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Disproportionate Rise in *C. difficile*-Associated Hospitalizations Among U.S. Youth with Inflammatory Bowel Disease, 1997-2011

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Abstract

Objectives—Our aim was to characterize the temporal changes in burden that *Clostridium difficile* infection (CDI) added to the hospital care of children and young adults with inflammatory bowel disease (IBD) in the United States.

Methods—Retrospective analysis of annual, nationally-representative samples of children and young adults with IBD.

Results—There was a five-fold increase in IBD hospitalizations with CDI from 1997 to 2011 (P for trend <0.01). Over the same period, IBD hospitalizations without CDI increased two-fold (P for trend <0.01). Mean length of stay (LOS) for IBD hospitalizations with CDI was consistently longer than hospitalizations without CDI and did not significantly change over time (P for trend = 0.47). CDI-related total hospital days in the US rose from 1,702 to 10,194 days per million individuals per year from 1997 to 2011 (P for trend <0.01). Children and young adults hospitalized with CDI had a significantly lower odds of colectomy (0.31) compared to those without CDI. Total charges for CDI-related hospitalizations among children and young adults in the U.S. rose from \$8.7 million in 1997 to \$68.2 million in 2011.

Conclusions—A widening gap in burden has opened between IBD hospitalizations with and without CDI over the last decade and a half. CDI-related hospitalizations are associated with disproportionately longer lengths of stay, more hospital days, and more charges than hospitalizations without CDI over time. Further work within health systems, hospitals, and practices, can help us better understand this enlarging gap to improve clinical care for this vulnerable population.

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Keywords

national trends; *Clostridium difficile*; inflammatory bowel disease; Nationwide Inpatient Sample; variance-weighted regression

INTRODUCTION

Increased hospitalizations have been reported due to hypervirulent *Clostridium difficile* strains in adults, with increased risk for patients with inflammatory bowel disease (IBD).¹ This added burden results in more days spent in the hospital, prolonged recovery from illness, and overall greater need for immunosuppression.^{2–7} The reasons for increasing rates of CDI in hospitalized adults may be multifactorial, and may include increase in community-acquired infections, increased use of immune-suppressing medications, and reliance on early therapeutic regimens.⁸

Children and young adult IBD patients with *C. difficile* infection (CDI) are assumed to have a similar trend in recent years, but this has not been fully investigated. We have reported elsewhere that overall hospitalizations of pediatric patients with IBD are increasing on a national level.⁹ It is unclear how much CDI contributes to this increase. Previous work by Pant, *et al.* indicates that CDI is associated with longer lengths of stay and higher charges compared to hospitalizations of pediatric IBD patients without CDI, and seems to be most pronounced for patients with ulcerative colitis,¹⁰ but in the current body of literature, it is not clear whether the differential burden apparent with CDI has been changing over time. A more complete understanding of temporal trends of CDI and associated burdens of hospital care would better guide future research efforts and inform policy decisions.

The central aim of this study was to characterize the temporal trends of CDI-related burden to hospital care of children and young adults with IBD across the United States. To examine this hypothesis, we used a national, annual, all-payer hospital dataset for the time period 1997–2011.

MATERIALS AND METHODS

Data Source

We identified children and young adults with IBD from annual cross-sectional analyses of discharges using the Healthcare Cost and Utilization Project's (HCUP) Nationwide Inpatient Sample (NIS), compiled by the Agency for Healthcare Research and Quality (AHRQ). Data from the NIS are generalizable to the broader U.S. population.¹¹ We used the NIS rather than the Kids' Inpatient Database (KID), also compiled by AHRQ, in order to include young adults in our analysis and to compare year-over-year patterns that are not available from the KID.^{12–14} The same variables that appear in the KID are also available in the NIS.¹¹ Additionally, the NIS includes samples from all community and academic hospitals, whereas the KID excludes samples from hospital units within other institutions.¹¹ Years before 1997 were excluded due to small numbers in younger age subsets, as required by AHRQ.¹⁵

