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Original Article

Oral vancomycin prophylaxis against recurrent *Clostridioides difficile* infection: Efficacy and side effects in two hospitals

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Abstract

Objective: The data regarding the effectiveness of chemical prophylaxis against recurrent *C. difficile* infection (CDI) remain conflicting.

Design: Retrospective cohort study on the effectiveness of oral vancomycin for prevention of recurrent CDI.

Setting: Two academic centers in New York.

Methods: Two participating hospitals implemented an automated alert recommending oral vancomycin 125 mg twice daily in patients with CDI history scheduled to receive systemic antimicrobials. Measured outcomes included breakthrough and recurrent CDI rates, defined as CDI during and 1 month after initiation of prophylaxis, respectively. A self-controlled, before-and-after study design was employed to examine the effect of vancomycin prophylaxis on the prevalence of vancomycin-resistant *Enterococcus* spp (VRE) colonization and infection.

Results: We included 264 patients in the analysis. Breakthrough CDI was identified in 17 patients (6.4%; 95% confidence interval [CI], 3.8%–10.1%) and recurrent in 22 patients (8.3%; 95% CI, 5.3%–12.3%). Among the 102 patients with a history of CDI within the 3 months preceding prophylaxis, 4 patients (3.9%; 95% CIs, 1.1%–9.7%) had breakthrough CDI and 9 had recurrent disease (8.8%; 95% CIs, 4.1%–16.1%). In the 3-month period following vancomycin prophylaxis, we detected a statistically significant increase in both the absolute number of VRE (χ^2, 0.003) and the ratio of VRE to VSE isolates (χ^2, 0.003) compared to the combined period of 1.5 months preceding and the 3–4.5 months following prophylaxis. This effect persisted 6 months following prophylaxis.

Conclusions: Prophylactic vancomycin is an effective strategy to prevent CDI recurrence, but it increases the risk of VRE colonization. Thus, a careful selection of patients with high benefit-to-risk ratio is needed for the implementation of this preventive policy.

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In 2011, the Centers for Disease Control and Prevention (CDC) and the Emerging Infections Program estimated that 4% of all hospitalized patients in the United States met criteria for a hospital-acquired infection (HAI).[1] *Clostridioides difficile* (*C. difficile*) was the most frequently reported pathogen, causing 12.1% of these HAIs. This high prevalence, together with the high mortality and morbidity of the emerging hypervirulent NAP-1 strain,[2] prompted the CDC in 2013 to feature *C. difficile* as an urgent public health threat that requires aggressive action.[3] Significant efforts to decrease the burden of *C. difficile* infection (CDI) have been made since, including the establishment of antimicrobial stewardship programs,[4] newer methods of decontamination,[5] and novel CDI treatments.[6] However, the repeat study by Magill et al[7] indicated that, despite an overall decrease in the prevalence of HAIs, the CDI prevalence remained unchanged between 2011 and 2015.[7]

A cardinal concern of CDI is the high risk of recurrence, typically within the first 2–4 months after the initial episode.[8] Age >65 years, use of proton pump inhibitors, and especially systemic antibiotics for an indication other than CDI have been shown to confer an increased risk for recurrent CDI.[9] Multiple approaches, including the use of fidaxomicin,[10] restoration of the microbiome with probiotics,[11] or fecal microbiota transplantation,[12] and mandatory establishment of antimicrobial stewardship programs,[13] have been employed to decrease the risk of recurrent CDI, with variable effectiveness.

Because the risk of recurrence is known to increase in patients who are on systemic antimicrobials,[14] the use of chemical prophylaxis for the duration of antimicrobial use has recently received attention.[15,16] The effectiveness of prophylactic vancomycin as a strategy for secondary prevention in patients with history of CDI[17–19] has been studied with conflicting results. Most recently, oral vancomycin has been used for primary prevention of CDI in high-risk allogeneic stem-cell transplant recipients.[20] In this study, we present our experience from the use of prophylactic vancomycin in all patients with history of CDI who are on systemic antimicrobials in 2 hospitals over a 4.5-year period as part of a quality improvement protocol.

