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Hospitalization With Clostridioides difficile in Pediatric Inflammatory Bowel Disease: a Population-Based Study

*†M. Ellen Kuenzig, PhD, *†‡§‖¶#Eric I. Benchimol, MD, PhD, **††Charles N. Bernstein, MD, ‡‡Alain Bitton, MD, §§Matthew W. Carroll, BMed, MHSc, *†§Anne M. Griffiths, MD, ‖‖Gilaad G. Kaplan, MD, MPH, ‡¶¶##Geoffrey C. Nguyen, MD, PhD, ***Anthony R. Otley, MD, MSc, ‡##Therese A. Stukel, PhD, †††Trevor J.B. Dummer, PhD, ‡‡‡Wael El-Matary, MD, MSc, §§§Kevan Jacobson, MBBCh, ‖‖‖Jennifer L. Jones, MD, MSc, ¶¶###Lisa M. Lix, PhD, ‖¶#David R. Mack, MD, ****††††‡‡‡‡§§§§Sanjay K. Murthy, MD, MSc, ‖‖‖‖Juan-Nicolás Peña-Sánchez, MD, MPH, PhD, ¶¶Laura E. Targownik, MD, MSHS, ‡¶#Stephen G. Fung, MPH, ‡††††Sarah Spruin, MSc, ‖‖Stephanie Coward, PhD, ‖‖‖Yunsong Cui, MSc, ¶¶¶Christopher Filliter, MSc, **Zoann Nugent, PhD, ‡¶#Shabnaz Siddiq, MSc, and **††#####Harminder Singh, MD, MPH, on behalf of the Canadian Gastro-Intestinal Epidemiology Consortium (CanGIEC)

ABSTRACT

Objectives: Several studies have demonstrated higher rates of *Clostridioides difficile* infection (CDI) in adults with inflammatory bowel disease (IBD). We conducted a population-based study comparing the risk of hospitalization with CDI in children with and without IBD.

Methods: Using health administrative data and validated algorithms, we identified all children (<16 years) diagnosed with IBD in 5 Canadian provinces, then age and sex matched to 5 children without IBD. Province-specific 5-year incidence rates of hospitalization with CDI were pooled and generalized linear mixed-effects models were used to estimate the crude incidence rate ratio (IRR) comparing (1) children with and without IBD and (2) children with Crohn disease and ulcerative colitis. Hazard ratios (HR) from Cox proportional hazards models adjusting for age, sex, rural/urban household, and income were pooled using fixed-effects models.

Results: The incidence rate of CDI identified during hospitalization was 49.06 [95% confidence interval (CI), 39.40–61.08] per 10,000 person-years (PY) in 3593 children with IBD compared to 0.39 (95% CI, 0.13–1.21) per 10,000 PY in 16,284 children without IBD (crude IRR, 133.4, 95% CI, 42.1–422.7; adjusted HR, 68.2, 95% CI, 24.4–190.4). CDI was identified less often in children with Crohn disease than ulcerative colitis (crude IRR, 0.51, 95% CI, 0.32–0.82; adjusted HR, 0.69, 95% CI, 0.46–1.05).

Conclusions: Children with IBD have a markedly higher incidence of CDI identified during a hospitalization relative to children without IBD. Consequently, symptomatic children with IBD who are hospitalized should be screened for CDI.

An infographic is available for this article at *http://links.lww.com/MPG/C842*.

What Is Known

- Adults with inflammatory bowel disease (IBD) are at increased risk of *Clostridioides difficile* infection (CDI).
- Less is known about the incidence of CDI in children with IBD and how it compares to the incidence of CDI in children without IBD.

What Is New

- The incidence rate of hospitalization with CDI in a population-based incident cohort of children with IBD was 49.06 (95% confidence interval, 39.40–61.08) per 10,000 person-years and was nearly 70-fold than in age- and sex-matched children without IBD.
- These data suggest that children with IBD should be screened for CDI during hospitalization.

Key Words: Crohn disease, distributed network meta-analysis, health administrative data, ulcerative colitis

(*JPGN* 2022;75: 173–180)

Received December 7, 2021; accepted February 25, 2022.

From the *SickKids Inflammatory Bowel Disease Centre, Division of Gastroenterology, Hepatology and Nutrition, The Hospital for Sick Children, Toronto, Ontario, Canada, the †Child Health Evaluative Sciences, SickKids Research Institute, Toronto, Ontario, Canada, the ‡ICES, Toronto, Ontario, Canada, the §Department of Paediatrics, University of Toronto, Toronto, Ontario, Canada, the ‖Department of Pediatrics, University of Ottawa, Ottawa, Ontario, Canada, the ¶CHEO Inflammatory Bowel Disease Centre, Division of Gastroenterology, Hepatology and Nutrition, CHEO, Ottawa, Ontario, Canada, the #CHEO Research Institute, Ottawa, Ontario, Canada, the **Univeristy of Manitoba IBD Clinical and Research Centre, University of Manitoba, Winnipeg, Manitoba, Canada, the ††Department of Internal Medicine, Max Rady College of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada, the ‡‡McGill University Health Centre, Division of Gastroenterology and Hepatology, Montreal, Québec, Canada, the §§Division of Pediatric Gastroenterology, Hepatology and Nutrition, Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada, the ‖‖Departments of Medicine and Community Health Sciences, University of Calgary, Calgary, Alberta, Canada, the ¶¶Mount Sinai Hospital Centre for Inflammatory Bowel Disease, Department of Medicine, University of Toronto, Toronto, Ontario, Canada, the ##Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Ontario, Canada, the ***Department of Pediatrics, Dalhousie University, Halifax, Nova Scotia, Canada, the †††School of Population and Public Health, University of British Columbia, Vancouver, British Columbia, Canada, the ‡‡‡Department of Pediatrics, University of Manitoba, Winnipeg, Manitoba, Canada, the §§§Department of Pediatrics,