Our analyses included de-identified national data, and were therefore considered exempt from institutional review board approval by the University of Michigan Medical School. We employed the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) checklist in reporting this study.¹⁶

Study Population and Definitions of Variables

Using the NIS, discharges for patients with IBD were identified using the International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnosis codes of 555.x (Crohn disease, CD) and 556.x (ulcerative colitis, UC). The combination of diagnosis codes used in defining the sample has been described previously.^{9,17–19} We excluded discharges with codes of other forms of colitis (eosinophilic, allergic, microscopic, and ischemic) as well as discharges with codes for both CD & UC. Discharges with CDI were captured using the ICD-9-CM code of 008.45; this is the only code devoted to CDI, has been previously validated as an accurate determinant of active CDI.^{4,5,10,20–22} We also utilized surgical codes for colectomy, used previously.²¹ When evaluating associations with CDI, we controlled for disease type (CD vs. UC), colectomy, length of stay (days), age of patient at admission (years), gender, expected primary payer type, and U.S. census region.

Individuals aged 5 to 24 years were identified. Age groupings were used to permit adjustment with U.S. Census data in 5-year increments (5–9, 10–14, 15–19, and 20–24 years). We excluded patients younger than 5 years of age to protect privacy, per AHRQ requirements when reporting small numbers.¹⁵ We included young adults greater than 18 years of age, as many pediatric gastroenterologists provide care for this age group. Hospital discharges were divided by Census population for each respective age group and calendar year and reported as the rate of discharges per million individuals.¹⁵

Annual mean lengths of stay data were collected. As a secondary marker of hospitalization burden, we calculated total hospital days for patients with IBD with and without CDI, determined by multiplying the annual mean length of stay by the population-adjusted discharge rate. We then determined proportion of IBD hospital days attributable to CDI by dividing CDI hospital days by total hospital days. We also obtained hospital charges, which were adjusted to 2014 dollars using the consumer price index for inpatient hospital services.²³

Statistical Analysis

All analyses were performed using STATA version 12.0 (StatCorp, College Station, TX). Survey estimations were used in STATA to account for the stratified sampling technique of the NIS and provided weighted, nationally-representative estimates.¹¹ To evaluate trends over time, the *P* for trend test was conducted using variance-weighted least-squares regression, demonstrated previously.^{9,24–26} Trends were analyzed over 1997–2011 as yearly point estimates with 95% confidence intervals.

Associations between CDI and colectomy, hospital length of stay, and hospital charges were examined. Odds ratios were calculated for colectomy, adjusting for the above variables. The association between CDI and hospital length of stay and charges were examined using

negative binomial regression, used for count data. These yielded incidence rate ratios (IRR), which are interpreted as a multiplier of the reference count when the independent variable increases by one.

RESULTS

Characteristics of the study population are presented in Table 1. We identified a total of 1,747 discharges (95% CI: 5,747 – 7,382) for young persons aged 5 to 24 years with IBD and CDI during the study period. This represented 2.4% (95% CI: 2.2 % – 2.6 %) of all IBD hospitalizations of the same age group from 1997 to 2011; the proportion of IBD hospitalizations in 1997 was 1.4% (95% CI: 0.9 – 1.9), compared with 4.1% (95% CI: 3.4 – 4.7) in 2011. There were missing data for 0.1% of discharges for payer type, and no missing data for gender, age, hospital region, disease type, or colectomy.

National rates of IBD hospitalizations with CDI increased 5-fold from 1997 through 2011, while hospitalizations without CDI increased 2-fold (*P* for trend < 0.01 for both hospitalizations with and without CDI; Figure 1). Increases in CDI hospitalization rates for children and young adults with UC were similar to those with CD (*P* for trend < 0.01 for UC and CD, Figure 2). The bulk of the overall rise in CDI-related hospitalizations over time occurred in older age groups (*P* for trend < 0.01 for each age group; Supplemental Figure 1).

