Outcomes of *Clostridium difficile* Infection caused by the NAP1/BI/027 strain vs. Non Hypervirulent Strains: A Propensity Score Analysis

A thesis submitted by

Lauren Epstein, MD

In partial fulfillment of the requirements for the degree of

Masters in Clinical and Translational Science

TUFTS UNIVERSITY
Sackler School of Graduate Biomedical Sciences

May, 2013

Advisers:
DAVID SNYDMAN, MD
YOAV GOLAN, MD
ROBIN RUTHAZER

Abstract

Clostridium difficile infection (CDI) is a serious cause of infectious diarrhea in the United States. The new epidemic of CDI has been associated with the emergence of the NAP1/BI/027 strain, which has been linked to severe disease outcomes. It is unknown whether having the NAP1/BI/027strain as the cause of CDI is associated with increased morbidity and mortality, independent of the effect of host risk factors. This was a post hoc analysis of two phase 3 clinical trials comparing fidaxomicin vs. vancomycin for treatment of CDI. A propensity score for patients with CDI caused by the NAP1/BI/027 strain versus patients who did not have the strain was calculated. The outcomes assessed were disease severity, clinical cure and disease recurrence. Three different applications of the propensity score were used to assess disease outcomes: logistic regression (using quintiles of propensity score), matching and inverse probability weighting. Of the 792 patients with typed strains, 283 (35%) patients had the NAP1/BI/027 strain. Based on univariate analysis, patients with the NAP1/BI/027 strain were older, more likely to have a chronic disease and be exposed to antibiotics within two weeks of study enrollment. After controlling for the quintile of propensity, having the NAP1/BI/027 strain as the cause of CDI was associated with decreased cure (OR 0.42, 95% CI 0.27-0.64) as compared with not having the strain. However, having the NAP1/BI/027 strain as the cause for disease was not associated with disease severity (OR 1.08; 0.72-1.63). There was a trend towards higher disease recurrence rates among the patients with the NAP1/BI/027 strain (OR 1.33; 95% CI 0.86-2.04). After propensity score adjustment, patients with the NAP1/BI/027 strain do not have more severe disease than patients without the strain but appear to have reduced cure rates, regardless of underlying risk factors for disease. Patients with the

NAP1/BI/027 strain as the cause of CDI may be at higher risk of recurrence compared to patients without the strain.

Acknowledgements

The project described was supported by the National Institutes of Health T32 training grant, 5T32AI05412-07, the National Center for Research Resources (Grant ULIRR025752) and the National Center for Advancing Translational Sciences, National Institutes of Health (Grant ULI TR000073). The content is solely the responsibility of the authors and does not necessarily represent the official views of the NIH.

Table of Contents

List of tables

List of Figures

List of abbreviations

***Clostridium difficile* infection (CDI)**

North American pulsed field type 1(NAP1), restriction endonuclease analysis (REA) group BI, polymerase chain reaction (PCR) ribotype 027 (NAP1/BI/027 strain)

Modified intent-to-treat (mITT)

Restriction endonuclease analysis (REA)

Infectious Diseases Society of America (IDSA)

Introduction

Clostridium difficile infection (CDI) is a serious cause of infectious diarrhea in the United States. Clinical symptoms range from asymptomatic carriers to severe disease resulting in pseudomembranous colitis and death.[1] Recurrent CDIs have become a significant problem linked to prolonged hospitalizations and high medical costs as well as future recurrences.[2,3] Hospital discharges in the United States with CDI listed as a diagnosis increased from 31/100,000 to 61/100,000 between 1998 and 2003.[4]

Historically, CDI was primarily a healthcare infection affecting an elderly population associated with antimicrobial use.[5] However, CDIs now threaten a larger, healthier population with increased morbidity and mortality.[6-11] This epidemic of CDI coincides with the emergence of the NAP1/BI/027 strain (North American pulsed field type 1 (NAP1), restriction endonuclease analysis (REA) group BI, polymerase chain reaction (PCR) ribotype 027).[7-13] There are several traits of the NAP1/BI/027 strain which may contribute to its hypervirulence, including fluoroquinolone resistance, increased binary toxin production, heightened sporulation and surface layer protein adherence. [14] However, it is unknown whether the NAP1/BI/027strain is associated with increased morbidity and mortality, independent of the effect of host risk factors. Some known host risk factors for acquiring the NAP1/BI/027 strain include advanced age, previous hospitalizations, recent fluoroquinolone exposure and proton pump inhibitor use. [13] If having the NAP1/BI/027 strain alone is a risk factor for worse CDI outcomes, this would have a major impact on clinical diagnosis and management of disease.

Therefore, the goal of this study was to evaluate the association between CDI caused by the NAP1/BI/027 strain and several disease outcomes including clinical severity, clinical cure and recurrence while using a propensity score approach to adjust for potential confounding by host factors associated with NAP1/BI/027 strain susceptibility. The cohort of patients was from the modified intent-to-treat (mITT) population from two phase 3 clinical trials comparing the efficacy of fidaxomicin vs. vancomycin for treatment of CDI. [15,16] The mITT population includes 792 patients with CDI typed strains, including 283 subjects with the NAP1/BI/027 strain identified.

We used a propensity score approach to evaluate the association of the NAP1/BI/027 strain and disease outcomes. Propensity score based analysis is traditionally used to reduce indication bias in observational studies, most commonly when therapeutic regimens are not applied to patients at random.[17] In this study, we estimated the probability of having the NAP1/BI/027 strain using covariates to create a propensity score. We then built models to evaluate the association between NAP1/BI/027 strain and disease outcomes and used the propensity score to adjust for differences between patients who had the NAP1/BI/027 strain and patients who did not have the strain. We hypothesized that patients with CDI caused by NAP1/BI/027 are higher risk for worse disease outcomes than patients without this strain after adjusting for confounding by baseline host factors.

Materials and Methods

2.1 Study Population

This analysis used an observational cohort design nested in a database of two recent clinical trials evaluating the efficacy of fidaxomicin vs. vancomycin in the treatment of CDI. The design, methods and outcomes of the clinical trials been previously published in *The New England Journal of Medicine* and *The Lancet* in 2011 and 2012 respectively. [15,16] Briefly, patients included in this database were enrolled in two phase 3 clinical trials comparing the efficacy and safety of fidaxomicin in the treatment of CDI. Both trials were multicenter, double-blind, randomized, international non-inferiority trials which were conducted between May 2006 and December 2009. Eligible patients were 16 years of age or older with a diagnosis of CDI, defined as presence of diarrhea (change in bowel habits with >3 unformed bowel movements in the 24 hours prior to randomization) and either *C. difficile* toxin A, B, or both in the stool within 48 hours of randomization. Patients could have received up to 4 doses but no more than 24 hours of vancomycin or metronidazole prior to randomization, and no doses of other potentially effective treatments for CDI. Patients with life-threatening or fulminant CDI, toxic megacolon, previous exposure to fidaxomicin, a history of ulcerative colitis or Crohn's disease, and >1 occurrence of CDI within 3 months of study start were excluded. The modified intent-to-treat population (mITT) was defined as patients with documented CDI who underwent randomization and received at least one dose of study medication.

