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BRIEF REPORT

# Risk Factors for BI/NAP1/027 *Clostridioides difficile* Infections and Clinical Outcomes Compared With Non-NAP1 Strains

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We aim to describe the characteristics, risk factors, and clinical outcomes associated with NAP1 strain *Clostridioides difficile* infection (CDI) in this single-center, retrospective, case–control (1:1) study. We found that the NAP1 strain accounted for 19.7% of CDI, and risk factors for acquisition included residence in skilled nursing facilities, previous CDI, and proton pump inhibitor use.

**Keywords.** *Clostridium difficile*; NAP1; outcomes; risk factors.

The clinical profile of *Clostridioides difficile* infection (CDI) has been complicated by a hypervirulent strain, known as the North American pulsed-field gel electrophoresis type 1 (NAP1) strain. Risk factors for the NAP1 strain include prior fluoroquinolone use, admission from a skilled nursing facility, and advanced age [1–3]. Clinical outcomes of patients based on CDI ribotype have been investigated, but the findings have been mixed. Although some studies have demonstrated that the NAP1 strain is a predictor of disease severity, recurrence, or increased mortality [2, 4–6], others have shown no association between NAP1 strains and clinical outcomes [3, 7–9]. Our study aimed to describe the clinical features and risk factors associated with NAP1 and to further characterize the clinical outcomes of NAP1 strains in our patient population.

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## METHODS

A single-center, retrospective, case–control (1:1) study was conducted at a 413-bed university-affiliated urban teaching hospital and level 1 trauma and burn center, Harborview Medical Center, located in Seattle, Washington. Medical records of hospitalized patients who were ≥18 years old with a positive *C. difficile* polymerase chain reaction (PCR) detected by Xpert CDI Epi assay between February 2014 and May 2015 were reviewed.

CDI was defined as an episode of clinically significant diarrhea that warranted PCR testing and required antimicrobial treatment. For each patient diagnosed with NAP1 CDI, 1 control patient with non-NAP1 CDI was randomly selected by a computer-generated program matched for admitting medical service and intensive care unit (ICU) stay. Hospital-acquired CDI and community-acquired CDI were defined as a positive CDI PCR ≥72 or <72 hours from hospital admission, respectively. Hospital-acquired CID and community-acquired CDI were defined in accordance with internal definitions used by the Infection Prevention and Control team at our institution.

Severity of disease was assessed based on the 2010 Society for Healthcare Epidemiology and Infectious Disease Society of America (SHEA-IDSA) criteria [10]. Chart review was conducted to identify potential risk factors for CDI, including age, broad-spectrum antibiotic use in the 30 days preceding diagnosis (defined as cephalosporins, carbapenems, piperacillin-tazobactam, clindamycin, or fluoroquinolones), hospitalization in the preceding 90 days, residence at a skilled nursing facility, proton pump inhibitor (PPI) use, and CDI in the preceding 12 months. Prior CDI was not further categorized as NAP1 or non-NAP1, due to the fact that NAP1 testing was introduced just before the study period. Clinical cure was defined as resolution of diarrhea (ie, ≤3 unformed stools for 2 consecutive days) after the end of the course of therapy. The primary objectives were to describe disease severity and determine risk factors associated with CDI due to the NAP1 strain. Secondary outcomes included clinical cure rate, 90-day CDI recurrence rate, and hospital mortality.

The institutional review board of the University of Washington approved this study and waived written informed consent.

Variables were compared using the Student *t* test for continuous variables and the chi-square test or Wilcoxon rank-sum test for categorical variables. A 2-sided *P* value of <.05 was considered statistically significant. Multivariate logistic regression models with robust variance estimates were performed using Stata Software (Stata Corporation, College Station, TX, USA). A parsimonious model adjusting for covariates, including age, gender, ethnicity, medical comorbidities, prior CDI in the past 12 months, hospitalization in the past 90 days, admission from