Mean lengths of stay decreased over time for non-CDI hospitalizations (*P* for trend < 0.01), but did not change for CDI-related hospitalizations (*P* for trend = 0.47; Figure 3). Further, annual mean lengths of stay for IBD hospitalizations with CDI were consistently higher than hospitalizations without CDI (IRR 1.65, 95% CI: 1.56 – 1.75). CDI-related total hospital days for IBD patients increased from 1,702 (95% CI: 1,345 – 2,058) days per million individuals per year in the US in 1997 to 10,194 (95% CI: 8,763 – 11,625) in 2011 (*P* for trend < 0.01; Figure 3). Stated another way, the proportion of CDI-related patient days spent in the hospital was 1.9% of all IBD-related hospital days in 1997 and increased to 6.5% by 2011.

Overall, children and young adults hospitalized with CDI had a decreased odds of colectomy (0.31, 95% CI: 0.23 – 0.44) compared to those without CDI. Table 2 presents further comparisons of associations of colectomy and hospital lengths of stay among patients with and without CDI. For those patients hospitalized with CDI, the odds of colectomy were no different in patients with Crohn disease as compared to patients with ulcerative colitis (0.95, 95% CI: 0.57 – 1.56). In contrast, for those patients hospitalized without CDI, odds of colectomy were 1.71 higher in patients with Crohn disease compared to patients with ulcerative colitis (95% CI: 1.54 – 1.90). In the West Census region, length of stay was significantly longer in those hospital stays with CDI (1.36 times longer as compared with the Northeast, IRR 95% CI: 1.10 – 1.69).

Total charge burden expressed in 2014 \$US for all CDI-related hospitalizations among U.S. patients with IBD rose from \$8.7 million (95% CI: 4.6 – 13.0) in 1997 to \$68.2 million (95% CI: 44.3 – 92.3) in 2011 (*P* for trend < 0.01). In 2011, mean charges for hospitalizations with IBD with CDI were \$58,343 (95% CI: \$44,592 – \$72,094), compared

with \$40,226 (95% CI: \$36,775 – \$43,678) for hospitalizations with IBD without CDI (*P* for trend <0.01 across all years, Figure 4). Overall, hospital charges were 1.74 times greater (95% CI: 1.57 – 1.94) for hospitalizations with CDI as compared to hospitalizations without CDI, after controlling for colectomy and other covariates. Mean hospital charges over time were consistently higher in hospitalizations with CDI compared to non-CDI hospitalizations (Figure 4). When controlling for length of stay, however, IBD patient hospitalizations with CDI had annual mean charges per hospital day that were equivalent to those without CDI (Supplemental Figure 2; overall IRR 1.03, 95% CI: 0.97 – 1.09), indicating that the higher charges with CDI hospitalizations is largely due to longer length of stays compared with non-CDI hospitalizations.

DISCUSSION

Hospitalization rates for children and young adults with IBD and CDI increased 5-fold from 1997 through 2011, as compared to less than a doubling of the hospitalization rates for IBD without CDI. The rise seen over this time period is consistent with other studies of CDI among hospitalized IBD patients. However, this national study provides a more complete picture than previous studies which were over shorter time periods, did not include pediatric patients, or described only local trends.^{4,5,10,20,27–30} Additionally, this study includes young adults for whom many pediatric gastroenterologists provide care, and in whom the changes in disease burden over time are most pronounced. Great strides have been made in improving care for children and young adults with IBD who are hospitalized with CDI, but more work clearly remains to be done, as hospitalizations for IBD with CDI constitute a progressively larger share of IBD hospitalizations.

Widening Gap Between Hospitalizations With and Without CDI

The increasing rate of CDI-related hospitalizations seen in the study is likely multifactorial. One possible explanation may be readmissions. CDI is well known to cause recurrent disease and readmission, especially among patients with IBD.^{30,31} Discharge data in the NIS are available at the encounter level, rather than the patient level, and therefore we could not assess the frequency of readmissions. Characterization of the subset of readmitted patients within individual hospitals or regional systems could highlight specific areas of focus for interventions.

