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ORIGINAL ARTICLE

The Prevalence of *Clostridium difficile* Infection in Pediatric and Adult Patients with Inflammatory Bowel Disease

S. K. Hourigan · M. Oliva-Hemker · S. Hutfless

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Abstract
Objectives Adults with inflammatory bowel disease (IBD) have a high prevalence of *Clostridium difficile* infection (CDI). CDI in children with IBD may differ from adults. We aim to compare the prevalence of CDI in hospitalized pediatric and adult IBD patients and patients without IBD.
Methods The rates of CDI per 1,000 IBD and non-IBD hospitalizations between 1993 and 2012 were examined using the Maryland Health Services Cost Review Commission database. Age, sex and calendar year adjusted incidence rate ratios comparing CDI in pediatrics and adults by type of IBD and with patients without IBD were calculated. p values for trend identifying changes in rates over time were calculated.
Results Among children, the rate of CDI was over 12 times greater in IBD than non-IBD hospitalizations ($p < 0.0001$) and among adults, the rate of CDI was four times greater in IBD than non-IBD hospitalizations ($p < 0.0001$). In adults, CDI was significantly higher in ulcerative colitis (UC) than Crohn's disease (60.4 per 1,000 vs. 19.8 per 1,000, $p < 0.0001$) but in children there was no difference in CDI in UC compared with Crohn's disease (32 per 1,000 vs. 27 per 1,000, $p = 0.45$). The prevalence of CDI increased in pediatric and adult IBD patients, and patients without IBD, between 1993 and 2012 (p for trend <0.0001).
Conclusions CDI was more common in adult patients with UC, and no difference was found between CDI and IBD type in pediatrics. There may be different risk factors for CDI during hospitalization between adults and children with IBD.

Keywords Inflammatory bowel disease · Clostridium difficile · Pediatric

Introduction

Clostridium difficile infection (CDI) is the leading cause of nosocomial diarrhea in the USA and is increasing in prevalence in the community [1]. In the past two decades, there has been an increase in prevalence of CDI in both the adult and pediatric population [2, 3]. Traditional risk factors for CDI include being elderly, prolonged hospitalizations, recent antibiotic use, systemic comorbidities and being immunocompromised [4]. Evidence from the adult literature has demonstrated that patients with inflammatory bowel disease (IBD) have a higher prevalence of CDI than the general population [5]. There has been a rise in incidence in hospitalized adult patients with IBD and CDI [6] and increased morbidity [6], and mortality [7] has been shown in patients with both IBD and CDI.

This work is exempt from IRB approval, as per the Johns Hopkins Hospital IRB, because is uses de-identified data from a database accessible to the public.

S. K. Hourigan (✉) · M. Oliva-Hemker
Division of Pediatric Gastroenterology and Nutrition, Johns Hopkins School of Medicine, Brady 320, 600 N. Wolfe Street, Baltimore, MD 21287, USA
e-mail: suchihourigan@gmail.com

S. K. Hourigan
Pediatric Gastroenterology, Hepatology and Nutrition, Pediatric Specialists of Virginia, 8505 Arlington Blvd, Suite 400, Fairfax, VA 22031, USA

S. Hutfless
Division of Gastroenterology, Johns Hopkins School of Medicine, Baltimore, MD, USA

There is a paucity of literature regarding CDI in the pediatric IBD population, which in theory may differ from adult IBD patients for several reasons including increased asymptomatic carriage of *C. difficile* in young children [8], infrequent use of antibiotics to treat pediatric IBD, and different patterns of IBD in children compared with adults with a predominance of colonic Crohn's disease in young children [9]. In single-center studies, hospitalized pediatric patients with both IBD and diarrhea were found to have a higher prevalence of CDI compared with pediatric patients with diarrhea alone [10]. CDI recurrence is also more likely in children with both IBD and CDI compared with those with CDI alone [11]. Moreover, hospitalized children with CDI and IBD had longer hospital stays and charges compared with IBD alone [12].