2.2 Exposure

Baseline demographic data, significant medical history, previous CDI episodes, medications and lab values were collected through chart review at enrollment into to the trial. Antibiotic medication history for the past 30 days was also obtained upon enrollment. Medications were initially characterized by the trial study investigators. Antibiotics were further subdivided into specific classes for the purposes of this analysis. Medication use was ascertained at the time of trial enrollment, concomitantly during the course of treatment, as well as at follow-up visits.

2.3 Clostridium difficile culture and REA typing

Fecal samples to verify CDI and microbiologic testing were obtained at screening, at early termination or the end-of-therapy visit in patients with clinical failure and at visits for diagnosis and treatment of recurrent infections. Restriction endonuclease analysis (REA) typing was performed on recovered isolates at the Edward Hines Jr. VA Hospital (Hines, Illinois) to determine strain type.[18]

2.4 Statistical Analysis

All statistical analysis was performed using the R software, version 2.15.1. Descriptive statistics summarized characteristics of patients with CDI caused by the NAP1/BI/027 strain in comparison to patients with CDI not caused by the NAP1/BI/027 strain. All patient characteristics were analyzed as categorical variables and the

distributions of these characteristics were compared between the two CDI strain groups (NAP1/BI/02 vs. non NAP1/BI/027) using the Pearson's chi-square test of independence.

2.5 Propensity Score

A propensity score for the 3 outcomes was created using variables related to having the NAP1/BI/027 strain and the outcomes. A logistic regression model was fitted with the NAP1/BI/027 strain as the binary outcome and baseline patient characteristics prior to acquisition of disease as covariates to develop the propensity score. The estimated probability of having the NAP1/BI/027 strain based on this model was referred to as the propensity score. Performance of the propensity score model was evaluated using the concordance (C) statistic. A propensity score was generated for each patient to evaluate the propensity-adjusted effect of the NAP1/BI/027 strain on the disease outcomes. Three patient subgroups were created based on the status of the 3 disease outcomes: clinical severity, clinical cure and recurrence. A propensity score were generated for each patient using the same covariates in each subgroup.

2.6 Quintile analysis

In this analysis, a categorical variable representing the five propensity score quintiles was created. The baseline covariates were compared within quintiles (between patients with and without the NAP1/BI/02 strain) and between each quintile. Multivariable logistic regression models, adjusted for the propensity quintile, were built to evaluate the association of the NAP1/BI/027 strain and 3 principle clinical outcomes of disease severity, clinical cure and recurrence.

Two models were created for each outcome. The first model utilized only the propensity score quintile category as the sole adjuster with 4 degrees of freedom. The other model included the propensity score quintile and also controlled for other covariates that had unadjusted associations with the outcomes. Specifically, covariates with a p value of <0.1 were included in this model and a final model was built based on a combination of forced and backward selection of the covariates**.** The propensity score quintile was forced in all models. The results of the association of the NAP1/BI/027 strain on the outcome between the two models were compared.

2.7 Matched Analysis

We matched each patient with the NAP1/BI/027 strain with the nearest propensity-matched neighbor without the NAP1/BI/027 strain. To account for matching in the final analysis, a conditional logistic regression model was built to evaluate the association of strain type and the disease outcomes**.**

2.8 Inverse probability weighting

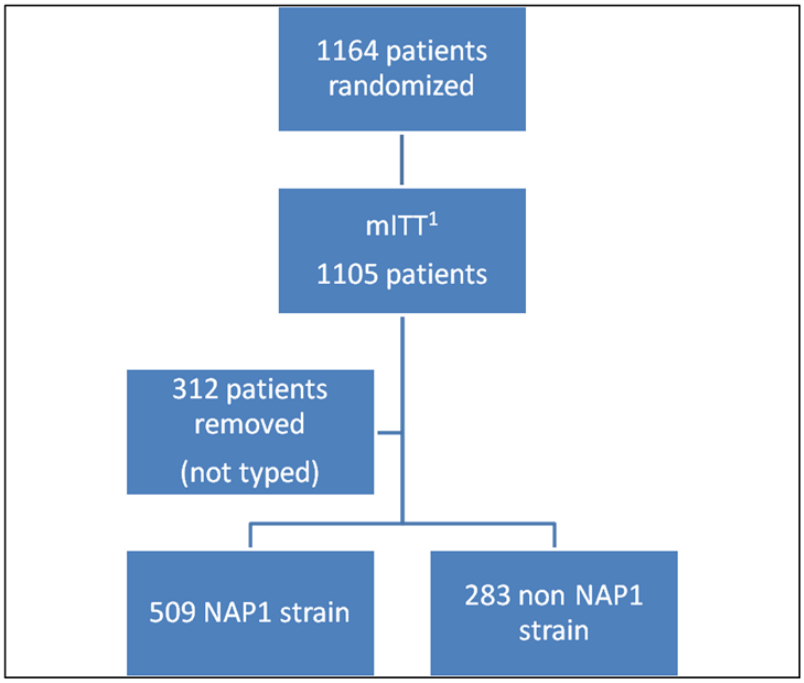
In this analysis, each patient was assigned a weight based on the propensity score and the presence of the NAP1/BI/027 strain. For patients with the strain, the weight was (1/propensity to have the strain). For patients without the strain, the weight was equal to 1/(1-propensity to have the strain). In order to account for extreme weights of patients with very low or very high probability of having the strain, the weights were stabilized by dividing each weight by the average weight. Finally, the weights were incorporated into a final logistic regression model to evaluate the association of strain and outcome.

2.9 Ancillary Analysis

As an additional analysis to assess generalizability of these results, characteristics of patients included in these analysis who had strain data will be compared to the sample of patients without strain data using descriptive statistics to compare both groups.

Results

Figure 1: Study Population flow diagram



[1] modified intent to treat population

3.1 Study Population

A total of 1164 patients were initially randomized in the study and 1105 patients were included in the modified intent-to-treat population (mITT). From the miTT population, no strain was isolated in 313 (26%) patients. Of the 792 patients with strain typed, 283 (36%) patients had the NAP1/BI/027 strain and 509 (64%) did not have the NAP1/BI/027 strain.

3.2 Descriptive Analysis

Patients with the NAP1/BI/027 strain were more likely to be older males, hospitalized (at the time of enrollment) and residing in North America. Furthermore, based on univariate analysis, patients with the NAP1/BI/027 strain were more likely to have recurrent disease and fail treatment for CDI. Patients with the NAP1/BI/027 strain were also more likely to have received antibiotics within two weeks of enrolling in the clinical trial and have some type of chronic disease. Finally, patients on any acid lowering medications prior to enrollment were more likely to have NAP1/BI/027 strain as the cause of CDI **(Table 1).**