**Table 1. Characteristics and Outcomes of NAP1 vs non-NAP1 Patients**

| | NAP1 (n = 42), No. (%) | Non NAP1 (n = 42), No. (%) | *P* Value[b] |
|---|---|---|---|
| Patient demographics | | | |
| Median age, IQR, y | 60.5, 54–66 | 61, 51–69 | NS |
| Male sex | 20 (47.6) | 24 (57.1) | NS |
| Ethnicity | | | NS |
| Non-Hispanic Caucasian | 31 (73.8) | 31 (73.8) | |
| African American | 7 (16.7) | 1 (2.4) | |
| Asian/Pacific Islander | 1 (2.4) | 5 (11.9) | |
| Native American | 1 (2.4) | 3 (7.1) | |
| Hispanic | 2 (4.8) | 2 (4.8) | |
| Hospitalized in the last 90 d | 27 (64.3) | 16 (38.1) | .0170 |
| Nursing home before admission | 16 (38.1) | 4 (9.5) | .0022 |
| Medical history | | | |
| Cardiovascular disease | 1 (2.4) | 7 (16.7) | .0266 |
| Any malignancy | 10 (23.8) | 6 (14.3) | NS |
| COPD | 12 (28.6) | 4 (9.5) | .0271 |
| Chronic kidney disease | 13 (31.0) | 8 (19.1) | NS |
| Diabetes mellitus | 17 (40.5) | 11 (26.2) | NS |
| Recent surgery within the last 30 d | 13 (31.0) | 22 (52.4) | .0477 |
| HIV | 1 (2.4) | 0 (0.0) | NS |
| Cirrhosis | 3 (7.1) | 0 (0.0) | NS |
| Heart failure | 9 (21.4) | 1 (2.4) | .0074 |
| Markers of CDI severity | | | |
| Median WBC at time of diagnosis, IQR, 1000 cells/μL | 18.3, 7.9–20.1 | 12.9, 7.2–16.0 | .0468 |
| Median Peak WBC during hospitalization, IQR, 1000 cells/μL | 21.6, 12.2–35.6 | 17.3, 12.8–22.0 | .0110 |
| Abdominal tenderness at diagnosis | 10 (23.8) | 8 (19.1) | NS |
| Presence of shock at diagnosis | 9 (21.4) | 5 (11.9) | NS |
| Presence of ileus at diagnosis | 7 (16.7) | 1 (2.4) | .0266 |
| Presence of megacolon at diagnosis | 3 (7.1) | 0 (0.0) | NS |
| Mechanical ventilation during CDI | 18 (42.9) | 14 (33.3) | NS |
| IDSA/SHEA severity[a] [10] | | | NS |
| Mild/moderate | 18 (42.9) | 22 (52.4) | |
| Severe and severe and complicated | 24 (57.1) | 20 (47.6) | |
| Hospital-acquired | 24 (57.1) | 27 (64.3) | NS |
| Community-acquired | 18 (42.9) | 15 (37.5) | |
| Risk factors For CDI | | | |
| Prior antibiotics in the last 30 d | 31 (73.8) | 25 (59.5) | NS |
| Prior CDI in the last 12 mo | 10 (23.8) | 2 (4.8) | .0132 |
| PPI use in the last 30 d (inpatient) | 9 (21.4) | 11 (26.2) | NS |
| PPI use in the last 30 d (outpatient) | 15 (35.7) | 6 (14.3) | .0242 |
| CDI treatment | | | |
| Metronidazole alone | 10 (23.8) | 6 (14.3) | NS |
| Vancomycin alone | 18 (43.9) | 15 (36.6) | NS |
| Combination therapy | 6 (14.6) | 10 (24.4) | NS |
| Therapy escalation | 7 (17.1) | 10 (24.4) | NS |
| Clinical outcomes | | | |
| Recurrence of CDI within 90 d | 7 (16.7) | 2 (4.8) | NS |
| Second recurrence of CDI within 90 d | 1 (2.4) | 0 (0.0) | NS |
| Alive at hospital discharge | 32 (76.2) | 36 (85.7) | NS |
| Clinical cure | | | NS |
| Yes | 22 (52.4) | 27 (64.3) | |
| No | 13 (31.0) | 8 (19.1) | |
| Indeterminate | 7 (16.7) | 7 (16.7) | |
| Hospital length of stay, mean ± SD [range], d | 20.9 ± 25.1 [2–106] | 21.0 ± 18.5 [2–78] | NS |
| ICU length of stay, mean ± SD [range], d | 10.0 ± 11.2 [1–42] | 11.2 ± 9.3 [1–33] | NS |

Abbreviations: CDI, *Clostridium difficile* infection; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IDSA, Infectious Diseases Society of America; IQR, interquartile range; NS, nonsignificant; PPI, proton pump inhibitor; SHEA, Society of Healthcare Epidemiology of America; WBC, white blood cell.

[a]Two patients did not receive therapy for *C. difficile* due to transition to comfort care.

