highly selected patients in whom oral regimens are chosen, clinicians must assure close follow up after discharge to monitor adherence and tolerability.

OVIVA Trial

Li et al. recently performed a randomized trial to evaluate oral antibiotic therapy for osteomyelitis, titled "Oral versus Intravenous Antibiotic Therapy for Bone and Joint Infection" (hereafter referred to as OVIVA).[7] Li and colleagues hypothesized that oral antibiotic therapy was non-inferior to intravenous antibiotic therapy for the initial six weeks of therapy for complex orthopedic infections. Here, we review OVIVA methods and conclusions.

Participants included in the OVIVA trial included over 1000 patients with bone and joint infections who would normally

Figure 2. Differences in Risk According to Analysis Performed in the OVIVA Trial.



be treated with at least six weeks of intravenous antibiotic therapy. Inclusion criteria were relatively broad, allowing those with surgical management, explanted hardware, and those without surgical management and retained hardware to enroll. Injection drug users and patients with *S. aureus* bacteremia were not included. Patients were randomized to complete an initial 6-week course of either intravenous or oral antibiotic therapy. The primary endpoint for analysis was definitive treatment failure, assessed by either clinical, microbiologic, or histologic evidence of infection. The study results indicated that oral antibiotic therapy was, again, non-inferior to intravenous antibiotic therapy at a threshold of 7.5%. In fact, oral therapy may have been slightly favored in all analyses except a worst-case scenario sensitivity analysis, in which those randomized to oral therapy with missing data were assumed to have treatment failure (Figure 2). Treatment failure occurred in 13.2% of those randomized to oral therapy compared to 14.6% in the intravenous group. Secondary outcomes also trended towards favorability for the oral therapy group. Duration of antibiotic treatment was overall shorter for oral therapy (71 vs 78 days), hospitalization stays were shorter, and there were fewer IV-related complications. *C. difficile* infection was also higher in the intravenous group (1.7 vs 1.0%), however minor adverse reactions, including nausea or poor gastrointestinal tolerability, were not included in the study results.

Similar to POET, the largest limitation of the OVIVA trial is the lack of analysis for specific treatment regimens in the oral antibiotic cohort. The authors admit that they "did not seek to compare specific antibiotic agents or to stipulate which agents should be used." Regimens were determined at the discretion of supervising infectious disease physicians. As such, the large majority of antibiotics used for the oral therapy cohort were highly bioavailable agents: clindamycin, doxycycline, and fluoroquinolones. Very few patients were treated with oral penicillins, and no patients were treated with oral cephalosporins. Limited data was reported regarding specific dosing strategies. Thus, we would rephrase the study conclusion as follows: highly bioavailable antibiotics are non-inferior to intravenous therapy when treating bone and joint infections.

Key Points

In conclusion, these two trials bring important, dogma-challenging information favoring a potential transition away from traditional, prolonged intravenous courses for endocarditis and osteomyelitis. However, the studies were not designed to make definitive, practical, and specific recommendations for oral antibiotic treatment choices. Further studies should include specific dosing strategies and evaluate the efficacy of regimens that have less bioavailability. Until then, treatment decisions for endocarditis and osteomyelitis remain nuanced and requires special consideration of organism, host, antibiotic characteristics, and weighing the potential unintended consequences.[8] Where available, we recommend consultation with infectious disease experts for these complicated infections.

References

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