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Clostridium difficile infection in rural Ontario: a retrospective multisite population-based study

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Introduction: We conducted a retrospective, population-based study to assess the prevalence of *Clostridium difficile* infections and the associated risk factors among inpatients and outpatients in our region.
Methods: We used laboratory data over a 2-year period to identify inpatient and outpatient cases of *C. difficile* infection. Data were collected from 3 local catchment areas for rural hospital laboratories in Sioux Lookout, Mount Forest and the South Huron Hospital Association in Exeter. We gathered demographic data and infection-specific information, including recent antibiotic use and recent or current hospital admission or nursing home stay.
Results: During the study period, 34 cases of *C. difficile* infection occurred in 29 patients, with an estimated crude annual rate of 24.3/100 000 population. Of the cases, 47.1% were diagnosed in outpatients. Most patients (76.5%) had taken antibiotics within the previous 90 days, and antibiotic use and hospital admission accounted for 47.1% of cases. Clindamycin was more commonly associated with *C. difficile* infections at the northern site and ciprofloxacin at the southern sites. There were 2 deaths from comorbidities.
Conclusion: The estimated annual incidence of *C. difficile* infection in our study is similar to urban-based estimates. Almost half of the cases involved outpatients, indicating a need to recognize this illness as a serious outpatient condition. Antibiotic stewardship is an ongoing consideration, as most patients were exposed to antibiotic use before infection.

Introduction : Nous avons effectué une étude rétrospective basée dans la population pour évaluer la prévalence des infections à *Clostridium difficile* et les facteurs associés chez les patients hospitalisés et non hospitalisés de notre région.
Méthodes : Nous avons utilisé les données de laboratoire sur une période de 2 ans pour recenser les cas d'infections à *C. difficile* chez les patients hospitalisés et non hospitalisés. Les données ont été recueillies à partir de 3 bassins de population locaux pour les laboratoires hospitaliers ruraux de Sioux Lookout, de Mount Forest et de la South Huron Hospital Association à Exeter. Nous avons colligé les données démographiques et les renseignements spécifiques aux infections, y compris l'utilisation récente de l'antibiothérapie et les hospitalisations ou séjours en foyers de soins infirmiers récents ou en cours.
Résultats : Au cours de la période de l'étude, 34 infections à *C. difficile* ont été dénombrées chez 29 patients, pour un taux annuel brut estimé de 24,3/100 000 habitants. Parmi ces cas, 47,1 % n'étaient pas hospitalisés au moment du diagnostic. La plupart des patients (76,5 %) avaient pris des antibiotiques au cours des 90 jours précédents et l'antibiothérapie et l'hospitalisation caractérisaient 47,1 % des cas. La clindamycine a le plus souvent été associée aux infections à *C. difficile* dans le site le plus au Nord et la ciprofloxacine, dans les deux sites plus au Sud. On a déploré 2 décès par suite de comorbidités.
Conclusion : L'incidence annuelle estimée de l'infection à *C. difficile* au cours de notre étude a été similaire aux estimations obtenues en milieu urbain. Près de la moitié des cas s'observaient chez des patients non hospitalisés, rappelant la nécessité de considérer cette infection comme un grave problème de santé chez les patients externes. La bonne gestion de l'utilisation des antibiotiques demeure un enjeu constant puisque la plupart des patients avaient été exposés à des antibiotiques avant leur infection.

INTRODUCTION

Clostridium difficile infections as a cause of symptomatic diarrhea and colitis are reported in the literature to be on the rise.[1] Until relatively recently,[2] most published data consisted of reportable infections in hospital inpatients, whereas infections that were acquired in the community and treated on an outpatient basis went uncounted. In 2014, studies in Manitoba and Australia documented that about 40% of *C. difficile* infections were community-associated.[1,2] Data are lacking on estimates of *C. difficile* infections among inpatient and outpatient populations in rural Canada.

In northwestern Ontario, high rates of antibiotic-resistant bacterial illness, including invasive disease, that are sensitive to clindamycin have been identified.[3–5] Antibiotic use (and overuse) is a known risk factor for *C. difficile* infections. We conducted a retrospective, population-based study to assess the prevalence of *C. difficile* infections and the associated risk factors among inpatients and outpatients in our region. To add to the total number of cases and to compare our rates with those of other rural regions in the province, we enlisted researchers in 2 rural centres in southern Ontario.

