Risk Factors for Systemic Vancomycin Exposure Following Administration of Oral Vancomycin for the Treatment of *Clostridium difficile* Infection

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Objective To identify risk factors for systemic exposure to vancomycin (VAN) following administration of oral vancomycin (POV) for the treatment of *Clostridium difficile* infection (CDI).

Design Prospective, observational, single-center case series.

Setting Academic medical center.

Patients Hospitalized patients with suspected or confirmed CDI who received POV for at least 5 days.

Intervention Random VAN serum levels were obtained on days 5, 10, and weekly thereafter in patients treated for ≥ 5 days with POV without concomitant intravenous VAN.

Measurements and Results Of 117 random VAN serum levels from 85 patients, 58 patients (68.2%) had one or more detectable (≥ 0.05 μg/ml) levels and 15 (17.6%) of 85 patients had one or more levels > 2.5 μg/ml. Risk factors for detectable VAN exposure following administration of POV included POV dosages > 500 mg/day (odds ratio [OR] 35.83, 95% confidence interval [CI] 7.56–169.8), the presence of severe CDI (OR 4.11, 95% CI 2.76–10.83, p=0.028), intensive care unit (ICU) admission (OR 3.80, 95% CI 1.02–14.21, p=0.032), and the administration of POV ≥ 10 days (OR 6.71, 95% CI 1.81–24.83, p=0.0025). Risk factors for exposure to serum VAN concentrations > 2.5 μg/ml included the presence of gastrointestinal (GI) pathology (OR 5.22, 95% CI 3.45–18.3, p=0.031), ICU admission (OR 3.21, 95% CI 1.40–10.28, p=0.022), the use of VAN retention enemas (OR 4.73, 95% CI 2.42–20.39, p=0.036), and having a creatinine clearance ≤ 50 ml/minute or undergoing hemodialysis or continuous renal replacement therapy (OR 4.03, 95% CI 1.26–12.84, p=0.039).

Conclusions Serum VAN levels were detected in 58 (68.2%) of 85 patients receiving POV for CDI. Risk factors for systemic exposure to VAN following administration of POV included ICU admission; VAN dosages > 500 mg/day; administration ≥ 10 days or as retention enemas; and the presence of severe CDI, renal dysfunction, or inflammatory conditions of the GI tract. Unique to our study, we identified ICU admission and the concomitant use of VAN retention enemas to be significant risk factors for systemic exposure to VAN.

Key Words vancomycin retention enemas, intestinal absorption, biologic availability.

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Current practice guidelines for the management of *Clostridium difficile* infection (CDI) in adults recommend the use of oral vancomycin (POV) at a dosage of 125 mg every 6 hours in the setting of a severe initial episode of CDI (patients who present with white blood cell count [WBC] > 15,000 or serum creatinine [S_{cr}] ≥ 1.5 times the premorbid level).[1] In patients with an initial episode complicated by hypotension or shock, ileus, or megacolon, the dosage of POV should be 500 mg every 6 hours, given in combination with intravenous (IV) metronidazole 500 mg every 8 hours.[1, 2] The use of POV has significantly increased over the past several years as a result of increased rates of CDI in many health care institutions worldwide and the emergence and rapid spread of a previously rare strain, known synonymously as polymerase chain reaction ribotype 027, North American Pulse-field type 1, or restriction endonuclease analysis type BI.[3] At the University of Michigan Hospitals, use of POV increased steadily over the years from 0.5 unique POV starts per 1000 patient-days in 2005 to 2.6 in 2008.

