Infection Control & Hospital Epidemiology (2019), **40**, 662–667
doi:10.1017/ice.2019.88

Original Article

Oral vancomycin prophylaxis during systemic antibiotic exposure to prevent *Clostridiodes difficile* infection relapses

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Abstract

Objective: To determine whether oral vancomycin prophylaxis accompanying systemic antibiotics reduces the risk of relapse in patients with history of *Clostridioides difficile* infection (CDI).

Design: Retrospective cohort study.

Patients: Adult inpatients with a history of CDI who received systemic antibiotics in either of 2 hospitals between January 2009 and June 2015.

Methods: We compared relapse rates in patients who started oral vancomycin concurrently with systemic antibiotics (exposed group) versus those who did not. We assessed for CDI relapse by toxin or nucleic acid testing at 90 days. We used inverse probability weighting and machine learning to adjust for confounders, to estimate propensity for treatment, and to calculate odds ratios for CDI relapse. We performed secondary analyses limited to toxin-positive relapses, patients with 1 versus >1 prior CDI episodes, and patients who received oral vancomycin on each antibiotic day.

Results: CDI relapse occurred within 90 days in 19 of 193 exposed patients (9.8%) versus 53 of 567 unexposed patients (9.4%; unadjusted odds ratio [OR], 1.06; 95% confidence interval [CI], 0.60–1.81; adjusted OR, 0.63; 95% CI, 0.35–1.14). CDI relapses at 90 days were less frequent in exposed patients with only 1 prior episode of CDI (OR, 0.42; 95% CI, 0.19–0.93) but not in those with >1 prior episode (OR, 1.19; 95% CI, 0.42–3.33). Our findings were consistent with a lack of benefit of oral vancomycin when restricting results to toxin-positive relapses and to patients who received vancomycin each antibiotic day.

Conclusions: Prophylactic oral vancomycin was not consistently associated with reduced risk of CDI relapse among hospitalized patients receiving systemic antibiotics. However, patients with only 1 prior CDI episode may benefit.

(Received 23 October 2018; accepted 18 March 2019)

Clostridioides difficile infection (CDI) is the most common healthcare-associated infection in the United States,[1] with >450,000 cases and close to 30,000 deaths per year.[2] The rate of relapse is ~25%,[3,4] and 58% of the $4.8 billion in annual healthcare costs attributable to *C. difficile* is linked to recurrent disease.[2] Recurrent infection also causes significant morbidity due to repeat testing and treatment, rehospitalization, and possible colectomy.[5] Thus, there is a need to identify practical ways of reducing the risk of CDI relapse, especially during times of heightened risk such as exposure to systemic antibiotics.

One strategy to prevent relapse is the prophylactic use of oral antibiotics with activity against *C. difficile* in patients with a history of CDI who require systemic antibiotics for other indications. Two retrospective analyses of the impact of prophylactic vancomycin have suggested that this strategy may be protective against CDI relapse[6,7]; however, these analyses did not adjust for some confounders associated with CDI risk, including the number[8,9] and risk class[10] of systemic antibiotics given, severity of illness,[11] and use of gastric acid suppressants.[12,13] Therefore, we conducted a retrospective analysis of the impact of prophylactic oral vancomycin on the incidence of CDI relapse, using detailed electronic health record data to account for differences between patients who did and did not receive prophylaxis.