The trend of CDI prevalence in pediatric IBD over the past decades compared with adults with IBD and children without IBD is unknown. The aims of this study were two-fold. First, to compare the prevalence of CDI in hospitalized pediatric IBD patients, adult IBD patients and hospitalized patients without IBD between 1993 and 2012. Second, to compare the prevalence of CDI in Crohn's disease and ulcerative colitis (UC) between pediatric and adult patients. It was hypothesized that the prevalence of CDI would be significantly higher in pediatric IBD compared with the hospitalized children without IBD. Additionally, it was hypothesized that CDI would be higher in UC than Crohn's disease in adults, as previously shown, and that the pattern in children would mirror this.

Methods

The rates of CDI per 1,000 hospitalizations in the state of Maryland between 1993 and 2012 were examined using the Maryland Health Services Cost Review Commission database [13]. The database reflects all hospital discharges from 47 acute general, three specialty, and three private psychiatric hospitals in the state of Maryland. The database was created to regulate and monitor hospital costs, and the dataset is available for public access, researchers and policy makers.

Our analysis included six groups of hospital discharges between the years of 1993 and 2012: (1) Pediatric discharges with Crohn's disease; (2) Pediatric discharges with UC; (3) Pediatric discharges without Crohn's disease or UC; (4) Adult discharges with Crohn's disease; (5) Adult discharges with UC; and (6) Adult discharges without Crohn's disease or UC. The International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes, in any of 30 diagnostic positions, were used to identify discharges with Crohn's disease (555) or UC (556). ICD-9-CM code 008.45 in any diagnostic position was used to identify discharges with CDI. The non-IBD cohort were all patients admitted to hospital during the time period studied and therefore could have many possible underlying disease processes but not IBD. Pediatric patients were defined as less than 18 years of age on discharge. Pediatric patients under 1 year old were not included in this study because some of these children may have generalized immune deficiencies and not IBD [14, 15] and also because there is a high rate of asymptomatic carriage of *C. difficile* in this population [16], with animal studies suggesting a lack of toxin receptor in young infants [17], although this has not been demonstrated in humans. The year 1993 was chosen as the starting year for this study because the ICD-9-CM code for *C. difficile* appeared in 1992, so this gave some time for health care providers to become familiarized with the code. In addition, the same variables were analyzed over the more recent time period of 2009–2012, in order to describe recent prevalence rates. The year 2009 was selected because this is the first year that a Maryland Hospital began using a PCR-based assay. All hospitals had transitioned to this assay by 2012. Hospitalizations with missing male/female status were excluded from analysis.

The age, sex and calendar year adjusted rates of CDI were expressed per 1,000 hospitalizations. Incidence rate ratios (IRRs) comparing CDI in pediatrics and adults by type of IBD and with patients without IBD were calculated. Log negative binomial regression using the genmod procedure in SAS 9.2 was used to calculate all IRRs and associated p values. When assessing changes in prevalence over of CDI over the years studied, p values were p for trend accounting for changes over time. Demographic p values were calculated using the two sample t test with unequal variances (Satterthwaite approximation) or the Cochran–Mantel–Haenszel general association p value.

Results

Study Population

Overall between 1993 and 2012, 12,218,429 hospitalizations met the inclusion criteria including 97,553 IBD hospitalizations and 12,120,876 hospitalizations in patients without IBD, with 549,692 pediatric discharges and 11,668,737 adult discharges. Table 1 shows the demographic characteristics for the hospitalizations. There were no major differences between age and sex within the three pediatric and three adult groups. Patients with IBD were more likely to be Caucasian compared with those without IBD ($p < 0.0001$).

Table 1 Demographic characteristics for discharges between 1993 and 2012

	Pediatric Crohn's disease	Pediatric UC	Pediatric non-IBD	Adult Crohn's disease	Adult UC	Adult non-IBD
N	2,074	814	546,804	63,864	30,801	11,574,072
Median age (range)	15 (1–17)	15 (1–17)	10 (1–17)	46 (18–102)	54 (18–102)	57 (18–102)
Female %	50	52	50	60	58	60
Caucasian %	68	75	55	77	76	65
African-American %	27	20	37	21	20	30
Other race %	5	5	8	2	4	5
C. difficile cases/1,000	27.0	32.0	2.2	19.8	60.4	9.6

Table 2 Overall prevalence of *Clostridium difficile* between 1993 and 2012, and 2009 and 2012