Clostridioides difficile infection (CDI) remains the most commonly identified cause of nosocomial infections (1). Several studies have reported that an increasing proportion of cases are occurring outside of hospital settings and among individuals without traditional risk factors (2,3). In spite of infection control efforts, there continues to be substantial incidence of CDI in many countries (4,5). Importantly, there has been no reduction in in-hospital mortality among patients with CDI (6).

Individuals with inflammatory bowel disease (IBD) have an altered microbiome and an increased number of contacts with the health care system, likely contributing to their increased risk of CDI (7). Among individuals with IBD, CDI increases the risk of complications including hospitalizations and mortality. However, most studies evaluating the link between IBD and CDI have been conducted in adults (8). There are limited data on the risk of CDI and hospitalization with CDI among children with IBD. CDI in children with Crohn disease is associated with a higher risk of surgery (9). Thus, it is important to understand the epidemiology of CDI in children. We report the incidence of hospitalization with CDI in a population-based Canadian national cohort of children with IBD.

METHODS

This study was approved by the Research Ethics Boards at the Children's Hospital of Eastern Ontario, IWK Health Centre, the University of Calgary, the University of Alberta, and the Montreal Jewish General Hospital and the Health Research Ethics Board at the University of Manitoba. In addition, this study was reviewed for privacy concerns by Alberta Health Services, the Manitoba Health Information Privacy Committee, Health Data Nova Scotia, ICES, and the Commission d'Accès a l'Information du Québec.

BC Children's Hospital Research Institute, University of British Columbia, Vancouver, British Columbia, Canada, the ‖‖‖Department of Medicine, Dalhousie University, Halifax, Nova Scotia, Canada, the ¶¶¶Department of Community Health Sciences, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada, the ###George & Fay Yee Centre for Healthcare Innovation, University of Manitoba, Manitoba, Winnipeg, Manitoba, Canada, the ****Department of Medicine, University of Ottawa, Ottawa, Ontario, Canada, the ††††Ottawa Hospital Research Institute, Ottawa, Ontario, Canada, the ‡‡‡‡Division of Gastroenterology, The Ottawa Hospital IBD Centre, Ottawa, Ontario, Canada, the §§§§School of Epidemiology and Public Health, University of Ottawa, Ottawa, Ontario, Canada, the ‖‖‖‖Department of Community Health & Epidemiology, College of Medicine, University of Saskatchewan, Saskatoon, Saskatchewan, Canada, the ¶¶¶¶Lady Davis Institute of Medical Research, Jewish General Hospital, Montreal, Québec, Canada, and the ####Research Institute at CancerCare Manitoba, Winnipeg, Manitoba, Canada.

Address correspondence and reprint requests to Harminder Singh, MD, MPH, FRCP(C), Section of Gastroenterology, University of Manitoba, 805-715 McDermot Avenue, Winnipeg, Manitoba, Canada R3E3P4 (e-mail: Harminder.Singh@umanitoba.ca).

Sources of Funding: E.K. was supported by a Post-Doctoral Fellowship Award from the Canadian Institutes of Health Research (CIHR), Canadian Association of Gastroenterology (CAG), and Crohn's and Colitis Canada and a Mitacs Elevate Post-Doctoral Fellowship. D.R.M. receives partial funding through a University of Ottawa Faculty of Medicine Distinguished Clinical Research Chair in Pediatric Inflammatory Bowel Disease Award. L.M.L. was supported by a Tier I Canada Research Chair. E.I.B. was supported by a New Investigator Award from the CIHR, CAG, and Crohn's and Colitis Canada. E.I.B. was also supported by the Career Enhancement Program of the Canadian Child Health Clinician Scientist Program. Data availability statement: The data set from this study is held securely in coded form at ICES. While legal data sharing agreements between ICES and data providers (e.g., healthcare organizations and government) prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at *www.ices.on.ca/DAS* (email: das@ices.on.ca). The full data set creation plan and underlying analytic code are available from the authors upon request, understanding that the computer programs may rely upon coding templates or macros that are unique to ICES and are, therefore, either inaccessible or may require modification. This work was supported by a Grant-in-Aid of Research from Crohn's and Colitis Canada, a Foundation Grant from the Canadian Institutes of Health Research (grant number 201409FDN-333131-FDN-CECC-164898), and a Canadian Institutes of Health Research Project Scheme Grant (Reference number PJT-162393). This study was supported by the ICES, which is funded by an annual grant from the Ontario Ministry of Health (MOH) and the Ministry of Long-Term Care (MLTC). Parts of this material are based on data and information compiled and provided by MOH and CIHI. Parts of this material are based on data and information provided by Alberta Health Services, Manitoba Health, Health Data Nova Scotia, and Régie de l'assurance maladie du Québec. The analyses, conclusions, opinions, and statements expressed herein are solely those of the authors and do not reflect those of the funding or data sources; no endorsement is intended or should be inferred.