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Cite this article: Caroff DA, *et al.* (2019). Oral vancomycin prophylaxis during systemic antibiotic exposure to prevent *Clostridiodes difficile* infection relapses. *Infection Control & Hospital Epidemiology*, 40: 662–667, https://doi.org/10.1017/ice.2019.88

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https://doi.org/10.1017/ice.2019.88 Published online by Cambridge University Press

Methods

Study design

We conducted a retrospective cohort study of adults hospitalized at 2 academic medical centers in Boston, Brigham and Women's Hospital (BWH) and Massachusetts General Hospital (MGH). We identified all patients from January 1, 2009, through June 30, 2015, who tested positive for toxigenic *C. difficile* by either stool toxin enzyme immunosorbent assay (ELISA, formerly Alere, subsequently acquired by Abbott Laboratories, Chicago, IL) or nucleic acid amplification testing (NAAT, Cepheid, Sunneyvale, CA). The testing algorithm included a dual toxin and glutamate dehydrogenase (GDH) antigen test with NAAT used in the case of indeterminate results. Test results from either hospital, or outpatient primary care and specialty practices affiliated with either hospital, were eligible. Patients were included if they had any hospitalizations at BWH or MGH within the subsequent 150 days after a positive test during which at least 1 dose of a systemic antibiotic was administered. We chose 150 days to allow for a large sample of eligible patients while limiting patients with very remote infections who may not hve been considered candidates for prophylaxis. When multiple hospitalizations were eligible, only the first hospitalization was included. Patients with positive *C. difficile* testing within 30 days before or 2 days after admission were excluded to omit patients with active CDI.

Group assignment

Patients who received oral vancomycin within 1 calendar day before or after starting systemic antibiotics were included in the vancomycin exposure (exposed) group. Patients who began oral vancomycin on day 2 after systemic antibiotic exposure underwent chart review by 1 study physician (D.A.C.) to determine whether the intent was prophylaxis or active treatment for recurrent CDI. Cases in which documentation indicated prophylactic intent were included as part of the exposed group. Cases in which the treatment intent was therapeutic were included in the unexposed group and classified as instances of CDI relapse. In addition, all patients who did not receive oral vancomycin within 2 days of starting systemic antibiotics were included in the unexposed group.

Outcomes and subgroups

The primary outcome was positive *C. difficile* testing within 90 days after systemic antibiotic exposure by either toxin assay or NAAT. Secondary outcomes included CDI relapse within 180 days and toxin-positive CDI only. We performed a stratified analysis among patients with 1 versus 2 or more positive *C. difficile* tests within the previous 12 months based on a previous trial;[7] patients enrolled during calendar year 2009 were excluded from this analysis to ensure complete data. Finally, we analyzed rates of relapse after limiting the exposed group to those who received oral vancomycin on all systemic antibiotic days, and separately after excluding unexposed patients who received oral vancomycin after day 2 in the absence of a positive *C. difficile* test.

Data collection

We collected the following data from an institutional electronic database: age, sex, race, hospital admission and discharge dates, vital status upon discharge, hospital length of stay, patient comorbidities derived from diagnosis codes using the method of Elixhauser et al,[14] ICU utilization, *C. difficile* test results, daily inpatient medication administration records, and all outpatient prescriptions. The most abnormal serum laboratory values within 1 day of study inclusion were collected for hematocrit, albumin, creatinine, lactate, and total bilirubin; missing values were imputed with the mean for each group. White blood cell count was treated as a categorical variable (Table 1). Antibiotic risk was classified as high, medium, or low risk based on published data (Appendix 1 online).[10,15] The study was reviewed and approved by the Partners Healthcare Institutional Review Board.

Statistical analysis

Data were analyzed using R statistical software version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria). Baseline covariates were compared between groups using univariate logistic regression. We estimated the average effect of treatment using inverse probability weighting for each comparison. Inverse probability weights incorporate a propensity score for treatment and the probability of missing data using Super Learner, an ensemble machine-learning algorithm that assesses multiple machine-learning methods and then uses cross validation to select the most accurate method or combination of methods in the algorithm library specified by users.[16,17] Super Learner combines propensity score predictions from multiple algorithms; our analysis used Lasso, elastic-net regularized generalized linear models, classification and regression tree (CART), and random forest. Super Learner optimally combines the predicted values from each candidate learner through a weighted average and computes estimated predicted values that asymptotically outperform each of the candidate estimators in the library even if the "correct" parametric model is not included in the candidate library. Super Learner has been shown to reduce bias and improve propensity score prediction compared with traditional logistic regression.[18]

We assessed all available covariates, as well as a set of covariates proposed by the authors based on clinical experience, to calculate propensity score and conditional probability. The covariate set proposed by the authors included age, Elixhauser score, antibiotic risk class, days since most recent positive *C. difficile* test, number of prior positive *C. difficile* tests, and ICU admission.