[b]*P* values >.05 were considered nonsignificant.

a skilled nursing facility, prior antibiotics, and PPI use 30 days before CDI, was selected.

## RESULTS

Our study was conducted during a nonepidemic CDI time period, and the incidence of CDI at our institution was steady from 2012 to 2015. The incidence of nosocomial colonization or infection of *C. difficile* was 8.91/10 000 patient-days in 2012, 7.18/10 000 patient-days in 2013, 8.33/10 000 patient-days in 2014, and 7.97/10 000 patient-days in 2015. During the study period, a total of 213 stool specimens were positive for *C. difficile* by PCR, and 42 (19.7%) were positive for NAP1. Cases with NAP1 CDI were more likely to have been hospitalized in the preceding 90 days before CDI diagnosis (64.3% vs 38.1%), more likely to have been admitted from a skilled nursing facility (38.1% vs 9.5%), and more likely to have been prescribed PPIs (35.7% vs 14.3%) than controls with a non-NAP1 strain.

Cases with the NAP1 strain tended to have a higher median white blood cell count when compared with controls (Table 1). The presence of shock or megacolon at diagnosis was similar between the NAP1 and non-NAP1 groups, but the incidence of ileus at the time of CDI diagnosis (16.7% vs 2.4%) was higher among cases with the NAP1 strain (Table 1).

There was no observed difference in clinical cure rate or recurrence rate between the 2 groups (Table 1). The all-cause in-hospital mortality rate was 23.8% in the NAP1 group compared with 14.3% in the non-NAP1 group ($P$ = .27). The average hospital and ICU length of stay was similar between the 2 groups. Multivariate logistic regression analysis indicated risk factors for acquisition of NAP1 CDI, including residence in a skilled nursing facility (SNF; odds ratio [OR], 12.6; 95% confidence interval [CI], 2.6–60.9), CDI in the previous 12 months (OR, 17.2; 95% CI, 2.5–117.1), and PPI use in preceding month (OR, 5.6; 95% CI, 1.03–30.4), as outlined in Table 2.

**Table 2. Multivariate Logistic Regression Analysis for Risk Factors for NAP1 CDI**

| Risk Factors | Odds Ratio | 95% CI | *P* Value |
|---|---|---|---|
| Resident at a nursing home before hospitalization | 12.6 | 2.6–60.9 | .002 |
| Prior CDI during the last 12 mo of hospitalization | 17.2 | 2.5–117.1 | .004 |
| PPI use in the last 30 d in the outpatient setting | 5.6 | 1.03–30.4 | .045 |

Abbreviations: CDI, *Clostridium difficile* infection; CI, confidence interval; PPI, proton pump inhibitor.

## DISCUSSION

We observed a NAP1 prevalence of 19.7%, which is consistent with findings from other investigations that reported a NAP1 positivity rate ranging between 18% and 24% [3, 9, 11]. We did not observe any significant difference between the NAP1 and non-NAP1 groups in terms of disease severity, recurrence rates, hospital length of stay, or mortality.

Our study demonstrated that residence in a nursing facility, outpatient PPI use, and prior CDI within 12 months are significant risk factors for developing CDI caused by the NAP1 strain. Residence in a nursing facility has previously been reported as an independent predictor of NAP1 CDI, and our study further supports this observation [2, 3]. In a Veterans Affairs hospital and its affiliated long-term care facility (LTCF), the NAP1 strain was the most common strain recovered from CDI cases and asymptomatic carriers, and this strain also accounted for all transmission events [12]. These results suggest that LTCF residents with asymptomatic carriage of *C. difficile* or CDI may contribute significantly to transmission in LTCFs and during hospitalizations. We also showed that outpatient PPI use in the 30 days before admission was an independent risk factor for the development of CDI due to NAP1. This might relate to the enhanced expression of toxin in NAP1 strains in the presence of a PPI [13].

Notably, our study differed from prior studies, including that of Scardina et al., which included only incident cases of CDI [3]. We found that CDI in the preceding 12 months was an independent risk factor for the development of NAP1 CDI compared with those with no prior CDI in the last year.

Our study has significant limitations given the small sample size and the inherent constraints of a single-center retrospective chart abstraction. Additionally, due to the small sample size, multivariate logistic regression may have led to overestimation of the effect size. Larger-scale studies will need to be performed in order to better understand the relationship between the NAP1 strain and clinical outcomes and to determine whether treatment decisions should be impacted by strain type.


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