NAP1 Strain Type Predicts Outcomes From Clostridium difficile Infection

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(See the Editorial Commentary by Aronoff on pages 1401–3.)

Background. Studies are conflicting regarding the importance of the fluoroquinolone-resistant North American pulsed-field gel electrophoresis type 1 (NAP1) strain in Clostridium difficile infection (CDI) outcome. We describe strain types causing CDI and evaluate their association with patient outcomes.

Methods. CDI cases were identified from population-based surveillance. Multivariate regression models were used to evaluate the associations of strain type with severe disease (ileus, toxic megacolon, or pseudomembranous colitis within 5 days; or white blood cell count ≥15 000 cells/µL within 1 day of positive test), severe outcome (intensive care unit admission after positive test, colectomy for C. difficile infection, or death within 30 days of positive test), and death within 14 days of positive test.

Results. Strain typing results were available for 2057 cases. Severe disease occurred in 363 (17.7%) cases, severe outcome in 100 (4.9%), and death within 14 days in 56 (2.7%). The most common strain types were NAP1 (28.4%), NAP4 (10.2%), and NAP11 (9.1%). In unadjusted analysis, NAP1 was associated with greater odds of severe disease than other strains. After controlling for patient risk factors, healthcare exposure, and antibiotic use, NAP1 was associated with severe disease (adjusted odds ratio [AOR], 1.74; 95% confidence interval [CI], 1.36–2.22), severe outcome (AOR, 1.66; 95% CI, 1.09–2.54), and death within 14 days of positive test.

Conclusions. NAP1 was the most prevalent strain and a predictor of severe disease, severe outcome, and death. Strategies to reduce NAP1 prevalence, such as antibiotic stewardship to reduce fluoroquinolone use, might reduce CDI morbidity.

Keywords. Clostridium difficile; clinical outcomes; strain typing; epidemiology.

Increases in incidence and severity of Clostridium difficile infection (CDI) have been reported in the past decade and were initially attributed to the emergence of a “hypervirulent” strain, the North American pulsed-field gel electrophoresis type 1 (NAP1) strain, also described as polymerase chain reaction (PCR) ribotype 027 and restriction endonuclease analysis (REA) group BI [1–3]. This strain demonstrates increased toxin production in vitro and increased fluoroquinolone resistance compared with previously described strains.

Subsequent reports of the relationship between the NAP1 strain and patient outcomes have been in conflict. Although some studies suggest that infection with the NAP1 strain is associated with more severe disease [4–6], others reported no association [7–11]. These studies used different outcome measures (clinical...
Severity [10] as defined by clinical practice guidelines [12]; a composite of intensive care unit [ICU] admission, colectomy, and death [5,7,9]; and 14- or 30-day mortality [4,6,8,11], involved small sample sizes, or have focused on cases of infection from a single institution or community.

We sought to clarify the role of C. difficile strain type by determining the relationship between strain type and disease outcomes using a geographically diverse dataset from the United States. We used outcome measures similar to those in other studies to facilitate comparisons with prior reports.

METHODS

CDI Surveillance and Study Population

Data were obtained from the Centers for Disease Control and Prevention (CDC) Emerging Infections Program (EIP) C. difficile surveillance, which has been described elsewhere [13, 14]. The EIP CDI surveillance system is an active population-based and laboratory-based surveillance system that began in 2009 in selected counties of 6 US states (California, Colorado, Connecticut, Georgia, Minnesota, New York), expanded to 2 additional US states in 2010 (Tennessee and Oregon), and in 2011 expanded to an additional 2 states (Maryland and New Mexico). At each EIP site, trained surveillance officers investigate all positive C. difficile toxin assay or molecular assay reports from clinical, reference, and commercial laboratories for residents of surveillance catchment areas. A CDI case is defined as a positive C. difficile stool specimen in a surveillance area resident aged 1 year or older who did not have a positive test in the previous 8 weeks.

Cases are classified as community-associated if a positive specimen was collected as an outpatient or within 3 days of an acute care admission, without documentation of an overnight stay in a healthcare facility during the 12 weeks prior to stool collection; otherwise, cases are classified as healthcare-associated. Healthcare-associated cases are further classified as healthcare facility-onset if they occurred during a long-term care facility/nursing home stay or >3 calendar days after hospital admission; otherwise they are classified as community-onset healthcare facility-associated [15]. All CDI cases classified as either community-associated or community-onset healthcare facility-associated underwent a full medical record review to collect information on symptoms, coinfections, clinical comorbidities (Charlson index) [16], and outcomes, and a 10% sample of the healthcare facility-onset cases was fully reviewed.