Vancomycin (VAN) is a poorly absorbed antimicrobial agent. Oral administration of VAN to healthy individuals results in undetectable plasma and low (< 1 μg/ml) urine concentrations,[4–6] and low (≤ 1 μg/ml) serum levels in anephric subjects without inflammatory bowel disease.[6] However, previously published case reports and case series (including one from our institution[7]) suggested that certain patient populations may be at greater risk for systemic absorption of POV.[8–14]

VAN plasma concentrations as high as 58.7 μg/ml following administration of POV have been documented in patients with renal failure,[8–13] and in those administered POV at higher dosages (500 mg every 6 hr)[9, 11, 13, 15] or for prolonged durations (> 10 days) of therapy.[11, 13] Patients with severe pseudomembranous colitis,[13, 16] gastrointestinal (GI) graft-versus-host disease (GVHD),[7] or other inflammatory conditions of the GI tract such as Crohn disease or inflammatory bowel disease[6, 14, 17] have also experienced elevated plasma levels of VAN. Given reports of high serum concentrations in these settings, current Infectious Diseases Society of America (IDSA) practice guidelines for CDI in adults suggest monitoring serum VAN concentrations in patients with renal failure receiving long courses of 2 g/day.[1]

Although high VAN serum levels are concerning for toxicity and accumulation, levels < 10 μg/ml may also be of concern[9, 11, 15, 17, 18] because prolonged exposure to VAN at serum levels < 10 μg/ml may be associated with the development of resistant strains of *Staphylococcus aureus* including VAN-intermediate *S. aureus* (VISA) and VAN-resistant *S. aureus* (VRSA).[19–21]

Although a number of previous case reports or case series have proposed potential risk factors for the absorption of POV, none have statistically analyzed a large group of patients to determine independent risk factors associated with VAN exposure in patients with CDI. The goal of our study was to identify risk factors for systemic exposure to VAN following administration of POV for the treatment of CDI.

Materials and Methods

Study Design

All adult and pediatric patients with suspected or confirmed CDI between February 2010 and June 2011 who received POV (reconstituted from IV solution) for at least 5 days were included in this prospective observational single-center case series. Patients were excluded from the study if they were receiving concomitant IV VAN or had received IV VAN within the previous 30 days. Given the half-life of VAN in the setting of hemodialysis (HD) of 7 days, 1 month was determined to be an adequate washout period.

Data Collection

A random serum VAN level was obtained after at least 5 days of therapy. All samples were obtained as random concentrations irrespective of the timing of the level to the prior POV dose. Most of the serum concentrations were obtained from discarded samples initially obtained for routine clinical laboratory monitoring. Samples were stored immediately in the laboratory refrigerator, centrifuged within 4 hours, and placed into a freezer (−15°C to −20°C) to maintain sample integrity where they remained until enough samples were available to run as a batch to analyze serum concentrations. If patients remained on POV > 10 days, a serum VAN level was obtained every 7–10 days thereafter while the patients remained hospitalized. We prospectively collected data to assess potential risk factors for

VAN exposure including POV dosages > 500 mg/day or administration ≥ 10 days, the presence of severe CDI based on the Society for Healthcare Epidemiology of America (SHEA)/IDSA guidelines (i.e., findings of WBC > 15,000 or S_{cr} > 1.5 times the premorbid level),[1] intensive care unit (ICU) admission, the presence of GI pathology (e.g., inflammatory bowel disease, Crohn disease, or GI GVHD), the use of VAN retention enemas, and the presence of renal dysfunction (defined as a creatinine clearance [Cl_{cr}] ≤ 50 ml/min, or the use of HD or continuous renal replacement therapy [CRRT]). The Cl_{cr} was calculated using the Cockcroft and Gault equation.[22]

The study was conducted in accordance with the ethical standards and approval of our institution's Human Research Protection Program. All VAN samples were batched for bulk analysis; thus clinicians caring for patients did not receive notification of VAN concentrations except in the two instances in which VAN levels had been obtained during routine patient care. VAN serum concentration assays were performed using the Roche Integra 800 Analyzer that has a limit of detection (at a 95% confidence level) of 1.39 μg/ml. Patient samples, which were analyzed in duplicate, displayed a coefficient of variation (CV) of VAN concentrations < 10% at concentrations of 1.39–20 μg/ml. At concentrations ≥ 0.05 μg/ml but < 1.3, VAN levels were detectable, but CVs were > 15%. None of the patients was receiving concomitant therapy with telavancin, which can cause false-positive VAN levels when utilizing a particle-enhanced turbidimetric inhibition immunoassay.[23]

