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EDITORIAL COMMENTARY

Perils, Pitfalls, and Promise of Primary Prophylaxis for *Clostridioides difficile* Infection

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(See the Major Article by Johnson et al on pages 1133–9.)

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Clostridioides difficile infection (CDI) is the most common healthcare-associated infection in the United States [1]. CDI has a wide spectrum of clinical presentation associated with death, colectomy, high healthcare costs, and poor patient-reported outcomes [2]. The pathophysiology of CDI involves disruption of the microbiome in a susceptible host, allowing for germination of *C. difficile* spores, toxin production, and infection. By far, the most common risk factor for microbiome disruption is use of high-risk, broad-spectrum antibiotics [3]. Given the high incidence and burden of the disease along with a known and identifiable risk factor, interest in primary prophylaxis for CDI in high-risk individuals given broad-spectrum antibiotics has been a keen research and clinical interest. Vancomycin has potent activity against *C. difficile*, does not have the long-term systemic adverse events associated with metronidazole, and has a lower acquisition cost than fidaxomicin. Thus, oral vancomycin is a logical choice for use as an antibiotic for primary prophylaxis of CDI. However, difficulties in identifying a population at high enough risk for development of CDI in order to properly power a study has been problematic. Thus, for the most part, data on primary prophylaxis for CDI have involved retrospective evaluations of clinical initiatives. The 2017 Infectious Diseases Society of America/Society for Healthcare Epidemiology of America CDI guidelines considered primary and secondary CDI prophylaxis as an important clinical area but had no high-quality evidence on which to base specific recommendations [4].

Primary prophylaxis with vancomycin does have several potential limitations. Oral vancomycin has a profound effect on the microbiome that by itself decreases colonization resistance to *C. difficile*, vancomycin-resistant *Enterococcus*, and other multidrug-resistant organisms (MDROs). Reduced rates of CDI while a patient is on vancomycin should be expected due to the known susceptibility of *C. difficile* to vancomycin. However, reduced colonization resistance of *C. difficile* and other MDROs can persist for weeks after discontinuation of vancomycin [5]. Thus, CDI may develop at the same rate or higher in patients given oral vancomycin as primary prophylaxis but be simply delayed during the vancomycin administration time period. The correct dose to use as prophylaxis is also problematic. Vancomycin clearance is almost exclusively via passing of feces. Thus, a dose that is lower than the standard 125 mg given 4 times daily may be effective as diarrhea subsides and bowel habits return to normal. This may also be beneficial to reduce the dysbiosis caused by vancomycin. However, *C. difficile* has shown increased resistance to vancomycin [6]. If primary prophylaxis with vancomycin was adopted widely, this would significantly increase the antibiotic selection pressure for increased resistance especially if lower doses are used. Thus, clinicians are faced with a double-edged sword in that too high of a dose may negate the CDI prevention aspects of vancomycin by increasing dysbiosis while too low of a dose may increase the likelihood of resistance development.

In the backdrop of these potential benefits and concerns, in this issue of *Clinical Infectious Diseases*, Johnson and colleagues [7] present the results from their randomized, open-label study of low-dose oral vancomycin 125 mg given once daily compared with no prophylaxis in a 961-bed tertiary community hospital. To be included, patients were aged ≥60 years, had a hospitalization in the past 30 days, and were rehospitalized and receiving high-risk systemic antibiotics. After signing an informed consent, 100 patients were randomized 1:1 to vancomycin prophylaxis or no prophylaxis. No patient developed CDI during hospitalization in the vancomycin prophylaxis arm, while

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6 (12%) developed CDI during the current hospitalization in the no-prophylaxis arm (P = .03). Medical records were reviewed for more than 80% of patients at 3 months. Telephone follow-up was also attempted 30 days after discharge, which was completed for 44% (no prophylaxis) and 48% (vancomycin prophylaxis) of patients. Two patients who experienced hospital-onset CDI in the no-prophylaxis group also experienced recurrent CDI on the outpatient basis. No cases of CDI were observed in the vancomycin prophylaxis group during the posthospitalization evaluation period. As noted by the authors, the major limitation to the study was the posthospitalization follow-up that may have led to missed diagnosis of community-onset, healthcare facility–associated CDI. The open-label nature of the study is also problematic as many patients given broad-spectrum antibiotics will experience antibiotic-associated diarrhea that may or may not be related to *C. difficile*. Although the investigators attempted to control for bias as much as possible, it is possible that knowledge of the assigned treatment groups could have influenced the results. We also recently created a risk score to identify a patient population at high risk for primary CDI [8]. Using the integrated electronic health records of an 11-hospital healthcare system, we were able to identify a patient population with a 30-day CDI risk of 7%. However the sensitivity of our algorithm at that incidence rate was only 0.15. Thus, the 12% risk of hospital-onset CDI in the study by Johnson et al was truly remarkable and will need to be validated in future studies. This is especially important given that overuse of oral vancomycin in high-risk patients will increase vancomycin-resistant selection pressure and could increase resistance rates in CDI, which has limited antibiotic options.

What might be the best method for primary prophylaxis for CDI? The lowest dose of an effective antibiotic that minimizes dysbiosis seems prudent and the best option for antibiotic prophylaxis. The narrow-spectrum antibiotic fidaxomicin was shown in subanalyses to be effective as a primary prophylaxis in the hematopoietic stem cell population [9]. Head-to-head comparisons between vancomycin and fidaxomicin would determine whether the reduced dysbiosis associated with fidaxomicin is cost-effective in relation to its higher acquisition cost. The challenge with antibiotic use as primary prophylaxis is development of resistance. The addition of a nonantibiotic option such as a biotherapeutic that restores colonization resistance to *C. difficile* and other MDROs has been shown to be effective as a secondary prophylaxis strategy [10], and use as a primary prophylaxis strategy should be studied. A number of nontraditional strategies could also be considered. The *C. difficile* toxin-binding agent tolevamer failed the primary endpoint of clinical cure in phase 3 trials but did demonstrate lower recurrence rates [11]. Likewise, bezlotoxumab demonstrated lower recurrence rates in patients with CDI with a window of CDI recurrence prevention of up to 3 months [12]. All of these strategies (biotherapeutics, toxin binder, monoclonal antibody) benefit in that they are nonantibiotic options that prevent further development of antimicrobial resistance. The study by Johnson et al provides a good starting point for future trials to further optimize therapy to prevent CDI.

Notes

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