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Concise Communication

Clostridioides difficile toxin testing and positivity in Manitoba, Canada

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Abstract

We assessed *Clostridioides difficile* toxin testing and positivity for all patients in Manitoba hospitals during June 2016–November 2018. The testing rate was 30 per 10,000 patient bed days (95% confidence interval [CI], 30–31) and the incidence rate was 3.5 per 10,000 patient bed days (95% CI, 3.3–3.7). The context of testing is essential to the interpretation of data among jurisdictions.

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Clostridioides difficile infection (CDI) remains a significant public health challenge in Manitoba and elsewhere in Canada.[1,2] Rates of reported CDI have been increasing,[3,4] and hospital and institutional outbreaks caused by CDI often cause significant disruption to the delivery of health services.[2] Control of CDI is hampered by a lack of harmonized information on disease burden and time trends.[5] The interpretation of surveillance data is difficult without a clear understanding of the intensity of testing. Analyses based solely on reported cases might lead to erroneous conclusions and decisions if the prevalence and predictors of testing are poorly understood.[6,7]

Although CDI has been reportable to public health authorities in Manitoba since April 2005, little is known about testing rates. A positive toxin test result should only be reported as CDI in Manitoba if it is accompanied by diarrhea. The lack of information about testing rates does not allow for an unbiased comparison of surveillance data with other jurisdictions because testing protocols differ within Canada.[8] We assessed the probability of testing and the toxin positivity rate for *Clostridioides difficile* in Manitoba hospitals.

Methods

Manitoba Health is the publicly funded health insurance agency providing comprehensive health insurance, including coverage for hospital and outpatient physician services, to the province's 1.3 million residents. Coverage is universal, with no eligibility distinction based on age or income, and participation rates are very high (>99%). Insured services include hospital and diagnostic services.

To measure the intensity of screening, we identified all inpatient tests for *C. difficile* for all Manitoba hospitals between June 1, 2016, and November 30, 2018, from the Shared Health Laboratory Information System (LIS; Delphic, Sysmex, New Zealand), including the collection dates, test results, and patient demographics. Since 2002, all in-hospital *C. difficile* testing in Manitoba has been done by a single provincial entity; this entity is fully funded by Manitoba Health and fully accountable to Manitoba Health and is currently named Shared Health, Diagnostic Services. All requested inpatient *C. difficile* tests in Manitoba and all test results are registered in the LIS. During the study period, stool specimens were screened using the glutamate dehydrogenase (GDH) membrane immunoassay using the C. Diff Quik Chek test (Techlab, Blacksburg, VA) following the manufacturer's recommendations. Specimens positive for GDH antigen were then subjected to a *C. difficile* toxin single nucleic acid amplification test (Illumigene C. diff; Meridian Bioscience, Cincinnati, OH).

We attributed all tests for a patient to the same episode of care if it was within 56 days of another test (in line with the provincial protocol and literature definitions of recurrent CDI[7]). We included 1 test per episode of care in our analysis, the first positive test for positive episodes (16% of all positives were recurrent) and the first negative test for negative episodes. We calculated testing and incidence (of positive toxin) rates using the number of patient bed days from Manitoba hospitals[9] as the denominator.

Because its proportion of elderly patients is relatively large, we retrospectively reviewed charts of 400 randomly selected patients discharged from the adult medicine ward at Grace Hospital in 2016, a 247-bed urban hospital in the main urban center of Winnipeg, Manitoba. A trained registered nurse reviewed the charts and extracted using a custom-designed Epi Info data form (Centers for Disease Control and Prevention, Atlanta, GA) to extract demographic information (age, gender, area of residence), diarrhea status at admission (as a symptom, regardless of whether it was the main reason for admission), diarrhea onset during hospitalization, collection of stool specimens, positive tests for *C. difficile* toxin, and other characteristics of the hospitalization for each patient. We summarized the extracted data using descriptive statistics.

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Table 1. Number and Crude Rate of *C. difficile* Toxin Testing and Positivity According to Gender, Age Group, and Year

Variable	Tested, No. (%)	Testing Rate (95% CI)[a]	No. Positive	% Positive	Incidence Rate (95% CI)[a]
Total	8,544 (100.0)	30 (30–31)	974	11.4	3.5 (3.3–3.7)
Gender					
Male	3,962 (46.4)	31 (30–32)	469	11.8	3.6 (3.3–4.0)
Female	4,582 (53.6)	30 (29–31)	505	11.0	3.3 (3.0–3.6)
Age, y					
<70	4,957 (58.0)	38 (37–39)	509	10.3	3.9 (3.6–4.3)
≥70	3,587 (42.0)	24 (23–25)	465	13.0	3.1 (2.8–3.4)
Year[b]					
2016	1,974 (23.1)	29 (28–30)	249	12.6	3.7 (3.2–4.2)
2017	3,342 (39.1)	29 (29–31)	381	11.4	3.4 (3.0–3.7)
2018	3,208 (37.5)	31 (30–32)	342	10.7	3.3 (3.0–3.7)

Note. CI, confidence interval.
[a]Per 10,000 patient bed days.
[b]Data only available June–December in 2016 and January–November in 2018.

We used Stata version 14 software (StataCorp, College Station, Texas) for all analyses. This study was approved by the University of Manitoba Research Ethics Board [no. HS 19565 (H2016:111)] and the Winnipeg West Integrated Health & Social Services Senior Leadership team.

Results

During the study period, 8,544 patients were tested. Among them, 11.4% (974) tested positive for *C. difficile* toxin (Table 1), and 37% (3,182) were tested ≤3 days from admission. Men tested positive at a slightly higher percentage than women, and the percent positive was ~25% higher for patients aged >70 years than for younger patients. Test positivity trended slightly downward during the study period, although different months were included for each calendar year.

