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Oral Vancomycin for the Prevention of *C. difficile* Infection

Introduction

Clostridioides (Clostridium) difficile infection (CDI) is the leading cause of hospital-onset, infectious diarrhea[1]. In 2017, approximately 223,900 cases of CDI occurred in the United States, resulting in an estimated 12,800 fatalities[1]. Significant attention has been rightly made to infection prevention strategies for the prevention of CDI, yet pharmaceutical prophylaxis for CDI prevention remains relatively unexplored. The most recent 2017 IDSA guidelines do not provide a recommendation for or against prophylaxis, and the available body of literature investigating oral vancomycin prophylaxis (OVP) is limited.[2] OVP is defined as antibiotic treatment before symptom onset or diagnosis of CDI. As a result, clinicians often prescribe OVP at various dosing intervals and durations for primary prophylaxis of CDI in different patient populations. Recently, the first randomized controlled trial[3] evaluating the efficacy of OVP for CDI prevention was published in *Clinical Infectious Diseases*, in an effort to shed light on this subject.

The First RCT for OVP!

From October 2018 to April 2019, Johnson and colleagues performed a single-center, open-label, prospective randomized controlled trial investigating the efficacy of daily dose oral vancomycin for the primary prevention of CDI in high risk individuals.[3] High-risk individuals needed to meet three criteria:

- Age ≥ 60 years AND
- Hospitalization ≤ 30 days prior to enrollment hospitalization AND
- Receipt of systemic antibiotics during prior hospitalization

If patients met these inclusion criteria, and were again receiving systemic antibiotics, they were eligible for enrollment. Researchers randomized eligible patients to prophylaxis with either oral vancomycin 125 mg daily for the duration of systemic antibiotic therapy plus five additional days, or no prophylaxis. Concomitant metronidazole therapy disqualified patients from randomization. The trial enrolled a total of 100 patients, with 50 patients participating in each arm.

Incidence of healthcare facility-onset CDI (HCFO-CDI) was measured as the primary endpoint, with CDI defined by the presence of diarrhea or ≥ 3 stools/day with a confirmatory PCR test for *C. difficile*. Secondary endpoints included rates of new vancomycin-resistant *Enterococci* (VRE) colonization, and community-onset, healthcare facility-associated CDI within 30 days of hospital discharge.

The two treatment arms consisted primarily of women with an average age of around 75 years. The two cohorts were well-balanced with respect to comorbidities, PPI and H2-blocker use, and antibiotic utilization, as measured by DOT. Only one trial participant reported a history of CDI prior to enrollment, allowing assessment of OVP for primary prevention of CDI.

At trial conclusion, zero patients in the OVP arm contracted HCFO-CDI, contrasted with six individuals (12%) in the no-prophylaxis arm (p = 0.03). This corresponded to a number-needed-to-treat of **9** to prevent one episode of illness. Additionally, the investigators estimated the cost of one OVP course at $26, assuming an average treatment duration of 12 days. For comparison, the authors provided the estimated cost of one episode of HCFO-CDI at $2,650, **a 100x difference**!

Taking a Look Back at OVP

While Johnson et. al. conducted the only randomized controlled trial of OVP for the primary prevention of CDI, several others have published retrospective cohort studies[4-11] on primary and secondary prophylaxis. Recently, Babar[12] and others published a systematic

review and meta-analysis assessing OVP in 8 retrospective studies and the Johnson RCT.

There was significant heterogeneity among the studies. Four studies investigated the effect of OVP on CDI recurrence in patients receiving systemic antibiotics, while the others evaluated primary or secondary prevention of CDI in patients with renal transplantation, hematopoietic stem cell transplant patients, and elderly patients. Additionally, each study utilized differing dosing strategies of vancomycin. Oral vancomycin 125 mg twice daily was the most commonly prescribed dosing frequency for prophylaxis.

The meta-analysis produced several findings. First, CDI recurrence was less likely in those receiving OVP with an overall odds ratio of 0.245 (95% CI, 0.13 – 0.48). When stratified by immunocompetency, this finding persisted. The authors calculated an OR of 0.32 (0.17 – 0.63) for immunocompetent individuals and an OR of 0.08 (0.02 – 0.37) in immunocompromised patients. Similarly, for primary prevention of CDI, the researchers presented an OR of 0.04 (0.01 – 0.23) and an OR of 0.36 (0.20 – 0.65) for recurrent CDI. All of these findings suggest a benefit of OVP for the prevention of CDI.