Using these propensity scores, we calculated the estimated treatment effect of oral vancomycin using a weighted logistic regression model, with the inverse probability weights calculated as: $I_{trt} \times [\Delta/\text{missingness probability}) + (1 - I_{trt}) \times (\text{PS}/(1 - \text{PS})] \times \Delta/\text{missingness probability}$, where $\Delta = 0$ indicates death before relapse, otherwise $\Delta = 1$. We truncated the inverse probability weights at the 99th percentile. A robust standard error estimate was used to calculate 95% confidence intervals on the log scale.

Results

In total, 760 patients met inclusion criteria. Of these, 193 of 760 (25%) received oral vancomycin within 1 calendar day of starting systemic antibiotics and 567 of 760 (75%) did not. (Table 1).

The mean duration of systemic antibiotic exposure was 5.99 days (SD, 6.29) for the exposed group versus 5.41 days (SD, 6.65) for the unexposed group ($P = .27$). Within the exposed group, oral vancomycin was administered on all systemic antibiotic days in 118 patients (61%) and on at least half of all antibiotic days in 152 patients (79%). The mean duration of oral vancomycin was 2.29 days (SD, 5.77). Outpatient antibiotic prescriptions (other than oral vancomycin) were given at discharge to 54.4% and 50.6% of patients in the exposed and unexposed groups,

https://doi.org/10.1017/ice.2019.88 Published online by Cambridge University Press