Table 1: Baseline characteristics of the NAP1/BI/027 patients vs. non NAP1/BI/027 patients (n=792)

	non NAP1 (n=283)	non NAP1 (%)	NAP1 (n=509)	NAP1 (%)	P-value
DIAGNOSIS (at enrollment)[1]					
Bone or Joint infection	9	2%	8	3%	0.33
GI or Abdominal Infection	101	20%	41	14%	0.06
Urinary Tract Infection	76	15%	65	23%	0.005
Lower Respiratory Infection	68	13%	72	25%	<0.001
Bacteremia or Sepsis	37	7%	18	6%	0.88
Fever (no definite source)	27	5%	16	6%	0.06
Pre Operative Prophylaxis	57	11%	38	13%	0.36
TYPES OF ANTIBIOTICS[2]		0%		0%	
Metronidazole	78	15%	54	19%	0.18
Beta Lactam	176	35%	115	41%	0.09
Fluoroquinolone	73	14%	94	33%	<0.001
Penicillin	100	20%	46	16%	0.24
Any Cephalosporin	77	15%	70	25%	<0.001
Cephalosporin 3rd or 4th generation	35	7%	37	13%	0.0042
OUTCOMES		0%		0%	
Severe Disease	86	17%	79	28%	<0.001
Clinical Cure	464	91%	230	81%	<0001
Recurrence	86	17%	61	22%	0.02
DEMOGRAPHICS		0%		0%	
Inpatient	249	49%	224	79%	<0.01
Males	182	36%	133	47%	0.002
Caucasians	464	91%	251	89%	0.26
North America	388	76%	269	95%	<0.001
CDI in 3 months prior to trial	72	14%	65	23%	0.001
Age (greater than 65)	216	42%	176	62%	<0.001
Albumin (less than 3.0)	234	46%	198	70%	<0.001
Creatinine (greater than 1.5)	73	14%	52	18%	0.14
WBC (greater than 15,000)	59	12%	64	23%	<0.001
Vancomycin[3]	256	50%	140	49%	0.82
PAST MEDICAL HISTORY[4]					
Alcohol Abuse	46	9%	6	2%	0.3
Diverticulosis	68	13%	12	4%	0.18
Appendectomy	90	18%	23	8%	0.26
Chronic Lung Disease	141	28%	38	13%	<0.001
Cardiovascular Disease	237	47%	63	22%	<0.001
Diabetes Mellitus	136	27%	31	11%	<0.001
Cirrhosis	19	4%	4	1%	0.73
Liver Disease	68	13%	9	3%	0.384
Chronic Kidney Disease	113	22%	35	12%	<0.001
Solid Cancer	133	26%	24	8%	0.02
Any Malignancy	148	29%	29	10%	0.06
Metastatic Cancer	17	3%	3	1%	0.687
Upper GI Abnormality	241	47%	50	18%	0.02
Lower GI Abnormality	128	25%	18	6%	0.192
Obesity	37	7%	12	4%	0.001
Active Smoker	84	17%	16	6%	0.47
Transplant (any type)	13	3%	2	1%	0.85
Hematologic Malignancy	38	7%	8	3%	0.89
MEDS (not antibiotics)		0%		0%	
Any Acid Lowering Agent	236	46%	174	61%	<0.001
PPI	135	27%	104	37%	0.003

[1]Diagnosis at enrollment in study as a reason for antibiotics

[2]Anbiotics were received within 2 weeks of enrollment in the study; timing and dosage not available

[3] Study drug received for treatment (randomized per study protocol)

[4]Past medical history as obtained from chart review at enrollment

3.3 Propensity Score Analysis

Propensity score models for the NAP1/BI/027 strain were created using the cohorts of patients with complete data for each of the three outcomes with the same 21 covariates. Each of the propensity scores achieved a C statistic of 0.78.

Table 2: Propensity Score (PS) Analysis (NAP1/BI/027 strain vs. nonNAP1/BI/027)

	Severe Disease (n = 702)	Clinical Cure (n = 792)	Recurrence (n = 694)
Univariate	1.82 (1.28-2.60)	0.42 (0.27-0.64)	1.58 (1.08-2.30)
PS ANALYSIS			
PS adjustment only	1.08 (0.72-1.63)	0.64 (0.30-0.81)	1.33 (0.86-2.04)
PS adjustment only with covariates[1]	1.15 (0.75-1.77)	0.47 (0.28-0.79)	1.36 (0.89-2.14)
Inverse Probability Weighting	0.86 (0.60-1.23)	0.62 (0.40-0.96)	1.06 (0.73-1.55)
PS matching[2]	1.33 (0.91-1.97)	0.42 (0.25-0.70)	1.71 (1.09 - 2.8)

Table 3: List of Covariates for the Propensity Score

Diagnosis GI or Abdominal Infection Pre Enrollment (as an indication for antibiotics)
Diagnosis of Urinary Tract Infection Pre Enrollment (as an indication for antibiotics)
Diagnosis of a lower respiratory infection Pre Enrollment
Received metronidazole antibiotic within 2 weeks of Enrollment
Received beta-lactam antibiotic within 2 weeks of Enrollment
Received fluoroquinolone antibiotic within 2 weeks of enrollment
Received 3rd or 4th generation cephalosporins within 2 weeks of enrollment
Received penicillin within 2 weeks of enrollment
Any acid lowering medication (prior to enrollment)
Sex
Race
Living in North America (yes/no)
History of prior episode of CDI
History of Cardiovascular disease
History of Diabetes Mellitus
History of Chronic Kidney Disease
History of Chronic Lung Disease
History of Solid Cancer
History of any malignancy
History of obesity
History of upper GI abnormality

Table 4: List of Covariates for Multivariate Analysis

Clinical Cure
Any Beta lactam at enrollment and continued
Previous History of CDI
History of upper GI abnormality
Any acid lowering agent
Age greater than 65
WBC at enrollment (greater than 15,000)
Creatinine at enrollment (greater than 1.5)
Study treatment (Fidaxomicin vs. Vancomycin)

Disease Severity
Recent history of Fever (no source defined)
Caucasian
Sex
History of Cardiovascular disease
History of Diabetes Mellitus
History of Upper GI abnormality
History of Organ transplant
Any Acid Lowering Agent
Age (greater than 65)

Disease Recurrence
Beta-lactam at enrollment and continued
History of CDI
History of Upper GI abnormality
Any acid lowering medication at enrollment
Age greater than 65
WBC on enrollment greater than 15000
Creatinine on enrollment greater than 1.5
Study Treatment (Fidaxomicin vs. Vancomycin