Methods

Study setting and population

We conducted a retrospective cohort study in 2 academic centers in New York: the 725-bed NYU Langone Medical Center and the

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450-bed NYU Langone Brooklyn Hospital. Since 2014, a best-practice advisory alert has been implemented to prompt providers to administer oral vancomycin to patients with history of CDI scheduled to receive systemic antimicrobial therapy. The protocol consists of the administration of vancomycin at a dose of 125 mg twice daily for the duration of antimicrobial therapy and 5 days thereafter, and it targets all patients with previous history of CDI regardless of age, comorbidities, and number and timing of previous infections.

Inclusion/Exclusion criteria

The list of patients who received the oral vancomycin prophylaxis protocol from January 2014 to June 2018 was obtained from pharmacy records. All hospitalized patients >18 years old with a laboratory confirmed history of CDI who were receiving systemic antimicrobials were included in the analysis. Patients were excluded if the vancomycin was administered to treat CDI, previous diagnosis of CDI was made within 14 days of the first dose of prophylaxis, first dose of prophylaxis was administered >24 hours after the first dose of systemic antimicrobials, or the last dose of prophylaxis was given >24 hours prior to the end of the course of systemic antimicrobials. Finally, patients who were approved for prophylaxis more than once during the study period were included only once in the final analysis.

Outcomes of interest

The primary outcome of interest was the rate of breakthrough CDI, defined as the onset of diarrhea while on prophylaxis, with laboratory confirmation of CDI and an associated change in the dose of vancomycin from prophylactic to therapeutic or initiation of an alternative CDI treatment. Secondary outcomes included the rate of CDI within 1 month after the initiation of prophylaxis and the rate of hospital readmission with CDI as the admission diagnosis. The rate of breakthrough CDI in patients with a history of CDI within 90 days prior to the initiation of prophylaxis was also calculated. The severity of CDI was defined according to the Infectious Diseases Society of America (IDSA) guidelines.[16] In an effort to elucidate any risk factors for failure of the chemical prophylaxis used in our hospitals, we examined the association of some well-described risk factors for recurrent CDI with the prevalence of breakthrough CDI. The following factors were examined: age >65 years,[9] gender, Charlson comorbidity index (CCI), concurrent use of metronidazole for an infection other than CDI,[15] use of fluoroquinolones as part of the systemic antimicrobial therapy,[9] proton pump inhibitors (PPIs),[9] renal insufficiency (defined as creatinine clearance <60 mL/min/1.73 m^2),[9] and number of previous CDI episodes.[16]

Finally, we assessed the association of prophylactic vancomycin with the subsequent isolation of vancomycin-resistant *Enterococcus* spp (VRE) from the patient. Because all of our patients were on prophylactic vancomycin, we selected a self-controlled before-and-after study design in which each patient acted as his or her own cohort. We hypothesized that a period of increased prevalence of VRE colonization or infection would occur after the administration of prophylaxis. Prior studies examining the natural history of VRE colonization estimated that ~50% of VRE-colonized patients lose their colonization within 6 months.[21] Thus, we compared the prevalence of VRE isolated from any source in the 3-month period following the initiation of oral vancomycin with the observed VRE prevalence in a combined 3-month period of 1.5 months preceding and 3–4.5 months following the administration of prophylaxis (Fig. 1). We included the 1.5-month period preceding the administration of prophylaxis in the comparator group to capture patients with antecedent VRE colonization or infection. Because the studied hospitals do not routinely perform surveillance cultures, we used urine and superficial wound swab cultures as surrogates for VRE colonization; isolation of VRE from other sterile sites or initiation of VRE-targeted therapy by the clinician were considered surrogates for VRE infection. As comparator outcomes, both the absence of VRE and the presence of vancomycin-sensitive *Enterococcus* spp (VSE) were examined. Finally, a sensitivity analysis was performed for which the prevalence of VRE was compared between the 6 months following the administration of oral vancomycin and the combined period of 3 months preceding and 6–9 months following the administration of prophylaxis.