A convenience sample of clinical laboratories in each catchment area (n = 37 laboratories) submitted all stool specimens from CDI patients with full medical record review to 3 reference laboratories (Edwards Hines Jr Veterans Affairs, New York State Department of Health, and Minnesota Department of Health Public Health Laboratory) for culture of C. difficile [17]. Recovered isolates were sent to the CDC for molecular typing by pulsed-field gel electrophoresis (PFGE). PFGE patterns were analyzed using BioNumerics version 5.10 (Applied Maths, Austin, Texas) and grouped into pulsed-field types using Dice/unweighted pair group method with arithmetic mean clustering. An 80% similarity threshold was used to assign North American PFGE (NAP) types [18]. Isolates also underwent PCR to detect the presence of tcdA, tcdB, and binary toxin (cdtA and cdtB) genes [19].

For this analysis, we limited the data to the CDI cases with stool specimens collected between 1 January 2009–31 December 2011. Only cases with full medical record review and strain typing results available were included. Cases whose isolates were negative for both tcdA and tcdB (n = 89) were excluded. During 2009–2011, only 8 EIP sites collected stool specimens (California, Colorado, Connecticut, Georgia, Minnesota, New York, Oregon, and Tennessee). These 8 EIP sites represented a surveillance catchment area of 9667103 persons in 2011.

Outcomes of Interest

Three separate outcome measures were evaluated: severe CDI disease, severe CDI outcome, and death within 14 days of infection. The definition of severe disease, adapted from current clinical practice guidelines [12], was development of ileus, toxic megacolon, or pseudomembranous colitis within 5 days of the positive C. difficile stool specimen or serum white blood count ≥15 000 cells/µL within 1 calendar day of collection of the stool specimen. Severe outcome was defined as ICU admission within 7 days after stool collection, colectomy for CDI, or death within 30 days of stool collection, in accordance with a recent study from Walk et al [7]. Death within 14 days was also evaluated based on the recent study from Walker et al [5].

Statistical Analysis

Multiple imputation was used to impute missing race (12.6% of cases) based on the distribution of known race by age, sex, and surveillance site. Analysis of imputed datasets was performed using PROC MIANALYZE (SAS Institute, Cary, North Carolina) to account for the uncertainty associated with imputation. Baseline differences between groups were evaluated using \(\chi^2\) or Fisher exact tests for categorical variables, as appropriate, and Wilcoxon rank-sum tests for continuous variables. Because a linear relationship between increasing Charlson index and outcome variables was seen (up to a Charlson comorbidity index of 3), the Charlson index was treated as an ordinal variable with levels 0, 1, 2, and ≥3.

For the outcomes studied, initial analyses of the association between individual variables and the outcome of interest were first performed with a univariate logistic regression model; a separate multivariate logistic regression model was then constructed for each of 3 outcome measures of interest using stepwise backward selection. Variables with \(P \leq .25\) in univariate
analysis were eligible for inclusion in the corresponding multivariate model. Possible confounding variables (ie, change of ≥10% to the estimated odds ratio for NAP1 strain) were added to respective multivariate models regardless of $P$ values. Charlson index was also included in all models regardless of $P$ value. To confirm the results found in multivariate models, analyses stratifying the data by age (patients ≤50 vs >50 years of age) and by epidemiologic classification (community-associated vs healthcare-associated) were performed. A sensitivity analysis was also performed excluding the EIP site contributing the largest number of NAP1 cases from models. A 2-tailed $P$ value <.05 was considered statistically significant. All analyses were performed with SAS software, version 9.3 (SAS Institute).

Human Subjects Review
The CDC and local institutional review boards approved the study. A waiver of informed consent was granted because the study posed no greater than minimal risk to participants.