	Pediatric IBD	Adult IBD	Total IBD	Pediatric non-IBD	Adult non-IBD	Total non-IBD
Overall prevalence of *Clostridium difficile* between 1993 and 2012						
C. difficile cases/1,000	28.6	33.0	32.9	2.2	9.6	9.3
Overall prevalence of *Clostridium difficile* between 2009 and 2012						
C. difficile cases/1,000	46.9	48.6	48.5	4.1	14.5	14.1

Overall Prevalence of CDI

A total of 115,759 hospitalizations with CDI were identified between 1993 and 2012. A total of 3,205 hospitalizations with CDI occurred in IBD patients and 112,554 in those without IBD. The rate of CDI per 1,000 hospitalizations was higher in hospitalizations with IBD than those without IBD (32.9 vs. 9.3, $p < 0.0001$; Table 2). Among pediatrics, the IRR of CDI in hospitalizations with IBD (28.6 per 1,000) compared with those without IBD (2.2 per 1,000) was 12.7 [95 % confidence interval (CI) 10.0–26.1, $p < 0.0001$]. Among adults, the IRR of CDI in hospitalizations with IBD (33.0 per 1,000) compared with those without IBD (9.6 per 1,000) was 4.0 (95 % CI 3.8–4.2, $p < 0.0001$). There was no significant difference in the overall rate of CDI between pediatric hospitalizations with IBD (28.6 per 1,000) and adult hospitalizations with IBD (33.0 per 1,000; $p = 0.65$).

Prevalence of CDI from 2009 to 2012

A total of 38,134 hospitalizations with CDI were identified between 2009 and 2012. A total of 1,438 hospitalizations with CDI occurred in IBD patients and 36,696 in those without IBD. The rate of CDI per 1,000 hospitalizations was higher in hospitalizations with IBD than those without IBD (48.5 vs. 14.1, $p < 0.0001$; Table 2). Among pediatrics, the IRR of CDI in hospitalizations with IBD (46.9 per 1,000) compared to those without IBD (4.1 per 1,000) was 13.3 [95 % confidence interval (CI) 9.28–19.1, $p < 0.0001$]. Among adults, the IRR of CDI in hospitalizations with IBD (48.6 per 1,000) compared with those without IBD (14.5 per 1,000) was 4.4 (95 % CI 3.9–4.9, $p < 0.0001$). There was no significant difference in the overall rate of CDI between pediatric hospitalizations with IBD (46.9 per 1,000) and adult hospitalizations with IBD (48.6 per 1,000; $p = 0.92$).

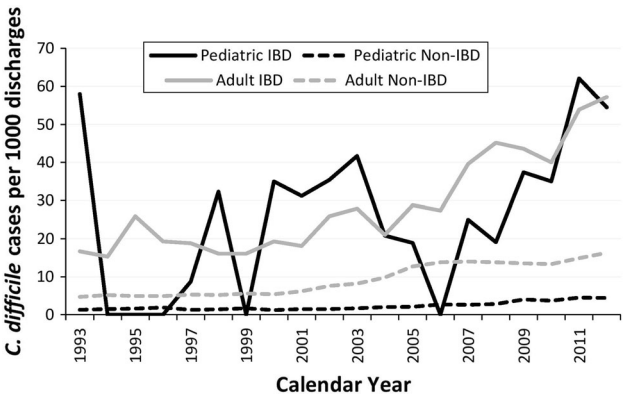

Fig. 1 *Clostridium difficile* cases in pediatrics and adults between 1993 and 2012

Prevalence Trends from 1993 to 2012

There was an increase in prevalence of CDI over time in all groups studied, $p < 0.0001$ (Fig. 1). There was more variation in CDI rates from year to year in pediatric IBD than other groups, but the overall trend showed an increase in rate of CDI over time in this population ($p < 0.0001$). Among all hospitalizations with IBD, both pediatric and