Variation in the use of immunosuppressive regimens, antibiotics, probiotics, and acid suppression could also contribute to rising CDI and consequent increases in hospitalization rates. It has been suggested that the use of systemic steroids more than other immunosuppressive regimens increases the risk of CDI.³² To what extent changes in the immunosuppressive armamentarium—in particular the use of steroids with the advent of other therapeutics—have altered risk of CDI is unclear and remains an important area for research. Likewise, understanding practice patterns of acid suppression can also inform our understanding of non-antibiotic-associated CDI.^{33,34} These could be investigated by practitioner surveys or by secondary data analysis within systems and networks.

Part of the increasing trend in hospitalizations could also be explained by known epidemiologic trends of IBD.³⁵ Older age groups (20 to 24-year-olds in our study) bear a

greater burden of hospitalization, which fits known epidemiology of IBD. This may represent the summation of cumulative risk (e.g. longer duration of IBD) versus risk factors inherent with aging. Longitudinal follow-up within population-based cohorts could help distinguish these potential causative factors, if studied over decades. Epidemiologic studies could also help elucidate the potential role that widespread use of antibiotics in agriculture (and therefore the human food supply) and the infiltration of acid suppressants into our public water supplies have in increasing CDI rates.^{36–41}

The rise in hypervirulent strains of *Clostridium difficile* may also be contributing to the increase in hospitalizations and shifting epidemiology of CDI infections and merits further investigation,¹ as does community-acquired CDI and its proposed risk factors, focusing on differences among age groups.³³ A better understanding of strain-specific epidemiology could provide further targets for improvement in care delivery, including efforts that span inpatient and outpatient arenas. Study at the health system level could provide valuable insights into such patterns.

Colectomy Among Hospitalized Patients with CDI

Children and young adults with IBD who were hospitalized with CDI were less likely to undergo colectomy than those hospitalized without CDI. Importantly, the odds presented here are for colectomy performed during the same hospitalization and do not address risk for colectomy during a subsequent hospitalization. Consequently, it is unclear whether there are increased numbers of patients being discharged with their colons intact. Currently, the literature is mixed on whether or not CDI conveys added risk for colectomy. One study finds that CDI does not affect risk for colectomy among adults by 5 years.⁴² Another study shows that adults admitted with CDI had significantly higher rates of colectomy compared to non-CDI patients.⁴³ There was no difference in rates of colectomy between patients with CD and UC hospitalized with CDI. Interestingly, among those admitted without CDI, patients with CD had higher odds of colectomy than those with UC; explanations for this contrast merit further investigation in cohorts with more detailed clinical information.

Persistently Unchanged Length of Stay in Hospitalizations with CDI

Mean length of stay decreased for IBD hospitalizations without CDI while remaining stubbornly unchanged for hospitalizations with CDI during the 15-year study period. Before considering risk stratification and other innovative strategies to decrease lengths of stay, factors associated with persistently prolonged length of stay must be elucidated.^{44–49} Several potential factors could prolong hospital stays, including delay in identifying infection, subsequent delay in initiating treatment, or a prolonging of hospital stays in attempt to decrease the likelihood of subsequent admission. Investigating physician practices with mixed method studies at the institutional level can illuminate whether such practice patterns are contributing to prolonged lengths of stay.

Alternatively, a stable mean length of stay in the face of hypervirulent strains of *C. difficile* may represent successful management of lengths of stay that may have increased otherwise. Though we cannot investigate this counterfactual possibility, regional or health system differences may provide helpful insights into understanding how variation in practice may

be associated with shorter lengths of stay or decreased readmission rates. For example, it appears that children and young adults with IBD in the West census region are hospitalized less frequently with CDI and stay longer than children and young adults in other U.S. geographic regions. Different explanations could include a regional difference in CDI virulence, variation in medication use (systemic steroids, antibiotics, probiotics, and acid suppressants), or variation in hospital utilization patterns. Future work investigating these differences may have important implications to outpatient and inpatient practice management for IBD with CDI.