Figure 2: Propensity Score Quintiles Comparison

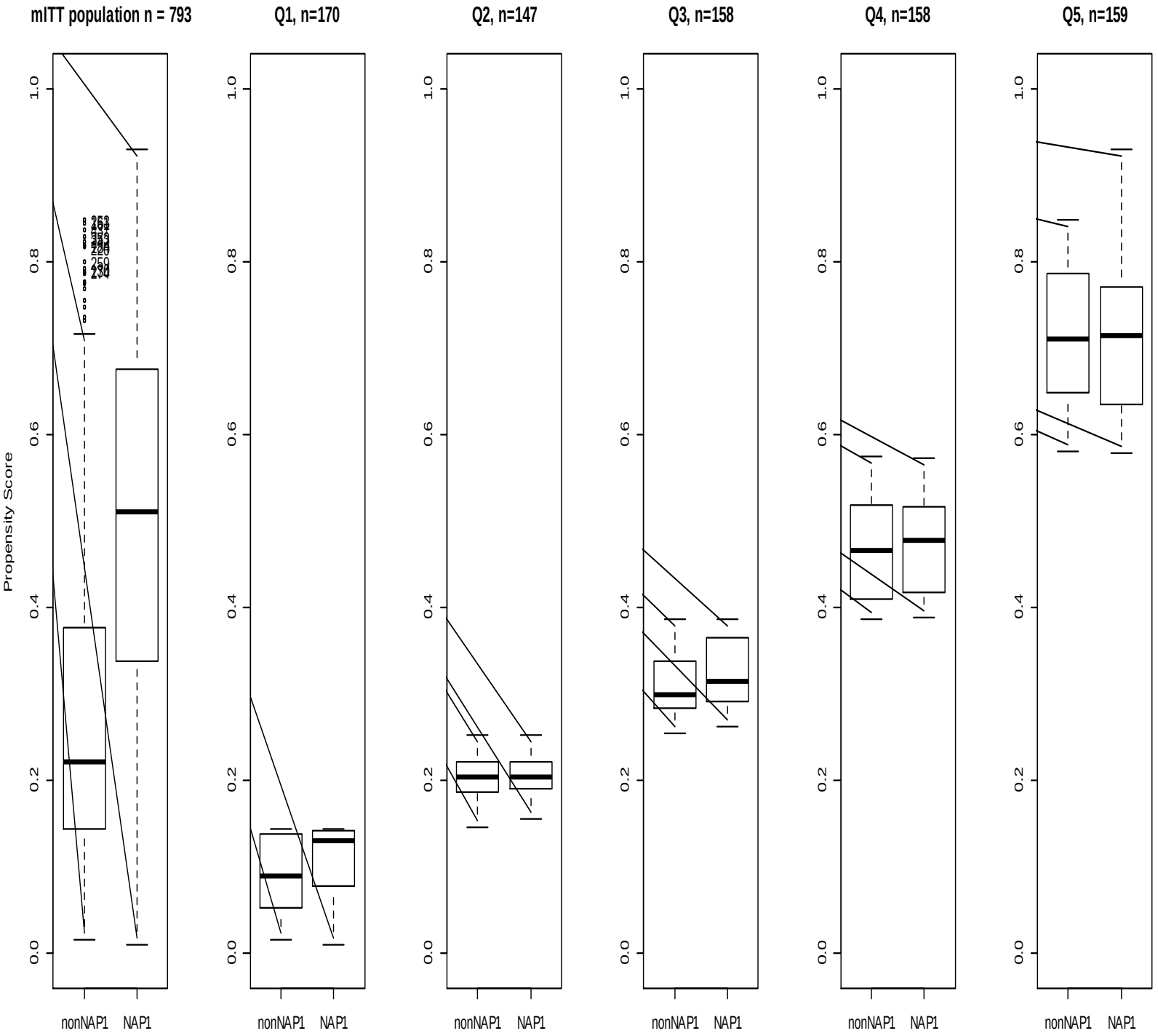


Table 5: Variable Distribution (per population and quintile)

	Entire population (n=792)		
	NAP1	**non NAP1**	**p value**
Lower Respiratory Infection	**72**	**68**	**<0.001**
FQ	**94**	**73**	**<0.001**
Any Cephalosporin	**70**	**77**	**<0.001**
Chronic Kidney Disease	**35**	**113**	**<0.001**
Solid Cancer	**24**	**133**	**<0.001**
Clinical Cure	**230**	**464**	**<0.001**
Any Acid Lowering Agent	**174**	**236**	**<0.001**
Chronic Lung Disease	**38**	**141**	**<0.001**
Obesity	**12**	**37**	**<0.001**
Cardiovascular Disease	**63**	**237**	**<0.001**
Diabetes Mellitus	**31**	**136**	**<0.001**

	Quintile 1 , n = 170		
	NAP1	**non NAP1**	**p value**
Lower Respiratory Infection	3	18	0.72
FQ	2	8	0.412
Any Cephalosporin	4	19	0.373
Chronic Kidney Disease	1	23	0.23
Solid Cancer	2	24	0.488
Clinical Cure	17	136	0.43
Any Acid Lowering Agent	2	58	0.002
Chronic Lung Disease	3	10	0.21
Obesity	0	4	0.99
Cardiovascular Disease	4	31	0.945
Diabetes Mellitus	2	22	0.58

	Quintile 2 , n = 147		
	NAP1	**non NAP1**	**p value**
Lower Respiratory Infection	0	10	0.99
FQ	7	19	0.533
Any Cephalosporin	1	9	0.651
Chronic Kidney Disease	0	8	0.991
Solid Cancer	3	17	0.996
Clinical Cure	19	116	0.31
Any Acid Lowering Agent	10	44	0.36
Chronic Lung Disease	1	19	0.20
Obesity	0	1	0.992
Cardiovascular Disease	2	23	0.295
Diabetes Mellitus	2	8	0.646

	Quintile 3, n = 158		
	NAP1	**non NAP1**	**p value**
Lower Respiratory Infection	2	8	0.516
FQ	7	19	0.788
Any Cephalosporin	9	15	0.329
Chronic Kidney Disease	9	8	0.02
Solid Cancer	6	20	0.46
Clinical Cure	36	106	0.04
Any Acid Lowering Agent	28	96	0.02
Chronic Lung Disease	3	15	0.28
Obesity	1	5	0.50
Cardiovascular Disease	11	21	0.464
Diabetes Mellitus	5	12	0.98

	Quintile 4, n = 158		
	NAP1	**non NAP1**	**p value**
Lower Respiratory Infection	18	10	0.07
FQ	10	13	0.59
Any Cephalosporin	18	22	0.58
Chronic Kidney Disease	19	23	0.59
Solid Cancer	17	17	0.97
Clinical Cure	64	71	0.42
Any Acid Lowering Agent	47	56	0.28
Chronic Lung Disease	20	21	0.99
Obesity	4	7	0.40
Cardiovascular Disease	41	49	0.36
Diabetes Mellitus	24	30	0.43

	Quintile 5, n = 159		
	NAP1	**non NAP1**	**p value**
Lower Respiratory Infection	49	22	0.18
FQ	73	26	0.86
Any Cephalosporin	38	12	0.72
Chronic Kidney Disease	42	15	0.91
Solid Cancer	40	11	0.40
Clinical Cure	94	35	0.42
Any Acid Lowering Agent	67	20	0.58
Chronic Lung Disease	68	19	0.21
Obesity	23	4	0.161
Cardiovascular Disease	89	29	0.55
Diabetes Mellitus	46	16	0.99

3.4 Disease Severity

To analyze the outcome of disease severity, 703 patients from the miTT population had complete information regarding strain type, white blood cell count and creatinine measurements at the time of enrollment. Based on the current *Clostridium difficile* guidelines, 165 (23%) patients met the criteria for severe disease [1]. From this population, 209 (30%) patients had the NAP1/BI/027 strain.

The presence of the NAP1/BI/027 strain was positively associated with clinical disease severity in the univariate analysis (OR 1.82; 95% CI, 1.28-2.60) but not in the quintile propensity-score adjusted analysis (OR 1.08; 95% CI 0.72-1.63). After further adjustment for covariates in addition to the quintiles of the propensity score, the presence of the NAP1/BI/027 strain was not associated with disease severity (OR 1.15; 95% CI 0.75-1.77). Similar results were observed using a propensity-weighted adjustment using the inverse probability weighting and the propensity-matched analysis **(Table 2).**

3.5 Clinical Cure

To analyze the outcome of clinical cure, 792 patients from the miTT population had complete information regarding strain type and clinical outcomes. According to the original study definitions for clinical cure, 694 (87%) patients met the criteria for clinical cure while 98 (12%) patients failed treatment.

