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Major Article

Clostridium difficile intervention timelines for diagnosis, isolation, and treatment

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Background: Developing timelines of nosocomial *Clostridium difficile* infection (CDI) is critical to improving control and preventive measures. The objective of this study was to provide data-driven estimates of CDI timelines of diagnosis, isolation, and treatment in a hospital setting.

Methods: We obtained data for all CDI inpatients with symptoms onset occurring between January 1, 2013, and December 30, 2017, from St Joseph's Healthcare in Hamilton, Canada. We analyzed full empirical distributions of timelines associated with the diagnosis, isolation, and treatment of CDI.

Results: A total of 683 inpatients with CDI symptoms were recorded, of which 243 cases were identified as health care–associated infection (HAI). The mean time intervals between the onset of CDI symptoms after admission and the release of laboratory results were 1.2 days and 1.9 days for the HAI and community-associated infection (CAI) patient groups, respectively. The mean time intervals from symptoms onset to the start of isolation were 1.5 days and 2.6 days for the corresponding patient groups. The initiation of treatment within 2 days of symptoms onset reduced the duration of first isolation (P value $< .0001$); however, the type of initial antibiotic used for CDI treatment was not associated with the duration of isolation.

Conclusions: Estimated timelines did not differ (P values $> .6$) between HAI and CAI patient groups with symptoms onset after admission. These estimates are useful for evaluating the effectiveness of CDI interventions.

BACKGROUND

Clostridium difficile infection (CDI) has become the leading cause of nosocomial diarrhea worldwide.[1-3] The costs of CDI management and health care resource utilization inflict a substantial economic burden, largely due to prolonged hospital stays, patient isolation, and recurrence.[4-7] Despite the availability of treatment options that are effective in most primary cases, CDI relapse or recurrence can occur, thereby increasing rates of transmission to other in-hospital patients by various means, including contaminated surfaces.[3,7-9]

Although there are well-documented published guidelines for diagnosis, treatment, and infection control practices pertaining to CDI hospital epidemiology and interventions,[10-12] descriptive analyses of a number of key CDI-associated timelines based on administrative databases are still lacking. These timelines relate directly to the costs and strategies for treatment and prevention of health care–associated CDI; for example, the onset of CDI symptoms marks the start of an observable window of opportunity for infection transmission, either through the shedding of spores into the environment or by direct contact with individuals. This time window can be restricted and transmission can be reduced through patient isolation. Initiation of treatment can reduce the severity of the disease and lead to the resolution of symptoms, further reducing CDI transmission.[10] Hence, a data-driven analysis of such timelines can also inform future studies that aim to evaluate the effectiveness and cost-effectiveness of CDI interventions.

The objective of this study was to provide estimates of CDI timelines of diagnosis, isolation, and treatment based on analysis of a database that was systematically recorded over a 5-year period in a Canadian hospital setting. We performed statistical analyses to

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quantify the incidence and stool frequency and are reporting summary statistics of the CDI-associated timelines.

METHODS

Data

We obtained 5 years of data for all CDI inpatients, with symptoms onset occurring between January 1, 2013, and December 30, 2017, from an internal database at St Joseph's Healthcare in Hamilton, Ontario, Canada. The Charlton Campus is a 600-bed, mixed medical/surgical hospital and is the regional care center for patients with complicated kidney and lung disease. The study protocol was approved by the Hamilton Integrated Research Ethics Board, and, due to the retrospective nature of the data review, the requirement for individual patient consent was waived.

The case definition of CDI in this database was as follows: (1) the patient had 3 or more stools of type 5, 6, or 7 on the Bristol scale over a 24-hour period, and (2) stool specimen was *C. difficile* positive using a laboratory-developed loop-mediated isothermal amplification assay targeting the *TCDC* gene. This rapid testing technique had a sensitivity of 95%, specificity of 100%, positive predictive value of 100%, and negative predictive value of 97%.[13]

Relapse was defined as a subsequent CDI that occurred within 8 weeks after the end of treatment and resolution of the previous CDI episode. Recurrence was defined as the occurrence of CDI at least 8 weeks after recovery from the last episode. The dates of admission, CDI symptoms onset, laboratory results, and start of treatment and isolation were recorded for all patients. A case was categorized as a health care–associated infection (HAI) by the Infection Prevention and Control (IPAC) department if the onset of CDI symptoms occurred more than 72 hours after admission or CDI symptoms were present at the time of admission with a previous stay in this hospital within the past 4 weeks. If these criteria were not met, the case was categorized as a community-associated infection (CAI); in particular, a CDI case suspected to be associated with a hospital stay other than St Joseph's Healthcare was categorized as CAI. For patients with the CAI classification, infection control relied on patient-provided data when the patient was admitted from the community. In our analysis of CDI timelines, we divided the dataset into 2 groups of patients based on whether the onset of CDI symptoms occurred prior to or following hospital admission. For each group, we applied the classification of HAI and CAI to determine the CDI timelines.

