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What is the role for metronidazole in the treatment of *Clostridium difficile* infection? Results from a national cohort study of Veterans with initial mild disease

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Running title: Metronidazole for mild CDI

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Key summary: In our national cohort of Veterans with initial mild *Clostridium difficile* infection (CDI) and treated with metronidazole, age $\leq$ 65 years was the only predictor of success 30-days post treatment (absence of

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mortality or recurrence). Among these younger patients with mild CDI, success rates were similar with metronidazole and vancomycin.

Brief 40-word summary: Age $\leq$ 65 years was predictive of success (absence of mortality or recurrence 30 days post-treatment) among Veterans with initial mild *Clostridium difficile* infection treated with metronidazole. Among patients aged $\leq$65 years, success rates were similar with metronidazole and vancomycin.

Author Contributions:

Conception and design of the study: HA, AC, KL

Data generation: HA, AC

Analysis and interpretation of the data: HA, AC, KL

Preparation or critical revision of the manuscript: HA, AC, KL

ABSTRACT

Background: Metronidazole may still be an appropriate therapeutic option for mild *Clostridium difficile* infection (CDI) in select patients, but data is limited to guide clinicians in identifying these patients.

Methods: Our two-stage study included a national cohort of Veterans with a first episode of mild CDI (2010-2014). First, among those treated with metronidazole, we identified predictors of success, defined as absence of all-cause mortality or recurrence 30-days post-treatment, using multivariable unconditional logistic regression. Second, among a subgroup of patients with characteristic/s predictive of success identified in the first-stage, we compared clinical outcomes among those treated with metronidazole compared with vancomycin, using Cox proportional hazards models for time to 30-day all-cause mortality, CDI recurrence, and failure.

Results: Among 3,656 patients treated with metronidazole, we identified 3,282 patients with success and 374 patients without success (failure). Younger age was the only independent predictor of success. Age $\leq$65 years was associated with an odds of success 1.63 times higher (95% confidence interval [CI] 1.29 – 2.06) than age >65 years. Among 115 propensity-score matched pairs $\leq$65 years of age, no significant differences were observed between metronidazole and vancomycin (reference) for all-cause mortality (hazard ratio [HR] 0.29, 95% CI 0.06-1.38), CDI recurrence (HR 0.62, 95% CI 0.26-1.49), or failure (HR 0.50, 95% CI 0.23-1.07).

Conclusion: Among patients $\leq$65 years of age with initial mild CDI, clinical outcomes were similar with metronidazole and vancomycin. These data suggest metronidazole may be considered for the treatment of initial mild CDI among patients 65 years of age or younger.

BACKGROUND

Clostridium difficile has become the most common cause of healthcare associated infections in the United States.[1] For over three decades metronidazole has been the mainstay of treatment for initial cases of mild to moderate *Clostridium difficile* infection (CDI).[2] Until recently, metronidazole was recommended as the first-line treatment option over vancomycin for initial cases of mild-moderate CDI.[2, 3] In early 2018, updated clinical practice guidelines from the Infectious Diseases Society of America (IDSA) and the Society for Healthcare Epidemiology of America (SHEA) were released, which no longer recommend metronidazole for initial non-severe CDI as per previous guidelines from 2010.[2, 3] Updated guidelines only distinguish severe disease from non-severe disease (previously defined as mild-moderate disease), and 2010 guidelines do not distinguish between mild and moderate disease.[2, 3]

This substantial change in non-severe CDI treatment recommendations is largely based off evidence demonstrating better outcomes associated with vancomycin as compared to metronidazole in patients with severe CDI.[4, 5] Among patients with mild CDI, several studies have demonstrated no difference between vancomycin and metronidazole for mortality, CDI recurrence or clinical cure.[4-6] When metronidazole is used per 2010 CDI guidelines in certain patients with mild-moderate disease it may still have similar effectiveness to vancomycin. Metronidazole is less expensive and may be associated with lower colonization and/ or development of drug-resistant organisms compared with vancomycin.[7, 8]

Since publication of the updated guidelines, expert correspondence has recommended continued consideration of metronidazole as a first-line option for patients with mild CDI and a low risk for disease complications.[8] Limited data exists to guide clinicians in identifying in which patients metronidazole may still be used. As such, first we sought to identify independent predictors of success (defined as absence of mortality or recurrence) among a national cohort of Veterans with mild CDI treated with metronidazole per 2010 CDI guideline recommendations. Then, we sought to compare the effectiveness of metronidazole with vancomycin in patients with mild CDI. Characteristics associated with success were used to identify the subgroup for our comparative effectiveness analysis.

