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BRIEF REPORT

Efficacy of Oral Vancomycin in Preventing Recurrent *Clostridium difficile* Infection in Patients Treated With Systemic Antimicrobial Agents

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(See the Editorial Commentary by Johnson on pages 654–5.)

We compared rates of recurrent *Clostridium difficile* infection in patients receiving or not receiving oral vancomycin prophylaxis with systemic antimicrobial therapy. The incidence of *C. difficile* infection was significantly lower in patients receiving prophylaxis (4.2% vs 26.6% in those without prophylaxis; odds ratio, 0.12; 95% confidence interval, .04–.4; $P < .001$).

Keywords. prophylaxis; *Clostridium difficile*; vancomycin; antimicrobial agents.

Clostridium difficile infections (CDIs) may be associated with significant illness and occasional deaths and are characterized by frequent recurrences [1, 2]. Unfortunately, the optimal approach to reducing the risk of recurrence, particularly in high-risk patients who require systemic antimicrobial therapy, remains unclear. During the past several years, we observed an increasing number of patients with history of CDI who were given oral vancomycin prophylaxis (OVP) when systemic antimicrobial therapy was required and wondered whether this approach was effective in reducing the risk of recurrent CDI in this patient population.

METHODS

This was a retrospective cohort study performed at Mercy Hospital St Louis, a 979-bed community teaching hospital in St Louis, Missouri. Hospital electronic health records were used to identify all adult patients (aged ≥18 years) who had previous chart documentation of "loose stools" or "diarrhea" and concurrent positive stool test for *C. difficile* by polymerase chain reaction (PCR) (Xpert C. difficile/Epi; Cephied) and were subsequently hospitalized and treated with systemic antimicrobial therapy. The study period for previous CDI episode and subsequent hospitalization requiring systemic antimicrobial therapy was 1 January 2010 through 31 December 2014.

Recurrence of CDI was defined as symptoms of loose stools or diarrhea in a patient whose stool tested positive for *C. difficile* by PCR within 4 weeks after completion of systemic antimicrobial agents, based on inpatient and outpatient provider notes. We targeted the 4-week period after completion of systemic antimicrobial therapy because the highest incidence of CDI after hospital discharge occurs during this period [3] and longer surveillance periods might have increased the likelihood of including patients who acquired *C. difficile* after completion of OVP.

Systemic antimicrobial therapy was defined as ≥1 day of treatment with ≥1 agent. Exclusion criteria included pregnancy, vancomycin allergy, concurrent treatment with metronidazole for any indication during OVP, and diagnosis with inflammatory bowel disorder (eg, Crohn disease), diverticulosis, diverticulitis, or bacterial gastrointestinal infection with agents other than *C. difficile* (eg, *Salmonella* sp.). Fisher exact and Student *t* tests were used to compare categorical and continuous data, respectively, with differences considered statistically significant at $P < .05$. The study was approved by Mercy Hospital's institutional review board.

RESULTS

Of 580 patients initially screened, 377 had ≥1 exclusion criterion; 198 had inflammatory bowel disorder, 119 were receiving concurrent metronidazole therapy, 46 had bacterial gastroenteritis, 8 were <18 years old, and 6 were pregnant. Of the remaining 203 eligible patients, 71 received OVP (29 [41%] at a dose of 125 mg and 42 [59%] at a dose of 250 mg twice daily) during the course of their systemic antibiotic therapy and for up to 1 week after its completion, and 132 received no OVP (control group). The mean duration of OVP (including both inpatient and postdischarge days) was 13.7 days (range, 3–29 days).

Patient characteristics in OVP and control groups are shown in Table 1. There was no significant difference between the 2 groups with regard to age, sex, race, interval between previous CDI and hospital admission, probiotic use in the hospital, rate of discharge to home, mean duration of systemic antimicrobial therapy, or use of selected antimicrobials, including fluoroquinolones (levofloxacin or ciprofloxacin), cephalosporins, aminopenicillins, aztreonam, or a fixed combination therapy with intravenous vancomycin, levofloxacin, and piperacillin-tazobactam. The OVP group was significantly more likely to have received a carbapenem or a gastric acid-suppressive agent (ie, histamine-2 receptor antagonist [H2RA]) or a proton-pump inhibitor (PPI). The mean duration

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Table 1. Patient Characteristics in Oral Vancomycin Prophylaxis and Control Groups

