Prevalence and impact of *Clostridioides difficile* infection among hospitalized patients with coronavirus disease 2019

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Introduction

Coronavirus disease-19 (COVID-19), resulting from severe acute respiratory syndrome coronavirus (SAR-CoV-2), has rapidly emerged as a global pandemic. While most patients present with fevers and respiratory symptoms, increasing data highlight gastrointestinal manifestations as important hallmarks of disease, including up to a third with diarrhea.\(^1\) While there remains no currently approved therapy for COVID-19, patients hospitalized with moderate to severe disease are often empirically treated with broad-spectrum antibiotics, with escalation as clinical status deteriorates.

Nosocomial *Clostridioides difficile* infection (CDI) is associated with significant morbidity and mortality.\(^2\) Exposure to antibiotics is a known risk factor for CDI; therefore, hospitalized COVID-19 patients may be at higher risk given the routine use of broad-spectrum antibiotics.\(^3,4\) However, strict isolation and social-distancing protocols adopted by hospitals since the start of the pandemic may help mitigate this risk. Therefore, we aimed to evaluate the prevalence, patient characteristics, and clinical outcomes of CDI among hospitalized patients with COVID-19.

Methods

This was a retrospective cohort study of patients hospitalized with COVID-19 from 3 November 2020 to 4 February 2020 across nine hospitals in Massachusetts (two tertiary, seven community hospitals). A diagnosis of COVID-19 was confirmed by nasopharyngeal swab polymerase chain reaction (PCR). All patients who underwent stool testing for CDI were included. Testing was performed via glutamate dehydrogenase (GDH) and enzyme-linked immunosorbent assay (ELISA) immunoassay (EIA) for toxin and considered diagnostic if both tests were positive. For patients with inconclusive GDH/EIA results but high clinical suspicion, PCR was performed as a confirmatory test and, if positive, was considered diagnostic for CDI. Demographic data, presenting symptoms, medication including antibiotic use, and laboratory data were obtained from electronic medical records. Outcomes and mortality were also compared for hospitalized COVID-19 patients with and without CDI. Historical inpatient CDI testing data from Brigham and Women’s Hospital in 2019 were used as a control for comparison.

All continuous variables were reported as means with standard deviations. Categorical data were expressed using numbers and frequencies. Student’s t-test and Fisher’s exact test were performed for continuous variables and categorical variables, respectively, on univariate analyses. Two-tailed P-values of 0.05 or lower were considered statistically significant. Statistical analysis was performed using Statistical Analysis Software 9.4 (SAS Institute Inc., Cary, NC, USA). This study was approved by the Partners Healthcare Institutional Review Board (2020P0000983).

Results

Of 390 hospitalized patients with laboratory-confirmed COVID-19, 97 (24.9%) were tested for CDI (mean age: 62.4 ± 15.3 years, 38 [40.2%] women) (Table 1). Five patients (5.2%) tested positive for CDI, all via GDH/EIA. This was lower than the overall inpatient CDI-positive rate in 2019 (280 positives [159 GDH/EIA and 121 PCR] of 2984 tests performed, 9.8%).

Although statistical significance was not reached (P = 0.16). Specifically, GDH/EIA-positive rates were similar between the COVID-19 and historical cohort (5.2% vs 5.3%), while the PCR positive rate among GDH/EIA-indeterminate patients was significantly lower among COVID-19 patients (10/10, 0% vs 121/288, 42%); P = 0.02) (Table 2). The median number of antibiotics used for the entire COVID cohort was four [interquartile range (IQR) 2–5], with no significant difference between CDI and non-CDI patients (3 [3–6] vs 4 [2–5]; P = 0.57). All CDI patients were exposed to at least two (range 2–8) antibiotics prior to CDI diagnosis. Proton pump inhibitor (PPI) use during hospitalization was more common among CDI patients, although statistical significance was not reached (80% vs 51.7%; P = 0.22) (Table 2).