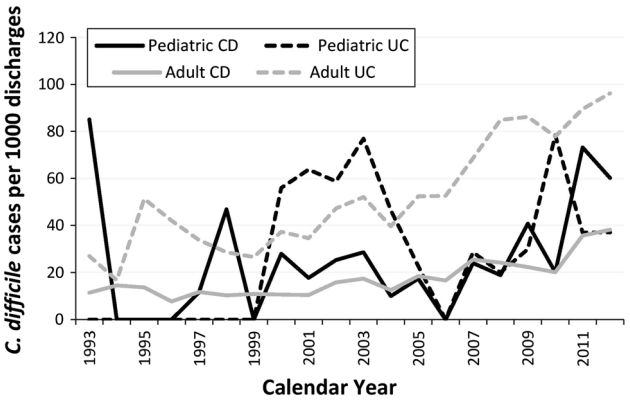

Fig. 2 *Clostridium difficile* cases in Crohn's disease compared with ulcerative colitis between 1993 and 2012. *UC* ulcerative colitis. *CD* Crohn's disease

adult, the rate of CDI increased from 19.9 per 1,000 in 1993 to 67.0 per 1,000 hospitalizations in 2012. In those without IBD, the rate of CDI increased from 4.6 per 1,000 in 1993 to 16.0 per 1,000 in 2012. The rate of increase in CDI over time was not significantly different between adults with and without IBD ($p = 0.80$) and children with and without IBD ($p = 0.90$). When looked up separately for the period 2009–2012, the pediatric population did not have a significant increase in the prevalence of CDI ($p = 0.42$), where as the adult population maintained a p value of 0.0001. Among all hospitalizations with IBD, both pediatric and adult, the rate of CDI increased from 43.4 per 1,000 in 2009 to 57.1 per 1,000 hospitalizations in 2012. In those without IBD, the rate of CDI increased from 13.2 per 1,000 in 2009 to 15.9 per 1,000 in 2012.

CDI and Inflammatory Bowel Disease Type

Among all hospitalizations with IBD, the rate of CDI was higher in UC (59.7 per 1,000) compared with Crohn's disease (20.0 per 1,000; $p < 0.001$). This pattern was seen when looking at the rates of CDI in adults with IBD (60.4 per 1,000 in UC vs. 19.8 per 1,000 in Crohn's disease, $p < 0.0001$). However, no difference in the rate of CDI was seen between pediatric Crohn's disease (27 per 1,000) and pediatric UC (32 per 1,000; $p = 0.45$). There was an increase in prevalence of CDI from 1993 to 2012 for Crohn's disease and UC, in both pediatrics and adults (Fig. 2).

Rates of CDI by Age

In adults without IBD, there was a higher prevalence of CDI in patients over 65 years of age (16.2 per 1,000), compared with those under 65 years (5.5 per 1,000). In adults with IBD, the prevalence of CDI in those over 65 years was 55.5 per 1,000 and in those under 65 years was 25.0 per 1,000. In children below 3 years of age (1 and under excluded), the prevalence of CDI in those without IBD was 2.8 per 1,000 and there was only one reported case of CDI in children with IBD under the age of 3. There were only 70 children with IBD under the age of 5 (1 and under excluded), which accounted for less than 2 % of all pediatric IBD patients.

Discussion

This study found that children with IBD were significantly more likely to have CDI during hospitalization than children without IBD. This finding is a similar trend to adults in this study and other adult IBD reports [5–7, 18, 19]. In general, CDI is more common in adults than children, and this was seen in the population without IBD in this study. However, the prevalence of CDI in pediatric hospitalizations with IBD was just as high compared with adults with IBD. Moreover, the magnitude of difference in CDI rates when comparing those with IBD to those without IBD was much higher in children than adults (12.7 vs. 4.0). CDI is most common in the elderly [4, 20, 21], and this was also found in out study, with adults over 65 years of age having an increased prevalence of CDI than younger adults, in both those with and without IBD.