The type of antibiotic treatment for *C difficile* (vancomycin or metronidazole) was recorded, as well as any switch in the type of initial treatment. Previous or concomitant antibiotic administration was not available for most cases; therefore, this variable was not included in our analysis. Laxative treatment prior to the onset of CDI symptoms also was not recorded. We calculated the total number of isolation days for each patient by summing up all the durations of isolation episodes. For the initial CDI episode (which may have been the only episode recorded if there was no relapse or recurrence), the daily number of stools was recorded for 14 days from the day before treatment was initiated. For the type of stool, records were available only for stools of type 6 and 7 on the Bristol scale. We defined 3 patient groups (A, B, and C) based on the total number of stools recorded during the entire duration of the patient's first CDI episode. Group A included patients who had at most 11 stools, group B was comprised of those who had between 11 and 24 stools, and group C included patients for whom the number of stools exceeded 24. The thresholds of 11 and 24 stools were chosen so the 3 groups would have the same number of patients.

Here, we present an analysis of timelines associated with CDI and its management during hospital stays. We also present the temporal evolution of stool frequency by the patients included in this study. The dates for our analysis were chosen such that each patient had at least 6 months of follow-up at the time of writing.

Descriptive statistics

The statistical analysis was performed using R 3.5.1 (R Core Team; R Foundation for Statistical Computing, Vienna, Austria). We report summary statistics (including mean, median, and quantiles) of the variables recorded in the dataset that are associated with CDI timelines. We used the Tukey honest significant difference (HSD) test when comparing multiple groups with their associated distributions.[14]

RESULTS

There were 683 cases of CDI identified during the study period, of which 54.6% were female. The mean age of patients was 70.9 years (median, 73 years; 25% and 75% quantiles of 62 years and 83 years, respectively).

Incidence

The number of CDI inpatients was in the range of 120 to 170 cases per year over the 5-year study period. Figure 1 shows the monthly CDI incidence decreasing from approximately 7.5 cases to 3 cases per 10,000 inpatient-days. A linear regression over the 5-year period indicates a decreasing trend at an annual rate of 0.57 (95% confidence interval, 0.29-0.86) cases per 10,000 inpatient-days. Although adherence to guidelines for CDI management can reduce the incidence, a combination of factors may have contributed to the observed year-to-year decline of incidence, including the Canada-wide decrease in hypervirulent NAP1 strains over the same study period.[15]

CDI-associated timelines

We excluded 84 cases from the analysis of timelines due to undetermined IPAC classification and lack of consistent records of dates for events of symptoms onset, laboratory results, and isolation. After these exclusions, there were 202 cases with symptoms onset prior to hospital admission and 397 cases who developed symptoms following admission. We analyzed the full empirical distributions of time intervals recorded from admission to CDI symptoms onset and from symptoms onset to laboratory results, to first isolation, and to start of treatment. Table 1 provides summary statistics of these timelines, including only the cases that had available and consistent records across all timelines (n = 599). We also tested whether there was a statistically significant difference in CDI timelines between HAI cases and CAI cases (Table 1).

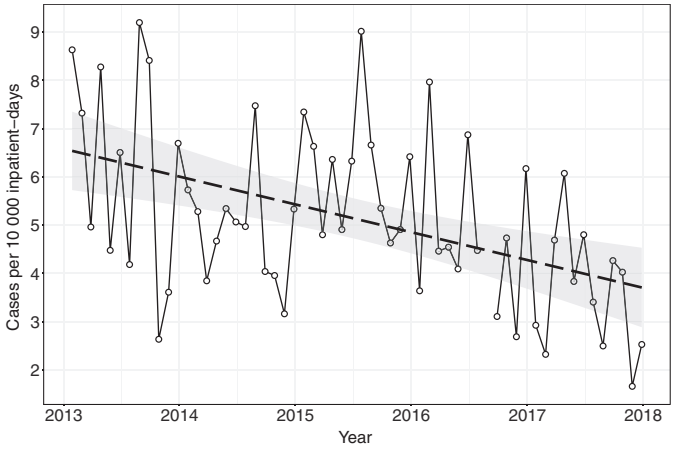

Fig 1. Incidence of *Clostridium difficile* infection per 10,000 inpatient-days (solid line with circles). The dashed line represents the linear regression, and the shaded area shows the 95% confidence interval of the linear regression.