Data extraction

The medical records of patients who were approved for prophylaxis were scrutinized and the following data were extracted: patient demographics, comorbidities, CCI, concomitant antimicrobials, duration of prophylaxis, date of last CDI episode and method of diagnosis, number of prior CDI episodes and episodes within 1 month after the administration of prophylactic vancomycin, 30-day readmission with a primary diagnosis of CDI, dates and results of all urine and superficial wound cultures from 3 months prior to 9 months following the administration of prophylaxis, as well as laboratory-confirmed VRE infections within 1.5 months preceding and 4.5 months following the administration of vancomycin.

Data analysis

Continuous data were presented as mean values with the standard deviation (SD) and range, and as median values with the 25th–75th interquartile range. Categorical data were presented as relative frequencies and were compared using the χ^2 test. Statistical significance was set at 0.05. Univariate and logistic regression analyses were used to detect any association between the continuous variables and prevalence of breakthrough CDI. Statistical analyses were performed using STATA version 14 software (StataCorp, College Station, TX).

Results

In a review of the pharmacy records, we identified 1,084 approvals for prophylactic vancomycin between January 2014 and September 2018. Of those, 270 were duplicates, meaning that the same patient was approved for prophylaxis more than once during the study period, and were excluded. Another 35 approvals were for patients aged <18 years and 57 were for nonhospitalized patients; these were also excluded from the final analysis. Among the remaining 722 patients, 266 were excluded because there was no laboratory confirmation of their CDI history. Another 97 were excluded because vancomycin was either started >24 hours after the initiation or ended >24 hours prior to the end of systemic antimicrobials. And 53 were excluded because the 125 mg twice daily dose of vancomycin was part of the treatment taper for a previous CDI episode. Another 42 patients were excluded for reasons presented in detail in the flow chart (Fig. 2), leaving 264 unique patients in the final analysis.

The characteristics of the 264 patients included in the study are shown in Table 1. The mean age of the included patients was 65.9 years (SD, 18.6; range, 18–98) and 53.4% were women. Their

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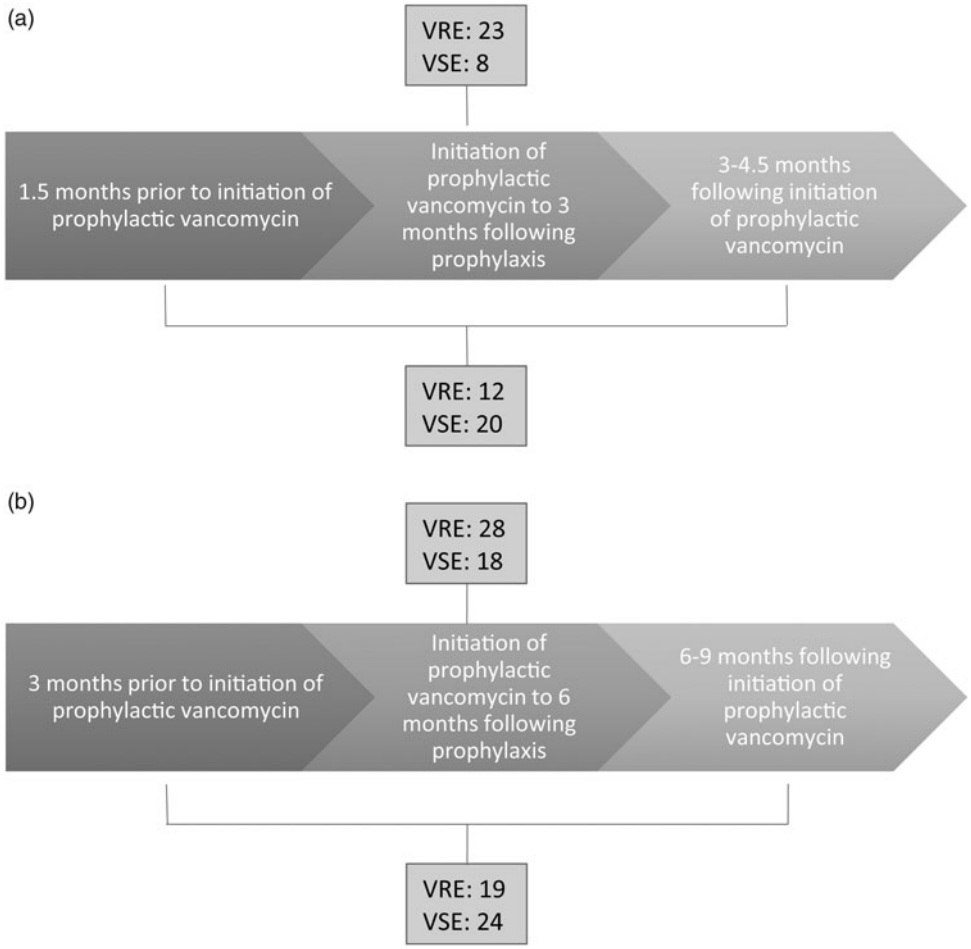