RESULTS

Description of Clostridium difficile Infection Cases
During 2009–2011, strain typing results were available for 2057 of the 14,091 total CDI cases identified. Two EIP sites (New York and Minnesota) contributed >50% of cases with strain typing results (Table 1). Compared with CDI cases without strain typing results but with clinical data available (n = 5324), those with strain typing results were similar with respect to age ($P = .41$) and the 3 clinical outcomes of interest: severe disease ($P = .05$), severe outcome ($P = .90$), and death within 14 days ($P = .18$). Although differences in sex ($P = .04$) and race ($P < .0001$) between CDI cases with and those without strain typing results reached statistical significance, the relative differences were <6% between groups.

Among the 2057 CDI cases included in the analysis, the majority (52.8%) were community-associated by design. Overall, the most common strain types were NAP1 (28.4% of cases), NAP4 (10.2%), NAP11 (9.1%), and NAP6 (6.6%) (Figure 1). Of the 585 NAP1 cases, 17 (2.9%) were negative for binary toxin. Compared with these 3 most common NAP types, and compared with all others, the NAP1 type was associated with a greater odds of severe disease in unadjusted analysis (Figure 2). Therefore, remaining analyses compare the NAP1 strain to all other strain types (ie, non-NAP1 strains).

NAP1 strain was associated with older age ($P < .0001$), healthcare-associated epidemiologic classification ($P < .0001$), emergency department visits ($P = .003$) in the prior 12 weeks, Charlson index ($P < .0001$), and prior receipt of antibiotics ($P < .0001$) in univariate analysis (Table 2). Inflammatory bowel disease ($P = .0003$) and prior immunosuppressive treatment ($P = .04$) were associated with non-NAP1 strains.

Outcomes
    Severe Disease
Criteria for severe disease were met for 363 cases (17.7%) with strain typing results. The majority of these cases (86.0%) met criteria for severe disease because of elevated white blood cell count alone. Infection with the NAP1 strain was significantly associated with severe disease in multivariate analysis (adjusted odds ratio [AOR], 1.74; 95% confidence interval [CI], 1.36–2.22) after controlling for age, epidemiologic classification, prior emergency department visits and hospitalizations,

**Figure 1.** Distribution of North American pulsed-field gel electrophoresis (PFGE) types among Clostridium difficile cases with strain typing results (n = 2057). The “unnamed” strain type consists of many (>200) unrelated PFGE patterns.

### Table 1. Clostridium difficile Infection Cases With Strain Typing Results by Emerging Infections Program Site, 2009–2011

<table>
<thead>
<tr>
<th>EIP Site</th>
<th>CDI Cases, All Strains (n = 2057)</th>
<th>NAP1 Strain (n = 585)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>% of Total</td>
</tr>
<tr>
<td>California</td>
<td>114</td>
<td>5.5</td>
</tr>
<tr>
<td>Colorado</td>
<td>346</td>
<td>16.8</td>
</tr>
<tr>
<td>Connecticut</td>
<td>184</td>
<td>9.0</td>
</tr>
<tr>
<td>Georgia</td>
<td>105</td>
<td>5.1</td>
</tr>
<tr>
<td>Minnesota</td>
<td>469</td>
<td>22.8</td>
</tr>
<tr>
<td>New York</td>
<td>689</td>
<td>33.5</td>
</tr>
<tr>
<td>Oregon</td>
<td>39</td>
<td>1.9</td>
</tr>
<tr>
<td>Tennessee</td>
<td>111</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Abbreviations: CDI, Clostridium difficile infection; EIP, Emerging Infections Program.
Charlson index, prior immunosuppressive treatment, and prior antibiotic use (Table 3).

### Severe Outcome
Severe outcomes occurred for 100 cases (4.9%). Of these cases, 41 were admitted to an ICU within 7 days after infection, 6 underwent colectomy, and 70 died within 30 days of infection. Cases developing severe outcomes were more likely to be infected with a NAP1 strain compared with those who did not develop severe outcomes (46.0% vs 27.5%, \( P < .0001 \)). NAP1 strain remained a predictor of severe outcomes in multivariate analysis (AOR, 1.66; 95% CI, 1.09–2.54) after controlling for older age, white race, healthcare-associated epidemiologic classification, Charlson index, and prior antibiotic use (Table 4).

