JGH Open Open Access An open access journal of gastroenterology and hepatology

JGHF Journal of Gastroenterology and Hepatology Foundation

doi:10.1002/jgh3.12497

BRIEF REPORT

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

Jessica R Allegretti,*,† Cheikh Nije,†,‡ Emma McClure,* Walker D Redd,†,‡ Danny Wong,†,‡ Joyce C Zhou,† Ahmad N Bazarbashi,*,† Thomas R McCarty,*,† Kelly E Hathorn,*,† Lin Shen,*,† Kunal Jajoo*,† and Walter W Chan*,†

*Division of Gastroenterology, Hepatology and Endoscopy, ‡Department of Medicine, Brigham and Women's Hospital and †Harvard Medical School, Boston, Massachusetts, USA

Key words
antibiotics, *Clostridioides difficile* infection (CDI), coronavirus disease 2019 (COVID-19), diarrhea, severe acute respiratory syndrome coronavirus (SAR-CoV-2).

Accepted for publication 13 January 2021.

Correspondence
Jessica R Allegretti, Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, USA.
Email: jallegretti@bwh.harvard.edu

Declaration of conflict of interest: Jessica R Allegretti is a consultant for Finch Therapeutics, Artugen, Pfizer, Takeda, Janssen, and Iterative Scopes and receives research support from Merck. She serves as an unpaid advisor to Openbiome. All the remaining authors have no conflicts to disclose.
Author contributions: Jessica R Allegretti, Kunal Jajoo, Walter W Chan: Study concept and design. Emma McClure, Cheikh Nije, Walker D Redd, Danny Wong, Joyce C Zhou, Ahmad N Bazarbashi, Thomas R McCarty, Kelly E Hathorn, Lin Shen: Data acquisition. Walter W Chan, Jessica R Allegretti, Cheikh Nije: Paper preparation and statistical analysis. Walter W Chan, Jessica R Allegretti, Cheikh Nije, Walker D Redd, Danny Wong, Joyce C Zhou, Ahmad N Bazarbashi, Thomas R McCarty, Kelly E Hathorn, Lin Shen, Kunal Jajoo: Critical revisions.

Funding support: National Institute of Diabetes and Digestive and Kidney DiseasesT32 DK007533-35.

Funding support: Merck

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.[2–4] 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.[5,6] 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-indeterminant patients was significantly lower among COVID-19 patients ([0/10, 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.[7,8] 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 controversary 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 indeterminant.

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 indeterminant 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,

Table 1 Demographics, presenting symptoms, admission laboratory results, and hospitalization course and outcomes of coronavirus disease 2019 (COVID-19) patients with or without *Clostridioides difficile* infection (CDI)

	All COVID-19 (*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/m^2, ±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 (×10^9/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 (×10^9/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.

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.[1] 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

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.

Acknowledgments

This work was funded, at least in part, by the NIH grant T32 DK007533-35.

REFERENCES

1 Redd WD, Zhou JC, Hathorn KE *et al*. Prevalence and characteristics of gastrointestinal symptoms in patients with SARS-CoV-2 infection in the United States: a multicenter cohort study. *Gastroenterology*. 2020; **159**: 765–767.e2.
2 Karaoui WR, Rustom LBO, Bou Daher H *et al*. Incidence, outcome, and risk factors for recurrence of nosocomial *Clostridioides difficile* infection in adults: a prospective cohort study. *J. Infect. Public Health*. 2020; **13**: 485–90.
3 Bartlett JG. Narrative review: the new epidemic of *Clostridium difficile*-associated enteric disease. *Ann. Intern. Med.* 2006; **145**: 758–64.
4 Gravel D, Miller M, Simor A *et al*. Health care-associated *Clostridium difficile* infection in adults admitted to acute care hospitals in Canada: a Canadian Nosocomial Infection Surveillance Program Study. *Clin. Infect. Dis.* 2009; **48**: 568–76.
5 Lessa FC, Mu Y, Bamberg WM *et al*. Burden of *Clostridium difficile* infection in the United States. *N. Engl. J. Med.* 2015; **372**: 825–34.
6 McDonald LC, Gerding DN, Johnson S *et al*. Clinical Practice Guidelines for *Clostridium difficile* infection in adults and children: 2017 update by the Infectious Diseases Society of America (IDSA) and Society for Healthcare Epidemiology of America (SHEA). *Clin. Infect. Dis.* 2018; **66**: 987–94.
7 Guh AY, Mu Y, Winston LG *et al*. Trends in U.S. Burden of *Clostridioides difficile* infection and outcomes. *N. Engl. J. Med.* 2020; **382**: 1320–30.
8 Bagdasarian N, Rao K, Malani PN. Diagnosis and treatment of *Clostridium difficile* in adults: a systematic review. *JAMA*. 2015; **313**: 398–408.
9 Siegel JD, Rhinehart E, Jackson M, Chiarello L, and the Healthcare Infection Control Practices Advisory Committee. 2007 Guideline for Isolation Precautions: Preventing Transmission of Infectious Agents in Healthcare Settings. Accessed 15 May 2020. Available from URL: https://www.cdc.gov/infectioncontrol/guidelines/isolation/index.html.
10 Rutala WA, Weber, JD, and the Healthcare Infection Control Practices Advisory Committee (HICPAC). Guideline for Disinfection and Sterilization in Healthcare Facilities, 2008. 2019. Accessed 12 May 2020. Available from URL: https://www.cdc.gov/infectioncontrol/guidelines/disinfection/.