Fig. 1. Number of patients with isolated vancomycin-resistant *Enterococcus* (VRE) and vancomycin-sensitive *Enterococcus* (VSE) in urine cultures and superficial wound cultures. Comparison between (A) the 3 months following and the combined period of 1.5 months preceding and the 3.0–4.5 months following the administration of vancomycin prophylaxis (B) the 6 months following and the combined period of 3 months preceding and the 6–9 months following the administration of vancomycin prophylaxis.

mean Charlson comorbidity score was 4.6 (SD, 3.1; range, 0–14), and 75% had a CCI ≥2. At the time of vancomycin approval, the patients had history of a mean number of 1.34 CDI episodes (SD, 0.82; range, 1–7), with the last episode at a median of 147 days (interquartile range, 54–461) before the initiation of prophylaxis. Furthermore, 102 patients (38.6%) had had a CDI within 3 months prior to the administration of prophylaxis. In nearly all patients (261 patients, 98.9%), the CDI diagnosis was made with PCR. Moreover, 168 patients (63.6%) were receiving cephalosporins; 105 (39.8%) were receiving penicillins and/or penicillin combinations; 53 (20.0%) were receiving carbapenems; and 27 (10.2%) were receiving fluoroquinolones; and 220 patients (83.3%) were receiving multiple systemic antibiotics. The mean duration of prophylaxis during hospitalization was 8.4 days (SD, 7.2; range, 1–48).

Among the 264 patients who received prophylactic vancomycin while on systemic antimicrobials, 17 were diagnosed with breakthrough CDI (6.4%; 95% CI, 3.8%–10.1%). The mean age of the patients with breakthrough CDI was 59.9 years (SD, 22.6; range, 19–84); 58.8% were aged >65 years and 12 were women (70.6%). Their mean Charlson comorbidity score was 3.2 (SD, 2.4; range, 0–8), and 64.7% of the patients (11 patients) had a moderate to severe CCI. The following factors were not significantly associated with the prevalence of breakthrough CDI: gender (χ^2, 2.16; $P = .14$), age >65 years (χ^2, 0.05; $P = .82$), number of prior CDI episodes (χ^2, 2.49; $P = .87$), use of metronidazole in the antimicrobial regimen for reasons other than a *C. difficile* infection (χ^2, 0.13; $P = .72$), use of fluoroquinolones (χ^2, 0.03; $P = .87$), proton pump inhibitors (χ^2, 0.23; $P = .63$), renal insufficiency (χ^2, 0.67; $P = .41$), and the severity of CCI (χ^2, 1.29; $P = .52$). The logistic regression analysis did not show a statistically significant association between any of the aforementioned risk factors with the prevalence of breakthrough CDI. Of the 102 patients with a history of CDI within 3 months from the vancomycin prophylaxis, 4 had breakthrough CDI during incident hospitalization (3.9%; 95% CI, 1.1%–9.7%). Among the 264 patients included in the study, 239 (90.5%) had follow-up in the included hospitals for at least 1 month after the initiation of prophylaxis. During the 1-month follow-up, another 5 patients were diagnosed with CDI, for a total prevalence of recurrent CDI of 8.8% (95% CI, 4.1%–16.1%), with 3 severe infections detected. Among the 264 included patients, 70 (26.5%) had a 30-day readmission in the participating hospitals, among whom 2 had CDI as the readmission diagnosis (2.9%; 95% CI, 2.0%–9.9%).