### Death Within 14 Days
Fifty-six deaths occurred within 14 days of stool collection. The NAP1 strain was more common among those who died within 14 days than among those who survived (51.8% vs 27.8%, \( P < .0001 \)). The 14-day mortality of NAP1 cases was 5.0% and for non-NAP1 cases was 1.8%. In particular, in cases with NAP7/8, which corresponds to ribotype 078, the 14-day mortality was 1.5% (95% CI, 0.4%–8.0%; 1 of 66). In univariate analyses, older age (odds ratio [OR], 5.6; 95% CI, 2.87–10.86), healthcare-associated epidemiologic classification (OR, 5.41; 95% CI, 2.43–12.07 for community-onset healthcare facility–associated vs community-associated; OR, 10.38; 95% CI, 4.59–23.43 for healthcare facility–onset vs community-associated), Charlson index (OR 2.68; 95% CI, 1.94–3.70), prior proton pump inhibitor use (OR, 2.18; 95% CI, 1.28–3.71), and prior antibiotic use (OR, 2.31; 95% CI, 1.30–4.11) were also associated with death within 14 days. In multivariate analysis, age, race, epidemiologic classification, and Charlson index were retained in the final model. After controlling for these risk factors, NAP1 strain remained a significant predictor of 14-day mortality (AOR, 2.12; 95% CI, 1.22–3.68; Table 5).

### Sensitivity Analyses
In analyses stratified by age group, NAP1 infection remained a predictor of poor outcomes in both younger (<50 years) and older patients (>50 years) (data not shown). When stratifying by epidemiologic class (healthcare- vs community-associated), NAP1 remained significantly associated with the 3 outcomes of interest for healthcare-associated cases, whereas for community-associated cases, all NAP1 ORs were >1.0 but \( P \) values were >.05. Finally, the associations between the NAP1 strain and severe disease, severe outcome, and 14-day mortality remained significant after excluding cases from the EIP site (New York) that contributed the largest number of NAP1 cases.
Disease Among Cases With Strain Typing Results, 2009

epidemiologic classes did not have significantly different odds of severe disease than other NAP types in our dataset. NAP1 was associated with greater odds of severe disease than other NAP types related to differences in sample size. However, our results differ from a recent study from the United States by Walk et al that found no association between the NAP1/027 strain and severe outcome [7]. In the US study, the number of patients with NAP1 was small (approximately 40) and <50 patients met the outcome measure. Although the US study reported a lack of association, the odds for severe outcome were increased among NAP1/027 cases, albeit not achieving statistical significance. Thus, as suggested by others [20, 21], lack of association between the NAP1/027 strain and severe outcome reported in the US study might be largely related to differences in sample size.

The proportion of patients who died in our study (3.8%) is lower than that reported from other studies of CDI outcomes [5, 22]. This discrepancy is likely a result of a larger proportion of community-associated CDI cases in our study, which are associated with better outcomes than healthcare-associated cases [14]. This is unlikely to bias our study toward detection of and a variety of healthcare exposures. After controlling for potential confounders, the NAP1 strain remained a significant predictor of severe disease, severe outcome, and 14-day mortality. Our results represent the largest study to date to examine the association between strain type and disease outcomes. Furthermore, inclusion of cases from a wide geographic spread reduces bias due to regional variation in C. difficile strain type or patient characteristics.

We chose the outcome measures of severe outcome and 14-day mortality to facilitate comparisons with 2 recent studies on CDI outcome related to the NAP1 strain. Our findings agree with those in a recent report from the United Kingdom showing that the NAP1/027 strain is associated with increased 14-day mortality [5]. However, our results differ from a recent study from the United States by Walk et al that found no association between the NAP1/027 strain and severe outcome [7]. In the US study, the number of patients with NAP1 was small (approximately 40) and <50 patients met the outcome measure. Although the US study reported a lack of association, the odds for severe outcome were increased among NAP1/027 cases, albeit not achieving statistical significance. Thus, as suggested by others [20, 21], lack of association between the NAP1/027 strain and severe outcome reported in the US study might be largely related to differences in sample size.