Notably, none of the patients with CDI initially presented with diarrhea on admission. There were no differences in laboratory values between CDI and non-CDI patients on presentation, including markers of inflammation such as C-reactive protein, ferritin, D-dimer, platelets, and lactate dehydrogenase (LDH). Otherwise, there were no significant differences in baseline demographics, comorbidities, and presenting symptoms between CDI and non-CDI patients (Table 1).

Three of the five patients (60%) with CDI received treatment, all with fidaxomicin and one with concomitant metronidazole. The remaining two patients died prior to receiving therapy. The majority (70.1%) of patients who underwent CDI testing required intensive care unit-level care, with no difference between CDI versus non-CDI cohorts (80% vs 69.6%; P = 0.62). The overall mortality was significantly higher among CDI patients compared to those without CDI (80% vs 12.2%; P < 0.0001).

Discussion

While hospital-associated case burden seems to be decreasing in the United States, CDI continues to be a significant cause of diarrhea among hospitalized patients, especially in the setting of broad-spectrum antibiotic use.\(^5,6\) In the year prior to the COVID-19 pandemic, the overall inpatient positive CDI rate among patients tested at our institution was 9.8%, encompassing both GDH/EIA-positive and PCR-positive patients. While there remains controversy around PCR testing and whether this represents clinically significant CDI versus colonization, at our institution, PCR is only used if clinical suspicion is high and GDH/EIA results are indeterminate.

In comparison, rates of confirmed CDI were lower among patients hospitalized with COVID-19. This difference was entirely driven by patients who were PCR positive but GDH/EIA indeterminate as the rates of GDH/EIA positivity were similar between COVID-19 and the historical cohorts. This may suggest lower rates of *C. difficile* colonization despite a similar risk of CDI. These findings are notable as all the patients in the COVID-19 cohort received ≥2 systemic antibiotics, placing them at significant risk. With strict isolation of COVID-19 patients in most hospitals, together with aggressive hand washing and donning and doffing protocols, it is possible that such rigorous measures resulted in the unintended benefit of reducing nosocomial transmission and mitigating the risk of colonization and subsequent CDI.\(^9,10\) This highlights the importance of hand hygiene,
contact precautions, and appropriate isolation of patients in lowering hospital-acquired CDI.

Many patients with COVID-19 experience diarrhea as part of their clinical presentation. The patients who developed CDI in our cohort began experiencing diarrhea after admission. These symptoms may go unrecognized or be mistakenly attributed to COVID-19 itself, resulting in a delay in diagnosis and management. Importantly, albeit small in number, we found that patients with CDI in our cohort had significantly higher mortality rates compared to hospitalized COVID-19 patients without CDI. In fact, two patients were so ill by the time diagnosis was made that they ultimately died prior to receiving CDI therapy, further