METHODS

Study Population

A cohort of Veterans with a first CDI episode (defined as a stool sample positive for *C. difficile* toxin(s) and $\geq$ 2 days of CDI treatment) from May 1, 2010 to December 30, 2014 was used.[9] CDI episodes from inpatient and outpatient settings from 125 VA centers nationally were included. Only patients with mild disease (defined as a white blood cell count (WBC) $\leq$15 x 10^3/µL and a serum creatinine (SCr) was $\leq$1.5 mg/dL within 7 days of CDI treatment) and those treated per guidelines (10-14 days of monotherapy with oral metronidazole or oral vancomycin) were included.[2] Patients with missing WBC or SCr were excluded.

Study Design

We conducted a two-stage analysis among our large national cohort of Veterans with mild CDI, first conducting a predictive analysis and second a comparative effectiveness analysis.

Predictive Analysis.

We compared patients with and without successful outcomes with a mild first CDI episode treated with metronidazole monotherapy. Patients with success were those who did not die or have a CDI recurrence at day 30, and patients without success were those who died or had a CDI recurrence within 30 days post-treatment (failures). CDI recurrence was defined as another CDI positive stool sample or CDI diagnosis code (008.45) and at least two days of subsequent CDI treatment at least 14 days after the initial positive stool sample and within 30 days post-treatment of the initial episode. Our a priori definition of recurrence was a subsequent episode within 30 days post-treatment, as recurrence risk is greatest within 10 days post-treatment and in clinical trials recurrence is commonly defined within 28-30 days post-treatment.[10, 11]

Predictors assessed are presented in Table 1. Treatment setting (acute, long-term care, or outpatient) was defined based on patient location at the time of positive stool sample. Comorbidities were identified using International Classification of Diseases, 9th Revision (ICD-9) diagnosis and procedure codes within the one year prior to the first CDI episode or during treatment. The Clinical Classifications Software of the Agency for

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Healthcare Research and Quality and previously described disease categorizations were used to group specific diagnoses and procedures into broader disease state groups.[12, 13] ICD-9 codes were also used to identify previous and current infections and other acute events. Comorbidity burden was assessed using Charlson comorbidity index and Elixhauser score. All medication exposures were defined as binary variables and windows of exposure were selected based on clinical relevance or previous work.[14-16] Inpatient and outpatient pharmacy data were utilized to determine all medication exposures and CDI treatment duration. Hypervirulent strain was defined as presence of NAP1/027 where strain type data was available and not hypervirulent/unknown strain in the absence hypervirulent strain type or where strain type was missing. Overall, 45 potential predictors were selected a priori and assessed.[2, 14, 17-19]

Comparative Effectiveness Analysis.

In the second phase of our study, we conducted a comparative effectiveness analysis of metronidazole versus vancomycin on outcomes among Veterans in a select subgroup of our mild CDI cohort. We used characteristic/s predictive of success with metronidazole identified in the first stage of our study, to select the subgroup to compare clinical outcomes with metronidazole and vancomycin. The primary exposure of interest was CDI treatment (metronidazole or vancomycin). The outcomes of interest were 30-day all-cause mortality, 30-day CDI recurrence, and a composite failure outcome (lack of success as defined above). Numerous covariates, which may confound the association between CDI treatment and poor clinical outcomes in patients with CDI, were identified and measured a priori based on underlying causal beliefs.[2, 14, 17-19]

Statistical Analysis

Predictive Analysis.

We used backwards, manual, stepwise unconditional logistic regression to identify independent predictors of success among patients with a mild first CDI episode treated with metronidazole.[20] Variables from univariate analysis with a p-value of <0.10 were included in subsequent multivariable analysis and removed one-by-one from the multivariable model until all remaining variables had a p-value <0.05.[20] Tolerance and variance inflation were used to confirm the absence of collinearity between potential predictors.[20]

Comparative Effectiveness Analysis.

