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Risk of *Clostridium difficile* Infection in Patients with Celiac Disease: a Population-Based Study

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Abstract

Background & Aims—Patients with celiac disease are at increased risk for infections such as tuberculosis, influenza, and pneumococcal pneumonia. However, little is known about the incidence of *Clostridium difficile* infection (CDI) in patients with celiac disease.

Methods—We identified patients with celiac disease based on intestinal biopsies submitted to all pathology departments in Sweden over a 39-year period (from July 1969 through February 2008). We compared risk of CDI (based on stratified Cox proportional hazards models) among patients with celiac disease vs without celiac disease (controls) matched by age, sex, and calendar period.

Results—We identified 28,339 patients with celiac disease and 141,588 controls; neither group had a history of CDI. The incidence of CDI was 56/100,000 person-years among patients with celiac disease and 26/100,000 person-years among controls, yielding an overall hazard ratio (HR) of 2.01 (95% CI, 1.64–2.47; $P<.0001$). The risk of CDI was highest in the first 12 months after diagnosis of celiac disease (HR, 5.20; 95% CI, 2.81–9.62; $P<.0001$), but remained high, compared to that of controls, 1–5 years after diagnosis (HR, 1.85; 95% CI, 1.22–2.81; $P=.004$). Among 493 patients with CDI, antibiotic data were available for 251; there were no significant differences in prior exposures to antibiotics between patients with celiac disease and controls.

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Acquisition of data: BL, JFL

Analysis and interpretation of data: BL, YRN, PHRG, MJB, JFL

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Conclusions—In a large population-based cohort study, patients with celiac disease had significantly higher incidence of CDI than controls. This finding is consistent with prior findings of higher rates of other infections in patients with celiac disease, and suggests the possibility of altered gut immunity and/or microbial composition in patients with celiac disease.

Keywords

bacteria; celiac disease; epidemiology; immune response

Introduction

Patients with celiac disease (CeD) are at increased risk for infections and their complications, including influenza, ¹ pneumococcal infections, ² community-acquired pneumonia, ³ tuberculosis, ⁴ and sepsis.^{5,6} Differential rates of infections may reflect a variety of factors, including hyposplenism, malnutrition/vitamin D deficiency, altered gut immunity or mucosal permeability. ⁵ Given this heightened susceptibility, it is important to assess the impact of clinically relevant pathogens in patients with CeD.

Clostridium difficile infection carries a heavy burden of morbidity and mortality in Western countries, with an estimated 453,000 incident cases and 29,300 associated deaths in the United States in 2011. ^{7,8} Rates of incident infection, both hospital- and community-acquired, are increasing. ⁹ In addition to female, white, and elderly (≥ 65 years old) patients,⁷ studies also have identified patients with inflammatory bowel disease (IBD) as a population at higher risk for *C. difficile* infection and its sequelae.^{10–14} While CeD shares characteristics with IBD, including being both immune-mediated and associated with altered microbiota,^{15,16} the incidence of *C. difficile* infection in patients with CeD compared to the general population has not been evaluated to date. Therefore, using a well-characterized national Swedish patient cohort, we assessed the risk of *C. difficile* infection in patients with CeD compared to non-CeD controls.

Methods

Study population

We performed a population-based cohort study of patients in Sweden with duodenal villous atrophy consistent with CeD. The study population was derived as described previously.^{17,18} Patients with CeD were identified via Systematized Nomenclature of Medicine (SnoMed) codes corresponding to villous atrophy among all small intestinal biopsy specimens submitted to Swedish pathology departments from July 1969 to February 2008. Time of entry into the study was defined as date of biopsy for patients with CeD or the corresponding date for matched controls. Patients who had already been diagnosed with *C. difficile* infection prior to that index date (date of diagnosis of CeD or corresponding date for controls) were excluded from the analysis. The follow-up period continued for each patient until development of *C. difficile* infection, death (identified via the Swedish Total Population Register), emigration, or December 31, 2009. Via the government agency Statistics Sweden, each patient with CeD was matched with up to 5 controls (mean 4.82) without CeD based on age (in years), gender, and county.