E.I.B. has acted as a legal consultant for Hoffman La-Roche Limited and Peabody & Arnold LLP for matters unrelated to a medication used to treat inflammatory bowel disease or *C. difficile* infection. He has also acted as a consultant for McKesson Canada. G.G.K. has received honoraria for speaking or consultancy from Abbvie, Janssen, Pfizer, Amgen, and Takeda. He has received research support from Ferring, Janssen, Abbvie, GlaxoSmith Kline, Merck, and Shire. He shares ownership of a patent: TREATMENT OF INFLAMMATORY DISORDERS, AUTOIMMUNE DISEASE, AND PBC. UTI Limited Partnership, assignee. Patent 62/555,397. A.R.O. has been on advisory boards of AbbVie Canada, Janssen Canada, and Nestle. He has received unrestricted educational grants from AbbVie Canada and Janssen Canada. His site is involved with clinical trials for AbbVie, Pfizer, Takeda, Eli Lily, and Celgene. A.M.G. has been a consultant for Abbvie, Amgen, BristolMyersSquibb, Janssen, Lilly, Pfizer, Roche; has received speaker fees from Abbvie, Janssen, Nestle, and investigator-initiated grant support from Abbvie. L.E.T. has received investigator initiated funding from Janssen Canada, and served on advisory boards for AbbVie Canada, Sandoz Canada, Takeda Canada, Merck Canada, Pfizer Canada, Janssen Canada, and Roche Canada. C.N.B. has been on the advisory boards of Abbvie Canada, Amgen Canada, Bristol Myers Squibb Canada, Janssen Canada, Pfizer Canada, Sandoz Canada, Takeda Canada, Roche Canada, and consulted to Takeda and Mylan Pharmaceuticals. He has been on the speaker's bureau for Abbvie Canada, Janssen Canada, Takeda Canada and Medtronic Canada. He has received unrestricted educational grants from Abbvie Canada, Janssen Canada, Pfizer Canada, and Takeda Canada and has done contract research with Abbvie, Janssen, Pfizer, Celgene, Boeringher Ingelheim, and Roche. K.J. has been on Advisory boards of Abbvie Canada, Janssen Canada, Merck Canada, and Mylan Pharmaceuticals. He has been on the speaker's bureau of Abbvie Canada and Janssen Canada. He has received investigator-initiated research support from Abbvie Canada and Janssen Canada. W.E.M. has received honoraria for speaking or consultancy from Abbvie and MERCK. H.S. has consulted to Amgen Canada, Bristol-Myers Squibb Canada, Sandoz Canada, Roche Canada, Takeda Canada, and Guardant Health. The remaining authors report no conflicts of interest.

Supplemental digital content is available for this article. Direct URL citations appear in the printed text, and links to the digital files are provided in the HTML text of this article on the journal's Web site (*www.jpgn.org*).

DOI: 10.1097/MPG.0000000000003489

Data Sources

We conducted a matched cohort study using health administrative data from Alberta, Manitoba, Nova Scotia, Ontario, and Québec. All Canadian provinces have universal healthcare coverage for all residents (>99% of the population). These included 5 provinces representing 79% of the Canadian population (10). A detailed description of the data sources in each province, including the dates of data availability, is provided in Table 1, Supplemental Digital Content 1, *http://links.lww.com/MPG/C843*. Briefly, health administrative data in each province includes information on resident demographics and healthcare encounters (outpatient visits and hospitalizations in all provinces; emergency department visits in Alberta, Ontario, Nova Scotia, and Québec). Health administrative data are linked deterministically using encrypted personal identification numbers. In Ontario, all health administrative data are maintained by ICES according to an agreement with the Ontario Ministry of Health and Ministry of Long-Term Care (11). In Manitoba, all administrative health data are maintained by Manitoba Health; the study utilized the population-based cohort of persons with IBD and matched controls in the University of Manitoba IBD Epidemiology Database. In Nova Scotia, the administrative health data were made available through Health Data Nova Scotia. In Alberta, the administrative health data were made available through Alberta Health Services. In Québec, data were made available through the Commission d'Accès du Québec. The databases in each province are available to researchers in an uncleaned and unedited format after obtaining approvals from the local research ethics boards and the respective provincial health agencies.