METHODS

We collected laboratory data for positive *C. difficile* test results for inpatients and outpatients over a 2-year period, from Apr. 1, 2012, to Apr. 1, 2014, from 3 sites in rural Ontario: Sioux Lookout, Mount Forest and the South Huron Hospital Association in Exeter. In-house *C. difficile* toxin tests and Public Health Ontario laboratory test results were collated. The catchment area populations for the 3 rural hospital laboratories were estimated from regional strategic plans.

We gathered demographic data and infection-specific information, including recent antibiotic use, and recent or present hospital admission or nursing home stay. Hospital-associated cases were defined by onset of symptoms and positive testing more than 48 hours after admission. Community-associated cases were defined by no hospital admission or by onset of symptoms and positive testing within 48 hours of a hospital admission. We defined recurrence by a positive specimen result 2–8 weeks after previous positive testing. Positive results beyond 8 weeks were considered a new case.

The Sioux Lookout Research Review and Ethics Committee granted ethics approval for this study.

RESULTS

The 3 rural laboratory sites had a total estimated population of 70 000 in the catchment areas (Table 1). A total of 34 cases (in 29 patients) of *C. difficile* infection were encountered during the study period (Table 2). This is an estimated crude annual rate of 24.3/100 000 population. These cases included both inpatients and outpatients. The northern site (Sioux Lookout) had the same number of cases as the 2 southern sites (Mount Forest and South Huron Hospital Association) combined; taking into account the populations (29 000 for the northern site v. 41 000 for the southern sites combined) the difference in rates of *C. difficile* infection was not significant ($p = 0.6$).

Most *C. difficile* infections were new cases (78.8%) and 7 were recurrences. The mean age was 61.7 (range 2–93) years, with one outlier at 2 years of age (Table 2). Of the patients, 76% were older than 50 years, and 50% were older than 65 years. Outpatient diagnosis occurred 47.1% of the time (Table 2) and outpatient treatment occurred 41.2% of the time (Table 3).

Most patients (76.5%) had taken an antibiotic within 90 days of their diagnosis. Antibiotic use and

Table 1: Estimated population service areas for laboratory services*

Service area	Population catchment area for laboratory services
Sioux Lookout	29 000
South Huron Hospital Association, Exeter	19 000
Mount Forest	22 000
Total	70 000

*The estimates came from Statistics Canada and internal hospital audits, according to which communities the laboratory served and/or from internal strategic planning documents developed by each laboratory service.

Table 2: Patient characteristics at presentation, *n* = 34 infections

Characteristic	No. (%)*
Age, mean (range), yr	61.7 (2–93)
New cases	26 (76.5)
Recurrent cases	7 (20.6)
Diagnosed in outpatient	16 (47.1)
Diagnosed in inpatient	17 (50.0)
Days of diarrhea before diagnosis	
Mean (range)	11.7 (1–40)
1–3	6 (17.6)
1–7	13 (38.2)

*Unless stated otherwise.

hospital admission accounted for 47.1% of cases. Only a small portion of our identified cases had no hospital admission or antibiotic use (14.7%). Of the patients, 38.2% were concurrently taking proton pump inhibitors (PPIs) (Table 4).

The associated antibiotics used within 90 days of case detection was almost evenly distributed: ciprofloxacin (26.5%), clindamycin (23.5%) and cephalosporins (20.6%). Clindamycin was more commonly associated with *C. difficile* infections at the northern site and ciprofloxacin at the southern sites (Table 5). Treatment was commonly metronidazole (64.7%) (Table 3).

There were 2 deaths, both in older, immunocompromised patients with other infections and end-stage renal disease or cancer.

DISCUSSION

Our population-based incidence is similar to those quoted in urban-based North American studies, which commonly quote a rate of 20–30/100 000 population.[6] Outpatients amounted to almost half of the total cases in our study, which is also in keeping with recent estimates for urban populations. A 2006 Manitoba study of 1006 cases of *C. difficile* infection found a similar rate in their provincial population data of 23.4/100 000 and a 40% outpatient incidence.[2,6]

Advanced age is a known risk factor for *C. difficile* infection.[7,8] Our study supports this, with a mean age of 61.7 years and half of the patients being older than 65 years.

