


Original Article

Screening of *Clostridioides difficile* carriers in an urban academic medical center: Understanding implications of disease

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Abstract

Objective: Efforts to reduce *Clostridioides difficile* infection (CDI) have targeted transmission from patients with symptomatic *C. difficile*. However, many patients with the *C. difficile* organism are carriers without symptoms who may serve as reservoirs for spread of infection and may be at risk for progression to symptomatic *C. difficile*. To estimate the prevalence of *C. difficile* carriage and determine the risk and speed of progression to symptomatic *C. difficile* among carriers, we established a pilot screening program in a large urban hospital.

Design: Prospective cohort study.

Setting: An 800-bed, tertiary-care, academic medical center in the Bronx, New York.

Participants: A sample of admitted adults without diarrhea, with oversampling of nursing facility patients.

Methods: Perirectal swabs were tested by polymerase chain reaction for *C. difficile* within 24 hours of admission, and patients were followed for progression to symptomatic *C. difficile*. Development of symptomatic *C. difficile* was compared among *C. difficile* carriers and noncarriers using a Cox proportional hazards model.

Results: Of the 220 subjects, 21 (9.6%) were *C. difficile* carriers, including 10.2% of the nursing facility residents and 7.7% of the community residents ($P = .60$). Among the 21 *C. difficile* carriers, 8 (38.1%) progressed to symptomatic *C. difficile*, but only 4 (2.0%) of the 199 noncarriers progressed to symptomatic *C. difficile* (hazard ratio, 23.9; 95% CI, 7.2–79.6; $P < .0001$).

Conclusions: Asymptomatic carriage of *C. difficile* is prevalent among admitted patients and confers a significant risk of progression to symptomatic CDI. Screening for asymptomatic carriers may represent an opportunity to reduce CDI.

(Received 10 July 2019; accepted 5 October 2019; electronically published 11 December 2019)

Annually, >400,000 cases and almost 30,000 deaths from *Clostridioides difficile*-associated diarrhea occur in the United States.¹ Efforts to reduce the spread of *C. difficile* have focused on reducing transmission from patients with symptomatic *C. difficile*-associated diarrhea.^{2,3} However, many patients are *C. difficile* carriers who do not have diarrhea. Asymptomatic carriers may serve as a reservoir and spread *C. difficile* to those around them.^{4–7} However, patients who are carriers are not routinely identified on hospital admission. In addition, though some

research suggested that asymptomatic carriage is protective against symptomatic *C. difficile*,⁸ other studies demonstrated that patients can progress from carrier state to symptomatic *C. difficile* infection (CDI).⁹ Data demonstrating how frequently and how quickly this occurs are limited.¹⁰ Therefore, identification of asymptomatic carriers could reduce the spread of *C. difficile* through 2 mechanisms: first, isolation of *C. difficile* carriers could reduce transmission to uninfected patients, and second, interventions targeting *C. difficile* carriers could potentially prevent progression to symptomatic *C. difficile*.

Clostridioides difficile is a spore-forming, gram-positive anaerobic bacillus spread by fecal–oral transmission of spores, which remain viable for long periods of time ex vivo.^{11,12} Although *C. difficile* carriers do not have diarrhea, they do shed spores that can contaminate environmental surfaces.⁴ The proportion of symptomatic infection resulting from transmission from asymptomatic carriers remains unknown, but research indicates that this does occur.¹³

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PREVIOUS PRESENTATION: Portions of this research were presented at the Annual Meeting of the Society of Hospital Medicine on March 25, 2019, in National Harbor, Maryland, and at the Annual Meeting of the Society of General Internal Medicine on April 13, 2018, in Denver, Colorado.

Cite this article: Baron SW, et al. (2020). Screening of *Clostridioides difficile* carriers in an urban academic medical center: Understanding implications of disease. *Infection Control & Hospital Epidemiology*, 41: 149–153, <https://doi.org/10.1017/ice.2019.309>

Previously, *C. difficile* carriage was thought to be protective against the future development of symptomatic *C. difficile*,⁸ and progression was understood to be rare. However, recent evidence suggests otherwise.^{6,13–16} Progression to symptomatic *C. difficile* often follows acquired immunocompromise (eg, steroids or severe illness) or administration of antibiotics which disrupt the gut flora.¹⁷ Both are frequently encountered in hospitalized patients. Hospitals are responsible for reporting “healthcare-facility onset” *C. difficile*,¹⁸ diagnosed 3 or more days after hospital admission, which does not account for symptoms or carrier status before the admission. Identifying a high rate of progression from *C. difficile* carrier to symptomatic *C. difficile* could change what we consider a “hospital-acquired infection,” especially if the bacteria was not necessarily acquired in the hospital but was present on admission and only the diarrhea began in the hospital.