| Demographics (n = 97) | CDI (n = 5) | No CDI (n = 92) | P-value |
|----------------------|------------|----------------|---------|
| Age (years, ±SD)     | 62.4 ± 15.3| 73.6 ± 14.8     | 61.8 ± 15.1 | 0.09  |
| Male (n, %)          | 58 (59.8%) | 4 (80.0%)       | 54 (58.7%)  | 0.34  |
| Body mass index (BMI) (kg/m², ±SD) | 31.8 ± 6.7 | 30.5 ± 2.8 | 31.9 ± 6.9 | 0.66  |
| Presenting symptoms (n, %) | | | |
| Diarrhea             | 39 (40.2%) | 0 (0%)          | 39 (42.4%)  | 0.06  |
| Nausea               | 28 (28.9%) | 1 (20.0%)       | 27 (29.4%)  | 0.65  |
| Vomiting             | 13 (13.4%) | 0 (0%)          | 13 (14.1%)  | 0.37  |
| Abdominal pain       | 12 (12.4%) | 0 (0%)          | 12 (13.0%)  | 0.39  |
| Fever                | 81 (83.5%) | 1 (20.0%)       | 80 (87.0%)  | <0.0001 |
| Dyspnea              | 65 (67.0%) | 2 (40.0%)       | 63 (68.5%)  | 0.19  |
| Sore throat          | 20 (20.6%) | 0 (0%)          | 20 (21.7%)  | 0.24  |
| Medical comorbidities (n, %) | | | |
| Coronary artery disease | 10 (10.3) | 1 (20.0) | 9 (9.8) | 0.46  |
| Cardiac arrhythmia   | 15 (15.5)  | 2 (40.0)        | 13 (14.1)  | 0.12  |
| Hypertension         | 50 (51.6)  | 4 (80.0)        | 46 (50.0)  | 0.19  |
| Hyperlipidemia       | 44 (45.4)  | 2 (40.0)        | 42 (45.7)  | 0.80  |
| Diabetes             | 33 (34.0)  | 1 (20.0)        | 32 (34.8)  | 0.50  |
| Pulmonary disorders  | 20 (20.6)  | 2 (40.0)        | 18 (19.6)  | 0.27  |
| Presenting laboratory results | | | |
| White blood cell count (x10⁹/L) | 7.5 ± 4.8 | 11.3 ± 5.2 | 7.3 ± 4.8 | 0.07  |
| Hemoglobin (g/L)     | 17.3 ± 10.8| 15.4 ± 9.0     | 17.4 ± 10.9| 0.70  |
| Platelets (x10⁹/L)   | 196.0 ± 84.8| 147.6 ± 65.7  | 198.6 ± 85.3| 0.19  |
| C-reactive protein   | 112.0 ± 80.0| 70.5 ± 83.8    | 114.6 ± 79.5| 0.23  |
| D-dimer (nmol)       | 2513 ± 9167| 1579 ± 588     | 568 ± 9435 | 0.82  |
| Ferritin             | 894 ± 778  | 465 ± 296      | 915 ± 789  | 0.26  |
| LDH                  | 371 ± 146  | 346 ± 118      | 373 ± 148  | 0.70  |
| Hospitalization course and outcomes medication received | | | |
| Antibiotics (median [IQR]) | 4 [2−5.5] | 3 [3−6] | 4 [2−5] | 0.57  |
| Proton pump inhibitor (n, %) | 51 (53.1) | 4 (80.0) | 47 (51.7) | 0.22  |
| Hospitalization outcome (n, %) | | | |
| Intensive care unit stay | 68 (70.1) | 4 (80.0) | 64 (69.6) | 0.62  |
| Mechanical ventilation | 65 (67.0) | 4 (80.0) | 61 (66.3) | 0.53  |
| Death                | 15 (15.8)  | 4 (80.0)       | 11 (12.2)  | <0.0001 |

Table 2 Clostridioides difficile infection (CDI) stool testing of coronavirus disease 2019 (COVID-19) patients compared to all inpatient CDI tests in 2019

|          | COVID-19 (n = 97) | All inpatient CDI tests in 2019 (n = 2984) | P-value |
|----------|------------------|---------------------------------------------|---------|
| Stool antigen and toxin (glutamate dehydrogenase [GDH]/ELISA immunoassay [EIA]) (n, %) | | | |
| Positive | 5 (5.2)          | 159 (5.3)                                   | 0.94    |
| Indeterminant | 10 (10.3) | 288 (9.7)                                   | 0.93    |
| Stool polymerase chain reaction (PCR)† (n, %) | | | |
| Positive | 0/10 (0)         | 121/288 (42.0)                              | 0.02    |
| Overall stool CDI positive (n, %) | 5 (5.2) | 280 (9.4) | 0.16   |

†Stool PCR only performed with GDH/EIA-indeterminant samples.
highlighting the importance of early identification and aggressive treatment in this patient population.

In conclusion, the prevalence of CDI among hospitalized COVID-19 patients was not higher despite widespread use of multiple antibiotics, likely due to aggressive contact precaution and isolation measures implemented for COVID-19. The development of CDI was associated with poor outcomes and a high mortality rate among hospitalized COVID-19 patients. A low threshold for early CDI testing should be implemented among COVID-19 patients to ensure prompt diagnosis and appropriate therapeutic intervention.

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