Antibiotic use has long been considered a risk factor for *C. difficile* infection, and our study does nothing to challenge that assumption. In more than three-quarters of cases, an antibiotic had been used within the previous 90 days. We did find that clindamycin use in the northern site was more commonly associated with *C. difficile* infection than at the other sites. This may represent a prescribing difference, with clindamycin being prescribed more commonly at the northern location. Recently, higher rates of community-associated methicillin-resistant *Staphylococcus aureus* have occurred in that region, including serious invasive bacteremias. Clindamycin is 1 of 3 possible early treatments (along with sulfamethoxazole–trimethoprim and doxycycline), and this finding may reflect an increased use of this antibiotic relative to other rural sites in the province.[3–5]

In the 1970s, clindamycin was commonly associated with *C. difficile* infection and its usage declined as a result. In the 1980 and 1990s, cephalosporins were the commonly identified culprit. More recently,[9] fluoroquinolones have been associated with *C. difficile* infection (including the 2002/03 Quebec outbreak of a highly virulent strain).[10] We see all 3 offending antimicrobials in equal numbers in our study.

Proton pump inhibitors are statistically associated with increased rates of *C. difficile* infection in large US and UK population studies.[11–15] Although this is still controversial, the US Food and Drug Administration has issued a warning to patients taking long-term PPI therapy about an increased risk of *C. difficile* infection. A 2013 Scottish study calculated a 1.7-fold increase in risk of *C. difficile* infection with chronic PPI use.[16] The proposed mechanism is the protective effect of normal stomach acidity and the change in stomach and large

Table 3: Treatment of *Clostridium difficile* infection, *n* = 34 infections

Variable	No. (%)
Medication	
Metronidazole	22 (64.7)
Vancomycin	4 (11.8)
Vancomycin and metronidazole	4 (11.8)
Data unavailable	4 (11.8)
Patient status at time of treatment	
Outpatient	14 (41.2)
Inpatient	17 (50.0)
Data unavailable	3 (8.8)

Table 4: Exposures before *Clostridium difficile* infection, *n* = 34 infections

Preinfection exposure	No. (%)
Antibiotic use within 90 d	26 (76.5)
Recent hospital admission plus antibiotic use	16 (47.1)
Outpatient antibiotic use	10 (29.4)
Outpatient status, with or without antibiotic use	15 (44.1)
Antibiotic use within 90 d in 26 new cases	18/26 (69.2)
Hospital admission, without antibiotic use	2 (5.9)
No hospital admission or antibiotic use	5 (14.7)
Recent PPI use	13 (38.2)

PPI = proton pump inhibitor.

Table 5: Antibiotic use within 90 days of diagnosis of *Clostridium difficile* infection, *n* = 34 infections

Antibiotic	No. (%)
Ciprofloxacin*	9 (26.5)
Clindamycin*	8 (23.5)
Cephalosporin*	7 (20.6)
Penicillin, amoxicillin	3 (8.8)
Other	8 (23.5)
Data unavailable	9 (26.5)

*Ciprofloxacin: 6/9 cases were at southern sites; clindamycin: all cases were at the northern site; cephalosporin: cases at northern and southern sites.

intestine flora by PPIs.[17–19] Our study sheds no light on this developing discussion, as PPIs were used in 38.2% of cases, but most of these patients had also received antibiotics (11/13).

Given that outpatient diagnosis and treatment often occur in office practice settings, it is sobering to know that recent studies indicate that spore shedding can occur up to 4 weeks after treatment initiation and can inhabit any skin location and high contact environmental areas, such as door handles and examination tables.[20,21] Attention to hand washing and hand protection, and use of sporicidal-containing cleansers may be warranted in attending to affected patients in our office settings.

Limitations

Our catchment-area populations were estimates from regional service planning sources. These are not directly comparable to province-wide census population figures. Our methods were similar to those of other population-based studies that also used laboratory-based catchment areas as a starting point. Cases were identified if their tests were processed in the identified laboratory. We did not cross-check those cases with home addresses, so we may have included some visitors to the community in our case detection. Because we were able to access most inpatient records from the hospital associated with the laboratory, this effect may be minimal. Alternatively, patients from 1 of our 3 catchment areas may have been tested elsewhere, and we would have missed those cases. Our rates of *C. difficile* infection are therefore considered estimated crude rates.

CONCLUSION

The estimated annual incidence of *C. difficile* infection is similar to other existing urban population-based figures. The northern rural site in the study had a higher incidence than the 2 southern sites, which was not significant. Most cases were associated with antibiotic use. Antibiotic stewardship is an important consideration in our communities.

Almost half of the identified cases of *C. difficile* infection involved outpatients. Although we have traditionally viewed *C. difficile* infection as a hospital-acquired infection, this is no longer accurate. Care will have to be taken with hygiene in our office examination rooms and other outpatient clinic settings.

Competing interests: None declared.

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