Table 1
Summary statistics for selected time intervals during *Clostridium difficile* infection

	Mean time interval, d (2.5% quantile; 97.5% quantile)					
	Symptoms onset following admission(n = 397)			Symptoms onset prior to admission(N = 202)		
	HAI (n = 264)	CAI (n = 133)	*P* value (HAI vs CAI)	HAI (n = 69)	CAI (n = 133)	*P* value (HAI vs CAI)
Hospital admission to symptoms onset	21.6 (5; 100.7)	2.1 (0; 5.7)	<.001	−5.8 (−7; −1)	−9.9 (−11; −1)	.594
Symptoms onset to laboratory results	1.4 (0; 9.4)	1.7 (0; 10.1)	.989	5.8 (2; 22.3)	10.2 (3; 51)	<.001
Symptoms onset to start of isolation	1.7 (0; 10.4)	2.8 (0; 16)	.697	5.8 (2; 18.5)	10.2 (3; 50.7)	.012
Laboratory results to start of isolation	0.2 (0; 1.4)	1.1 (0; 6.5)	.668	0 (-1; 12)	0.1 (−1; 7.7)	1.000
Symptoms onset to start of treatment	2.1 (1; 9.9)	2.3 (1; 10.5)	.992	7 (3; 23)	11.1 (4; 51.7)	.001

NOTE: *P* values were calculated using the Tukey honest significant difference test for comparing groups of HAI and CAI. Negative sign indicates the start of the event prior to hospital admission.
HAI, health care–associated infection; *CAI*, community-associated infection.

Time interval from admission to CDI symptoms onset

The mean time interval between admission and CDI symptoms onset was 21.6 days for HAI cases and 2.1 days for CAI cases who presented symptoms after hospital admission. For the group with CDI symptoms prior to admission, the corresponding mean time intervals from symptoms onset to hospital admission were 5.8 days for HAI cases and 9.9 for CAI cases (Table 1).

Time interval from CDI symptoms onset to laboratory results

For the patient group with symptoms onset following hospital admission, the mean time intervals between the onset of symptoms and the release of laboratory results were 1.4 days (median of 0 day) for HAI cases and 1.7 days for CAI cases. The corresponding mean time intervals for patients with symptoms onset prior to admission were 5.8 days for HAI cases and 10.2 days for CAI cases (Table 1).

Time interval from CDI symptoms onset to first isolation

For the patient group with symptoms onset following admission, the mean time intervals between the onset of symptoms and first isolation were 1.7 days for HAI cases and 2.8 days for CAI cases. For patients with symptoms onset prior to admission, the corresponding mean time intervals were 5.8 days for HAI cases and 10.2 days for CAI cases (Table 1).

Time interval from CDI symptoms onset to CDI treatment initiation

For patients who presented CDI symptoms following admission, the mean time intervals for start of treatment after symptoms onset were 2.1 days for HAI cases and 2.3 days for CAI cases. The corresponding mean time intervals for patients with symptoms onset prior to admission were 7.0 days for HAI cases and 11.1 days for CAI cases.

Duration of isolation

Patients could be isolated several times, especially in the case of CDI relapses, but 74.5% had only 1 isolation event. The duration of the first isolation had a mean of 20.5 days and a median of 14 days, with 25% and 75% percentiles of 14 days and 26 days, respectively. The mean and median of the total duration of all isolation episodes (including relapses) were 27 days and 17 days, respectively, with 25% and 75% quantiles of 7 days and 34 days, respectively. Duration of the first isolation increased with stool frequency. The median durations of isolation were 6 days, 13.5 days, and 23 days for patients in groups A, B, and C, respectively (Table 2) (analysis of variance and Tukey HSD test *P* values <.0001); however, this duration was not associated with the type of CDI antibiotic used for treatment. The duration of isolation for successive isolation events varied between 1 week and 3 weeks (Table 2).

The mean duration of the first isolation with respect to the initial CDI antibiotic treatment was 24.4 days (25% and 75% quantiles of 8 and 27, respectively) for vancomycin, 20.3 days (25% and 75% quantiles of 6 and 26, respectively) for metronidazole, and 16.6 days (25% and 75% quantiles of 6 and 25, respectively) when both vancomycin and metronidazole were used together for more severe disease. We did not infer any statistically significant differences among the durations of isolation for these treatment regimens (Tukey HSD test *P* values >.11). However, we observed a longer duration of the first isolation (*P* value <.0001) for cases when treatment was initiated with a delay longer than 2 days after the onset of CDI symptoms (mean, 24.8 days) compared to patients who started treatment within 2 days of symptoms onset (mean, 15.0 days).