Identifying Children With IBD

Previously validated province-specific algorithms were used to identify children diagnosed with IBD before 16 years of age (12–15). These algorithms use health care encounters associated with International Classification of Diseases (ICD)-9 and ICD-10-CA diagnostic codes for Crohn disease (ICD-9: 555, ICD-10-CA: K50) and ulcerative colitis (ICD-9: 556, ICD-10-CA: K51) and physician billing codes for endoscopy (Ontario only). The relative number of diagnostic codes for Crohn disease and ulcerative colitis was used to differentiate between the 2 IBD subtypes. Children with diagnostic codes for both Crohn disease and ulcerative colitis in whom established algorithms could not differentiate between the 2 IBD subtypes were labeled as having IBD unclassifiable. The details of these algorithms and their accuracy are described in Table 1, Supplemental Digital Content 1, *http://links.lww.com/MPG/C843*.

Incident cases were distinguished from prevalent cases using a 3-year washout period, meaning that all individuals had ≥3 years of continuous follow-up in their province of diagnosis without a diagnostic code for IBD prior to their first IBD diagnostic code. Children who were continuously eligible for provincial health care coverage from birth until IBD diagnosis did not require a washout period since all encounters with the health care system would be included within the health administrative data for the province in which they were born. The date of diagnosis was the date of the first health care encounter with an IBD code that qualified the child as a case of IBD.

We included children newly diagnosed with IBD during the following fiscal years (April 1 to March 31): Alberta, 2005 to 2015; Manitoba, 2004 to 2014; Nova Scotia, 2001 to 2011; Ontario, 2002 to 2014; Québec, 2006 to 2008. Study start dates were selected based on (1) start of provincial adoption of ICD-10-CA coding in hospital records to allow for identification of CDI; and (2) ensuring a validated washout period (i.e., ≥3 years) for all cases to distinguish incident from prevalent cases of IBD (12). Children were followed until death, migration out of the province in which they were diagnosed with IBD (i.e., their coverage for universal provincial health care coverage ended), or the end of the study (Alberta: 2017; Manitoba; 2018; Nova Scotia: 2016; Ontario: 2017; and Québec: 2010). Follow-up extended beyond the latest possible date of IBD diagnosis to ensure all cases had sufficient a sufficient look-forward period to meet the requirements of their province's algorithm for identifying cases of IBD. Study end dates varied across provinces due to data availability.

Study Design

Using a matched cohort design, we matched each child with IBD to five children without IBD based on birthdate (± 30 days), sex, and duration of eligibility for provincial healthcare coverage in Alberta, Manitoba, Nova Scotia, and Ontario. Controls in Manitoba were additionally matched based on the first 3 digits of their postal code. These controls were randomly identified from province-wide databases of children eligible for provincial healthcare coverage. Québec did not have data available on children without IBD. Children without IBD were followed forward from the date of diagnosis for their matched child with IBD.

Identifying Children Hospitalized for *Clostridioides difficile* Infection

Children with and without IBD who were hospitalized with CDI were identified using the ICD-10-CA code A04.7. We limited our analyses to those admissions where CDI was flagged as a most responsible diagnosis, a preadmission comorbidity, a postadmission comorbidity, secondary diagnosis, or admitting diagnosis when different from the most responsible diagnosis so as to increase the likelihood of CDI being contributory to that person's hospitalization. We included both nosocomial and community-acquired infections severe enough to require hospitalization. This code has been previously validated to identify hospitalizations for CDI in Ontario and Alberta (16,17). We have also recently demonstrated in Manitoba that using this code provides similar epidemiological patterns to the patterns produced when using the toxin assay (18). We only included a child's first hospitalization with CDI.

Statistical Analysis

Percentages and means (with standard deviations) were used to describe the categorial and continuous characteristics, respectively, of children with and without IBD included in the study.

Outcomes included the incidence rate of hospitalization for CDI among children with and without IBD within 1, 3, and 5 years of IBD diagnosis (cases) or index date (controls). All incidence rates are reported per 10,000 person-years. The 5-year incidence rates of CDI in children with and without IBD were compared using crude incidence rate ratios (IRR) and incidence rate differences (IRD). When there were a sufficient number of hospitalizations for CDI among both children with and without IBD to allow for model convergence, we also estimated hazard ratios (HR) and their 95% confidence intervals (95% CIs) from Cox proportional hazards regression adjusting for mean neighborhood income quintile (a validated proxy for individual-level socioeconomic status (19)) and residence location (rural or urban), both at the time of IBD diagnosis/index date. Analyses included all children with IBD, then were stratified by subtype of IBD (Crohn disease and ulcerative colitis). Children with IBD unclassifiable were included in the analysis of all children with IBD but excluded from the analyses stratified by subtype. The incidence of CDI in children with Crohn disease and ulcerative colitis were compared using the same analytic approach.

Privacy regulations prevent the sharing of individual-level data across provinces. To obtain overall estimates of the incidence

of *C. difficile* and its association with IBD, we used a distributed network analysis. This approach has been used previously in research conducted by the Canadian Gastro-Intestinal Epidemiology Consortium (20–23) and involves identical conducting analyses with identical code in each province (adapted to each provincial data set) then pooled with meta-analyses. A validation study using real-world health administrative data demonstrated this approach produces similar results to multivariable regression models conducted using individual-level data (24).