Propensity-score matched Cox proportional hazards models were used to quantify the effect of vancomycin versus metronidazole on time to 30-day all-cause mortality, CDI recurrence, and failure among a subgroup of patients with characteristic/s associated with metronidazole success.[21] Propensity scores were developed for exposure to metronidazole compared with vancomycin as function of all potential confounders which was modeled using logistic regression.[21] The predicted probability of exposure for each patient (propensity score) was estimated using this model. We assessed common support (overlapping distributions of the propensity score between exposure groups) using visual comparison.[21, 22]   We performed nearest-neighbor 1:1 propensity score matching within 0.01 caliper. To assess balance of potential confounders, standardized biases (absolute standardized difference in means) were examined for the original and matched samples.[22] Crude and matched hazard ratios were calculated using Cox proportional hazard regression models. Cox proportional hazard regression proportionality assumptions were assessed.

RESULTS

Predictive Analysis.

Among 3,656 patients with mild CDI and treated with metronidazole, we identified 3,282 patients with success at day 30 post-treatment and 374 patients without success (failure). Several significant differences between patients with and without success were observed (Table 1). In multivariable analysis, younger age was the only independent predictor of success identified (Table 2). The odds of success was 1.63 times (95% confidence interval [CI] 1.29 – 2.06) higher among patients 65 years of age or younger as compared to those over 65 years of age. There were several predictors of failure identified (odds ratios <1, Table 2) including: a principle diagnosis of CDI, current intestinal infection, current respiratory failure, malignancy, previous hospital or long-term care exposure, hypoalbuminemia, body mass index (BMI) > 30 kg/m^2, and previous probiotic exposure.

Comparative Effectiveness Analysis.

For the comparative effectiveness analysis, a mild CDI cohort of younger patients 65 years of age or younger was selected. Predictors of treatment and of failure were included in the propensity score model. Baseline characteristics were well balanced in the propensity score matched cohort (115 matched pairs, Table 3). Among

the propensity-score matched cohort, no significant differences were observed between metronidazole and vancomycin (reference) for the outcomes assessed (Table 4).

DISCUSSION

To our knowledge this study is the first to focus specifically on identifying predictors of success and comparing treatment options in patients with an initial episode of mild CDI. This work suggests that metronidazole may still be an appropriate treatment option for younger patients with initial mild CDI.

Age was the only predictor of success identified and may be one of the most important factors when considering which patients with initial mild disease may still be candidates for metronidazole therapy. Several factors may contribute to the increased risk observed in older patients, such as immunosenescence, decreased functional status, and underlying comorbidities.[23] Previous work has demonstrated that older age is an independent risk factor for mortality and recurrence in patients with CDI.[15, 24, 25] Age 65 years or older was among the strongest predictors of all-cause mortality identified in a recent national analysis of adults hospitalized with CDI.[25] A systematic review of 39 studies which assessed the impact of age on treatment failures and recurrence, found higher rates of treatment failures and CDI recurrences in older patients aged >65 years as compared to younger patients (treatment failure: 24.7% vs. 19.6%; p=0.005; recurrence: 23.4% vs 19.4%; p=0.003).[26] For patients with mild disease it may be important to avoid metronidazole treatment in older patients, however for younger patients metronidazole may still be an option.

Predictors of failure with metronidazole in mild CDI (odds ratio <1) may indicate patient subgroups where metronidazole should be avoided. Similar to previous findings, a principal diagnosis of CDI (as compared to those hospitalized without a principal diagnosis of CDI or outpatients) was identified as a significant predictor of failure likely related to CDI severity.[9, 27, 28] Previous hospital or long-term care exposure was also a predictor of poor outcomes. The association between CDI and exposure to healthcare settings is well recognized.[29, 30] Within hospital and long-term care settings, the patients are typically older, have an increased exposure to antibiotics and gastric acid suppressants, and environmental exposure to *C. difficile* spores, thus are at an

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increased risk for the development of initial and recurrent CDI.[10] These factors may also contribute to an increased risk for severe disease and mortality.