Primary outcome

The primary outcome was incident *C. difficile* infection, as identified by outpatient or inpatient visits with corresponding International Classification of Disease Codes indicating *C. difficile* infection (ICD-10 A047). This diagnosis code was introduced in Sweden on January 1, 1997, and was first diagnosis code to be specific to *C. difficile*; individuals whose follow-up time ended before that date were therefore excluded from the analysis.

Statistical analysis

We performed stratified Cox proportional hazards models to compare patients with CeD to matched controls with regard to their risk of incident *C. difficile* infection. As socioeconomic status may be associated with CeD diagnosis, results were adjusted for the subject's educational attainment level (or for subjects <18 years, their parents).^{19,20} We then performed stratified analyses based on age of CeD diagnosis, gender, and calendar period of study entry.

To assess robustness of our findings, we performed several sensitivity analyses. First, so as to increase the chance that the use of a *C. difficile* diagnosis code represented a true infection, we restricted the definition of the outcome of *C. difficile* infection to subjects with at least 2 visits with a diagnosis code of *C. difficile*. Second, we repeated the overall risk assessment, now without adjusting for education level.

Time-stratified analysis (1997–2009)—In addition to the overall Hazard Ratio (HR), we subsequently recalculated the overall risk assessment, now restricting the population to those CeD patients and their corresponding controls whose date of biopsy/study entry occurred on or after January 1, 1997, since ascertainment of the date of *C. difficile* diagnosis was available from that date onward. We then calculated HR's stratified according to time elapsed since CeD diagnosis (less than 1 year, 1–5 years, or greater than 5 years) based on the finding that risk of morbidity diminishes over time following CeD diagnosis.^{32,12,22,23}

Healthcare utilization (2001–2009)—Patients with CeD may be more likely to be diagnosed with *C. difficile* infection because of increased opportunities for testing, given that CeD is a chronic condition that entails contact with the healthcare system. This increased contact with healthcare may in turn increase the risk for the development of *C. difficile* infection, given the exposure to antibiotics or the presence of *C. difficile* in the healthcare setting. We therefore calculated the mean number of annual outpatient visits (excluding visits associated with a diagnosis of *C. difficile* infection) in CeD patients and matched controls; we limited this analysis to January 1, 2001 onward, since visit volume data were only available since that date. We then measured the association between CeD and *C. difficile* infection after adjusting for the number of outpatient visits.

Medication use (2005–2009)—We performed two additional analyses that incorporated medication use as confounding or mediating the association between CeD and *C. difficile* infection. First, we adjusted for exposure to at least one prescription for a proton pump inhibitor (PPI) from July 1, 2005 (the date of inception of the Swedish Prescription Drug Register) and December 31, 2009 (the study end). This register records prescriptions from

both inpatient and outpatient care (including prescriptions from general practitioners)²⁴ but not drugs administered in the hospital or sold over the counter. We then assessed recent antibiotic use (defined as occurring in the 180 days preceding the *C. difficile* infection) in patients with CeD and controls to examine associations with particular agents. Among subjects with *C. difficile* infection during that time period, we compared CeD patients to controls using the chi-square test with regard to recent exposure to one of four antibiotic classes or groupings: penicillins, fluoroquinolones, macrolides, and other antibiotics.

We performed statistical calculations using SAS version 9.4 (Cary, NC). All Hazard Ratios are reported with corresponding 95% confidence intervals, and all reported p-values are 2-sided. This study was approved by the Regional Ethical Review Board in Stockholm, Sweden which required no informed consent since this was a strictly register-based study.²⁵

Results

Patient characteristics

Of 28,375 patients with CeD and 141,631 matched controls, 36 patients with CeD and 43 controls were excluded due to prior *C. difficile* infection. The resulting study populations included 28,339 patients with CeD and 141,588 controls, matched for age, sex, and calendar year of entry (Table 1).