When there were between 1 and 5 children hospitalized with CDI in a province, the actual number of events could not be shared due to privacy regulations. In these situations, the number of events was assigned as a random number between 1 and 5. Known person time at risk was then used with the random number of events to calculate the incidence of hospitalization with CDI. We have previously demonstrated that this approach results in similar effect estimates as would be observed with a prespecified number of events (e.g., 1 or 5 events) (23).

Province-specific incidence rates of CDI were pooled using generalized linear mixed-effects models (GLMM) which extract individual patient data from the number of events and person time to obtain an overall estimate of the incidence of CDI (25). Unconditional fixed-effects GLMM were used to estimate an overall crude IRR (25) and fixed-effects Mantel-Haenszel methods were used to pool IRDs (26). Fixed-effects meta-analyses using inverse-variance weighting (27) were used to pool adjusted HRs, when there were a sufficient number of events to ensure convergence in province-specific models. Fixed-effects models were selected a priori because our use of a distributed network design minimized methodological heterogeneity across provinces. This approach has previously validated in scenarios with varying levels of heterogeneity (24). Between-province heterogeneity was estimated using the I^2 statistic.

Statistical analyses were conducted using the GENMOD and PHREG procedures in SAS 9.4 (SAS Institute Inc, Cary, USA). Meta-analyses were conducted using the meta and metafor packages in R (28–30).

Sensitivity Analyses

As data on children without IBD were not available in Québec, we conducted a sensitivity analysis in which we excluded Québec from the pooled incidence rate of hospitalization for CDI.

RESULTS

A total of 3593 children with IBD and 16,284 without IBD were included. The mean age at IBD diagnosis was similar across the 5 provinces; the overall mean (standard deviation) was 11.7 (0.3) years (Table 1). Over half of the children with IBD who were hospitalized with CDI within 5 years of IBD diagnosis were hospitalized within the first year following IBD diagnosis (Fig. 1). This translated to CDI hospitalization incidence of 131.5 (95% CI, 98.8–175.1) per 10,000 person-years of follow-up within the first year and 49.1 (95% CI, 39.4–61.1) per 10,000 person-years of follow-up within the first 5 years (Table 2; Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/C843*). There was little heterogeneity in the incidence of hospitalization with CDI across provinces. There were no hospitalized CDI cases among the children without IBD in the first year and an incidence of 0.4 (95% CI, 0.1–1.2) per 10,000 person-years of follow-up over 5 years after the index (diagnosis date of matched child with IBD). In the 5 years after IBD diagnosis (index date in children without IBD), children with IBD had a significantly higher incidence of hospitalization with CDI (IRR, 133.42, 95% CI, 42.11–422.69; IRD 51.35 per 10,000 person-years, 95% CI, 39.86–62.83). Throughout the study, the relative incidence of hospitalization with CDI among children with Crohn disease was approximately half of that observed in children with ulcerative colitis (IRR, 0.51, 95% CI, 0.32–0.82) (Table 2; Figure 1, Supplemental Digital Content, *http://links.lww.com/MPG/C843*).

Regression analyses adjusted for neighborhood income quintile and living in a rural or urban household showed results consistent with unadjusted analyses, though the magnitude of effect was attenuated (Table 2). The adjusted HR for IBD was 68.15, 95% CI, 24.40 to 190.39. In stratified adjusted analysis, the relative risk was higher among those with ulcerative colitis than those with Crohn disease (Figure 1, Supplemental Digital Content, *http://links.lww.com/MPG/C843*). The comparison of Crohn disease and ulcerative colitis was no longer statistically significant in the adjusted model (HR, 0.69, 95% CI, 0.46–1.05) (Fig. 2).

In a sensitivity analysis excluding data from the province of Québec, incidence of CDI hospitalization among children with IBD (Table 3, Supplemental Digital Content, *http://links.lww.com/MPG/C843*) was similar to that in the primary analysis (Table 2; Table 2, Supplemental Digital Content, *http://links.lww.com/MPG/C843*).

DISCUSSION

In this large population-based multiprovince Canadian study, we report a markedly increased risk of hospitalization with CDI among children with IBD. While an increased risk was observed among both children with Crohn disease and ulcerative colitis, the risk among children with Crohn disease was lower than that of children with ulcerative colitis. Children with IBD had the highest risk of hospitalization with CDI in the first year after IBD diagnosis. The high risk of CDI in children with IBD highlights the importance of screening for CDI during hospital admission for both Crohn disease and ulcerative colitis.