Factors, such as hypoalbuminemia, respiratory failure and intestinal infection, which may be markers of severe or complicated disease, were also predictive of failure. Underlying comorbidities and hypoalbuminemia are among the most commonly reported risk factors for poor outcomes.[15] While not included in the IDSA/SHEA definitions for severity, hypoalbuminemia is included in other criteria to define severe disease.[5, 31] While antibiotic use was not identified as an independent predictor in our study, antibiotic use is another frequently reported risk factor for poor outcomes in patients with CDI.[15] Patients with comorbid respiratory failure or intestinal infections during a CDI episode may be exposed to non-CDI active antibiotics for these conditions during their CDI treatment. It is also possible an intestinal infection diagnosis may not be due to another infection but may be due to CDI symptoms themselves. Our findings suggest that severe underlying comorbidities and other markers of severity in addition to those of the IDSA/SHEA, particularly albumin level, should be considered when determining which patients have mild disease that can be treated with metronidazole.[31] Continued work is needed to investigate which severity criteria are most useful in defining mild disease that can be successfully treated with metronidazole.

Obesity (BMI $\geq$ 30 kg/m^2) was also identified as a predictor of failure. Previous work has identified obesity as a risk factor for the development of CDI.[30] There is also evidence that obesity is associated with more severe disease.[32] Among a weighted sample of 22,937 patients with CDI presenting to the emergency department, extreme obesity (BMI > 40 kg/m^2) was associated with an increased risk of in-hospital mortality.[33] The relationship between obesity, severe disease, and mortality is largely unclear at this time, however in general, obesity is associated with increased risk of death compared to normal weight BMI categories.[34] It may be advisable for clinicians to avoid use of metronidazole for mild disease in obese patients.

Among patients 65 years of age or younger, we found no difference between metronidazole and vancomycin for the treatment of initial mild CDI. Existing studies focusing on patients with mild disease are limited. In a single center retrospective analysis of 168 cases of mild to moderate CDI, metronidazole and vancomycin yielded

similar recurrence rates (13% vs. 9%, p=0.4), however treatment responses were lower for patients treated with metronidazole (82% vs 97%, p=0.002).[35] When stratified by strain, a difference in treatment response was only identified among 83 patients with non-NAP1 CDI (78% metronidazole vs. 98% vancomycin, p=0.007) while similar rates were observed among 85 patients with NAP1 CDI (86% metronidazole vs. 97% vancomycin, p=0.13). Another retrospective cohort study was conducted in patients with solid organ transplants who had mild to moderate CDI.[36] Similar to our findings, this study found no difference between metronidazole and vancomycin for treatment failure (metronidazole 16% vs. vancomycin 10%, p=0.71), 90-day CDI recurrence (metronidazole 14% vs. vancomycin 14%, p=0.99), or 30 day all-cause mortality (0 in both groups). This was a small, single center study of 71 patients with limited power to detect significant differences. A larger national VA study was conducted among 10,137 patients with a first episode of CDI treated in the VA healthcare system between 2005-2012 that included non-severe and severe CDI.[6] This study demonstrated that in the overall cohort, not stratified by severity, patients treated with vancomycin had a lower risk of mortality versus metronidazole (adjusted RR, 0.86; 95% CI, 0.74 to 0.98) but no difference in the risk of recurrence.[6] Mortality differences observed were largely driven by those with severe disease.[6] In secondary analyses, vancomycin was only associated with a decreased risk of mortality in those with severe disease and not in those with mild-moderate disease (adjusted RR 0.91; 95% CI 0.72-1.14).[6] Two randomized controlled trials have also compared metronidazole vs. vancomycin.[4, 5] These studies, which did not use IDSA/SHEA criteria to define severity, have consistently demonstrated no difference in small subgroups of patients with mild CDI for recurrence and clinical cure.

There are limitations to our retrospective study. We were interested in assessing guideline concordant treatment thus required a CDI treatment duration of 10 to 14 days per guideline recommendations and that laboratory values be measured to assess disease severity. Our results may not be generalizable to more mild cases that resolve sooner than 10 days or more severe or complicated cases that require treatment longer than 14 days or those in which SCr and WBC were not collected. The VA population consists primarily of older White males and as such generalizability of this study to the general population may be limited.