The mean follow-up time for all patients was 11.5 years. *C. difficile* infection was documented in 493 patients: in 136 (0.48%) patients with CeD, (yielding an incidence of 56 per 100,000 person-years), and in 357 (0.25%) controls, (26 per 100,000 person-years). The adjusted HR of *C. difficile* infection among patients with CeD compared to controls was 2.01 (95% CI 1.64–2.47, $p<0.0001$). When the HR was calculated without adjustment for education level, findings were essentially the same (HR 2.00, 95% CI 1.64–2.45; $p<0.0001$). When we redefined *C. difficile* infection as requiring two or more separate visits with a relevant diagnosis code, the association remained between CeD and *C. difficile* (HR 2.16, 95% CI 1.50–3.10; $p<0.0001$). The association between CeD and *C. difficile* infection was present when considering separately those cases of *C. difficile* infection ($n=445$) first diagnosed in the inpatient setting (HR 1.93; 95% CI 1.56–2.40, $p<0.0001$) and those cases ($n=48$) first diagnosed in the outpatient setting (HR 2.72; 95% CI 1.52–4.87, $p=0.0008$). On stratified analysis (Table 2), significantly increased risk of *C. difficile* infection was present in both genders, across age groups, and across calendar periods. Formal tests for interaction showed no significant differences between categories of gender, age group, or calendar period with regard to the association between CD and the development of *C. difficile* infection.

Time-stratified analysis—When we examined the subset of this cohort diagnosed with CeD on or after January 1, 1997, the association between CeD and *C. difficile* remained similar (HR 2.05, 95% CI 1.54–2.72; $p<0.0001$). The risk of infection was highest in the first 12 months after CeD diagnosis (HR 5.20, 95% CI 2.81–9.62; $p<0.0001$), but remained elevated in the 1–5 years after diagnosis compared to controls (HR 1.85, 95% CI 1.22–2.81; $p=0.004$, see Table 3 and Supplementary Figure 1). Beyond 5 years after CeD diagnosis, the association between CeD and *C. difficile* infection was no longer statistically significant

(HR 1.42; 95% CI 0.85–2.38). This change in HR over time was significant (p value for heterogeneity = 0.003).

Healthcare utilization—We examined the subset of this cohort diagnosed with CeD on or after January 1, 2001, now adjusting for the mean number of outpatient visits. Patients with CeD had a mean 2.8 outpatient healthcare visits per year (excluding visits with a diagnosis code indicating *C. difficile* infection), compared to controls, who had a mean 1.7 outpatient visits per year ($p < 0.0001$). After adjusting for outpatient healthcare visits, the association between CeD and *C. difficile* infection was no longer statistically significant (HR 1.08, 95% CI 0.64–1.80), while each additional annual outpatient visit was associated with an increased risk of *C. difficile* infection (HR 1.23, 95% CI 1.16–1.30).

Medication use—At least one prescription for a PPI (omeprazole, esomeprazole, pantoprazole, lansoprazole, or rabeprazole) was noted in 5,998 (21%) of 28,339 CeD patients and 19,215 (14%) of 141,588 controls ($p < 0.0001$). After adjusting for PPI exposure, the association between CeD and the development of *C. difficile* infection remained significant (HR 1.68, 95% CI 1.32–2.14, $p < 0.0001$).

Antibiotic data were available for 251 (50.9%) of the 493 patients with *C. difficile* infection, based on temporal overlap with the Swedish Prescription Drug Registry. Of these 251 subjects, 165 (66%) had been prescribed an antecedent antibiotic. (None of these 165 subjects was prescribed >1 class of antibiotic.) Although patients with CeD were less likely than controls to have taken penicillins and more likely to have taken quinolones, these differences were not statistically significant ($p = 0.32$, Table 4). There were no significant differences in the distribution of antibiotic exposure between CeD patients and controls across all treatment categories: penicillins, quinolones, macrolides, other antibiotics, or no antibiotics.

Discussion

C. difficile infection is associated with a high burden of morbidity and mortality in Western countries, but its incidence among patients with CeD has not been assessed previously. In this population-based cohort study, patients with CeD had double the risk of *C. difficile* infection compared to that of controls with findings that remained significant regardless of adjustment for education level and PPI use, as well as stratification by age, sex, and study period of enrollment. Among the strengths is the large statistical power (and tight 95% CI=1.64–2.47) but also our access to data on potential confounders and a comparison of antibiotic exposures among individuals who developed *C. difficile* infection.