Table 1. Baseline Characteristics

	Raw Sample						After IPTW					
	Unexposed Group (n = 567)		Exposed Group (n = 193)		Absolute Difference	*P* Value	Unexposed Group (n = 567)		Exposed Group (n = 193)		Absolute Difference	*P* Value
Age, mean y (SD)	58.9	(17.6)	63.6	(16.9)	4.7	<.01	62.9	(17.3)	62.6	(17.2)	0.3	.85
Male sex, no. (%)	261	(46.0)	81	(42.0)	4.0	.33	255	(44.9)	81	(42.2)	2.7	.49
Admitting hospital BWH, no. (%)	269	(47.4)	98	(50.8)	3.4	.42	290	(51.2)	99	(51.5)	0.3	.78
Race, no. (%)												
White (referent)	471	(83.1)	163	(84.5)	1.4	. . .	490	(86.4)	164	(84.9)	1.5	. . .
Asian	16	(2.8)	6	(3.1)	0.3	.52	21	(3.7)	7	(3.5)	0.2	.92
Black	38	(6.7)	11	(5.7)	1.0	.80	25	(4.4)	11	(5.8)	1.4	.43
Hispanic	26	(4.6)	2	(1.0)	3.6	.12	9	(1.6)	1	(0.7)	0.9	.28
Other	16	(2.8)	11	(5.7)	2.9	.27	22	(3.9)	10	(5.2)	1.3	.44
Year of study inclusion, no. (%)												
2009	48	(8.5)	11	(5.7)	2.8	. . .	51	(8.9)	11	(5.6)	3.3	. . .
2010	68	(12.0)	19	(9.8)	2.2	.61	55	(9.7)	17	(8.8)	0.9	.36
2011	87	(15.3)	21	(10.9)	4.4	.90	76	(13.5)	20	(10.2)	2.3	.62
2012	104	(18.3)	23	(11.9)	6.4	.93	78	(13.7)	26	(13.3)	0.4	.25
2013	123	(21.7)	67	(34.7)	13	.02	175	(30.9)	72	(37.4)	6.5	.05
2014	110	(19.4)	41	(21.2)	1.8	.20	106	(18.7)	40	(20.7)	2.0	.11
2015	27	(94.8)	11	(5.7)	0.9	.24	26	(4.6)	8	(4.2)	0.4	.44
Elixhauser Score, mean (SD)	2.4	(1.4)	2.3	(1.4)	0.1	.36	2.3	(1.4)	2.3	(1.4)	0.0	.78
Hospital LOS, mean d (SD)	12.3	(13.8)	11.5	(11.5)	0.8	.87	12.6	(13.6)	11.8	(12.6)	0.8	.47
Serum Laboratory Values on study inclusion, mean (SD)												
Lowest hematocrit, g/dL	28.7	(5.2)	28.1	(5.4)	0.6	<.01	28.1	(4.8)	27.4	(5.2)	0.7	.07
Highest bilirubin, mg/dL	1.0	(2.5)	0.9	(1.1)	0.1	.72	0.8	(1.0)	1.0	(1.2)	0.2	.08
Lowest albumin, g/dL	3.2	(0.5)	3.0	(0.7)	0.1	<.01	3.1	(0.6)	3.0	(0.6)	0.1	.15
Highest creatinine, mg/dL	1.5	(1.7)	1.4	(1.4)	0.1	.20	1.4	(1.6)	1.3	(1.3)	0.1	.45
Highest lactate, mmol/L	2.1	(1.2)	2.2	(1.7)	0.1	.39	2.0	(0.9)	2.0	(1.2)	0.0	.74
Serum white blood cell count on study inclusion, no. (%)												
4,000–12,000/dL (referent)	308	(54.3)	87	(45.1)	9.2	. . .	264	(46.5)	83	(43.0)	3.5	. . .
<4,000/dL	62	(10.9)	43	(22.3)	11.4	<.01	77	(13.6)	35	(18.4)	4.8	.26
>12,000/dL	184	(32.5)	59	(30.6)	1.9	.51	220	(38.8)	72	(37.3)	1.5	.71
Missing	13	(2.3%)	4	(2.0)	0.3	.88	6	(1.1)	3	(1.4)	0.3	.30
Antibiotic Exposure Risk Class, no. (%)[a]												
Low risk	113	(20.0)	33	(17.0)	3.0	.34	34	(17.4)	93	(16.5)	0.9	.75
Medium risk	164	(29.0)	41	(21.0)	8.0	.04	43	(22.3)	124	(21.9)	0.4	.90
High risk	374	(66.0)	164	(85.0)	19.0	<.01	155	(80.1)	470	83.0)	2.9	.36
Unique antibiotics received at index date, mean, SD	2.0	(0.8)	2.3	(0.9)	0.3	<.01	2.1	(0.9)	2.2	(0.8)	0.1	.11
Days since last positive *C. difficile* test, mean SD	75.2	(31.1)	117.7	(165.0)	42.5	<.01	65.3	(27.7)	61.1	(29.2)	4.2	.07
Positive *C. difficile* tests in prior 12 mo, no. (%)												
1 (referent)	338	(68.4)	126	(65.3)	3.1	. . .	380	(67.1)	128	(66.6)	0.5	. . .
2 or more	179	(31.6)	67	(34.7)	3.1	<.01	187	(32.9)	72	(33.4)	0.5	.89
Critical care CPT code within 1 d of index	108	(19.0)	44	(23.0)	4.0	.22	120	(21.1)	41	(21.1)	0.0	1.00
PPI given within 1 d of index	296	(52.0)	93	(48.0)	4.0	.36	267	(47.1)	93	(48.4)	1.3	.75

(*Continued*)

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Table 1. (*Continued*)