Misclassification of outcomes and covariates may impact our results. A priori, we chose to study 30-day CDI recurrence from the end of therapy, because most cases of CDI recur within 1-3 weeks after treatment.[10, 29, 37-39] Moreover, a consensus definition for CDI recurrence has not been established and most previous CDI clinical trials have assessed outcomes at 28-30 days post-treatment.[11] Follow up time among studies assessing risk factors for CDI recurrence have ranged widely from 21-180 days from the previous CDI episode.[16] Misclassification of CDI recurrence that occurred greater than 30 days after treatment is likely. However, the previous national VA study that compared vancomycin and metronidazole assessed for recurrence up to 56 days after the initial CDI diagnosis and similar to our findings found no difference between therapies on risk of recurrence.[6] We only accounted for treatment and care in the VA system, therefore there is the potential that we may of misclassified recurrence in patients who received care for their recurrent episode outside the VA system. Our success and failure outcomes are composite outcomes that include mortality and recurrence and they have not been used previously. We were not able to assess the resolution in CDI symptoms, so composite endpoints did not include treatment failure (continued diarrhea) which is another common poor outcome of CDI.[40] As a consensus definition for CDI-attributable mortality is not established, we measured all-cause mortality. It is possible that some of the deaths we observed were attributable, at least in part, to diseases other than CDI.

In our observational comparative effectiveness analysis, since there was no randomization of patients to either metronidazole or vancomycin, confounding by indication is a chief concern. During the study time period metronidazole was recommended first-line for mild-moderate disease and vancomycin was recommended for severe disease.[2] Due to the differences in treatment recommendations, patients treated with vancomycin at baseline were inherently different than those treated with metronidazole, and at a higher baseline risk of poor outcomes. We used restriction and propensity score matching in an attempt to reduce this confounding bias. Facility was included in the propensity score as there is no national VA policy for the treatment of CDI, and CDI treatment decisions could vary by facility. While our propensity score included all observed confounders related to the use of metronidazole and vancomycin in our study population, there is the potential for residual confounding due to unknown factors and known but unmeasurable factors, such as cytokine responses to CDI.

Due to the small sample size in the propensity score matched analysis, random error may have impacted the observed results.

Our findings among a national cohort of Veterans with an initial episode of mild CDI provide clinicians guidance on patients in whom metronidazole therapy may still be considered. Age was the only predictor of success identified and among patients aged $\leq$65 years we found no difference between metronidazole compared with vancomycin on risk of 30-day all-cause mortality, CDI recurrence, or a composite of the two outcomes. Other factors, such as a primary diagnosis of CDI on hospital admission, severe underlying comorbidities, and hypoalbuminemia were associated with failure and in patients with these conditions, alternative therapy with vancomycin or fidaxomicin should be considered.

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Table 1. Baseline characteristics among a national cohort of Veterans with an initial episode of mild CDI treated with metronidazole with and without successful outcomes

	Patients with success		Patients without success (failure)		
	n=3,282	%	n=374	%	p value
Demographics					
Age ≤ 65 years	1985	60.5	148	39.6	<0.001
Male gender	2982	90.9	357	95.5	0.003
White race	2494	76.0	281	75.1	0.714
Hispanic ethnicity	148	4.5	16	4.3	0.838
Married	1459	44.5	159	42.5	0.474
Treatment setting					
Acute care	401	12.2	109	29.1	<0.001
Long term care	84	2.6	21	5.6	
Outpatient	2797	85.2	244	65.2	
Principal diagnosis of CDI on hospital admission[a]	92	2.8	31	8.3	<0.001
Body mass index 30 or greater	1995	60.8	278	74.3	<0.001
Albumin less than 1.5	1292	39.4	244	65.2	<0.001
Hypervirulent CDI strain	190	5.8	22	5.9	0.942
Charlson comorbidity score at the median or above	2281	69.5	310	82.9	<0.001
Elixhauser score at the median or above	2055	62.6	289	77.3	<0.001
Comorbidities					
Cardiopulmonary disease	1871	57.0	261	69.8	<0.001
Chronic renal disease	362	11.0	75	20.1	<0.001