The presence of the NAP1/BI/027 strain was associated with decreased clinical cure in the univariate analysis (OR 0.42; 95% CI 0.27-0.64) as well as in the quintile propensity-score adjusted analysis (OR 0.64; 95% CI 0.30-0.81). After further adjustment for

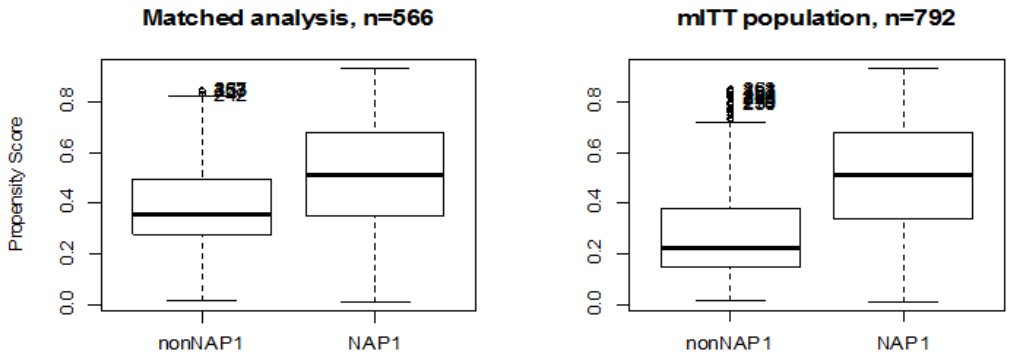
covariates in addition to the propensity score, the presence of the NAP1/BI/027 strain was still associated with decreased cure rates (OR 0.47, 95% CI 0.28-0.79). Similar results were observed with propensity-weighted adjustment using the inverse probability weighting or using a propensity-matched analysis **(Table 2)**.

3.6 Recurrence

To analyze the outcome of recurrent disease, 694 patients from the miTT population had strains typed and met the criteria for clinical cure and therefore could be evaluated for recurrence. Of this population, 147 (21%) patients had at least one recurrence of disease while 547 (78%) patients had no recurrence.

The presence of the NAP1/BI/027 strain was associated with recurrent disease in the univariate analysis (OR1.58; 95% CI 1.08-2.30). The presence of the NAP1/BI/027 strain was not statistically associated with recurrence in the propensity-score adjusted analysis (OR 1.33; 95% CI 0.86-2.04). After adjustment for covariates in addition to the propensity score, the presence of the NAP1/BI/027 strain was not statistically associated with recurrence (OR 1.36; 95% CI 0.89-2.14). These results were confirmed using a propensity-weighted adjustment using the inverse probability weighting (OR 1.06; 95% CI 0.73-1.55). However, using a propensity-matched analysis, the presence of the NAP1/BI/027 strain was statistically associated with recurrent disease (OR 1.71; 95% CI 1.09-2.80) **(Table 2).**

Figure 3: Matched population vs. mITT population propensity score comparison (overall and by a selection of variables)



	Matched population = 566		
	NAP1 N=283	non NAP1 n=283	p value
Lower Respiratory Infection	72 (25%)	44 (17%)	0.004
FQ	94 (33%)	61 (10%)	0.002
Any Cephalosporin	70 (25%)	50 (18%)	0.05
Chronic Kidney Disease	71 (25%)	51 (18%)	0.04
Solid Cancer	68 (24%)	55 (19%)	0.186
Clinical Cure	230 (98%)	258 (91%)	0.001
Any Acid Lowering Agent	174 (61%)	147 (52%)	0.02
Chronic Lung Disease	95 (34%)	59 (21%)	<0.001
Obesity	28 (10%)	16 (6%)	0.062
Cardiovascular Disease	147 (51%)	109 (39%)	<0.001
Diabetes Mellitus	79 (28%)	63 (22%)	0.121

	mITT population n=792		
	NAP1 N=283	non NAP1 N=509	p value
Lower Respiratory Infection	72 (25%)	68 (13%)	<0.001
FQ	94 (33%)	73 (14%)	<0.001
Any Cephalosporin	70 (24%)	77 (15%)	<0.001
Chronic Kidney Disease	71 (25%)	113 (22%)	<0.001
Solid Cancer	68 (24%)	133 (26%)	<0.001
Clinical Cure	230 (98%)	464 (91%)	<0.001
Any Acid Lowering Agent	174 (61%)	236 (46%)	<0.001
Chronic Lung Disease	95 (34%)	141 (28%)	<0.001
Obesity	28 (10%)	37 (7%)	<0.001
Cardiovascular Disease	147 (51%)	237 (46%)	<0.001
Diabetes Mellitus	79 (28%)	136 (27%)	<0.001

3.7 Ancillary Analysis

The sub-group of patients without typed strains was compared to patients who had typed strains (both the NAP1/BI/027 strains and the non-NAP1/BI/027 strains) (Table7). There were few differences in baseline demographics between the two groups. There were slight differences in proportions of patients between the typed vs. the non-typed group in terms of clinical cure, recurrent disease, antibiotic exposure prior to enrollment, sex, inpatient status and geographic distribution **(Table 6).**

Table 6: Comparison of patients with strains typed vs. patients without typed strains (n=1164)

	Typed N=814	% total	Non Typed N=350	% total
DIAGNOSIS (at enrollment)[1]				
Bone or Joint infection	19	2%	4	1%
BI or Abdominal Infection	144	18%	49	14%
Urinary Tract Infection	146	18%	50	14%
Lower Respiratory Infection	146	18%	56	16%
Bacteremia or Sepsis	51	6%	21	6%
Fever (no definite source)	46	6%	29	8%
Pre Operative Prophylaxis	97	12%	37	11%
TYPES OF ANTIBIOTICS[2]				
Metronidazole	133	16%	39	11%
Beta Lactam	292	36%	110	31%
Fluoroquinolone	169	21%	67	19%
Penicillin	146	18%	55	16%
Any Cephalosporin	147	18%	46	13%
Cephalosporin 3rd or 4th generation	73	9%	34	10%
OUTCOMES				
Modified intent to treat population	792	97%	313	89%
CDI severity	170 (92 unknown)	20%	54 (64 unknown)	15%
Death	52	6%	22	6%
Clinical Cure	709	87%	281	80%
Recurrence	150	18%	49	14%
Received vancomycin (vs. fidaxomicin)[3]	410	50%	155	44%
DEMOGRAPHICS				
Inpatient	500	61%	246	70%
Males	328	40%	164	47%
Caucasians	79	10%	42	13%
North America	141	18%	72	24%
Previous History of CDI	149	18%	46	13%
Age (greater than 65)	527	65%	227	65%
Albumin (less than 3.0)	418	51%	194	55%
Creatinine (greater than 1.5)	119	15%	34	9%
WBC (greater than 15,000)	124	15%	32	9%
PAST MEDICAL HISTORY[4]				
Alcohol Abuse	56	7%	47	13%
Diverticulosis	82	10%	38	11%
Appendectomy	113	14%	47	13%
Chronic Lung Disease	184	23%	93	27%
Cardiovascular Disease	309	38%	144	41%
Diabetes Mellitus	177	22%	98	28%
Cirrhosis		0%	10	3%
Liver Disease	81	10%	39	11%
Chronic Kidney Disease	184	23%	60	17%
Solid Cancer	160	20%	65	19%
Any Malignancy	181	22%	83	24%
Metastatic Cancer	20	2%	5	1%
Upper GI Abnormality	302	37%	159	45%
Lower GI Abnormality	151	19%	66	19%
Obesity	50	6%	17	5%
Active Smoker	104	13%	42	12%
Transplant (any type)	15	2%	20	6%
Hematologic Malignancy	48	6%	30	9%
MEDS (not antibiotics)[5]				
Any Acid Lowering Agent	422	52%	198	57%
PPI prior to enrollment	239	29%	123	35%