Of the 264 patients in the study, 142 (53.8%) had at least 1 available urine culture or superficial wound culture in the 3-month period following the administration of prophylaxis, and 195 (73.9%) had at least 1 in the combined period of 1.5 months preceding and 3–4.5 months following prophylaxis. In the 3-month follow-up period, 23 patients (16.2%) had VRE isolated in either urine or superficial wound cultures compared to 12 (6.2%) in the comparator combined period of 1.5 months preceding and 3.0–4.5 months following prophylaxis (Fig. 1A). The difference was statistically significant not only in comparison to patients who did not have VRE (χ^2, 0.003) but also in comparison to

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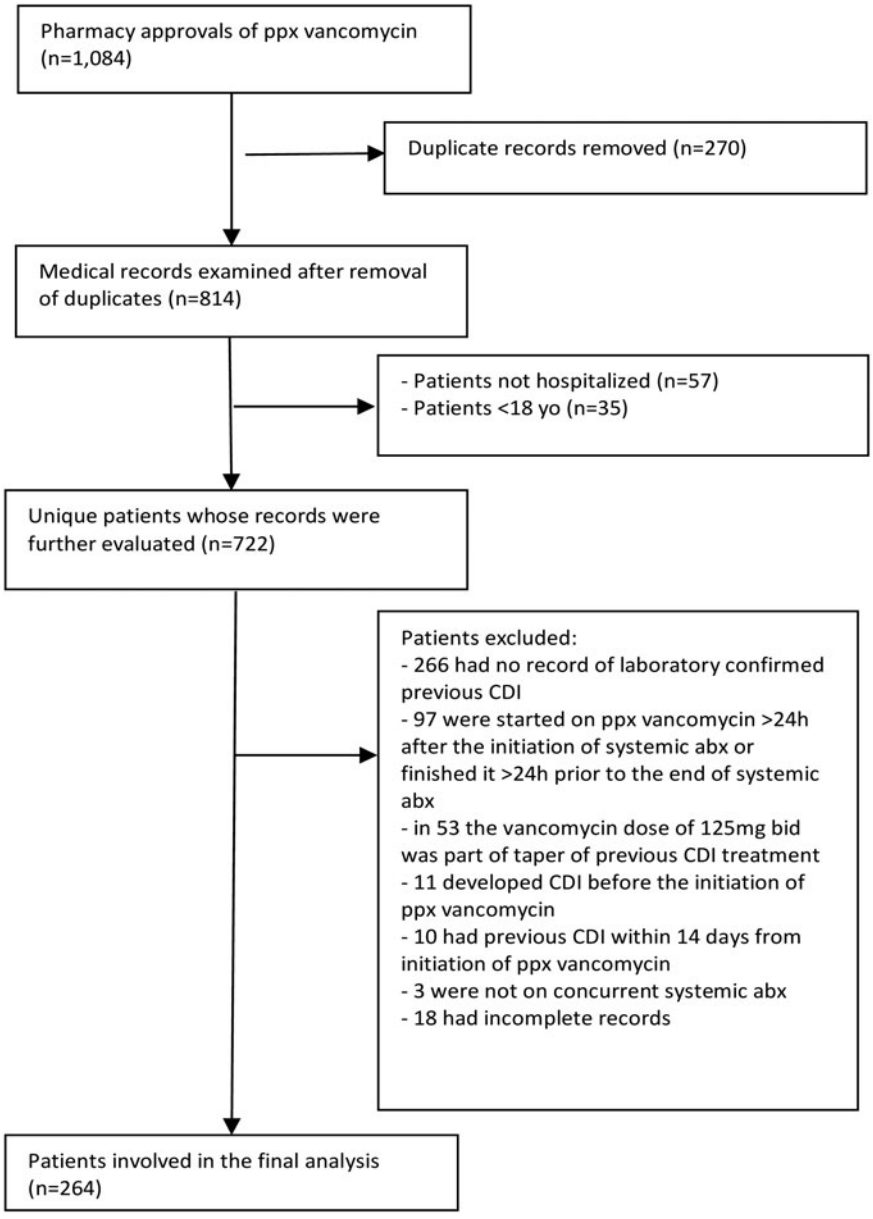