Dementia	127	3.9	22	5.9	0.062
Diabetes	1108	33.8	130	34.8	0.699
Gastrointestinal/ nutritional disorder	1412	43.0	175	46.8	0.164
Liver disease	344	10.5	56	15.0	0.008
Malignancy	620	18.9	133	35.6	<0.001
Paralysis	137	4.2	26	7.0	0.014
Rheumatic disease	1263	38.5	167	44.7	0.021
Current acute event or infection					
Meningitis	<5		<5		0.277
Gram negative	136	4.1	27	7.2	0.006
Intestinal infection	769	23.4	148	39.6	<0.001
Acute bronchitis	12	0.4	<5		0.625
Pneumonia	121	3.7	35	9.4	<0.001
Septicemia	100	3.0	27	7.2	<0.001
Bacteremia	46	1.4	10	2.7	0.058
Shock	13	0.4	7	1.9	0.003
Skin and soft tissue	198	6.0	45	12.0	0.001
MRSA	18	0.5	8	2.1	0.003
Pseudomonas	20	0.6	6	1.6	0.043
Urinary tract infection	167	5.1	42	11.2	<0.001
Respiratory failure	64	2.0	36	9.6	<0.001
Acute renal failure	171	5.2	50	13.4	<0.001
Fever of unknown origin	76	2.3	6	1.6	0.379
Previous acute event or infection					
Meningitis	11	0.3	<5		1.00
Gram negative	155	4.7	26	7.0	0.060
Influenza	24	0.7	<5		0.752

Intestinal infection	883	26.9	173	46.3	<0.001
Acute bronchitis	177	5.4	12	3.2	0.071
Pneumonia	382	11.6	87	23.3	<0.001
Septicemia	246	7.5	62	16.6	<0.001
Bacteremia	118	3.6	22	5.9	0.029
Shock	40	1.2	16	4.3	<0.001
Skin and soft tissue	692	21.1	106	28.3	<0.001
MRSA	78	2.4	16	4.3	0.028
Pseudomonas	51	1.6	9	2.4	0.219
Urinary tract infection	515	15.7	93	24.9	<0.001
Respiratory failure	164	5.0	56	15.0	<0.001
Healthcare exposures					
Surgery, during CDI treatment	133	4.1	23	6.1	0.057
VA Hospitalization or long-term care, prior 90 days	1152	35.1	241	64.4	<0.001
Medication exposures					
Non-CDI antibiotic use, 30 days before or during CDI treatment	2082	63.4	277	74.1	<0.001
Gastric acid suppressant use, 7 days before or during CDI treatment	1123	34.2	189	50.5	<0.001
Immunosuppressant use, 7 days before or during CDI treatment	192	5.9	61	16.3	<0.001
Probiotic use, 7 days before or during CDI treatment	110	3.4	43	11.5	<0.001

CDI= *Clostridium difficile* infection; IQR= interquartile range; SD= standard deviation

Success was defined as absence of death from any cause or CDI recurrence within 30 days from the end of treatment of the initial episode. Patients with success were those who experienced success at day 30, and those without success (failures) were those who died or recurred within 30 days from end of treatment.

[a]A principal diagnosis of CDI on hospital admission was compared to those without a principal diagnosis of CDI on hospital admission/ outpatients.

Table 2. Independent predictors of success and failure at 30 days post-CDI treatment with metronidazole monotherapy

Predictor	Adjusted Odds ratio	Lower 95% confidence limit	Upper 95% confidence limit
Predictors of success - absence of mortality or CDI recurrence at day 30 post treatment (odds ratio > 1)			
Age ≤ 65 years	1.63	1.29	2.06
Predictors of failure - mortality or CDI recurrence within 30 post treatment (odds ratio > 1)			
Probiotic exposure, 7 days prior or during CDI treatment	0.33	0.22	0.49
Current respiratory failure	0.34	0.22	0.54
VA hospital or long-term care exposure, 90 days prior	0.52	0.41	0.67
Hypoalbuminemia[a]	0.53	0.42	0.68
Principal diagnosis of CDI on hospital admission	0.54	0.34	0.85
Malignancy	0.60	0.47	0.77
Body mass index greater ≥ 30 kg/m^2	0.74	0.57	0.96
Current intestinal infection	0.74	0.58	0.95

CDI= *Clostridium difficile* infection

The adjusted odds ratios are estimated from multivariable analysis of the data. The final multivariable unconditional logistic regression model included all variables in Table 2. Success was defined as absence of death from any cause or CDI recurrence within 30 days from the end of treatment of the initial episode. Those with success were those who experienced success at day 30, and those without success (failures) were those who died or recurred within 30 days from end of treatment. Thus, variables with an odds ratio greater than one were independent predictors of success, and those with an odds ratio less than one were predictors of failure.