Chandrakumar et al (31) reported a CDI incidence (community or hospital-acquired) rate of 5.04 cases per 1000 person-years among an incident cohort of 261 children with IBD diagnosed and followed prospectively between 2011 and 2019 at the only pediatric IBD center in Manitoba, Canada. This corresponded to a 65-fold increased risk compared to the incidence of CDI previously reported among the general pediatric population in Manitoba and consistent with the findings of our study. The magnitude of this association is much greater than has been previously reported in the United States, where children with IBD were approximately 10 times more likely to have CDI than children without IBD (32). However, the American study compared hospitalized children with IBD to hospitalized children without IBD, rather than all children without IBD. By only including hospitalized children (with and without IBD), the American study likely introduced bias that attenuated the true impact of IBD on the risk of CDI. Further, our study only included incident cases of IBD, while the American study did not differentiate between incident and prevalent cases. This increased incidence of CDI among children with IBD relative to the general population is much greater in magnitude than when comparing the risk of CDI in adults with and without IBD (7,32).

We found the highest risk of hospitalization with CDI among children with IBD occurred in the first year after IBD diagnosis. This is consistent in previous studies for CDI in both children and adults (7,31). This heightened risk early in newly diagnosed IBD patients may result from increased use of antibiotics early in IBD diagnosis, higher rates of dysbiosis of the gut microbiome at IBD diagnosis, untreated altered humoral immune responses, or epithelial dysfunction predisposing to CDI. In IBD, dysbiosis occurs independent of predisposing factors, such as the use of antimicrobials. Perhaps, all newly diagnosed IBD cases should be investigated for CDI.

TABLE 1. Characteristics of children with and without IBD included in the study, stratified by province

	Alberta		Manitoba		Nova Scotia		Ontario		Québec*	Overall	
Characteristics	With IBD (N = 703)	Without IBD (N = 3515)	With IBD (N = 163)	Without IBD (N = 814)	With IBD (N = 255)	Without IBD (N = 1275)	With IBD (N = 2136)	Without IBD (N = 10,680)	With IBD (N = 336)	With IBD (n = 3593)	Without IBD (n = 16,284)
Age at IBD diagnosis or index date, mean (SD)	10.8 (4.1)	10.8 (4.1)	11.8 (2.8)	11.9 (2.8)	11.6 (3.7)	11.6 (3.7)	11.4 (3.4)	11.5 (3.4)	12.9 (2.7)	11.7 (0.3)†	11.4 (0.2)†
Female, n (%)	307 (43.7)	1535 (43.7)	71 (43.6)	354 (43.5)	112 (43.9)	560 (43.9)	899 (42.1)	4495 (42.1)	150 (44.6)	1539 (42.8)	6944 (42.6)
Type of IBD, n (%)											
Crohn disease	407 (57.9)	-	103 (63.2)	-	159 (62.4)	-	1247 (58.4)	-	285 (84.8)	2201 (61.3)	
Ulcerative colitis	217 (30.9)	-	60 (36.8)	-	80 (31.4)	-	738 (34.6)	-	36 (10.7)	1131 (31.5)	
IBD unclassifiable‡	79 (11.2)	-	-	-	16 (6.3)	-	151 (7.1)	-	15 (4.5)	261 (7.3)	
Rural, n (%)‡	140 (19.9)	866 (24.6)	38 (23.3)	180 (22.1)	75(29.4)	461 (36.2)	223 (10.4)	1276 (11.9)	60 (17.9)	536 (14.9)	2783 (17.1)
Mean neighborhood income quintile, n (%)§											
Q1	115 (16.4)	734 (20.9)	15 (9.2)	75 (9.2)	63 (24.7)	292 (22.9)	277 (13.0)	2104 (19.7)	45 (13.4)	515 (14.3)	3205 (19.7)
Q2	142 (20.2)	721 (20.5)	23 (14.1)	133 (16.3)	47 (18.4)	257 (20.2)	374 (17.5)	2011 (18.8)	62 (18.4)	648 (18.0)	3122 (19.2)
Q3	141 (20.1)	611 (17.4)	34 (20.9)	136 (16.7)	50 (19.6)	262 (20.6)	429 (20.1)	2191 (20.5)	49 (14.6)	703 (19.6)	3200 (19.7)
Q4	115 (16.4)	626 (17.8)	37 (22.7)	197 (24.2)	43 (16.9)	244 (19.1)	501 (23.5)	2219 (20.8)	105 (31.2)	801 (22.3)	3286 (20.2)
Q5	180 (25.6)	714 (20.3)	52 (31.2)	259 (31.8)	52 (20.4)	218 (17.1)	550 (25.7)	2095 (19.6)	70 (20.8)	904 (25.2)	3286 (20.2)
C. difficile infection, n (%)											
Within 1 y of IBD diagnosis or index date	14 (2.0)	0 (0.0)	1–5‖ (0.6–3.1)	0 (0.0)	1–5‖ (0.4–2.0)	0 (0.0)	25 (1.2)	0 (0)	1–5‖ (0.3–1.5)	42–54‖ (1.2–1.5)	0 (0)
Within 3 y of IBD diagnosis or index date	18 (2.6)	0 (0.0)	1–5‖ (0.6–3.1)	0 (0.0)	6 (2.4)	0 (0.0)	36 (1.7)	0 (0.0)	1–5‖ (0.3–1.5)	62–70‖ (1.7–1.9)	0 (0.0)
Within 5 y of IBD diagnosis or index date	19 (2.7)	0 (0.0)	1–5‖ (0.6–3.1)	0 (0.0)	11 (4.3)	1–5‖ (0.08–0.4)	44 (2.1)	1–5‖ (0.01–0.05)	1–5‖ (0.3–1.5)	76–84‖ (2.1–2.3)	2–10‖ (0.01–0.06)