[1]Diagnosis at enrollment in study as a reason for antibiotics

[2]Anbiotics were received within 2 weeks of enrollment in the study; timing and dosage not available

[3] Study drug received for treatment (randomized per study protocol)

[4]Past medical history as obtained from chart review at enrollment

[5]Medications patients received at enrollment

Table 7: Severe CDI vs. non Severe CDI from mITT population

Variables	Non Severe	% Non Severe	Severe	% Severe	P-value
DIAGNOSIS[1]					
Bone or Joint infection	14	2%	3	0%	0.568
GI or Intra Abdominal Infection	92	12%	31	4%	0.618
Urinary Tract Infection	82	10%	37	5%	0.302
Lower respiratory infection	81	10%	47	6%	<0.001
Bacteremia or sepsis	29	4%	15	2%	0.09
Fever (no source)	20	3%	18	2%	<0.001
Pre-Op prophylaxis	68	9%	19	2%	0.701
ANTIBIOTICS[2]					
Metronidazole	82	10%	34	4%	0.106
Beta-lactam	188	24%	71	9%	0.06
Fluoroquinolone	104	13%	44	6%	0.0441
Penicillin	92	12%	38	5%	0.0872
Any Cephalosporin	96	12%	37	5%	0.19
Cephalosporin (3rd or 4th generation)	43	5%	24	3%	0.013
OUCOMES					
Clinical Cure	490	62%	124	16%	<0.001
Recurrence	96	12%	29	4%	0.349
Vancomycin[3]	272	34%	80	10%	0.641
DEMOGRAPHICS		0%		0%	
Inpatient	293	37%	139	18%	<0.001
SEX	204	26%	76	10%	0.05
Race (Caucasian)	495	63%	142	18%	0.023
Living in North America	444	56%	139	18%	0.609
History of CDI	88	11%	36	5%	0.109
Age (greater than 65)	60	8%	70	9%	<0.001
Albumin (less than 3.0)	3.12	0%	2.69	0%	<0.001
PAST MEDICAL HISTORY[4]					
Alcohol Abuse	31	4%	12	2%	0.48
Diverticulosis	57	7%	15	2%	0.578
Appendectomy	74	9%	27	3%	0.404
Chronic Lung Disease	109	14%	52	7%	0.002
Cardiovascular Disease	178	22%	98	12%	<0.001
Diabetes Mellitus	91	11%	59	7%	<0.001
Cirrhosis	16	2%	6	1%	0.67
Liver Disease	50	6%	17	2%	0.699
Chronic Kidney Disease	69	9%	65	8%	<0.001
Solid Cancer	107	14%	34	4%	0.84
Any Malignancy	119	15%	42	5%	0.373
Metastatic Cancer	13	2%	5	1%	0.663
Upper GI abnormality	187	24%	74	9%	0.019
Lower GI abnormality	103	13%	27	3%	0.421
Obesity	27	3%	17	2%	0.01
Actively smoking	65	8%	24	3%	0.406
Organ transplant	5	1%	10	1%	<0.001
Hematologic malignancy	30	4%	14	2%	0.18
MEDS (not antibiotics)[5]		0%		0%	
Any acid lowering agent	262	33%	103	13%	0.002
PPI during pre-treatment	154	19%	64	8%	0.014

[1]Diagnosis at enrollment in study as a reason for antibiotics

[2]Anbiotics were received within 2 weeks of enrollment in the study; timing and dosage not available

[3] Study drug received for treatment (randomized per study protocol)

[4]Past medical history as obtained from chart review at enrollment

[5]Medications patients received at enrollment

Table 8: Patients who were cured vs. patients who were not cured (mITT)

Variables	Fail	% Fail	Cure	% Cure	P-value
DIAGNOSIS[1]					
GI or Abdominal infection	21	3%	121	15%	0.904
Urinary Tract Infection	25	3%	116	15%	0.336
Lower Respiratory Infection	27	3%	113	14%	0.35
Bacteremia or Sepsis	10	1%	39	5%	0.007
Fever (no source)	8	1%	35	4%	0.08
Pre Operative Prophylaxis	7	1%	88	11%	0.2
ANTIBIOTICS[2]		0%		0%	0.12
Metronidazole	16	2%	116	15%	0.923
Beta lactam	46	6%	245	31%	0.03
Beta lactam (received at enrollment and cont'd)	13	2%	34	4%	0.001
Fluoroquinolone	27	3%	140	18%	0.1
Fluoroquinolone (received at enrollment and cont'd)	3	0%	14	2%	0.51
Any Cephalosporin	23	3%	124	16%	0.183
Cephalosporin (received at enrollment and cont'd)	3	0%	10	1%	0.248
Penicillin	22	3%	124	16%	0.275
Penicillin (received at enrollment and cont'd)	5	1%	14	2%	0.07
Cephalosporin (3rd or 4th generation)	15	2%	57	7%	0.02
Cephalosporin (3rd or 4th gen received at enrollment and cont'd)	5	1%	4	1%	0.001
OUTCOMES		0%		0%	
CDI severity	41	5%	124	16%	0.009
Vancomycin (vs. fidaxomicin)[3]	46	6%	350	44%	0.518
DEMOGRAPHICS		0%		0%	
Inpatient	91	11%	393	50%	<0.001
Sex (males)	46	6%	269	34%	0.123
Race (Caucasian)	93	12%	622	79%	0.107
Living in North America	78	10%	579	73%	0.345
History of CDI	53	7%	230	29%	<0.001
Age (greater than 65)	68	9%	61	8%	0.0003
Albumin (less than 3.0)	86	11%	346	44%	<0.001
Creatinine (greater than 1.5)	1.55	0%	1.11	0%	0.008
WBC (greater than 15,000)	14	2%	10	1%	<0.001
PAST MEDICAL HISTORY[4]		0%		0%	
Alcohol Abuse	11	1%	41	5%	0.05
Diverticulosis	11	1%	69	9%	0.69
Appendectomy	14	2%	99	13%	0.99
Chronic Lung Disease	33	4%	146	18%	0.005
Cardiovascular Disease	52	7%	248	31%	0.001
Diabetes Mellitus	23	3%	144	18%	0.537
Cirrhosis	5	1%	18	2%	0.175
Liver Disease	15	2%	62	8%	0.05
Chronic Kidney Disease	27	3%	121	15%	0.02
Solid Cancer	26	3%	131	17%	0.078
Any Malignancy	29	4%	148	19%	0.07
Metastatic Cancer	4	1%	16	2%	0.301
Upper GI abnormality	53	7%	238	30%	<0.001
Lower GI abnormality	27	3%	119	15%	0.014
Obesity	6	1%	43	5%	0.977
Actively smoking	18	2%	82	10%	0.0701
Organ transplant	3	0%	12	2%	0.372
Hematologic malignancy	7	1%	39	5%	0.547
MEDS (not antibiotics)[5]					
Any acid lowering medications	68	9%	342	43%	<0.001
PPI during pre-treatment	41	5%	198	25%	0.008
PPI during treatment	54	7%	248	31%	<0.001