Fig. 2. Flow chart.

patients who had VSE isolation (χ^2, 0.003). In the 3-month follow-up period, there were 16 VRE-associated infections, including 4 episodes of UTI, 2 of pyelonephritis, 2 wound infections, 2 intra-abdominal abscesses, 2 episodes of bacteremia, and 1 case of CLABSI, CAUTI, peritonitis, and tricuspid valve endocarditis each. In the comparator combined period of 1.5 months preceding and 3.0–4.5 months following prophylaxis, the relevant number of VRE infections was 9, including 5 episodes of UTI, 2 of bacteremia, and 2 wound infections.

In a sensitivity analysis, the follow-up period was extended to 6 months following the administration of vancomycin, and the comparator combined period was changed to 3 months preceding and 6–9 months following prophylaxis. Furthermore, 161 patients (61%) had a urine or superficial swab culture available in the 6 months following prophylaxis, compared to 210 (79.5%) patients in the before and after period. In this analysis, a higher numbers of both absolute VRE (χ^2, 0.02) and VRE/VSE isolates (χ^2, 0.12) were identified in the immediate 6-month period following the administration of vancomycin (Fig. 1B), but only the absolute number of VRE isolates was significantly higher in the period following exposure to prophylactic vancomycin.

Discussion

In this study, we retrospectively reviewed the medical records of all patients who received vancomycin prophylaxis to prevent recurrent CDI in 2 New York academic hospitals over a 4.5-year period. The administration of prophylaxis is part of an institutional best-practice advisory that has been implemented since 2014 in our hospitals and recommends chemical prophylaxis for CDI prevention in all patients with history of CDI scheduled to receive systemic antimicrobial therapy. Among the 264 patients included in the final analysis, 6.4% developed breakthrough CDI, meaning that they experienced changes in bowel movements while on prophylaxis with laboratory confirmation of CDI and subsequent change from prophylactic to therapeutic dose of vancomycin or

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Table 1. Patient Characteristics, Type of Antibiotic Exposure, Duration of Prophylactic Vancomycin, and Characteristics of the History of *Clostridioides difficile* Infection

Demographics/Patient Characteristics	No. of Patients (%)[a]
Age >65 years old	162 (61.4)
Gender	
Male	123 (46.6)
Female	141 (53.4)
Race	
White	162 (61.4)
Black	33 (12.5)
Asian	23 (8.7)
Other/Unknown	46 (17.4)
Charlson comorbidity score; mean (SD, range)	4.6 (3.1, 0–14)
Charlson comorbidity index ≥2, %	75
Systemic antimicrobials	
Cephalosporins	168 (63.6)
Penicillins/penicillin combinations	105(39.8)
Carbapenems	53 (20.0)
Fluoroquinolones	27 (10.2)
Duration of inpatient ppx vancomycin, mean d (SD, range)	8.4 (7.2, 1–48 d)
Prior CDIs, mean (SD, range)	1.34 (0.82, 1–7)
Days from prior CDI; median (IQR)	147 (54–461)

Note: CDI, *Clostridioides difficile* infection; ppx, prophylaxis; SD, standard deviation; IQR, interquartile range.
[a]Unless otherwise specified.

alternative CDI treatment. In the 1-month follow-up, the prevalence of CDI was 8.3%. Importantly, we observed a significant increase in VRE colonization in the 3-month period following prophylaxis compared to baseline; an effect that also persisted 6 months thereafter.