	Raw Sample						After IPTW					
	Unexposed Group (n = 567)		Exposed Group (n = 193)		Absolute Difference	*P* Value	Unexposed Group (n = 567)		Exposed Group (n = 193)		Absolute Difference	*P* Value
Probiotic given within 1 d of index	23	(4.0)	15	(8.0)	4.0	.03	39	(6.9)	14	(7.4)	0.5	.79
Vasopressor within 1 d of index	62	(11.0)	19	(10.0)	1.0	.77	50	(8.8)	14	(7.1)	0.3	.42
Prior colectomy	40	(7.0)	6	(3.0)	4.0	.05	21	(3.6)	6	(3.3)	0.3	.82

Note. IPTW, inverse probability weighting; SD, standard deviation; BWH, Brigham and Women's Hospital; LOS, length of stay; CPT, current procedural terminology; PPI, proton pump inhibitor.
[a]See Appendix 1 for antibiotic risk class assignments.

Table 2. Unadjusted and Adjusted Results

	90 d From Antibiotic Exposure		180 d From Antibiotic Exposure	
Variable	Relapses per Patient (%)	OR (95% CI)	Relapses per Patient (%)	OR (95% CI)
Unadjusted analysis				
No prophylactic antibiotic (referent)	53/567 (9.35)	. . .	54/567 (9.52)	. . .
Oral vancomycin	19/193 (9.84)	1.06 (0.60–1.81)	22/193 (11.40)	1.22 (0.71–2.04)
Adjusted analysis				
No prophylactic antibiotic (referent)	53/567 (9.35)	. . .	54/567 (9.52)	. . .
Oral vancomycin	19/193 (9.84)	0.63 (0.35–1.14)	22/193 (11.40)	0.72 (0.41–1.29)
Relapse defined by toxin test (ELISA) only				
No prophylactic antibiotic (referent)	42/567 (7.41)	. . .	43/567 (7.58)	. . .
Oral vancomycin	14/193 (7.25)	0.58 (0.30–1.15)	17/193 (8.81)	0.67 (0.35–1.28)
1 positive *C. difficile* test in the prior 12 months				
No prophylactic antibiotic (referent)	37/353 (10.48)	. . .	37/353 (10.48)	. . .
Oral vancomycin	10/118 (8.47)	0.42 (0.19–0.93)	11/118 (9.32)	0.44 (0.20–1.0)
≥2 positive *C. difficile* tests in the prior 12 months				
No prophylactic antibiotic (referent)	13/166 (7.83)	. . .	14/166 (8.43)	. . .
Oral vancomycin	7/64 (10.94)	1.19 (0.42–3.33)	9/64 (14.06)	1.29 (0.49–3.38)
Patients treated for 100% of antibiotic days				
No prophylactic antibiotic (referent)	53/567 (9.35)	. . .	54/567 (9.52)	. . .
Oral vancomycin	12/118 (10.17)	0.76 (0.38–1.52)	14/118 (11.86)	0.82 (0.42–1.60)
Patients treated for 100% of antibiotic days, excluding unexposed patients who received oral vancomycin ≥3 d following antibiotic exposure				
No prophylactic antibiotic (referent)	46/489 (9.41)	. . .	47/489 (9.61)	. . .
Oral vancomycin	12/118 (10.17)	0.86 (0.44–1.69)	14/118 (11.86)	0.81 (0.41–1.59)

Note. OR, odds ratio; CI, confidence interval; ELISA, enzyme-linked immunosorbent assay.

respectively ($P = .41$). Also, 78 patients in the unexposed group received oral vancomycin 3 or more days after antibiotic exposure, either preceding or in the absence of a positive *C. difficile* test. No patients began oral vancomycin on day 2, so no chart reviews were performed.