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<table>
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<th>Table 3. Multivariate Analysis for Severe Clostridium difficile Disease Among Cases With Strain Typing Results, 2009–2011</th>
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<tr>
<td><strong>Risk Factors</strong></td>
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<tr>
<td>Cases with strain typing results (n = 2057)</td>
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<tr>
<td>Age &gt;65 y</td>
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<tr>
<td>Healthcare-associated epidemiologic classification</td>
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<tr>
<td>Emergency department visit during 12 wk prior to infection</td>
</tr>
<tr>
<td>Charlson index</td>
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<tr>
<td>Medications during 14 d prior to infection</td>
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<tr>
<td>Immunosuppressive treatment</td>
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<tr>
<td>Any antibiotic</td>
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<tr>
<td>NAP1 strain</td>
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</tbody>
</table>

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

* Candidate variables included in the severe disease model: age; epidemiologic classification; surgery or emergency department visit during 12 weeks prior to infection; diverticular disease; Charlson index; proton pump inhibitor use, immunosuppressive treatment, or antibiotic use during 14 days prior to infection; strain type.

** Healthcare facility–onset and community-onset healthcare facility–associated epidemiologic classes did not have significantly different odds of severe disease and were collapsed into a single “healthcare-associated” category.

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<th>Table 4. Multivariate Analysis for Severe Outcome of Clostridium difficile Infection Among Cases With Strain Typing Results, 2009–2011</th>
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<tr>
<td><strong>Risk Factors</strong></td>
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<td>Cases with strain typing results (n = 2057)</td>
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<tr>
<td>Age &gt;65 y</td>
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<tr>
<td>White race</td>
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<tr>
<td>Healthcare-associated epidemiologic classification</td>
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<tr>
<td>Charlson index</td>
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<tr>
<td>Any antibiotic during 14 d prior to infection</td>
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<tr>
<td>NAP1 strain</td>
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</tbody>
</table>

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

* Candidate variables included in the severe outcome model: age; race; epidemiologic classification; chronic hemodialysis; emergency department visit during 12 weeks prior to infection; Charlson index; proton pump inhibitor use, H2 blocker use, or antibiotic use during 14 d prior to infection; strain type.

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<table>
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<tr>
<th>Table 5. Multivariate Analysis for 14-Day Mortality After Clostridium difficile Infection Among Cases With Strain Typing Results, 2009–2011</th>
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<tbody>
<tr>
<td><strong>Risk Factors</strong></td>
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<td>Age &gt;65 y</td>
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<tr>
<td>White race</td>
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<tr>
<td>Epidemiologic classification</td>
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<td>Healthcare facility–onset</td>
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<tr>
<td>Community-onset healthcare facility–associated</td>
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<tr>
<td>Community-associated (reference)</td>
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<tr>
<td>Charlson score</td>
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<td>NAP1 strain</td>
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</table>

Abbreviations: AOR, adjusted odds ratio; CI, confidence interval.

* Candidate variables included in the model: age; race; epidemiologic classification; chronic hemodialysis; emergency department visit during 12 weeks prior to infection; Charlson index; proton pump inhibitor use, H2 blocker use, or antibiotic use during 14 d prior to infection; strain type.

** Healthcare facility–onset and community-onset healthcare facility–associated epidemiologic classes did not have significantly different odds of severe disease and were collapsed into a single “healthcare-associated” category.

DISCUSSION

We found NAP1 to be the most common strain, accounting for more than one-quarter of cases in our dataset. NAP1 was associated with greater odds of severe disease than other NAP types in unadjusted analysis and was also associated with older age and a variety of healthcare exposures. After controlling for potential confounders, the NAP1 strain remained a significant predictor of severe disease, severe outcome, and 14-day mortality. Our results represent the largest study to date to examine the association between strain type and disease outcomes. Furthermore, inclusion of cases from a wide geographic spread reduces bias due to regional variation in C. difficile strain type or patient characteristics.

We chose the outcome measures of severe outcome and 14-day mortality to facilitate comparisons with 2 recent studies on CDI outcome related to the NAP1 strain. Our findings agree with those in a recent report from the United Kingdom showing that the NAP1/027 strain is associated with increased 14-day mortality [5]. However, our results differ from a recent study from the United States by Walk et al that found no association between the NAP1/027 strain and severe outcome [7]. In the US study, the number of patients with NAP1 was small (approximately 40) and <50 patients met the outcome measure. Although the US study reported a lack of association, the odds for severe outcome were increased among NAP1/027 cases, albeit not achieving statistical significance. Thus, as suggested by others [20, 21], lack of association between the NAP1/027 strain and severe outcome reported in the US study might be largely related to differences in sample size.