Statistical Analysis

The primary and secondary outcomes of interest were identification of risk factors associated with systemic exposure to VAN following administration of POV and the incidence of systemic exposure following the administration of POV among those treated for confirmed CDI, respectively. Bivariate and multivariate analyses were performed to determine identifiable risk factors associated with systemic exposure to VAN. Potential risk factors assessed included age, gender, weight in kilograms, renal function (calculated Cl_{cr} or requirement of renal replacement therapy), comorbid disease states (e.g., renal failure, GVHD, etc.), concomitant medications (specifically other nephrotoxins), dosage/duration of POV, and GI pathology (GVHD of the GI tract, inflammatory bowel disease, or Crohn disease).

Bivariate analysis was completed using *t* tests or the Mann-Whitney *U* test for continuous variables and the χ^2 or Fisher exact test for categorical variables to identify factors associated with systemic exposure to VAN. Given the limitations of our VAN assay, and the variability of the assay at low (< 1 μg/ml) concentrations, we chose to analyze risk factors for both detectable levels and levels > 2.5 μg/ml. The 2.5 μg/ml threshold value was selected by the investigators as clinically relevant, monitorable, and above the lower limit of detection at most institutions. Measurement of this level in a patient not receiving IV VAN would indicate systemic accumulation and exposure. In addition, available evidence suggests that VAN levels < 10 μg/ml are associated with the development of VAN resistance.[19–21] However, analyses after selection of other VAN threshold concentrations yielded similar results (data not shown). Crude odds ratios (ORs) and 95% CIs were calculated for categorical data variables, and ORs for continuous variables were obtained using a simple logistic regression. Variables with p values ≤ 0.20 in the bivariate analysis or that had a priori clinical significance were included separately in multivariate modeling and maintained if their inclusion changed the OR for the primary risk factor of interest by ≥ 15%.[24] A two-tailed test of significance with a p value ≤ 0.05 was considered statistically significant. All statistical analyses were performed using SPSS software v.21 (IBM, Las Vegas, NV) and StatView v.5.0.1 (SAS institute, Inc., Cary, NC).

Results

A total of 85 patients receiving POV were included in the analysis (79 adults and 6 children). Almost 50% of the patients were male, and the mean age of all patients was 54.8 ± 21.9 years. However, patients with detectable (≥ 0.05 μg/ml) levels of POV were significantly older than patients with undetectable levels (61.5 + 20.2 yrs and 40.3 + 19.2 yrs, respectively, p<0.005). The six children in the study were 18, 17, 15, 15, 8, and 6 years of age. Daily POV dosages and the maximum plasma levels measured in the children were 500, 1000, 2000, 2000, 735, and 880 mg, and 1.6 μg/ml, nondetectable, nondetectable, 1.0 μg/ml, nondetectable, and 0.91 μg/ml, respectively.

POV dosages ranged from 62.25–2000 mg/day; the median dosage was 500 mg/day. Of

note, only eight patients (two of whom were children, 15 yrs of age) received high (2000 mg/day) POV dosages. During the analysis period, 117 random VAN levels were obtained from the 85 patients; VAN levels were detectable in 74 (63.2%; Table 1). Fifty-eight patients (68.2%) had one or more detectable (≥ 0.05 μg/ml) levels, ranging from 0.05 to 9.94 μg/ml, and 15 patients (17.6%) had one or more VAN levels > 2.5 μg/ml. Of the 58 patients with one or more detectable serum concentrations, 26 (44.8%) had received POV therapy ≥ 10 days and 39 (67.2%) had severe CDI (based on findings of a WBC > 15,000 or S_{cr} > 1.5 times the premorbid level). Of 14 patients with other (nonsevere CDI) GI disease, only 2 (14.3%) had GI GVHD (one each with stage 1 and stage 2 disease); the remaining 12 patients (85.7%) had other GI pathologies such as Crohn disease or ulcerative colitis.