These results extend the prior literature that patients with CeD are at increased risk for infections, including influenza, community-acquired pneumonia, and tuberculosis.^{1–5} Possible etiologies for these trends, including hyposplenism, malnutrition, vitamin D deficiency, and increased mucosal permeability, have been posited. It is possible that the increased risk of developing *C. difficile* infection is related to the higher rate of these other infections, in that antibiotic use to treat the latter may increase the risk of the former. Another biologically plausible explanation may be that CeD patients are at increased risk for

C. difficile infection due to the altered colonic microbiota that accompanies *C. difficile* infection.^{8,26} Although disrupted microbiota may be attributable to antibiotic exposure, in our study, antibiotic use occurred at similar rates in those who developed *C. difficile* infection, regardless of whether they had CeD or were controls. This finding contrasts with data in patients with IBD, who are less likely to have been exposed to antibiotics than controls with *C. difficile* infection.^{11,27} Gut microbiota composition differs in patients with CeD compared with healthy controls, with an increase of certain *Clostridia* species.^{16,28,29} One possible explanation for the increased risk of *C. difficile* infection among patients with CeD relates to the treatment with a gluten-free diet. Although this diet carries clinical and histologic benefit to patients with CeD, gluten restriction may have downstream consequences with regard to pathogen defense. In a study of healthy volunteers without CeD, the gluten-free diet was associated with a reduction of *Bifidobacterium* and *Lactobacillus* populations, bacteria that may be protective against enteric infections, including those due to *C. difficile*.³⁰ In one study of 120 patients with CeD, of 10 who had refractory diarrhea thought to be due to uncontrolled CeD, 6 were found to have *C. difficile*; the CeD patients may have been at increased risk due to decreased diversity involving *Bacteroides*, *Prevotella*, and *Bifidobacteria*.³¹ One previous study found that children with inflammatory bowel disease had carriage rates of *C. difficile* nearly 10 times greater than those of children with CeD, though in that study those with inflammatory bowel disease included inpatients (which likely included patients in the midst of a disease flare) while those with CeD were restricted to outpatients.¹¹

We found that the risk of incident *C. difficile* infection was highest at the time closest to CeD diagnosis: the HR for *C. difficile* infection was 5.20 in the first year following diagnosis, and decreased to 1.85 in the 1–5 years following diagnosis. Although the point estimate remained elevated beyond 5 years after diagnosis, the difference was not significant. These findings are consistent with prior studies showing that patients with CeD have highest rates of co-morbid diseases in the initial time period following diagnosis. This might reflect protopathic bias, e.g. patients with pre-existing *C. difficile* whose evaluation for diarrhea reveals previously asymptomatic CeD. However, this also might reflect that patients have the greatest degree of intestinal inflammation at the time of initial CeD diagnosis and prior to treatment.^{22,23,32} Nevertheless, we found that the overall risk estimate was similar regardless of whether we included the cohort diagnosed from 1969–2008 (HR 2.01, 95% CI 1.64–2.07), or when we restricted the analysis to those subjects whose date of inclusion occurred in the year 1997 and onward, when we were first able to ascertain the presence of *C. difficile* infection (HR 2.05, 95% CI 1.54–2.72). The fact that those diagnosed prior to 1997 had an increased risk of the outcome of *C. difficile* infection raises the possibility that there is a long-term risk of *C. difficile* that diminishes but does not resolve in the long term. Patients presenting for evaluation of persistent diarrhea are likely to be tested for both infectious and non-infectious etiologies, which may boost identification of *C. difficile* around the time of CeD diagnosis. Regardless of cause for the stronger association during the peri-diagnosis period, the persistently increased risk of *C. difficile* infection beyond the first year of CeD diagnosis suggests a biological basis for the association.