The proportion of patients who died in our study (3.8%) is lower than that reported from other studies of CDI outcomes [5, 22]. This discrepancy is likely a result of a larger proportion of community-associated CDI cases in our study, which are associated with better outcomes than healthcare-associated cases [14]. This is unlikely to bias our study toward detection of
association between strain type and outcomes, given that we adjusted for epidemiologic classification as a confounder in our analyses.

We found baseline differences between the patient populations infected by C. difficile NAP1 vs non-NAP1 strains. Although we adjusted for patient comorbidities, unmeasured patient-level confounders might still account for some of the relationship we found between the NAP1 strain and patient outcomes. However, our findings persisted in analyses stratified by age, supporting that C. difficile strain is an important predictor of patient outcome independent of patient age. Associations between NAP1 strain and patient outcomes did not remain significant for community-associated cases when stratifying the data by epidemiologic classification. This lack of significance is likely related to low statistical power, as outcomes of interest were uncommon among community-associated cases (10.8% for severe disease, 1.5% for severe outcomes, and 0.7% for death within 14 days), and the NAP1 strain was less prevalent in the community.

Our analysis therefore provides additional support for the conclusion that infection by the NAP1 strain adversely affects patient outcomes. The practical implications of this finding remain to be determined. Host-related factors play an important role in the development of CDI, and other studies have suggested that clinical scores or biomarkers based on the immune response of the host (eg, albumin, serum white blood count, C-reactive protein), rather than strain type, should be the basis for decisions about severity of disease for treatment [12, 23, 24].

Nevertheless, strategies that account for strain-specific factors might complement treatment strategies based on host response and further reduce morbidity due to CDI. The specific virulence factors possessed by the NAP1/027 strain that lead to worsened outcomes remain to be more clearly elucidated. As such research progresses, vaccines being developed for C. difficile might target such factors.

In addition, antimicrobial stewardship might further aid in preventing infections from the NAP1 strain. Although more judicious antimicrobial use would likely reduce C. difficile infections in general, including those caused by NAP1, stewardship efforts might also be leveraged to have a greater impact on NAP1 prevalence. For example, given that the NAP1/027 strain is more resistant than other strains to the fluoroquinolones [1, 3, 5, 25, 26], antimicrobial stewardship aimed at reducing the overall use of fluoroquinolones might also reduce the prevalence of infections from NAP1 and decrease patient morbidity from CDI. Indeed, fluoroquinolone use has been found to be a risk factor for infection by the NAP1/027 strain [27–29], and the development of fluoroquinolone resistance by the NAP1/027 strain has been suggested to be the primary genetic factor facilitating its spread [29]. Fluoroquinolone restriction has also been reported to be an important component of efforts to control outbreaks of C. difficile from the NAP1/027 strain [30, 31], but further research is needed to determine the utility of the application of this strategy to nonoutbreak settings.

We should note the following limitations of our study. First, all clinical data collected were obtained by retrospective review of medical charts, potentially leading to underestimation of mortality rates if patients died soon after discharge. Second, we were not able to control for differences in treatment, which might affect patient outcomes. However, as noted earlier, because our data encompass a diverse geographic area, it is unlikely that our findings are driven by individual institutional treatment practices. Third, we could not fully evaluate the potential role of the NAP7/8/ribotype 078 strain, which has also been reported to have increased virulence [5, 32], on outcomes due to limited numbers of these cases in our dataset. Fourth, our analysis might not be representative of all C. difficile infections. For example, only a sample of healthcare facility–onset CDI cases are fully reviewed. However, even though patients with strain typing results represent a convenience sample of the total, comparison to patients without strain typing results suggests that our sample is representative of those cases with full medical record review. Fifth, we do not have data on all cases about the type of diagnostic test that was used to identify each CDI case (eg, toxin assay vs nucleic acid amplification test [NAAT]). As CDI cases detected by toxin assays have been reported to have higher mortality than cases detected solely by NAAT [33], we could not account for this potential effect modifier of CDI outcomes.

In conclusion, analysis of a large, geographically diverse set of CDI cases from the United States corroborates that the C. difficile NAP1 strain type is an important determinant of patient outcomes. Disease from C. difficile results from a complex interplay between host-related factors and pathogen-specific factors. Efforts to reduce the burden of CDI likely will need to consider both.

Notes

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All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References