To estimate the prevalence of asymptomatic *C. difficile* carriage at the time of hospital admission and to determine the rate and time to progression to symptomatic CDI, we tested and prospectively followed asymptomatic patients being admitted with no diarrhea. The objectives of our 2-part study were (1) to identify asymptomatic *C. difficile* carriers and (2) to observe carriers and noncarriers for progression to symptomatic *C. difficile*. We hypothesized (1) that admission from a nursing facility would be positively associated with *C. difficile* carriage and (2) that asymptomatic *C. difficile* carriers would be at increased risk for developing symptomatic *C. difficile* compared to asymptomatic noncarriers.

Methods

Study design and setting

We performed a prospective cohort study on a sample of patients being admitted to a large university hospital in the Bronx, New York, between July 2017 and March 2018. The hospital contains >800 beds and receives >45,000 hospital admissions annually. To determine the prevalence of *C. difficile* carriage, patients being admitted to the hospital without diarrhea were tested for *C. difficile*. To follow these patients prospectively, we utilized our unified electronic medical record shared among multiple hospitals and outpatient clinics in the health system. All patients were followed within our system for 6 months or until death for the subsequent diagnosis of symptomatic CDI.

Participants

All patients with an admission order from July 2017 to March 2018 were eligible for inclusion. During the study period a convenience sample of days including weekends, was used for screening and testing. On screening days, all patients admitted within the previous 24 hours from a nursing facility were approached for inclusion. On those same days, a work list was generated, and any patient admitted from the community within the previous 24 hours was assigned a number. Random-number generators were used to determine a random sample of community patients. Because previous studies have suggested that nursing facility residents have a high prevalence of *C. difficile* carriage, patients from the community were sampled in a 1:4 ratio with patients from nursing facilities. For inclusion in the study, subjects were ≥ 21 years old and required an admission order from the emergency department within the previous 24 hours. The research team queried any patient, family, or staff and excluded patients with active diarrhea defined as ≥ 3 episodes of loose stool in the previous

24 hours or ≥ 2 episodes in the previous 12 hours. Subjects were excluded if there was documentation of comfort care only status, if they had a colostomy, or if they were admitted to the pediatrics, obstetric/gynecologic, or psychiatry services.

Because screening admitted patients for infectious diseases is part of standard infection prevention and control practice, we did not seek consent from each study subject, but we offered the option of dissenting (declining) when approached for participation. Following testing, participants were observed for 6 months or until death. The Montefiore/Einstein Institutional Review Board approved the study, granting a waiver of informed consent.

Data collection methods

Eligible subjects underwent swabbing of their perirectal area with an ESwab collection and transport system (Copan Diagnostics, Murrieta, CA) by a single member of the study team. No invasive rectal swabbing was performed. Rectal swabbing or direct testing of stool specimens are the accepted clinical standards, but previous studies have demonstrated the utility of perirectal swabbing.¹⁹ If stool was available, a separate swab was performed directly on stool. Test swab soilage, as defined by any visible material on the swab, was recorded as recommended.¹⁹

Specimens were processed by the study team (S.B. and D.D.) on the same day as collection. Two testing methodologies were used for all specimens: (1) *C. difficile* Quik Chek Complete (Abbott, Chicago, IL) to test for glutamate dehydrogenase (GDH) and toxins A and B and (2) XPert *C. difficile*/Epi (Cepheid, Sunnyvale, CA) real-time polymerase chain reaction (PCR) assay that detects the toxin B gene.^{20,21} All specimens were also tested by toxigenic culture using spore-enriched specimens in cultures with selective chopped meat broth incubated for 48–72 hours followed by repeat GDH and toxin A/B testing.^{22,23}

Demographic and clinical characteristics were extracted from the electronic medical record, which included all inpatient and outpatient visits and lab tests sent from the medical center.