[1] Diagnosis at enrollment in study as a reason for antibiotics

[2] Anbiotics were received within 2 weeks of enrollment in the study; timing and dosage not available

[3] Study drug received for treatment (randomized per study protocol)

[4] Past medical history as obtained from chart review at enrollment

[5] Medications patients received at enrollment

Table 9: Patients who had a recurrence of CDI vs. patients who did not recur from the mITT population (n=695)

Variables	No recur	% no recur	recur	% recur	p value
DEMOGRAPHICS					
Inpatient	304	38%	89	11%	0.281
Males	205	26%	64	8%	0.181
Caucasians	486	61%	136	17%	0.198
North America	450	57%	129	16%	0.114
Previous History of CDI	169	21%	61	8%	0.02
Age (greater than 65)	248	31%	74	9%	0.281
Albumin (less than 3.0)	242	31%	80	10%	0.03
Creatinine (greater than 1.5)	56	7%	26	3%	0.02
WBC (greater than 15,000)	77	10%	17	2%	0.43
DIAGNOSIS[1]		0%		0%	
Bone or Joint infection	14	2%	1	0%	0.196
BI or Abdominal Infection	97	12%	24	3%	0.69
Urinary Tract Infection	77	10%	39	5%	<0.001
Lower Respiratory Infection	84	11%	29	4%	0.204
Bacteremia or Sepsis	28	4%	11	1%	0.272
Fever (no definite source)	27	3%	8	1%	0.803
Pre Operative Prophylaxis	68	9%	20	3%	0.7
ANTIBIOTICS[2]		0%		0%	
Metronidazole	90	11%	26	3%	0.722
Beta Lactam	197	25%	48	6%	0.45
Fluoroquinolone	105	13%	35	4%	0.217
Penicillin	100	13%	24	3%	0.583
Any Cephalosporin	123	16%	24	3%	0.583
Cephalosporin (3rd or 4th generation)	43	5%	14	2%	0.515
OUTCOMES		0%		0%	
CDI severity	96	12%	29	4%	0.108
Vancomycin (vs. fidaxomicin)[3]	299	38%	51	6%	<0.001
PAST MEDICAL HISTORY[4]		0%		0%	
ALCOHOL ABUSE	27	3%	14	2%	0.04
DIVERTICLOSIS	52	7%	17	2%	0.46
APPENDECTOMY	75	9%	24	3%	0.421
Chronic Lung Disease	113	14%	33	4%	0.636
Cardiovascular Disease	181	23%	67	8%	0.005
Diabetes Mellitus	109	14%	35	4%	0.303
Cirrhosis	15	2%	3	0%	0.636
Liver Disease	46	6%	16	2%	0.352
Chronic Kidney Disease	88	11%	33	4%	0.07
Solid Cancer	97	12%	34	4%	0.139
Any Malignancy	111	14%	37	5%	0.201
Metastatic Cancer	12	2%	4	1%	0.71
Upper GI Abnormality	189	24%	49	6%	0.782
Lower GI Abnormality	94	12%	25	3%	0.959
Obesity	29	4%	14	2%	0.06
Active Smoker	69	9%	13	2%	0.211
Transplant (any type)	8	1%	4	1%	0.306
Hematologic Malignancy	0	0%	9	1%	0.76
MEDICATIONS[5]		0%		0%	
Any Acid Lowering Agent	269	34%	73	9%	0.91
PPI prior to enrollment	149	19%	49	6%	0.147

[1] Diagnosis at enrollment in study as a reason for antibiotics

[2] Anbiotics were received within 2 weeks of enrollment in the study; timing and dosage not available

[3] Study drug received for treatment (randomized per study protocol)

[4] Past medical history as obtained from chart review at enrollment

[5] Medications patients received at enrollment

Discussion

In this post-hoc analysis of the fidaxomicin vs. vancomycin clinical trials, we used a propensity score adjusted analysis to evaluate the association of the NAP1/BI/027 strain with several disease outcomes including disease severity (based on the IDSA guidelines), clinical cure and recurrence. We conclude that having the NAP1/BI/027 strain as the cause of CDI is not associated with more severe disease as compared with not having the strain as the cause of CDI. However, having the NAP1/BI/027 strain as the cause of CDI was significantly associated with decreased cure rates. These results remain robust through multiple analysis including propensity-adjusted logistic regression, propensity-matched conditional logistic regression and inverse probability weighting. Having the NAP1/BI/027 strain was not statistically associated with increased recurrence rates based on the propensity-adjusted model. However, the matched propensity score analysis showed a statistically significant association between the NAP1/BI/027 strain and recurrence.

Traditionally, the propensity score has been utilized extensively in observational treatment studies to reduce confounding when patients are not randomly assigned to receive a specific treatment, which can be influenced by baseline characteristics. Thus, the propensity score incorporates pretreatment variables and assigns an appropriate weight to each individual based on the probability that a patient will receive a given treatment instead of the alternative. Using a propensity adjusted analysis, the baseline treatment characteristics of patients who received a treatment vs. patients who did not receive a specific treatment in theory are balanced (based on the characteristics). Therefore, the true association between the specified treatment and outcomes is measured. [17]

In this study, we used a different approach to propensity score analysis to evaluate the association between the presence of the NAP1/BI/027 strains and outcomes. Similar to baseline characteristics of treatment groups in observational studies, having the NAP1/BI/027 strain as the cause of CDI is associated with certain baseline subject characteristics. In our study population, the patients that acquired the NAP1/BI/027 strain as the cause of CDI were an older and sicker cohort with more exposure to antimicrobials than patients with CDI not caused by the NAP1/BI/027 strain. More specifically, fluoroquinolone and beta-lactam exposure in the 2 weeks prior to enrollment is a statistically significant risk factor for acquisition of the NAP1/BI/028 strain as the cause of CDI in the univariate analysis. Any acid-lowering medication at the time of enrollment, including histamine blockers, proton pump inhibitors and antacids, were also associated with having the NAP1/BI/027 strain. Therefore, in order to estimate the effect of the NAP1/BI/027 strain on the disease outcomes, the propensity score accounts for these baseline characteristics that may affect the outcomes.

We utilized three different propensity adjusted analyses (quintile of propensity score propensity, inverse probability weighting and matched propensity analysis) to evaluate the association of the NAP1/BI/027 strain and the outcomes. All three methods showed similar results regarding the outcomes of clinical severity and clinical cure.