Temporal change in CDI-associated timelines

We tested whether the CDI timelines changed over the study period. We found no significant change in the time intervals and

Table 2
Summary statistics for number and duration of isolation episodes

		Duration (d) of isolation for the first *Clostridium difficile* infection episode for each patient group			
Patient group	n	Mean	Median	25% quantile	75% quantile
A	212	11.0	6.0	3.0	14.0
B	260	20.1	13.5	7.0	24.3
C	211	30.5	23.0	14.0	37.5

		Duration (d) of isolation for the number of isolation episodes			
Number of isolation episodes	n	Mean	Median	25% quantile	75% quantile
1	683	20.5	14.0	6.0	26.0
2	127	27.4	15.0	7.0	35.0
3	32	15.8	8.5	5.0	19.0
4	11	39.0	18.0	8.0	63.0
5	2	3.0	3.0	2.0	4.0
6	1	23.0	23.0	23.0	23.0
7	1	10.0	10.0	10.0	10.0

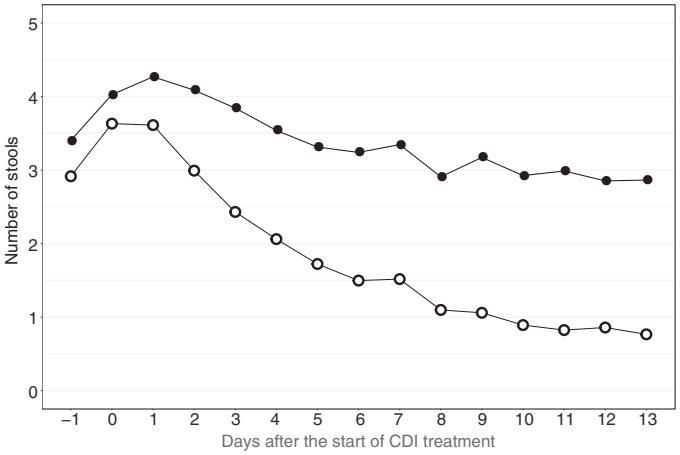

Fig 2. Daily number of stools during CDI treatment. The horizontal axis represents the number of days after the start of treatment (with 1 day prior to start of treatment). The filled circles represent the mean number of stools across all patients for each treatment day. The open circles are the mean number of stools of type 6 and 7 on the Bristol scale for each treatment day. *CDI*, *Clostridium difficile* infection.

isolation durations over time (Kruskal-Wallis test, *P* value >.25). When grouping variables by calendar year (ie, 5 groups from 2013 to 2017 for each variable), there was no significant change in the time intervals from admission to the onset of CDI symptoms, from symptoms onset to the start of isolation or CDI treatment, and the total duration of isolation episodes (Kruskal-Wallis test, all *P* values >.25). The only exception was the duration of isolation in 2016, which was slightly shorter (*P* <.01) than for other years in the study period.

Stools frequency

We performed an analysis of stool frequency for 669 patients in the database (excluding 14 patients for whom stool frequency was not recorded). The mean number of stools of type 6 and 7 on the Bristol scale over the full length of CDI was 21.1 stools (median, 17; 25% and 75% quantiles of 8 and 27, respectively). Figure 2 shows the daily distribution of the number of stools for all patients during their CDI antibiotic treatment.

The mean number of stools of type 6 and 7 with respect to the initial antibiotic treatment was 20 (25% and 75% quantiles of 8 and 26, respectively) for metronidazole, 26.4 (25% and 75% quantiles of 12 and 32, respectively) for vancomycin, and 25.2 (25% and 75% quantiles of 12 and 35, respectively) when both metronidazole and vancomycin were used together. A Tukey HSD test found a statistically significant difference between patient groups that were treated with metronidazole only and those treated with vancomycin only (adjusted *P* value = .003). We did not infer any statistically significant difference in the total number of stools when comparing the start of treatment with a delay longer or shorter than 2 days after the onset of CDI symptoms onset (*P* value = .6).

Relapse and recurrence

Of 683 cases of CDI, 576 (84.3%) experienced no relapse, 611 (89.5%) encountered no recurrence, 88 (12.9%) had only 1 episode of relapse within 8 weeks, and 42 (6.1%) had only 1 recurrence after 8 weeks. Isolation and relapse dates were recorded for 73 out of 100 patients who had at least 1 relapse episode. For these patients, the mean time interval between the end of their first isolation episode and the first relapse was 19.1 days (median, 15 days; 25% and 75% quantiles of 8 and 24, respectively).