Our study has several limitations. The *C. difficile* diagnoses reflected patient visit diagnosis codes, which may have been falsely coded and we did not have access to stool samples. Although the specificity for the use of a single diagnosis code for *C. difficile* has been found to be high,³³ there is the possibility that in clinical practice it might be used as a “rule out” code. For example, in a patient being evaluated for *C. difficile* infection, although test results were not yet available, the diagnosis code for *C. difficile* might nevertheless be used. To minimize this effect, sensitivity analysis requiring that *C. difficile* diagnosis be present during at least two patient visits showed an even stronger association between CeD and *C. difficile* infection (HR 2.16, 95% CI 1.50–3.10). As we were only able to ascertain the diagnosis of *C. difficile* infection starting in 1997, it is possible that patients with CeD with a history of *C. difficile* infection preceding their CeD diagnosis were included in this cohort if the infection occurred prior to 1997; however, given that the observed prevalence of *C. difficile* infection was <0.5% of the cohort, such misclassification is likely to be rare.

Given the limited overlap between the Swedish Prescription Drug Register (established on July 1, 2005) and our cohort (in which the last new entrants were recorded in 2008), our analysis of antecedent antibiotic use was focused on a subset of subjects infected with *C. difficile*, and our adjustment for PPI use could not take into account prescriptions for those agents that preceded 2005. Patients with CeD are more likely to be prescribed antibiotics before their CeD diagnosis,¹⁵ and thus differential antibiotic utilization after diagnosis may account for some of the increased *C. difficile* risk. We have previously reported that patients with CeD were more likely to have been prescribed PPIs prior to their CeD diagnosis than were controls,³⁴ and in the present analysis, PPI use was more common after diagnosis with CeD among those patients followed during the period covered by the Prescription Drug Register. Nevertheless, after adjusting for PPI the association between CeD and subsequent *C. difficile* remained significant (HR 1.68, 95% CI 1.32–2.14). Indeed, it is unlikely that differential PPI use is driving a large difference in *C. difficile* risk, given the relatively modest risk magnitude of the association between that class of medications and *C. difficile* infection.³⁵

Differential rates of healthcare consumption (as evidenced by a larger mean number of outpatient visits per year among CeD patients compared to controls) may be contributing to the observed difference in *C. difficile* diagnosis rates. Since patients with CeD may be more likely to seek evaluation for diarrhea than healthy controls, they may be more likely to be diagnosed with *C. difficile* infection. Indeed, we found that the association between CeD and *C. difficile* infection was no longer significant after adjusting for the number of healthcare visits. This raises the possibility that healthcare contact may be mediating the relationship between CeD and *C. difficile*. Even without personal receipt of antibiotics, exposure to healthcare, both in outpatient and inpatient settings, may be a risk factor for the development of *C. difficile* infection.^{36,37} However, this also raises the possibility that the association between CeD and *C. difficile* is, at least in part, driven by increased clinical evaluation in patients with CeD compared to the general population. Nevertheless, the association between CeD and *C. difficile* infection was significant when considering separately outpatient and inpatient visits, the latter of which may be less likely to reflect self-reporting of symptoms. This finding suggests that health care visits are serving as a mediator on the causal pathway between CeD and the development of *C. difficile* infection.

In conclusion, in this population-based cohort study, we found that the incidence of *C. difficile* infection was significantly increased in patients with CeD than in controls, and that risk of *C. difficile* infection was highest in the first year after CeD diagnosis. Among patients who developed *C. difficile* infection, exposure to antibiotics did not differ between CeD patients and controls. These findings add to a growing literature demonstrating that patients with CeD are at increased risk for infections. When evaluating patients with CeD with persistent or recurrent diarrhea clinicians should consider testing for *C. difficile* infection. Given that concomitant *C. difficile* infection has been linked a poorer prognosis in inflammatory bowel disease,¹⁰ outcomes in patients with CeD who develop *C. difficile* infection should be studied further. Additionally, the mechanism of increased susceptibility to *C. difficile* infection among patients with CeD needs elucidation, as does the contribution of an altered gut microbiota.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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STUDY HIGHLIGHTS**WHAT IS CURRENT KNOWLEDGE**

- Patients with celiac disease are at increased risk of infections including influenza, pneumonia, and tuberculosis
- Infection with *C. difficile* is increasingly common, and patients with inflammatory bowel disease have increased susceptibility to this infection, but the risk in celiac disease has not been quantified.