Measures

Prevalence analysis. Determination of active diarrhea status was queried directly of patients, family, or staff. All other demographic and clinical characteristics were recorded from the electronic medical record or an extracted replicate of the electronic medical record. *C. difficile* carrier status was defined as any positive PCR or toxin test or toxigenic culture for *C. difficile* without diarrhea (diarrhea was an exclusion criterion). If the primary clinical team ordered a subsequent *C. difficile* test, they were informed of any positive study testing result but otherwise were unaware of subject participation in the study. This allowed for the possibility of direct benefit to subjects in the form of hastened diagnosis and treatment. Independent variables examined included age, gender, nursing facility or community resident, season of enrollment, soilage of the test swab, previous admissions within 28 days,¹⁸ previous antibiotics within 90 days,²⁴ and previous CDI within 56 days.¹⁸

Outcomes analysis. The primary outcome, symptomatic CDI, was defined as any positive clinical test for *C. difficile* sent by the primary clinical team as part of usual care. The microbiology laboratory rejects solid stool specimens, so the presence of diarrhea in patients was assumed. The clinical algorithm used in this health-care system, in accordance with guidelines,¹⁸ is a combined GDH and toxin test (Quik Chek Complete) followed by PCR (XPert)

if the GDH and toxin results are discrepant. We compared time to *C. difficile*-positive testing among carriers versus noncarriers, censored at 6 months or death.

Statistical analysis

Baseline characteristics of nursing facility residents versus community residents were compared using the χ^2 and Fisher exact tests as appropriate. We calculated the prevalence of asymptomatic *C. difficile* carriage in the overall study population, in nursing facility residents, and community residents. The significance of the difference in prevalences was tested using a χ^2 test and univariate logistic regression model. The time of progression to symptomatic CDI or death, censored at 6 months, was plotted for carriers and noncarriers using the Kaplan-Meier method, and a log-rank test was used to test the differences between groups. Finally, a univariate Cox proportional hazards model was constructed to estimate the hazard of progressing to symptomatic CDI in carriers versus noncarriers. Given the small number of outcome events, no multivariate analyses were performed. Statistical analyses were performed using Stata version 14.2. software (StataCorp, College Station, TX). *P* values < .05 were considered statistically significant.

Results

Of the 351 potential subjects evaluated for inclusion, 220 subjects were enrolled (62.7%). Common reasons for nonenrollment included declined participation (*n* = 30), discharged before testing (*n* = 28), and excluded due to diarrhea (*n* = 14). Also, 28 patients were not eligible for 7 additional reasons based on the exclusion criteria. In addition, 31 patients who were included in random sampling and, thus, in the potential subject pool, but they were never approached for inclusion to maintain the 4:1 sampling strategy. In terms of acceptability to the subjects, only 30 of 351 of all eligible subjects (8.5%) declined participation.

Of the 220 enrolled subjects, most were female (54%), ≥ 65 years old (67%), enrolled in the summer (58%), did not have a soiled test swab (55%), and were nursing facility residents (76%), in accordance with the 4:1 enrollment strategy. The characteristics of the total study population and the nursing facility and community residents are presented in Table 1.

Prevalence analysis

Of 220 subjects tested, 21 (9.6%) were asymptomatic *C. difficile* carriers, which included 17 of 168 nursing facility residents tested (10.2%), and 4 of 52 community residents tested (7.7%), a difference that was not significant (*P* = .60).

The associations between subject demographic and clinical characteristics and the odds of asymptomatic carriage are presented in Table 2. Having a soiled swab was significantly associated with carriage (odds ratio [OR], 2.7; 95% confidence interval [CI], 1.03–6.9; *P* = .04). In addition, previous antibiotic exposure was nonsignificantly associated with asymptomatic carriage (OR, 2.3; 95% CI, 0.9–5.6; *P* = .08).

Outcomes study

Among 21 subjects identified as *C. difficile* carriers, 8 (38.1%) progressed to clinical CDI within 6 months. Among 199 subjects who were not carriers at enrollment, 4 (2.0%) developed symptomatic CDI within 6 months. Most carriers that progressed to symptomatic CDI did so within 2 weeks of enrollment (note that patients were

Table 1. Characteristics of Population by Nursing Facility Versus Community Residence and Population as a Whole