DISCUSSION

Our study provides estimates of key timelines associated with the diagnosis of CDI and control measures in a hospital setting. For patients who were admitted with CDI symptoms, our results indicate a relatively long duration of CDI symptoms (5 to 10 days on average) before hospital admission, highlighting the potential for significant *C difficile* transmission in the community and the potential for developing earlier intervention strategies to prevent hospitalization. For cases where the onset of CDI symptoms followed hospital admission, the delay for the initiation of CDI treatment was shorter (mean, 2.2 days) compared with previous estimates that ranged from 2.6 days to 7.7 days.[16,17] We did not infer statistically significant differences between the associated timelines for HAI and CAI patients who developed symptoms following admission (Table 1). We also found that the mean time interval for the release of laboratory results after symptoms appeared (ie, 1.5 days) for patients with symptoms onset following admission was lower than previous mean estimates of 1.8 to 2 days.[18,19] The timelines analyzed here were relatively constant over the 5-year study period, despite being in the context of a declining CDI incidence (Fig 1).

We found that the duration of isolation increased with the frequency of stools of type 6 and 7 (Table 2). Although the duration of isolation was not associated with the initial type of CDI treatment, it did increase with a delay in start of treatment longer than 2 days. This result provides supporting evidence that early antimicrobial CDI treatment remains an important component of infection control. Note that, prior to 2016, vancomycin was almost exclusively used as the first-line antibiotic for higher risk patients (those with moderate CDI and those at higher risk of relapse) but since 2017 has become the preferred initial choice for most inpatients with non-severe CDI. Vancomycin together with intravenous metronidazole has been the preferred regimen for severe disease.

To our knowledge, this is the first study to report a number of key timelines and their relevance to delays in the start of treatment for nosocomial CDI based on a single hospital database. Although we have provided a number of CDI-related timelines and stool frequency data that have not been documented in previous literature, we note that our estimates may be influenced by guidelines for infection control practices that may vary in different health care settings. At St Joseph's Healthcare Hamilton, an active IPAC service monitors timely isolation and testing of patients with diarrhea and assesses all laboratory-confirmed CDI cases. Patients receive education regarding isolation, and nursing and medical compliance with contact precautions and handwashing is monitored. All cases of CDI are classified as community or hospital associated based on a careful review of the patient's history. Testing for *C difficile* is available in a regional laboratory located at the hospital site; 3 daily batch-testing times result in testing turnaround times of 4 to 24 hours. Treatment for CDI is directed by 1 of 3 infectious diseases specialists. All CDI cases and rates of HAI are reported to the provincial Ministry of Health, and rates exceeding established thresholds result in outbreaks being declared on the ward, with implications for admission, transfer, and treatment. These important guidelines should be considered to contextualize our results.

This study will be useful to guide future efforts in improving guidelines for the diagnosis, treatment, and prevention of nosocomial CDI, particularly for modeling studies to evaluate the effectiveness of single or bundle interventions to reduce CDI transmission and the related economic impact.[20-23] For example, parameterization of dynamic models with estimates of time intervals for diagnosis and start of isolation or treatment after the onset of CDI symptoms could in turn influence disease transmission, the projection of within-hospital incidence of *C difficile*, and therefore the efficacy of interventions.[21] However, our findings here should be considered in the context of study limitations; for example, asymptomatic cases generally remain undiagnosed without testing.

For patients who acquire *C difficile* within their hospital stay and remain asymptomatic until discharge, such datasets may not accurately categorize them as HAI upon readmission after 4 weeks if CDI symptoms develop. Furthermore, the CAI classification based on patient-provided data may not be fully accurate because of patient recall bias. Our results on the increased duration of isolation corresponding to the increased frequency of stools should not be interpreted as longer hospital stays or as an indication of more severe disease. Our database did not include a control group of patients without CDI symptoms; therefore, the effect of CDI on the length of hospital stay could not be assessed. The database also lacked records on previous or concomitant antibiotic administration other than CDI treatment. The results presented here are based on a database specific to a Canadian hospital and may not be applicable to other settings where CDI management guidelines differ significantly. Nevertheless, our study provides estimates of several important timelines of nosocomial CDI that are critical to infection control and clinical decision-making in hospital settings.

Additional information on the full distribution of timelines presented here will be provided upon request.

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