^aHypoalbuminemia was defined as an albumin level < 1.5 mg/dL as compared to level above or missing.

Table 3. Patient characteristics of patients aged 65 years or under with mild disease treated with metronidazole or vancomycin: Unmatched and matched cohorts

	Unmatched cohort						Matched cohort					
	Met (n=2,133)		Van (n=118)				Met (n= 115)		Van (n= 115)			
	n	%	n	%	P value	SB	n	%	n	%	P value	SB
Demographics												
Age, years, median, IQR	57	47-62	59	51-64	0.003	0.23	59	52-63	59	51-64	0.436	0.04
Male gender	1853	86.9	105	89.0	0.507	0.06	101	87.8	103	89.6	0.677	0.05
White race	1576	73.9	82	69.5	0.291	0.10	77	67	81	70.4	0.570	0.08
Hispanic ethnicity	114	5.3	7	5.9	0.783	0.03	7	6.1	7	6.1	1.000	0.00
Married	857	40.2	39	33.1	0.124	0.15	32	27.8	39	33.9	0.318	0.13
Treatment setting												
Acute care	207	9.7	34	28.8		0.50	38	33	33	28.7		0.09
Long term care	35	1.6	9	7.6		0.29	7	6.1	7	6.1		0.00
Outpatient	1891	88.7	75	63.6	<0.001	0.62	70	60.9	75	65.2	0.769	0.00
Region												
Midwest	532	24.9	19	16.1		0.22	15	14.3	18	17.1		0.05
Northeast	233	10.9	17	14.4		0.10	17	16.2	15	14.3		0.02
West	534	25.0	39	33.1		0.18	40	38.1	31	29.5		0.11
South	834	39.1	43	36.4	0.050	0.05	33	31.4	41	39.0	0.824	0.09
Year												
2010	247	11.6	3	2.5		0.36	5	4.3	3	2.6		0.10
2011	456	21.4	31	26.3		0.12	20	17.4	30	26.1		0.21

2012	469	22.0	24	20.3		0.04	31	27	24	20.9		0.14
2013	439	20.6	30	25.4		0.12	28	24.3	28	24.3		0.00
2014	522	24.5	30	25.4	<0.028	0.02	31	27.0	30	26.1	0.492	0.00
Principal diagnosis of CDI	46	2.2	7	5.9	0.019	0.19	7	6.1	6	5.2	0.775	0.04
Body mass index 30 or greater	1190	55.8	85	72.0	<0.001	0.34	78	67.8	82	71.3	0.5667	0.08
Albumin less than 1.5	754	35.3	70	59.3	<0.001	0.49	57	49.6	67	58.3	0.186	0.18
Hypervirulent strain CDI	111	5.2	11	9.3	0.054	0.16	14	12.2	11	9.6	0.525	0.08
Treatment duration, days, median (IQR)	11	11-11	11	11-12	<0.001	0.31	11	11-12	11	11-12	0.792	0.03
Charlson comorbidity score at the median or above	1298	60.9	92	78.0	<0.001	0.38	84	73	89	77.4	0.445	0.10
Elixhauser score at the median or above	1215	57.0	90	76.3	<0.001	0.42	89	77.4	87	75.7	0.756	0.04
Comorbidities												
Cardiopulmonary disease	983	46.1	73	61.9	<0.001	0.32	69	60	72	62.6	0.685	0.05
Chronic renal disease	173	8.1	14	11.9	0.150	0.13	9	7.8	13	11.3	0.370	0.12
Dementia	14	0.7	<5		0.203	0.10	<5		<5		1.00	0.06
Diabetes	625	29.3	34	28.8	0.910	0.01	33	28.7	34	29.6	0.885	0.02
Gastrointestinal/ nutritional disorder	918	43.0	51	43.2	0.969	0.00	56	48.7	51	44.3	0.509	0.09
Liver disease	299	14.0	23	19.5	0.098	0.15	18	15.7	22	19.1	0.487	0.09
Malignancy	290	13.6	23	19.5	0.072	0.16	17	14.8	23	20	0.297	0.14