Characteristic	OVP Group (n = 71)	Control Group (n = 132)	*P* Value
Male, No. (%)	36 (51)	67 (51)	>.99
Age, mean (range), y	73 (41–97)	69 (25–9)	.07
White race, No. (%)	58 (82)	105 (80)	.85
Probiotics, No (%)[a]	31 (14)	21 (16)	.84
Systemic antimicrobials, No. (%)			
Fluoroquinolones	31 (43.7)	47 (35.6)	.29
Aminopenicillins[b]	35 (49.3)	63 (47.7)	.88
Cephalosporins	25 (35.2)	59 (44.7)	.23
Carbapenems	14 (19.7)	16 (12.1)	.15
Meropenem and imipenem	12 (16.9)	10 (7.6)	.06
Ertapenem	6 (8.5)	6 (4.5)	.35
Vancomycin, piperacillin-tazobactam, and levofloxacin[c]	16 (22.5)	21 (15.9)	.26
Duration of systemic antimicrobial therapy, mean (range), d	12.5 (2–56)	11.9 (3–42)	.67
H2RA or PPI, No. (%)			
Before admission	39 (54.9)	70 (53)	.77
Inpatient	58 (81.7)	90 (68.2)	.047
Prior CDI, mean (range), mo	6.14 (1–21)	7.61 (1–22)	.16
Discharged to home, No. (%)	40 (56.3)	74 (56.1)	1.0

Abbreviations: CDI, *Clostridium difficile* infection; H2RA, histamine-2 receptor antagonist; OVP, oral vancomycin prophylaxis; PPI, proton-pump inhibitor.

[a] *Saccharomyces boulardii* administered during inpatient stay.

[b] Ampicillin, ampicillin-sulbactam, amoxacillin, and amoxacillin-clavulanate.

[c] Intravenous vancomycin, piperacillin-tazobactam, and levofloxacin as a fixed combination.

of OVP after discontinuation of systemic antimicrobial therapy was 0.8 days (range, 0–6 days).

CDI was diagnosed in 3 (4.2%) patients in the OVP group, compared with 35 (26.6%) in the control group (odds ratio, 0.12; 95% confidence interval, .04–.4; $P < .001$). Of the 3 patients with CDI in the OVP group, 2 were in the 250-mg and 1 in the 125-mg twice-daily subgroup. Two of 3 CDI cases initially diagnosed in the OVP group (1 case in each subgroup), were eventually thought to have been "asymptomatic" based on clinician assessment.

DISCUSSION

Although antimicrobial agents remain the major risk factor for CDI [4], their use in hospitalized patients is often inevitable. Unfortunately, patient populations in need of antimicrobial therapy and those at high risk of CDI recurrence often overlap, making it imperative to explore ways by which CDI can be prevented in such patients. Our findings demonstrate the potential utility of OVP in reducing the risk of recurrent CDI in patients who require systemic antimicrobial therapy.

One potential strength of our study is that the OVP and control groups were largely comparable for several variables that might affect the risk of CDI, such as age, H2RA or PPI use, and the great majority of selected antibiotics. Although the in-hospital use of carbapenems and H2RA or PPIs was significantly higher in the OVP group, neither variable would be expected to reduce the rate of CDI. Another potential strength of our study is that testing of stool for CDI was based on the highly sensitive PCR method [5], minimizing the likelihood of false-negative cases. Our finding that 2 of 3 *C. difficile*–positive patients in the OVP group were eventually considered asymptomatic may reflect the suboptimal positive predictive value of PCR (as low as 71%) in populations with a relatively low prevalence of CDI [6, 7]. Another notable finding of our study was the frequently brief duration of OVP (mean, about 1 day) after completion of systemic antimicrobial therapy. Whether a longer duration of OVP would have been associated with even lower CDI rates is unclear.

Several limitations of our study are worthy of emphasis. First, because of the study was retrospective, the decision to initiate OVP was based solely on the treating physician's clinical judgment. We therefore cannot exclude the possibility that patients perceived to be high risk were more likely to be given OVP. However, this possibility would have negated, not enhanced, any potential protective effect of OVP. Another limitation of our study is that, for reasons already discussed, we restricted our surveillance period to 4 weeks after completion of systemic antimicrobial therapy, which could have missed subsequent CDI cases. Finally, we did not formally study the potential impact of OVP on changes in the fecal flora favoring colonization with multidrug-resistant organisms, such as vancomycin-resistant enterococci [8, 9].

In conclusion, OVP may be effective in reducing the risk of recurrent CDI in patients who require systemic antimicrobial therapy. Prospective studies are needed to better define the risks and benefits of OVP in this vulnerable patient population.

Notes

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