Overall, CDI relapse occurred in 76 of 760 patients (10%); at 90 days, there were 19 relapses among 193 patients (9.8%) in the exposed group and 53 relapses among 567 patients (9.4%) in the unexposed group (Table 2). At 180 days, there were 3 additional positive assays in the exposed group (total 22, 11.4%) and 1 additional positive assay in the unexposed group (total 54, 9.5%). At 90 days, there were 14 positive toxin assays in the exposed group (7.3%) and 42 in the unexposed group (7.4%). Mean days between antibiotic exposure and relapse were 34.47 days (SD, 28.64) in the exposed group and 29.40 days (SD, 28.70) in the unexposed group. At 90 days of follow-up, 31 of 193 (16.1%) patients in the exposed group had died and 99 of 567 (17.5%) in the unexposed group had died. At 180 days of follow-up, 42 of 193 (21.8%) patients in the exposed group had died and 130 of 567 (22.9%) in the unexposed group had died.

The unadjusted odds ratio (OR) for the primary outcome at 90 days was 1.06 (95% confidence interval [CI], 0.60–1.81) for the exposed versus unexposed group (Table 2). After inverse weighting, the adjusted odds ratio for relapse at 90 days was 0.63 (95% CI, 0.35–1.14) for the exposed versus unexposed group. The adjusted odds ratios were similar for risk of relapse within 180 days and when restricting the analysis to patients with toxin-positive CDI relapse (Table 2). For patients with only 1 prior positive *C. difficile*

https://doi.org/10.1017/ice.2019.88 Published online by Cambridge University Press

test in the preceding 12 months, the odds of relapse at 90 days were 0.42 (95% CI, 0.19–0.93) for the exposed versus unexposed group. For patients with 2 or more positive *C. difficile* tests in the preceding 12 months, the odds of relapse at 90 days were 1.19 (95% CI, 0.42–3.33) for the exposed versus unexposed group. Among patients in the exposed group who received oral vancomycin on all systemic antibiotic days, the odds of relapse were 0.76 (95% CI, 0.38–1.52) at 90 days and 0.82 (95% CI, 0.42–1.60) at 180 days versus the unexposed group. After excluding the 78 patients in the unexposed group who received oral vancomycin 3 or more days after antibiotic exposure, the odds of relapse at 90 days were 0.86 (95% CI, 0.44–1.69) and at 180 days were 0.81 (95% CI, 0.41–1.59) in the exposed versus unexposed group.

Discussion

Effective strategies are needed to prevent CDI, particularly in patients at high risk for recurrent disease. Oral antibiotic prophylaxis with vancomycin has gained attention in recent years, specifically in patients with a history of *C. difficile* who require systemic antibiotics for another infection. In this study, however, we found inconsistent short- and long-term benefits of prophylactic oral vancomycin for reducing the risk of CDI relapse when given alongside systemic antibiotics in hospitalized patients with a history of CDI. Although a potential protective effect of oral vancomcyin was seen in patients with only 1 previous CDI, we did not find any benefit among the full study population or in those with >1 prior episode of CDI.

Other investigators have reported more success with oral vancomycin for prevention of CDI relapse. In a retrospective study of 203 inpatients, Van Hise et al[6] reported an 88% reduced odds of CDI relapse within 4 weeks of antibiotic exposure in patients who received oral vancomycin alongside systemic antibiotics (OR, 0.12; 95% CI, 0.04–0.4).[6] This study did not include a multivariate analysis, and although both study groups were similar in distribution of certain CDI risk factors, the analysis did not include measures of comorbidities, severity of illness, number of previous CDIs, or number of systemic antibiotics given.

A second retrospective study by Carignan et al[7] evaluated 551 patients who received systemic antibiotics within 90 days following an initial or recurrent episode of CDI and followed them for relapse for 90 days after systemic antibiotic exposure. Overall, they reported a protective effect of oral vancomycin against relapse (adjusted hazard ratio [aHR], 0.59; 95% CI, 0.43–0.80), but the effect was limited to patients with ≥2 prior CDI episodes. They did not detect an effect among patients with only 1 previous CDI episode (aHR, 0.91; 95% CI, 0.57–1.45). This result contrasts with our findings, which only showed possible benefit in patients with 1 previous CDI and no benefit in those with ≥2 episodes. Our analysis included adjustments for several potential confounders that were not included in the prior study including gastric acid suppressants, antibiotic risk class, number of systemic antibiotics given, comorbid illness, and severity of illness. These factors may explain some of the differences in our findings.