CDI = *Clostridioides difficile* infection; IBD = inflammatory bowel disease; SD = standard deviation. *No data on children without IBD were available in Québec. †Province-specific means were pooled using a random effects model. ‡Only available in some provinces (Table 1, Supplemental Digital Content 1, *http://links.lww.com/MPG/C843*). §Totals may not add to 100% due to missing data for some children. ‖When there were between 1 and 5 children hospitalized with CDI in a given province, the exact number of events was suppressed due to provincial privacy regulations.

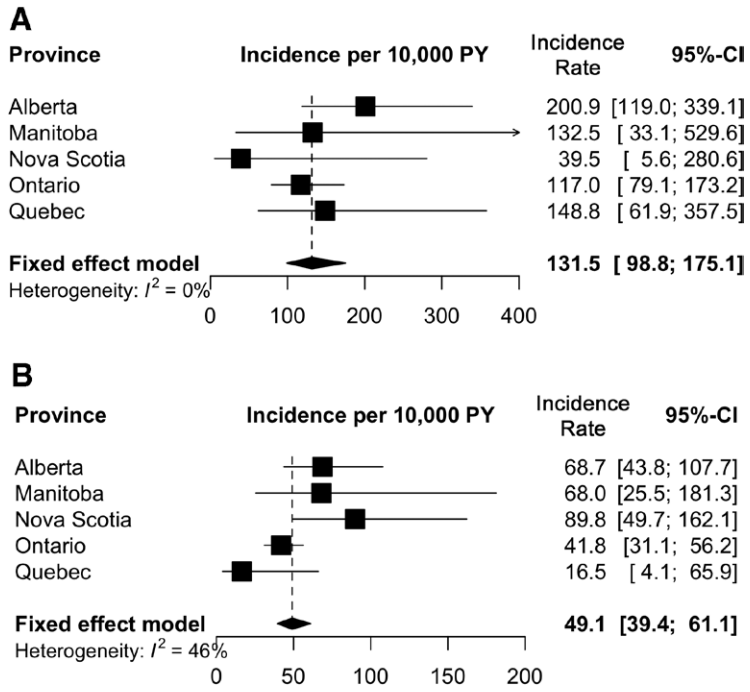

FIGURE 1. Incidence per 10,000 person-years (PY) of hospitalization with *Clostridioides difficile* infection among children with inflammatory bowel disease (IBD) in (**A**) the first year following diagnosis and (**B**) the first 5 y following diagnosis. CI = confidence interval.

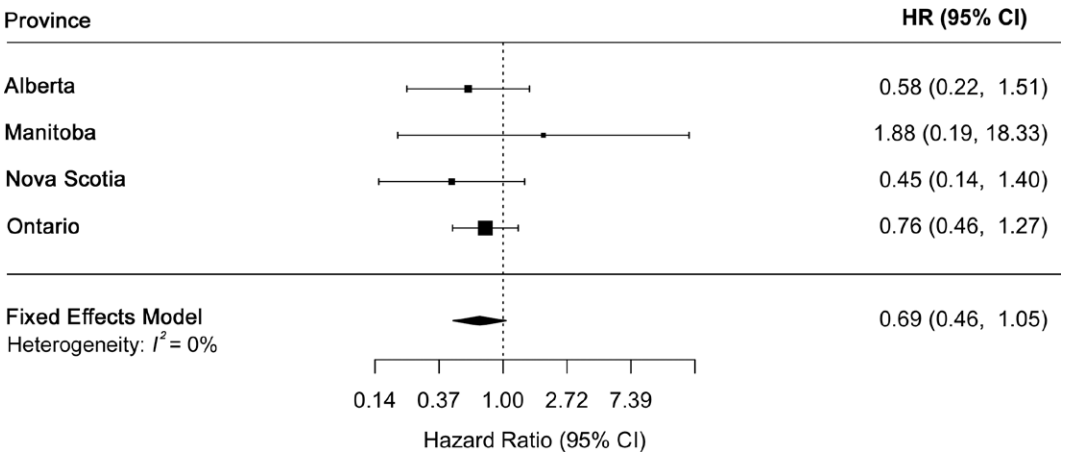

FIGURE 2. Hazard ratios (HRs) comparing the risk of hospitalization with *Clostridioides difficile* infection in children with Crohn disease relative to ulcerative colitis. CI = confidence interval.

Previous studies have reported similar rates of CDI among children with Crohn disease and ulcerative colitis (31,33,34), while most studies in adults suggest CDI occurs more often in patients with ulcerative colitis (8,35). In our unadjusted analyses, CDI occurred less often among children with Crohn disease than ulcerative colitis. However, the magnitude of this association was attenuated and no longer statistically significant when adjusting for age, sex, income, and living in a rural or urban household. Even if the CDI risk is 50% lower among hospitalized children with Crohn disease, the risk would remain markedly higher than that among children without IBD. Hence, hospitalized children with Crohn disease as well as those with ulcerative colitis should be screened for CDI.