To address heterogeneity, Babar and colleagues conducted a meta-regression analysis of several covariates, including vancomycin dosing. Interestingly, risk of CDI correlated directly with OVP dosing—that is, patients who received lower doses of oral vancomycin were at lower risk of resultant CDI (Figure 1).

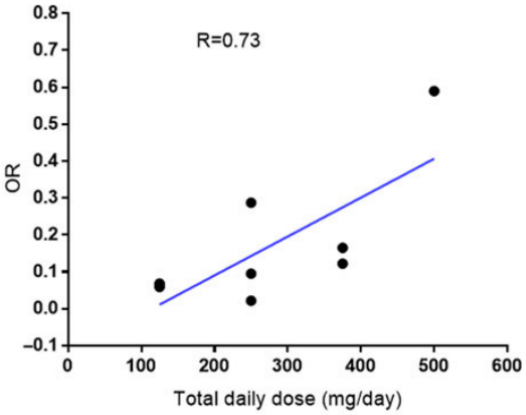

Figure 1. OR of CDI correlated with total daily dose of oral vancomycin prescribed.[12]

The authors hypothesized that higher doses of vancomycin resulted in increased disruption of healthy intestinal microbiota, creating an opportune environment for *C. difficile* to proliferate.

Unintended Consequences

Direct adverse drug effects and VRE acquisition are two significant concerns associated with oral vancomycin use. All studies confirm relatively minimal side effect profile of oral vancomycin. However, the data regarding VRE colonization is not as clear. In the recently published RCT, 42% of patients enrolled to receive OVP were colonized with VRE at baseline. While no uncolonized patients acquired VRE prior to hospital discharge, only 64% of patients were evaluated for this outcome, secondary to patient refusal of screening. Three retrospective studies assessing risk of VRE acquisition included in the Babar et al. meta-analysis also suggest no increased risk of VRE colonization on short term follow-up (Figure 2).

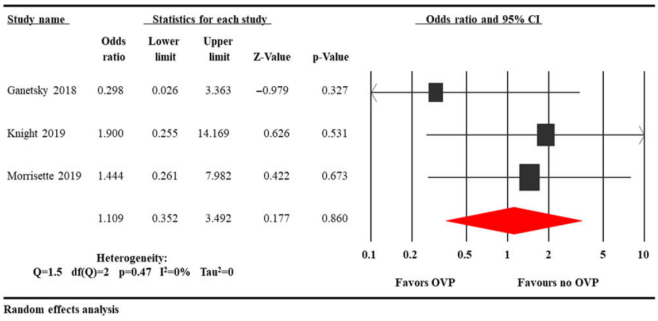

Figure 2. OR for VRE acquisition in association with OVP.[12]

However, in 264 patients with a history of CDI receiving OVP at 125 mg twice daily, a recently published retrospective study[13] found an increased risk in the absolute number of VRE-colonized patients at 6-month follow up. With low quality data demonstrating mixed results, it remains unclear whether OVP truly affects VRE colonization rates in a clinically significant manner.

Conclusion

Taken in aggregate, there is an accumulating body of evidence demonstrating the efficacy of OVP to prevent CDI. Questions remain to identify appropriate dosing strategy and patient populations, and a blanket recommendation for protocolization is yet out of reach.

However, sufficient evidence exists for clinicians to consider OVP at 125 mg daily or twice daily intervals in high-risk individuals to prevent potentially devastating episodes of CDI.

Key Points

- **OVP appears effective in reducing risk of CDI in high-risk patients, both as primary and secondary prevention**
- **Lower doses of oral vancomycin (125 mg daily or twice daily) may be more effective in preventing CDI than higher doses**
- **Clinicians could consider OVP (e.g., vancomycin 125mg PO daily or BID) in hospitalized patients over the age of 60, who are receiving systemic antibiotics and have a history of recent hospitalization and systemic antibiotic therapy within the past 30 days**

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