Paralysis	82	3.8	9	7.6	0.052	0.16	7	6.1	9	7.8	0.604	0.07
Rheumatic disease	745	34.9	54	45.8	0.017	0.22	49	42.6	52	45.2	0.690	0.05
Acute events or infections											
Current acute renal failure	83	3.9	9	7.6	0.055	0.16	6	5.2	9	7.8	0.423	0.11
Current fever of unknown origin	52	2.4	<5		1.0	0.05	<5		<5		1.00	0.06
Current infection	651	30.5	62	52.5	<0.001	0.46	64	55.7	60	52.2	0.597	0.07
Current septicemia/ bacteremia / shock	58	2.7	12	10.2	<0.001	0.31	7	6.1	11	9.6	0.326	0.13
Previous infection	1085	50.9	91	77.1	<0.001	0.57	90	78.3	88	76.5	0.753	0.04
Previous septicemia/ bacteremia / shock	152	7.1	21	17.8	<0.001	0.33	18	15.7	20	17.4	0.723	0.05
Healthcare exposures											
Surgery, 30 days before or during CDI treatment	79	3.7	10	8.5	0.024	0.20	10	8.7	9	7.8	0.811	0.03
VA Hospitalization or long-term care, prior 90 days	680	31.9	74	62.7	<0.001	0.65	72	62.6	72	62.6	1.00	0.00
Medication exposures											
Non-CDI antibiotic use, 30 days before or during CDI treatment	1320	61.9	77	65.3	0.463	0.07	65	56.5	75	65.2	0.177	0.18
Gastric acid suppressant use, 7 days	704	33.0	59	50.0	<0.001	0.35	57	49.6	58	50.4	0.895	0.02

before or during CDI treatment												
Immunosuppressant use, 7 days before or during CDI treatment	103	4.8	16	13.6	<0.001	0.31	17	14.8	15	13	0.703	0.05
Probiotic use, 7 days before or during CDI treatment	83	3.9	8	6.8	0.142	0.13	6	5.2	8	7	0.581	0.07

SB = Standardized bias; CDI= *Clostridium difficile* infection; IQR= interquartile range; MET= metronidazole treatment; VAN= vancomycin treatment

Data in the n % columns represent the number and percent, unless otherwise indicated.

Table 4. Unadjusted and propensity score matched hazard ratios for the effect of metronidazole versus vancomycin on outcomes among patients aged 65 years or under with an initial episode of mild CDI

Clinical Outcome	N event/ N met	N event/ N van	Unadjusted HR (95% CI)	N / N met	N events/ N van	Matched HR (95% CI)
All-cause mortality	33/2133	8/118	0.22 (0.10-0.48)	2/115	8/115	0.29 (0.06-1.38)
Recurrence	116/2133	15/118	0.42 (0.24-0.72)	8/115	14/115	0.62 (0.26-1.49)
Failure (mortality or recurrence)	148/2133	23/118	0.33 (0.21-0.51)	10/115	22/115	0.50 (0.23-1.07)

CI = confidence interval; HR = hazard ratio; N= number; Van- = Vancomycin treated patients; Met = Metronidazole treated patients.

Propensity score matched within 0.01 caliper.

The propensity was derived from an unconditional logistic regression model controlling for age, region, Charlson comorbidity index, Elixhauser score, BMI, race, ethnicity, marital status, principal diagnosis of CDI, albumin, CDI treatment duration, gender, gastric acid suppressant use, antibiotic use, probiotic use, immunosuppressant use, VA long-term care or hospital exposure prior 90 days, cardiopulmonary disease, gastrointestinal /nutritional disorder, liver disease, diabetes, rheumatic disease, chronic renal disease, dementia, current acute renal failure, HIV, current fever, surgery, current sepsis/shock/ bacteremia, history of sepsis/shock/ bacteremia, history of infection, current infection, treatment setting, virulent strain.