Our results should be interpreted in the context of its strengths and limitations. We used large population-based data sets which facilitated longitudinal follow-up of children from IBD diagnosis. By including data from multiple provinces, our study included a larger number of children with IBD than would be feasible in a single center or province study. We used hospitalization records, which are a rich data source and have been used extensively to assess comorbidities and outcomes among individuals with IBD. However, health administrative data are not without their limitations. As with all studies conducted using health administrative data, our study may have been at risk of misclassification bias. However, our use of previously validated province-specific algorithms to identify children with IBD and a validated diagnostic code for CDI minimized this risk. Diagnostic codes used for outpatient physician claims do not allow for the differentiation between CDI and other gastrointestinal infections. Therefore, we were not able to identify children with community-acquired CDI who were

TABLE 2. Comparison of the incidence of hospitalization with *Clostridioides difficile* infection per 10,000 person-years in children with and without IBD within 5 years of diagnosis

			Unadjusted*			Adjusted†		
Comparison	IR per 10,000 PY (95% CI)	I^2‡	IRR (95% CI)	I^2‡	IRD (95% CI)	I^2‡	HR (95% CI)†	I^2‡	Number of provinces
Inflammatory bowel disease vs control (ref)									
Inflammatory bowel disease	49.1 (39.4–61.1)	45.6%	133.42 (42.11–422.69)	0.0%	51.35 (39.86–62.83)	45.1%	68.15 (24.40–190.39)	65.5%	2 (NS, ON)
Control	0.4 (0.1–1.2)	52.5%							
Crohn disease vs control (ref)									
Crohn disease	34.3 (24.5–48.0)	0.0%	164.50 (22.50–1202.75)	0.0%	36.94 (24.24–49.63)	0.0%	23.69 (2.83–198.55)	-	1 (NS)
Control	0.2 (0.03–1.6)	64.1%							
Ulcerative colitis vs control (ref)									
Ulcerative colitis	70.8 (51.3–97.7)	0.0%	182.63 (25.06–1331.13)	0.0%	71.95 (48.61–95.29)	0.9%	65.64 (15.30–281.59)	8.5%	2 (NS, ON)
Control	0.4 (0.06–2.8)	67.7%							
Crohn disease vs ulcerative colitis (ref)									
			0.51 (0.32–0.82)	0.0%	−35.74 (−62.45 to −9.03)	0.0%	0.69 (0.46–1.05)	0.0%	4 (AB, MB, NS, ON)

AB = Alberta; CI = confidence interval; IBD = inflammatory bowel disease; IR = incidence rate; IRD = incidence rate difference; IRR = incidence rate ratio; MB = Manitoba; NS = Nova Scotia; ON = Ontario; PY = person-years. *Crude IRR and IRD compare the 5-y incidence of hospitalization with *C. difficile*. †Cox proportional hazards models compare the time to hospitalization with *C. difficile*. Models were adjusted for mean neighborhood income quintile and living in a rural or urban household at the time of IBD diagnosis or index date. Models did not converge in all provinces due to small number of events. ‡Measure of between-province heterogeneity.

not admitted to hospital. Additionally, we are unable to differentiate CDI from *C. difficile* colonization, although even in clinical practice it can be very difficult to distinguish bystander *C. difficile* from CDI among IBD individuals with diarrhea (36). Laboratory diagnostic algorithms restrict testing for *C. difficile* to those with diarrhea so as to reduce the chance of detecting colonization; although this criteria does not prevent detecting *C. difficile* colonization among those with IBD or other causes of diarrhea. However, in this context it is important to recall clinical difficulty in differentiating *C. difficile* colonization from active CDI in those with diarrhea. Clinicians almost always treat for CDI when the laboratory reports *C. difficile*, even when an IBD flare is suspected (then concomitantly or subsequently treat for IBD) (37,38). Of note, the diagnostic codes for CDI in Canadian administrative data were validated against reference standards of patients with ulcerative colitis admitted to hospital for CDI (17) and public health surveillance (16), and therefore are unlikely to occur in asymptomatic colonized patients. Further, we only included hospitalizations where CDI was the most responsible or a contributory diagnosis. Therefore, it is unlikely that patients colonized with *C. difficile* without clinically important CDI would be identified in our study. In addition, we did not have access to medical records, which would include information on IBD severity and phenotype, nor did we have access to inpatient or outpatient prescription medications in all provinces.

CONCLUSIONS

In conclusion, children with IBD have a markedly increased risk of hospitalizations with CDI, particularly within the first year of IBD diagnosis. While CDI occurs more frequently in children with both Crohn disease and ulcerative colitis, CDI may be more common in patients with ulcerative colitis. Children with IBD or who are suspected of having IBD and are hospitalized should be routinely screened for CDI.

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