Two retrospective cohort studies have previously examined the effectiveness of vancomycin prophylaxis with conflicting results.[17,18] The most recent IDSA guidelines acknowledge the results of these studies and point to the potential bias in the decision of administering or not vancomycin in both studies avoiding thus to recommend for or against this practice.[16] Van Hise et al[17] found a 4.2% prevalence of CDI in 1-month follow-up in patients with any history of CDI who received 125 mg or 250 mg prophylactic vancomycin twice daily while on systemic antimicrobials, compared to 26.6% in patients who did not receive prophylaxis. These estimates are comparable to the observed 8.3% rate of CDI in 1-month follow-up in our study. On the other hand, Carignan et al[18] studied CDI prevalence during the incident hospitalization in patients with recent history of CDI and reported a higher point prevalence of infection in those who received prophylaxis compared to those who did not (20.4% vs 19.4%). Notably, however, 83.7% of the patients who were placed on prophylaxis, actually received vancomycin at a treatment dose of 125 mg 4 times daily, and 27.3% of the included patients, received prophylaxis for <50% of the duration of antimicrobials. As these authors note, vancomycin was significantly less effective in patients that were on prophylaxis for <50% of the duration of antimicrobials.

Our study is, to the best of our knowledge, the first to report the results of the implementation of a universal policy for administration of prophylactic vancomycin at a standardized dose of 125 mg twice daily to all hospitalized patients on systemic antimicrobials who have any history of CDI, overcoming the potential biases of the previous studies. Patients who had started the prophylaxis late or finished it early in the course of systemic antimicrobials were excluded from the analysis to evaluate more precisely the effectiveness of this preventive policy. The observed 3.9% rate of CDI during the incident hospitalization in patients with a history of CDI within the 3 months preceding the admission highlights the effectiveness of chemical prophylaxis, with the relevant percentage in patients who have not received prophylaxis being reported as almost 20% in the study by Carignan et al.[18]

The transient increase in the prevalence of VRE colonization in the 6 months following the administration of vancomycin highlights the importance of targeting prophylaxis to the patients at the highest risk for CDI recurrence. The CDC has characterized VRE as a serious threat,[3] with recent estimates indicating that >1 in 3 enterococcal isolates in the United States are vancomycin resistant.[22] Despite the evidence that CDI treatment with vancomycin is shown to be equally associated with the growth of VRE in stool specimens as metronidazole[23] that led to the use of vancomycin as first-line agent for all episodes of CDI,[16] we should cautiously consider the increase in the risk of VRE colonization and potentially infection in the decision to administer vancomycin prophylaxis. Also, our finding of increased VRE/VSE ratio during the 3 months following prophylaxis should be taken into account when a patient who has been exposed to oral vancomycin has *Enterococcus* spp isolated from a clinical specimen.

This study has several limitations. First, the effectiveness of oral vancomycin prophylaxis was evaluated in comparison to previously published literature. Given the protocol-based administration of vancomycin in all eligible patients, the identification of a control group would necessitate comparison with historical cohorts before 2014. However, the fact that the diagnostic methods and antimicrobial stewardship recommendations were significantly different before 2014 would make the selection of an appropriately matched control group impossible. Second, we were not able to evaluate the reasons for the increase in CDI prevalence in the 1 month following the administration of prophylaxis. This number could be even higher if cases of recurrent CDI were diagnosed at another hospital. Finally, our hospitals do not have a surveillance protocol for VRE colonization, so we used urine and superficial swab cultures as surrogates of colonization. Given that not all patients had such a culture in both study periods, we cannot exclude the possibility that cases of VRE were missed. However, ~80% of patients had a culture in both time frames, which limits the possibility of systematic bias.

In conclusion, administration of prophylactic vancomycin at 125 mg twice daily seems to be an effective strategy in decreasing CDI recurrence. The observed increase in VRE colonization in the 6 months following the administration of vancomycin highlights the importance of a focused application of prophylaxis in patients who are at the highest risk for CDI, such as elderly patients with a recent history of CDI or patients scheduled to receive high-risk antimicrobials.

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