VAN levels > 2.5 μg/ml were measured in 18 samples from 15 adult patients (Table 2). Of the 15 patients with levels > 2.5 μg/ml, 6 (40%) received POV dosages of 500 mg/day, 9 (60%) received 1000 mg/day, and 14 (93.3%) experienced these levels at the time the first level was obtained (at a median of 6 days after initiation of POV therapy). Further, of six patients in this group in whom multiple VAN levels were obtained, five (83.3%) exhibited additional VAN levels > 2.5 μg/ml. Six (40%) of the 15 had GI disease (only one of whom had GVHD), 7 (46.6%) had been admitted to the ICU, 9 (60%) had renal dysfunction (Cl_{cr} < 50 ml/min or undergoing HD or CRRT), and 9 (60%) had received a POV dosage > 500 mg/day.

Variables significantly associated with any detectable VAN level in the bivariate analysis (Table 3) included POV dosages > 500 mg/day or administration ≥ 10 days, the presence of severe CDI, and ICU admission. Variables associated with VAN levels > 2.5 μg/ml included the presence of GI pathology, ICU admission, and the use of VAN retention enemas.

In the multivariate analysis (Table 4), independent risk factors significantly associated with detectable systemic VAN exposure included POV dosages > 500 mg/day (OR 35.83, 95% CI 7.56–169.8, p<0.001), the presence of severe CDI (OR 4.11, 95% CI 1.56–10.83, p=0.028), ICU admission (OR 3.80, 95% CI 1.02–14.21, p=0.032), and the administration of POV ≥ 10 days (OR 6.71, 95% CI 1.81–24.83, p=0.0025).

Risk factors for exposure to serum VAN concentrations > 2.5 μg/ml included the presence of

Table 1. Serum VAN Concentrations in 117 Levels from 85 Patients with CDI, Following Administration of POV

	VAN concentrations				
	1st	2nd	3rd	4th	Total
No. of concs measured	85	21	7	4	117
No. (%) detectable[a]	54 (63.5%)	13 (61.9%)	5 (71.4%)	2 (40.0%)	74 (63.2%)
No. (%) with level > 2.5	15 (17.6%)	3 (14.3%)	1 (14.3%)	0 (0%)	19 (16.2%)

	Day of therapy[b]	Conc μg/ml	Day of therapy	Conc μg/ml	Day of therapy	Conc μg/ml	Day of therapy	Conc μg/ml	Conc μg/ml
Median	6	1.2	13	1.7	42.6	1.7	46	1.0	0.05–9.9
Range	5–52	0.05–9.94	3–101	0.5–3.5	8–12	0.3–3.4	6–137	0.3–1.7	

CDI = *Clostridium difficile* infection; conc = concentration; POV = oral vancomycin; VAN = vancomycin.
[a]VAN levels that were detectable (≥ 0.05 μg/ml).
[b]"Day of therapy" refers to the number of days after the start of POV on which the vancomycin level was obtained. Levels were obtained after at least 5 days of therapy, then every 7–10 days thereafter if POV was continued. Samples were obtained from discarded samples initially obtained for routine clinical laboratory monitoring.

Table 2. Serum VAN Concentrations in 117 Levels from 85 Patients with CDI, Following Administration of POV

	Vancomycin levels			
Vancomycin daily dosage, mg	No. of patients	No. of levels obtained	No. of detectable[a] levels (%[b])	No. of levels > 2.5 μg/ml (%)
≤ 500	46	60	37 (61.7)	9 (15)
501–1000	31	43	28 (65.1)	5 (11.6)
2000	8	14	11 (78.6)	5 (35.7)
Total	85	117	76 (65)	19 (16.2)

[a]VAN levels that were detectable (≥ 0.05 μg/ml).
[b]As a percentage of the number of levels obtained in patients receiving that dosage.