There was an increase in prevalence of CDI in the pediatric IBD population from 1993 to 2012, a trend similar to that reported in the adult IBD population [5, 18]. There are several possible reasons for such a high increase in prevalence over time in patients with IBD. First, there may be a diagnostic bias with physicians becoming more aware that IBD is a risk factor for CDI [19]. Second, it is possible that underlying host factors in IBD may make this patient population more susceptible to the more virulent strains, for example, BI/NAP1/027, that have emerged more recently [1, 22]. Finally, there is increasing use of the highly sensitive [23] polymerase chain reaction test to detect *C. difficile* toxin genes, potentially leading to increased detection of CDI [24], compared with previously used diagnostic methods, which may explain the increase in CDI among hospitalizations patients with and without IBD. However, in our study, the first year that a Maryland Hospital began using a PCR-based assay was 2009 and all hospitals had transitioned to this assay by 2012; the overall trends in prevalence change of CDI were similar from 2009 to 2012 to the whole data set. Because the last hospital began using the assay in 2012, we are unable to examine trends after all hospitals were using the same assay.

Among pediatrics, there was no difference in CDI between Crohn's disease and UC. This lack of association in CDI prevalence with IBD type has also been reported in single-center pediatric studies [9, 25]. Our study also

confirmed that there was a significantly higher prevalence of CDI in adults with UC compared with Crohn's disease [5, 6, 18]. This difference in association with CDI and IBD type between the pediatric and adult population could be due to multiple factors including a higher prevalence of colonic Crohn's disease in children [9] and an increased lifetime use of antibiotics in adults to treat UC compared with children, with antibiotic use known to increase the risk of CDI [4]. These findings suggest that hospitalized pediatric patients with IBD may have different risk factors for CDI than adult patients with IBD. Other proposed IBD specific risk factors for CDI include disease severity and immunosupressive medication [26]; however, for our population this cannot be determined from the administrative data available from this data base. In addition, it was also not possible to determine whether patients with IBD were admitted for a flare of their disease or for other reasons.

The major limitation of our study was the absence of laboratory data to confirm the presence or absence of CDI in all hospitalized patients; the diagnosis of CDI was defined by an ICD-9-CM code. However, large hospital-based studies have shown that using ICD-9-CM was an accurate indicator of CDI, when compared to microbiological tests with a sensitivity of 71–78 % and specificity of 99 % [27, 28]. Additionally, it is known that there is an increased risk of asymptomatic *C. difficile* carriage both adults [29] and children [30] with IBD. Based on ICD-9 codes, this study cannot distinguish between asymptomatic carriage and infection; therefore, the difference in prevalence of CDI between IBD and healthy patients may be overstated. Moreover, children under 1 year of age are known to have increased asymptomatic carriage of *C. difficile* [16] and so were excluded from analyses; however, an increased rate of symptomatic carriage has also been described in the second and third year of life [16]. In our study, the rate of CDI in children under 3 years without IBD was 2.8 per 1,000, which is similar to the overall rate of CDI in the pediatric population, although some of these cases may have been due to asymptomatic carriage rather than CDI. Children under one were also excluded due to an increased prevalence of primary immune deficiencies rather than IBD [14, 15, 31], although there is still concern for primary immune deficiencies in children diagnosed with IBD up to 5 years of age. However, children under 5 years of age with IBD accounted for a very small proportion of the total number of pediatric patients with IBD in this study. It is also known that there is an increasing prevalence of community-acquired CDI [32]; although our study focuses on hospitalized patients, given that a diagnosis of CDI may have been given anytime during the hospitalization, it cannot discriminate between community-acquired and hospital-acquired CDI. Another limitation of our study was the use of hospitalization level and not person level data. The Maryland Health Services Cost Review Commission database is based on hospital discharges similar to the Nationwide Inpatient Sample and Kids' Inpatient Database. In these databases, it is possible that the same patient may be included more than once in the analysis. The overall rates of CDI in the adult population with and without IBD were similar to another nationally representative discharge database with the same limitation [18]. This database only looked at one state in the USA. There are known regional differences in the prevalence of CDI [33] and investigating whether the pediatric trends seen can be generalized to the rest of the USA could be addressed using a national inpatient database.

Conclusions

The prevalence of CDI in pediatric patients with IBD is higher than pediatric patients without IBD. This difference underscores the importance of having an increased index of suspicion in these patients as CDI can complicate the IBD disease course. The major difference found between pediatric and adult patients with IBD was that CDI was more common in adult patients with UC, and no difference was found between CDI and IBD type in pediatrics, possibly suggesting different risk factors for CDI during hospitalization between adults and children.

Conflict of interest None.

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