WHAT IS NEW

- In this population-based study, patients with celiac disease had an increased risk of developing *C. difficile* infection.
- Among patients who developed *C. difficile*, exposure to antibiotics did not differ between CeD patients and controls.

Table 1

Characteristics of patients with celiac disease and matched controls.

	Celiac Disease (n=28,339)	Controls (n=141,588)
Average age at study entry (years), Mean (SD)	31.3 (25.4)	31.4 (25.4)
Age (years), no. patients (%)		
0–19	11,777 (42)	58,554 (42)
20–39	5,267 (19)	26,233 (19)
40–59	6,332 (22)	31,801 (22)
60–79	4,419 (16)	22,265 (16)
80	544 (2)	2,735 (2)
Sex, no. patients (%)		
Male	10,679 (38)	53,450 (38)
Female	17,660 (62)	88,138 (62)
Calendar period of study entry, no. patients (%)		
1989	3,681 (13)	18,670 (13)
1990–1999	11,758 (41)	58,685 (41)
2000	12,900 (46)	64,233 (46)
Follow-up time (years), mean/median	11.4/10.1	11.5/10.2
Incident <i>C. difficile</i> infection, no. patients (%)	136 (0.48)	357 (0.25)

Table 2Association of celiac disease with *C. difficile* infection, stratified by gender, age, and year of study entry.

	Number of events	Adjusted* HR (95% CI)**	P-value	P- value for interaction
Overall				
Controls	136	1.0		
Celiac disease	357	2.01 (1.64–2.47)	<0.0001	
Gender				0.16
Male				
Controls	128	1.0		
Celiac disease	62	2.61 (1.91–3.59)	<0.0001	
Female				
Controls	229	1.0		
Celiac disease	74	1.72 (1.32–2.25)	<0.0001	
Age at Study Entry				0.36
0–19				
Controls	19	1.0		
Celiac disease	9	2.49 (1.12–5.57)	0.0259	
20–39				
Controls	32	1.0		
Celiac disease	16	2.71 (1.48–4.98)	0.0013	
40–59				
Controls	92	1.0		
Celiac disease	32	1.67 (1.11–2.50)	0.0134	
60–79				
Controls	189	1.0		
Celiac disease	69	2.03 (1.52–2.71)	<0.0001	
80				
Controls	25	1.0		
Celiac disease	10	2.59 (1.18–5.68)	<0.0001	
Calendar Year of Study Entry				0.91
1989 and before				
Controls	72	1.0		
Celiac disease	24	1.82 (1.11–2.98)	0.0172	
1990–1999				
Controls	180	1.0		
Celiac disease	72	2.17 (1.63–2.88)	<0.0001	
2000 and after				
Controls	105	1.0		
Celiac disease	40	1.91 (1.33–2.74)	0.0005	

* Adjusted for education level.

** HR: Hazards Ratio. CI: confidence interval.

Table 3

Subset of celiac disease patients diagnosed on or after January 1, 1997, stratified by follow-up time.

	Number of events	Adjusted* HR (95% CI)	P-value
Overall			
Controls	159	1.0	
Celiac disease	67	2.05 (1.54–2.72)	<0.0001
<1 year			
Controls	14	1.0	
Celiac disease	18	5.20 (2.81–9.62)	<0.0001
1–5 years			
Controls	79	1.0	
Celiac disease	30	1.85 (1.22–2.81)	0.004
>5 years			
Controls	66	1.0	
Celiac disease	19	1.42 (0.85–2.38)	0.18

Adjusted for education level.

HR: Hazards Ratio. CI: confidence interval.

Table 4

Subset of celiac disease patients (and corresponding controls) diagnosed on or after July 1, 2005: Antibiotic use within 180 days of *C. difficile* diagnosis, in patients who developed *C. difficile* infection.

	Celiac Disease (n=59) n (%)	Controls (n=192) n (%)	P-value
Antibiotic class			0.32
Penicillins	11 (19)	54 (28)	
Quinolones	7 (12)	13 (7)	
Macrolides	7 (12)	28 (15)	
Other antibiotics	14 (24)	31 (16)	
None	20 (34)	66 (34)	