Table 3. Bivariate Analysis of Demographic, Clinical, and Laboratory Features in 85 Patients with 117 VAN Levels Following Administration of POV

		VAN level			Any VAN level > 2.5 μg/ml		
Variable	N (%)	Undetectable	Detectable[a]	p	No (%)	Yes (%)	p
N		27 (31.8%)	58 (68.2%)		70 (82.4%)	15 (17.6%)	
Male gender	42 (49.4)	16 (38.1)	26 (61.9)	0.22	36 (85.7)	6 (14.3)	0.42
Age ≥ 60 yrs	41 (48.2)	14 (34.1)	27 (65.9)	0.65	34 (82.9)	7 (17.1)	0.89
POV > 500 mg/day[b]	40 (47.1)	2 (4.4)	43 (95.6)	< 0.001	39 (86.7)	6 (13.3)	0.27
Severe CDI[c]	48 (56.5)	9 (18.8)	39 (81.2)	0.003	37 (77.1)	11 (22.9)	0.15
GI disease[d]	14 (16.5)	5 (35.7)	9 (64.3)	0.73	8 (57.1)	6 (42.9)	0.0068
ICU admission	22 (25.9)	3 (14.3)	19 (86.4)	0.037	15 (68.2)	7 (31.8)	0.043
POV ≥ 10 days	29 (34.1)	3 (10.3)	26 (89.7)	0.0019	23 (79.3)	6 (20.7)	0.59
C. difficile positive	72 (84.7)	22 (30.6)	50 (69.4)	0.57	58 (80.6)	14 (19.4)	0.31
VAN retention enema	9 (10.6)	3 (33.3)	6 (66.7)	0.91	5 (55.6)	4 (44.4)	0.026
Cl_{cr} ≤50 ml/min or HD/CRRT	28 (32.9)	7 (25)	21 (75)	0.35	19 (67.9)	9 (32.1)	0.014

CDI = *Clostridium difficile* infection; Cl_{cr} = creatinine clearance; conc = concentration; GI = gastrointestinal; HD/CRRT = hemodialysis/chronic renal replacement therapy; ICU = intensive care unit; POV = oral vancomycin; VAN = vancomycin.
[a]VAN levels that were detectable (≥ 0.05 μg/ml).
[b]Of the 85 patients, 8 (9.4%) received 2000 mg/day, 29 (34.1%) received 1000 mg/day, and 42 (49.4%) received 500 mg/day. The remaining six patients (7.1%) received daily dosages of 880, 750, 735, 375, 125, or 62 mg. Of note, only three patients received dosages < 500 mg/day.
[c]Severe CDI was defined as patients with white blood cell count > 15,000 or serum creatinine > 1.5 times the premorbid level.
[d]GI disease was defined as inflammatory bowel disease, Crohn disease, GI graft-versus-host disease, or other GI process that could have affected the integrity of the GI tract.

GI pathology (OR 5.17, 95% CI 1.45–18.37, p=0.031); ICU admission (OR 3.21, 95% CI 1.00–10.28, p=0.022); the use of VAN retention enemas (OR 4.73, 95% CI 1.10–20.39, p=0.036); and a Cl_{cr} ≤ 50 ml/min, HD, or CRRT (OR 4.03, 95% CI 1.26–12.84, p=0.039).

Discussion

To our knowledge, this study includes the largest set of patient data assessing systemic VAN exposure following administration of large dosages of POV for CDI, and it is the first to evaluate independent risk factors for VAN exposure in this population. Similar to the findings of prior anecdotal case reports and small case series investigating systemic absorption of POV,[7, 9, 13, 15, 17, 18, 25] we found that the presence of renal failure, conditions that alter the integrity of GI tract, severe CDI, and the administration of high (> 500 mg/day) or prolonged (≥ 10 days) administration of POV are potential risk factors for exposure to systemic VAN after administration of POV. Unique to our study we identified that ICU admission and the concomitant use of VAN retention enemas were significantly associated with systemic exposure to VAN.