Regarding the outcome of disease recurrence, the matched propensity score analysis showed a statistically significant association between having the NAP1/BI/027 strain and disease recurrence which was not observed in the other 2 analysis (inverse probability weighting and propensity-adjusted logistic regression). One explanation for this is that in the matched analysis, the sample size was reduced (n = 566) as all of the patients with the

NAP1/BI/027 strains were matched and a significant number of controls were unmatched The matched cohort, while more similar than the full sample, still differed on multiple baseline characteristics which was due to our liberal matching strategy. Every patient with the NAP1/BI/027 stain was matched to a patient without it based on having the closest propensity score. In the matched cohort, the two populations (NAP1/BI/027 strain patients vs. non-NAP1/BI/027 patients) appeared slightly more balanced (based on the propensity score) when compared to the two groups in the unmatched population**.** However, this does not imply that the propensity score for the matched subjects was necessarily similar. Therefore, inverse probability weighting and propensity-adjusted logistic regression likely more validly estimate the true association between strain and recurrence, which was not statistically significant.

The identification of the NAP1/BI/027 strain has coincided with outbreaks of CDI but there has been no consistent data linking the strain with worse disease outcome. [12] One potential flaw is that the definition of disease severity has not been consistent across studies. [12] Our results indicate that patients with CDI caused by the NAP1/BI/027 strain do not have more severe disease (IDSA guidelines) than patients without the NAP/BI/027 strain. Therefore, baseline patient characteristics may predict disease severity, regardless of strain type. Our results also confirm previous reports of decreased cure rates in patients with the NAP1/BI/027 as the cause of CDI vs. patients without the strain.[18] This has clinical applications as knowledge of the type of strain causing CDI in patients may predict the clinical course irrespective of disease severity or type of treatment.

This study has several limitations. First, information regarding medication exposure prior to enrollment did not include the timing of the medication or the number of doses of

the medications. Therefore, patients that only received one dose of the medications were combined with patients who may have received many doses of medication prior to enrollment in the study which may have affected the results. Second, the definition of disease severity was based on the IDSA guidelines, defined as an elevated white blood cell count or an elevated creatinine level. The definition of disease severity did not include other factors such as age, temperature, number of stools, septic shock, ICU admission or 90-day mortality. Furthermore, outcomes associated with other hypervirulent strains, such as the ribotype 087, were not assessed in this study. Patients who acquired these strains as the cause of CDI may have developed worse disease outcomes in the control group. Finally, strain typing was not available for 30% of the modified intent-to-treat population. However, this population was similar to the typed population in descriptive analysis. Finally, the propensity score is most commonly used to predict the likelihood of treatment with a drug or implementation of a therapeutic procedure, both of which have well-defined dates of administration. The time of onset of disease caused by the NAP1/BI/027 strain is not known. Therefore, there is a chance that post-infection variables may have been inadvertently included in the propensity score.

The strengths of this analysis is the extensive information regarding baseline demographic information, laboratory values, underlying disease status, CDI presentation characteristics as well as extent and duration of CDI. Furthermore, the application of the propensity score in multiple analyses was an innovative approach to assessing CDI outcomes in relation to the presence of the NAP1/BI/027 strain. Finally, multiple applications of the propensity score further validated our findings.

In conclusion, our results show an association between CDI caused by the NAP1/BI/027

strain and decreased clinical cure compared. Risk factors for having the NAP1/BI/027 strain include older age, prior history of CDI, history of chronic disease and recent exposure to antimicrobials as well as exposure to any acid-lowering medications. However, having the NAP1/BI/027 strain as the cause of CDI, regardless of underlying host risk factors, is associated with decreased clinical cure and may be associated with increased recurrences. These results have significant clinical implications as patients who have the NAP1/BI/027 strain as the cause of CDI may be at risk for treatment failure and increased recurrence, regardless of type of treatment, baseline risk factors for disease or disease severity.

References

1. Cohen SH, Gerding DN, Johnson S, et al. Clinical practice guidelines for clostridium difficile infection in adults: 2010 update by the society for healthcare epidemiology of America (SHEA) and the infectious diseases society of America (IDSA). *Infect Control Hosp Epidemiol*. 2010;31(5):431-455.

2. Ghantoji SS, Sail K, Lairson DR, DuPont HL, Garey KW. Economic healthcare costs of clostridium difficile infection: A systematic review. *J Hosp Infect*. 2010;74(4):309-318.

3. Johnson S. Recurrent clostridium difficile infection: A review of risk factors, treatments, and outcomes. *J Infect*. 2009;58(6):403-410.

4. Zilberberg MD, Shorr AF, Kollef MH. Increase in adult clostridium difficile-related hospitalizations and case-fatality rate, united states, 2000-2005. *Emerg Infect Dis*. 2008;14(6):929-931.

5. Bartlett JG. Narrative review: The new epidemic of clostridium difficile-associated enteric disease. *Ann Intern Med*. 2006;145(10):758-764.

6. Redelings MD, Sorvillo F, Mascola L. Increase in clostridium difficile-related mortality rates, united states, 1999-2004. *Emerg Infect Dis*. 2007;13(9):1417-1419.

7. McDonald LC, Killgore GE, Thompson A, et al. An epidemic, toxin gene-variant strain of clostridium difficile. *N Engl J Med*. 2005;353(23):2433-2441.

8. Pepin J, Valiquette L, Alary ME, et al. Clostridium difficile-associated diarrhea in a region of quebec from 1991 to 2003: A changing pattern of disease severity. *CMAJ*. 2004;171(5):466-472.

9. Kelly CP, LaMont JT. Clostridium difficile--more difficult than ever. *N Engl J Med*. 2008;359(18):1932-1940.

10. Centers for Disease Control and Prevention (CDC). Surveillance for community-associated clostridium difficile--Connecticut, 2006. *MMWR Morb Mortal Wkly Rep*. 2008;57(13):340-343.

11. Abrahamian FM, Talan DA, Moran GJ, Pinner R. Update on emerging infections from the centers for disease control and prevention. severe clostridium difficile-associated disease in populations previously at low risk--four states, 2005. *Ann Emerg Med*. 2006;48(1):55-59.

12. Walk ST, Micic D, Jain R, et al. Clostridium difficile ribotype does not predict severe infection. *Clin Infect Dis*. 2012;55(12):1661-1668.

13. Goorhuis A, Bakker D, Corver J, et al. Emergence of clostridium difficile infection due to a new hypervirulent strain, polymerase chain reaction ribotype 078. *Clin Infect Dis*. 2008;47(9):1162-1170.

14. O'Connor JR, Johnson S, Gerding DN. Clostridium difficile infection caused by the epidemic BI/NAP1/027 strain. *Gastroenterology*. 2009;136(6):1913-1924.

15. Louie TJ, Miller MA, Mullane KM, et al. Fidaxomicin versus vancomycin for clostridium difficile infection. *N Engl J Med*. 2011;364(5):422-431.

16. Cornely OA, Crook DW, Esposito R, et al. Fidaxomicin versus vancomycin for infection with clostridium difficile in europe, canada, and the USA: A double-blind, non-inferiority, randomised controlled trial. *Lancet Infect Dis*. 2012;12(4):281-289.

17. Kurth T, Seeger J. Propensity score analyses in pharmacoepidemiology. In: Hartzema A, Tilson H, Chan K, eds. *Pharmacoepidemiology and theapeutic risk management.* Havey Whitney Books; 2008:301.

18. Petrella LA, Sambol SP, Cheknis A, et al. Decreased cure and increased recurrence rates for clostridium difficile infection caused by the epidemic C. difficile BI strain. *Clin Infect Dis*. 2012;55(3):351-357.