The overall testing rate was 30 (95% confidence interval [CI], 30–31) per 10,000 patient bed days (Table 1). Patients aged >70 years were tested approximately two-thirds as often as younger patients, and men were tested at approximately the same rate as women. Testing rates were stable (on an annual basis) during the study period.

The incidence rate of *C. difficile* toxin positivity was 3.5 per 10,000 patient bed days (95% CI, 3.3–3.7) (Table 1). The incidence rate for patients aged >70 years was 20% lower than the rate of younger patients, and men had a slightly higher rate than women. The incidence was stable during the study period, although it was slightly higher for 2016, the first year of the study that covered only June through December. CDI incidence rates vary by month in Manitoba, the rates are highest from August through October and lowest from January through March.[1]

The charts of 400 hospital patients were reviewed retrospectively (representing 402 hospitalizations). Among them, 10 patients (2.5%) were admitted with diarrhea (7 males and 3 females). The vast majority of patients (80%) resided in Winnipeg, the location of the hospital where the chart review was conducted. Stool specimens were collected for 27 (6.8%) patients, 18 of whom had diarrhea: 5 were admitted with diarrhea and 13 developed diarrhea during their hospitalization. Stools were collected for 5 of the 10 patients admitted with diarrhea and 13 of the 20 patients who developed diarrhea during their hospitalization. One patient tested positive for *C. difficile* toxin.

Discussion

For every 10,000 patient bed days, 30 patients were tested for *C. difficile* toxin and 3.5 tested positive; 11% of tested patients tested positive. Hospital-associated CDI decreased in Canada between 2009 and 2017 (from 5.9 to 3.9 per 10,000 patient bed days, in line with our results for 2016–2018), although those authors observed large regional differences.[10,11]

In our chart review, 18 patients of 400 had diarrhea and had stool samples collected, and 1 patient tested positive for *C. difficile* toxin (1 of 18 is 6%). This finding is in line with a 6,000-patient UK study in which 90% of samples tested negative for *C. difficile* toxin.[12] We found an 11% positivity rate in Manitoba. In a large European study, 58.4% of diarrhea samples were tested for CDI,[7] which is close to the prevalence of testing for the diarrhea patients in our chart review. Almost half of samples (40%) were collected for patients without diarrhea; the laboratory rejects formed stools for *C. difficile* testing. Our chart review was not set up to investigate other reasons for stool sample collection or to collect diarrhea characteristics (eg, duration or timing with respect to stool collection), so we were unable to assess the appropriateness of testing these samples.

We found an overall positivity rate of 11.4%. The positivity rate was reported to be 18% in Canadian hospitals in 1997,[13] although CDI practices (both in terms of testing protocols for CDI and volume of testing) were highly variable throughout Canada[8] and have changed since then. In a more recent European study, positivity rates differed by country. These rates were 9.6% in France, 14.9% in Italy, and 3.0% in the United Kingdom based on the number of positive results among tested patients, as reported by Davies et al.[7]

When we combined the 60% testing rate for patients with diarrhea and the 11% positivity rate, we noted that for every 100 patients with diarrhea, ~60 patients would be tested and ~7 patients would be positive. The 2-stage testing algorithm used in Manitoba leads to lower reported CDI rates than jurisdictions where standalone assays are used.[7,12] Rates of *C. difficile* testing and positivity, as well as positivity rates in Manitoba, resemble those in Italy and France more than those in the United Kingdom. A key difference could be earlier testing (within 48 hours of admission), which is more prevalent in the United Kingdom.[7]

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A major strength of this study is the availability of a high-quality, province-wide system for all hospital testing for CDI. These test protocols combine molecular and toxin immunoassay testing because relying on molecular tests alone would likely result in overdiagnosis of CDI.[12,14]

This study has several limitations. Two-step algorithms based on a GDH screen have a relatively low sensitivity in immunocompromised patients,[15] which may have resulted in underdiagnosis of CDI in this population. We were unable to determine rates for all community-tested CDI because we did not have data from a second laboratory that also tests these samples.

In 2005–2006, half of CDI infections were healthcare-acquired in Manitoba, an additional 15%–20% were hospital diagnosed and were community acquired or from an indeterminate origin.[1] A more recent Manitoba study found similar proportions by onset for patients with inflammatory bowel disease (IBD) and their matches.[16] We may have underestimated the postdischarge burden of community-onset, healthcare-associated CDI because we lacked information on testing after hospitalization. In 2011, two-thirds of CDIs in the United States were healthcare associated, although only a quarter had their onset during hospitalization.[17]

We lacked some important clinical information. We could not ascertain the province-wide prevalence of *C. difficile* testing for hospital patients with diarrhea, and we had no information about comorbidity (which may be particularly relevant for older patients). Patients with IBD have a higher risk of CDI[16] and might undergo more intense screening. We also lacked information on prior healthcare encounters to ascertain the onset of CDI. Because of these limitations, we were unable to assess the predictors and appropriateness of testing, which did not allow us to estimate the full burden of CDI in Manitoba. Based on our chart review, testing rates for *C. difficile* appeared to be low; only 50% of hospitalized patients with diarrhea were tested. This low rate of testing could explain some of the variability in CDI incidence rates. A better understanding of testing is important because *C. difficile* is the most common cause of hospital-acquired diarrhea and is treatable, and missing an early diagnosis can contribute to nosocomial spread.

In conclusion, increasing age was related to a lower rate (per patient bed day) of toxin testing and positivity. *C. difficile* incidence rates were in line with the literature, although the context of testing is essential to comparing data between jurisdictions. Although laboratory protocols have been standardized, initiation of testing is not standardized. The resulting variability in testing rates limits our understanding of CDI and ways to control it.

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