Current SHEA/IDSA guidelines for the management of CDI suggest monitoring serum VAN concentrations in patients with renal failure

Table 4. Multivariate Analysis in Patient Characteristics in 85 Patients with 117 VAN Levels Following Administration of POV

Variable	Odds ratio	95% CI	p
Any detectable VAN level[a]			
POV > 500 mg/day	35.83	7.56–169.8	< 0.001
Severe CDI[b]	4.11	2.76–10.83	0.028
ICU admission	3.80	1.02–14.21	0.032
POV ≥ 10 days	6.71	1.85–24.83	0.0025
VAN level > 2.5 μg/ml			
GI disease[c]	5.22	3.45–18.3	0.031
ICU admission	3.21	1.40–10.28	0.022
VAN retention enema	4.73	2.42–20.39	0.036
Cl_{cr} ≤ 50 ml/min or HD/CRRT	4.03	1.26–12.84	0.039

CDI = *Clostridium difficile* infection; Cl_{cr} = creatinine clearance; GI = gastrointestinal; conc = concentration; HD/CRRT = hemodialysis/chronic renal replacement therapy; ICU = intensive care unit; POV = oral vancomycin; VAN = vancomycin.
[a]Vancomycin levels that were detectable (≥ 0.05 μg/ml).
[b]Severe CDI was defined as patients with a white blood cell count > 15,000 or serum creatinine > 1.5 times the premorbid level.[1]
[c]GI disease was defined as inflammatory bowel disease (IBD), Crohn disease, GI graft-versus-host disease, or other process that could have affected the integrity of the GI tract. Of 14 patients with GI disease, there were four patients with Crohn disease, four with diverticulitis/diverticulosis, three with IBD, two with GI GVHD, and one with ulcerative colitis.

receiving ≥ 2 g/day for prolonged durations.[1] Similarly, the manufacturer's prescribing information for VAN capsules recommends serum VAN monitoring for patients with renal impairment or pseudomembranous colitis.[26] Although renal insufficiency (defined as an estimated Cl_{cr} < 50 ml/min) was previously suggested as a risk factor for systemic absorption of POV,[16] we found this to be an independent risk factor for a VAN level > 2.5 μg/ml. A recent abstract[8] reported that low concentrations of VAN, ranging from 0.052 to 1.71 μg/ml, were detectable in the plasma on days 1 or 10 of therapy in 25 of 102 patients (25%) with CDI following administration of POV 125 mg 4 times/day for 10 days. Patients with renal insufficiency (S_{cr} > 1.5 mg/dl) were more likely (79% vs 16%) to experience detectable VAN serum concentrations ($p<0.001$).[8] Similarly, in our study, 21 of 28 patients (75%) with an estimated Cl_{cr} < 50 ml/min had detectable levels, and 9 (32.1%) had VAN levels > 2.5 μg/ml. Of five patients who were undergoing HD or CRRT at the time a serum concentration was obtained, all had detectable VAN concentrations, and 60% had serum levels > 2.5 μg/ml obtained on more than one occasion, despite the ability of both HD and CRRT to remove significant amounts of VAN.[27, 28]

Severe inflammation of the GI tract that compromises the integrity of the mucosal lining, such as GVHD or severe CDI, can increase intestinal permeability, resulting in increased absorption of some orally administered drugs.[5, 6, 14, 16, 17] In a recent case report, a bone marrow transplant patient with stage IV GI GVHD was found to have a VAN serum concentration of 26.4 μg/ml after receiving POV at a dosage of 250 mg every 6 hours for 19 days.[7] Upon rechallenge with POV, the patient again experienced detectable VAN levels with associated acute renal insufficiency. In our study, the presence of inflammatory GI diseases such as GI GVHD or Crohn disease was an independent predictor of higher serum concentrations (> 2.5 μg/ml) of VAN, and severe CDI was a predictor of detectable VAN levels.