While mean hospital charges from CDI-associated hospitalizations are consistently higher than charges from non-CDI-associated hospitalizations, consistent with those from previous analyses,¹⁰ our analysis provides additional insight that the rate of rise in charges per hospital day is equivalent for CDI and non-CDI-associated hospitalizations. This finding indicates that hospital charges are more closely associated with a prolonged stay in the hospital (duration of IV therapies, ongoing need for nursing care), and less with use of distinct diagnostic or therapeutic interventions (assays or specific medications).

Limitations

This study has several limitations common to studies using hospital administrative data. First, we could not distinguish between readmissions of the same patient and admissions of multiple patients with the current dataset. Second, medication and laboratory data were not available for examination, which precludes direct assessment of different assays. Whereas new testing could account for added hospital-related expenditures, it would not likely account for the 5-fold increase in hospitalizations seen in our study. Third, we relied on the coding process, which may have under or overestimated counts of CDI or IBD. We are not aware of coding changes related to IBD or CDI during the study period that would have led to case identification at progressively higher rates over time.

Implications

A widening gap in burden has opened between IBD hospitalizations with versus without *Clostridium difficile* infection for children and young adults over the last decade and a half. Hospitalization rates for children and young adults with IBD, irrespective of disease type, infected with *Clostridium difficile* have risen five-fold since 1997, in contrast to the less than two-fold increase of rates in hospitalizations of IBD patients without *Clostridium difficile*. Total days spent in the hospital are rapidly increasing for CDI-related hospitalizations, creating increased burden on families, health systems, and payers. Further work within health systems, hospitals, and practices can help us better understand this enlarging gap to improve clinical care for this vulnerable population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1. Trends in hospitalization rates for IBD patients (A) with and (B) without *Clostridium difficile* infection (CDI) – United States, 1997-2011

Error bars represent 95% confidence intervals. Note different scales for y axes in panel (A) vs panel (B). Rates of hospitalization with CDI have increased over 5-fold, from 2.8 (95% CI: 1.7 – 3.8) per million population per year to 14.4 (95% CI: 10.5 – 18.2, P for trend < 0.01). Hospitalization rates without CDI have also increased, though less than 2-fold (P for trend < 0.01).

Figure 2. Trends in hospitalization rates for IBD with CDI, by disease type – United States, 1997-2011

Error bars represent 95% confidence intervals. Hospitalizations increased significantly for both ulcerative colitis (UC, P for trend <0.01) and Crohn disease (CD, P for trend <0.01).

Figure 3. Mean length of stay for IBD hospitalization with and without CDI – United States, 1997-2011

Note different scales for y axes in panels (A) and (B). Error bars represent 95% confidence intervals. (A) Trends in hospitalizations with CDI were not significant (P for trend = 0.47). Hospitalizations without CDI, however, significantly decreased (P for trend < 0.01). (B) CDI-related hospitalizations. Lengths of stay (P for trend = 0.47) are now plotted with total hospital days, which are significantly increasing (P for trend < 0.01).

Figure 4. Mean hospital charges per IBD-associated hospitalization, with and without CDI—United States, 1997-2011

Error bars represent 95% confidence intervals. P for trend <0.01 for both hospitalizations with and without CDI, though charges for CDI-associated hospitalizations appear to be rising at a greater rate than for hospitalizations without CDI.

Table 1

Characteristics of Patients with IBD, admitted with *Clostridium difficile* infection (CDI) – United States, 1997-2011.