Variable	Nursing Facility Residents (n = 168), No. (%)	Community Residents (n = 52), No. (%)	<i>P</i> Value ^a	Total Population (n = 220), No. (%) ^b
Age			<.001	
<65 y	40 (23.8)	32 (61.5)		72 (32.7)
≥ 65 y	128 (76.2)	20 (38.5)		148 (67.3)
Gender			.78	
Female	91 (54.2)	27 (51.9)		118 (53.6)
Male	77 (45.8)	25 (48.1)		102 (46.4)
Race/Ethnicity			.09	
White	24 (14.3)	3 (5.8)		27 (12.3)
Black	66 (39.3)	15 (28.9)		81 (36.8)
Hispanic	52 (31.0)	24 (46.2)		76 (34.5)
Unknown/Other	26 (15.5)	10 (19.2)		36 (16.4)
Season			.70	
Summer	99 (58.9)	28 (53.8)		127 (57.7)
Winter	19 (11.3)	8 (15.4)		27 (12.3)
Spring	50 (29.8)	16 (30.8)		66 (30.0)
Soiled test swab ^c	85 (50.9)	14 (26.9)	.002	99 (45.2)
Previous admission	49 (29.2)	7 (13.5)	.023	56 (25.5)
Previous antibiotics	64 (38.1)	12 (23.1)	.047	76 (34.5)
<i>C. difficile</i> carrier ^c	17 (10.2)	4 (7.7)	.60	21 (9.6)
Positive by toxin ^{c,d}	3 (1.6)	0 (0)	1.00	3 (1.4)

^aBold type face indicates statistical significance at *P* < .05.

^bUnadjusted statistics on total population.

^cIndicates that data is calculated based on 219 subjects total (missing data on 1 subject).

^dUsing the Fisher exact test.

Table 2. Odds Ratios for Being a *Clostridioides difficile* Carrier

Variable	Odds Ratio	95% CI	<i>P</i> Value
Nursing facility	1.4	0.4–4.2	.60
Male gender	1.06	0.4–2.6	.90
Age ≥ 65 y	1.6	0.6–4.6	.36
Soiled swab	2.7	1.03–6.9	.04
Season of Enrollment			
Summer enrollment	1.0	Reference	
Winter enrollment	0.4	0.05–3.1	.34
Spring enrollment	1.3	0.5–3.5	.54
Previous admission	1.2	0.4–3.2	.74
Previous antibiotics	2.3	0.9–5.6	.08

Note. CI, confidence interval.

assessed and excluded if diarrhea was present at enrollment). In the time-to-event analysis, *C. difficile* carriers had significantly increased risk of developing subsequent clinical CDI compared to noncarriers (hazard ratio [HR], 23.9; 95% CI, 7.2–79.6; *P* < .001) (Fig. 1).

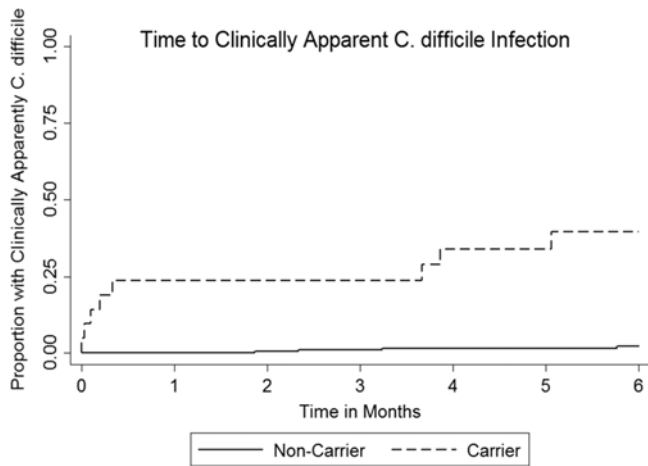


Fig. 1. Kaplan-Meier survival curve for time to symptomatic *C. difficile* infection for *C. difficile* carriers (dashed line) and noncarriers (solid line). There was a statistically significant difference ($P < .001$). The hazard ratio is 23.9 (95% CI, 7.2–79.6; $P < .001$).

Discussion

In this prospective cohort study, 9.6% of subjects admitted in a large academic medical center were asymptomatic *C. difficile* carriers, including 10.2% of nursing facility residents and 7.7% of community residents. Among *C. difficile* carriers identified at enrollment, 38.1% were subsequently diagnosed with symptomatic CDI, most progressing within 2 weeks, whereas only 2.0% of noncarriers were subsequently diagnosed with symptomatic CDI. Only 8.5% of potential subjects declined to participate despite the sensitive nature of perirectal swabbing, suggesting that screening of asymptomatic patients is feasible.