Previous case reports have documented significant absorption of VAN with the administration of higher (500 mg 4 times/day) dosages of POV in patients with CDI in the absence of renal failure, suggesting that higher dosages and/or prolonged administration are risk factors for the absorption of POV.[14, 16] We found both higher (> 500 mg/day) dosages and longer (≥ 10 days) durations of VAN therapy to be independent risk factors for achieving detectable VAN levels. In our study, 14 patients experienced levels > 2.5 μg/ml at the time the first level was obtained (at a median of 6 days after initiation of POV therapy); of these, 6 (40%) were receiving POV dosages of only 500 mg/day and 9 (60%) were receiving 1000 mg/day. Thus clinicians cannot rule out the possibility of drug exposure in patients receiving so-called lower dosages of POV typically administered to patients without severe CDI, if they have other risk factors[29] or if systemic absorption can be observed early in the course of therapy.[15]

VAN retention enemas, administered rectally at dosages of 500 mg 3 times/day, were administered to 9 (10.6%) of 85 patients in our study, and they were a significant risk factor for achieving VAN serum concentrations > 2.5 μg/ml. Although retention enemas are typically utilized in patients with severe disease in whom reduced gut integrity might be expected and most often in conjunction with high-dose POV therapy, only 5 (55.5%) of the 9 patients receiving enemas were receiving POV > 500 mg/day; 7 (77.7%) of 9 had severe disease.

ICU admission serves as a marker for the acuity of a patient's clinical status or condition. As such, these patients are more likely to have renal insufficiency or conditions that compromise the integrity of the GI tract, such as severe CDI, that could result in increased absorption and accumulation of generally poorly bioavailable orally administered medications.[30] ICU admission was a significant predictor of both measurable and elevated (> 2.5 μg/ml) levels of VAN. Of note, however, the dosage of POV was not significantly different in ICU versus non-ICU patients (730.7 ± 474.2 vs 838.1 ± 453.8 mg/day, respectively, $p=0.35$).

This prospective observational single-center case series has several limitations. Given that patients at the University of Michigan Hospital with confirmed or suspected CDI are administered the 100 mg/ml oral solution POV (reconstituted using the IV solution) as opposed to the VAN capsule, we could not determine if the dosage form might influence systemic absorption. By excluding all patients who had been exposed to IV VAN in the previous month, we may have eliminated many clinically labile patients who may have been at an increased risk for systemic absorption of POV. In addition, given that our analysis focused on factors found to be potentially associated with systemic absorption and exposure in previous case reports and case ser-

ies, other unknown or unanticipated factors may not have been identified. Lastly, it is important to note that this study was a qualitative assessment utilizing random serum samples to identify risk factors for detectable serum concentrations of VAN. As such, it was not a quantitative assessment of the pharmacokinetics of POV in high-risk patients. Because most of the serum VAN levels were obtained using serum from discarded samples initially obtained for routine clinical laboratory monitoring, they were unlikely to reflect peak systemic levels of VAN. Thus we do not know the extent or magnitude to which individual patients may accumulate VAN or whether higher plasma levels were achieved but not captured in our sampling.

The resurgence in CDI and resulting increased use of POV may place previously unidentified patient populations at risk of systemic exposure to VAN. We found that almost 70% of our patients receiving POV experienced one or more detectable serum concentrations of VAN, placing them at risk for further accumulation that could result in systemic toxicity including rash, redman syndrome, and elevated liver enzymes.[17, 25, 31–35] Because this was an observational study, we did not collect surveillance cultures to determine the impact of low-level vancomycin exposure on the host microbiome or the potential for isolation or development of resistant gram-positive organisms. Nor did we assess adverse reactions possibly due to VAN. However, published data suggest that VAN levels < 10 μg/ml may be associated with the development of resistant strains of *S. aureus* including VISA and VRSA.[19–21]

Conclusions

Based on the results of this study, clinicians should consider measuring VAN plasma concentrations early in the course of therapy in patients who display risk factors identified in the present study. Unique to our study, we identified that ICU admission and the concomitant use of VAN retention enemas were significantly associated with systemic absorption of POV. If measurable VAN levels are obtained, clinicians should consider decreasing the dosage of POV[2, 28, 29] because recent studies demonstrate that although fecal levels of vancomycin are proportional to the dosage of POV administered, they are much higher than the minimum inhibitory concentration for 90% of tested strains of *C. difficile*, even in patients with increased stool frequency.[28]

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