Characteristic	Unweighted Discharges N = 1,747	Sample-weighted Discharges N = 8,625 (95% CI)	Sample-weighted Percentage (95% CI)
Gender			
Female	939	4,657 (4,133 – 5,181)	54.0 (51.4 – 56.6)
Age			
5-9	87	433 (298 – 568)	5.0 (3.8 – 6.5)
10-14	291	1,450 (1,141 – 1,760)	16.8 (14.4 – 19.4)
15-19	575	2,837 (2,437 – 3,236)	32.9 (30.4 – 35.4)
20-24	794	3,904 (3,461 – 4,348)	45.3 (41.2 – 49.3)
Payer Type*			
Private	1,182	5,864 (5,119 – 6,609)	68.0 (65.0 – 71.0)
Public	372	1,832 (1,557 – 2,107)	21.2 (18.9 – 23.9)
Uninsured	191	920 (760 – 1,080)	10.7 (9.1 – 12.5)
Region			
Northeast	448	2,299 (1,734 – 2,863)	26.7 (21.7 – 32.3)
Midwest	474	2,354 (1,842 – 2,866)	27.3 (22.6 – 32.6)
South	547	2,599 (2,129 – 3,070)	30.1 (25.6 – 35.1)
West	278	1,373 (1,073 – 1,673)	15.9 (12.8 – 19.6)
Disease Type			
Crohn Disease	771	3,819 (3,324 – 4,313)	44.3 (41.6 – 47.0)
Ulcerative Colitis	976	4,806 (4,247 – 5,365)	55.7 (53.0 – 58.4)
Colectomy			
Yes	84	420 (315 – 524)	4.9 (3.9 – 6.1)
No	1,663	8,205 (7,303 – 9,108)	95.1 (93.9 – 96.1)

* 0.1% of data missing for payer type; weighted numbers may not sum to total.

Health burden indicators in children and young adults with IBD, hospitalized with and without CDI – United States, 1997-2011. Length of stay and age were treated as continuous covariates. The incidence rate ratio is interpreted as a multiplier of the reference count.

Table 2

		Colectomy (Odds ratio 95% CI)		Length of Hospital Stay (Incidence Rate Ratio 95% CI)	
		CDI	No CDI	CDI	No CDI
Disease Type	Ulcerative colitis	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
	Crohn disease	0.95 (0.57 – 1.56)	1.71 (1.54 – 1.90)	0.86 (0.77 – 0.96)	0.88 (0.86 – 0.90)
Colectomy	No	--	--	1 (Reference)	1 (Reference)
	Yes	--	--	2.25 (1.96 – 2.58)	2.15 (2.09 – 2.21)
Length of stay (days) *		1.04 (1.03 – 1.07)	1.11 (1.10 – 1.12)	--	--
Age (years)		1.07 (1.01 – 1.13)	1.05 (1.03 – 1.06)	0.98 (0.97 – 0.99)	0.98 (0.98 – 0.98)
Gender	Male	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
	Female	0.73 (0.45 – 1.19)	0.78 (0.73 – 0.82)	0.96 (0.86 – 1.07)	0.98 (0.96 – 1.00)
Insurance	Private	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
	Public	1.27 (0.74 – 2.16)	0.52 (0.48 – 0.58)	1.15 (1.01 – 1.31)	1.13 (1.10 – 1.15)
	Uninsured	1.31 (0.62 – 2.81)	0.70 (0.63 – 0.78)	1.02 (0.84 – 1.24)	1.01 (0.98 – 1.03)
Region	Northeast	1 (Reference)	1 (Reference)	1 (Reference)	1 (Reference)
	Midwest	1.26 (0.62 – 2.60)	1.25 (1.01 – 1.54)	0.94 (0.82 – 1.09)	0.91 (0.87 – 0.94)
	South	0.86 (0.41 – 1.78)	1.00 (0.82 – 1.23)	1.07 (0.94 – 1.22)	1.01 (0.98 – 1.05)
	West	0.86 (0.34 – 2.16)	1.03 (0.82 – 1.29)	1.36 (1.10 – 1.69)	0.99 (0.95 – 1.04)

* Convergence achieved after outliers (LOS > 279) excluded