Our study raises questions about the benefits of prophylactic oral vancomycin to prevent recurrent CDI in hospitalized patients receiving systemic antibiotics. This strategy might benefit patients with only 1 previous CDI, but the magnitude of this benefit is uncertain and contradicts results from a previous study. The rationale for oral prophylactic antibiotics in patients with a history of CDI seems intuitive and reflects extensive clinical experience using antibiotics to prevent infection in other circumstances such as severe immunosuppression and perioperative care, so it is understandable that this practice has become commonplace despite a lack of strong evidence. Importantly, however, the mechanism of CDI is unique compared to most other infections in that it requires a disturbed intestinal microbiome, a precondition which may be induced by antibiotics, including those with anti–*C. difficile* activity such as oral vancomycin. This concept is supported by a small randomized controlled trial of *C. difficile* decolonization in which use of oral vancomycin led to a significantly higher rate of recolonization after 2 months versus placebo.[19] Therefore, it is plausible that any prophylactic effect of oral vancomycin against *C. difficile* is counterbalanced by an adverse effect on other gut commensals and, thus, confers no long-term benefit against relapse.

This study has several limitations. As with all retrospective studies, our results could be affected by residual confounding; we attempted to mitigate this by including an extensive array of clinical variables and using a machine learning algorithm to identify the most consequential covariates, along with inverse probability weighting with propensity scoring to make robust estimates of treatment effect. These adjustments eliminated known differences between groups but unmeasured residual confounding could have remained. There was a slightly longer duration of antibiotic exposure in the exposed group (5.99 vs 5.41 days; $P = .27$), which could have biased results in favor of the unexposed group, although this difference was small and nonsignificant. We used laboratory testing alone to diagnose CDI relapse, leaving open the possibility that some positive *C. difficile* assays (ie, NAAT) may have merely represented colonization.[20] To address this possibility, we conducted a secondary analysis of relapse by toxin testing that yielded very similar results. Also, we could not determine the exact duration of antibiotic exposure after hospital discharge nor postdischarge antibiotic prescriptions due to the limitations of our institutional database. We did, however, show that rates of outpatient antibiotic prescriptions were similar across groups at discharge. We were only able to identify CDI relapse that was captured by laboratory testing at the 2 study hospital systems. Both study hospitals are large, academic medical centers, so our results may not be generalizable to other settings. Finally, confidence intervals for all effect estimates were wide and do not preclude the possibility that a study with more power could detect a positive effect of prophylaxis.

In conclusion, we found an inconsistent benefit of oral vancomycin for prevention of CDI relapse in patients with prior CDI and subsequent exposure to systemic antibiotics while hospitalized. Patients with only 1 prior CDI episode may have a reduced risk of CDI relapse from prophylactic oral vancomycin but there was no apparent benefit for patients with a history of ≥2 prior episodes of CDI. Prospective randomized trials are needed to determine whether this practice is truly beneficial.

Supplementary Material. To view supplementary material for this article, please visit https://doi.org/10.1017/ice.2019.88

Acknowledgments. The content is solely the responsibility of the authors and does not necessarily represent the official view of the Agency for Healthcare Research and Quality.

Financial support. Dr Rhee received support from the Agency for Healthcare Research and Quality for this study (grant no. K08HS025008).

Conflicts of interest. All authors report no conflicts of interest relevant to this article.

https://doi.org/10.1017/ice.2019.88 Published online by Cambridge University Press

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https://doi.org/10.1017/ice.2019.88 Published online by Cambridge University Press