Previous studies have reported widely varying prevalence estimates of asymptomatic *C. difficile* carriage in healthcare facilities. The overall raw prevalence of asymptomatic CDI in our sample (9.6%) is consistent with recent estimates of *C. difficile* carriage among admitted patients which vary from 0.6%–13%.^{25,26} In contrast, we found a lower prevalence of asymptomatic carriage among nursing facility residents (10.2%) than prior studies, which have reported up to 51%.^{9,27–29} Our lower prevalence may reflect a different underlying population, geographic variation, and/or the success of antibiotic stewardship programs.

Although *C. difficile* carriers shed fewer spores than symptomatic *C. difficile* patients,^{10,17,30,31} given their larger numbers, carriers may actually be responsible for a larger *C. difficile* spore burden and more transmission than symptomatic patients.^{5,32} Strategies to reduce transmission from asymptomatic carriers to uninfected individuals have included preemptive modified isolation,³³ heightened cleaning of units at risk,^{34,35} intensified antibiotic time outs for carriers,³⁶ or even prophylactic treatment for those at highest risk such as oncologic or chronically immunosuppressed patients.³⁷ Many of these strategies, however, require routine early identification of carriers.

In this study, the only clinical or demographic feature associated with carriage was swab soilage, which is visible fecal material staining the swab. We hypothesize that swab soilage represents improved testing sensitivity in the presence of frank fecal material or, instead, could mean stool incontinence, poor hygiene, or an inability to care for oneself effectively. Further study could elucidate the cause of this association.

The present study adds to the limited body of literature examining the rate of progression from *C. difficile* carriage to clinical

CDI. An older review of 810 patients in 4 studies admitted to large US hospitals⁸ found a lower rate of progression to symptomatic *C. difficile* among carriers than noncarriers; thus, *C. difficile* carriage was thought to be protective against symptomatic *C. difficile*. Newer studies show that carriers are at higher risk for subsequent CDI, though in each study the time frame in which carriers were followed was limited to 14 days,¹³ during the admission,^{6,15,16} or 1 month following discharge.¹⁴ We found a higher rate of progression from carrier to symptomatic CDI (38.1%) compared with only 2.0% among noncarriers when followed for up to 6 months. Due to the high rate of progression, it is possible that a substantial proportion of “healthcare-facility onset”¹⁸ *C. difficile* may actually result from the progression from *C. difficile* carriage to symptomatic *C. difficile*, especially within the first 2 weeks of hospitalization.

This study has several limitations. First, given the lower than expected number of *C. difficile* carriers, the study had limited power to detect a difference in the proportion of nursing facility and community residents who were *C. difficile* carriers. Second, inquiry about the subsequent development of diarrhea was left up to the primary team, which may have led to a symptomatic CDI going unnoticed and undiagnosed, leading to an underestimation of symptomatic CDI in carriers and noncarriers. Third, to screen for asymptomatic carriage, we used perirectal swabbing rather than rectal swabbing or stool specimens. Although perirectal swabbing may have underestimated the true prevalence of *C. difficile* carriers, the high frequency of soiled test swabs as well as the likely better acceptability of perirectal swabbing as a screening tool made this the preferred modality. Lastly, retrospective data on antibiotic use and prospective data on *C. difficile* diagnosis was limited to usage and diagnosis only within our healthcare system as recorded in the electronic medical record.

In conclusion, asymptomatic carriers may represent a significant reservoir for transmission of *C. difficile*, and progression from asymptomatic carriage to symptomatic CDI may account for a significant proportion of CDI that is classified as “healthcare-facility onset.” Therefore, identification of asymptomatic carriers could reduce the spread of *C. difficile*. Specific environmental, isolation, and stewardship strategies to prevent spread of *C. difficile* from carriers to uninfected patients as well as prevent progression to symptomatic CDI warrant further study.

Acknowledgments. The contents of this article are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health.

Financial support. The research described was supported by NIH/National Center for Advancing Translational Science (NCATS) Einstein-Montefiore CTSA (grant no. UL1TR001073). Additional support was provided by the Department of Medicine, Montefiore Medical Center, Albert Einstein College of Medicine.

Conflicts of interest. All authors report no conflicts of interest relevant to this article.

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