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High risk of post-infectious irritable bowel syndrome in patients with *Clostridium difficile* infection

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Abstract

Background—Infectious enteritis is a commonly identified risk factor for irritable bowel syndrome (IBS). The incidence of *Clostridium difficile* infection (CDI) is on the rise. However, there is limited information on post-infectious IBS (PI-IBS) development following CDI and the host- and infection-related risk factors are not known.

Aim—Our aim was to determine the incidence and risk factors for PI-IBS following CDI.

Methods—684 cases of CDI identified from Sep 2012–Nov 2013 were surveyed. Participants completed the Rome III IBS questionnaire and details on the CDI episode. Predictive modelling was done using logistic regression to evaluate risk factors for PI-IBS development.

Results—315 CDI cases responded (46% response rate) and 205 were at-risk (no pre-CDI IBS) for PI-IBS development. 52/205 (25%) met the Rome III criteria for IBS 6 months following

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MF. AlNahas: study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content

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CDI. IBS-mixed was most common followed by IBS-diarrhea. In comparison to those without subsequent PI-IBS, greater percentage of PI-IBS patients had CDI symptoms >7 days, nausea, vomiting, abdominal pain during CDI, anxiety, and a higher BMI. Using logistic regression, CDI symptoms >7 days {Odds ratio (OR):2.96, p=0.01}, current anxiety (OR:1.33, p<0.0001) and a higher BMI (OR:1.08, p=0.004) were independently associated with PI-IBS development; blood in the stool during CDI was protective (OR: 0.44, p=0.06).

Conclusions—In this cohort study, new-onset IBS is common after CDI. Longer CDI duration, current anxiety and higher BMI are associated with the diagnosis of *C. difficile* PI-IBS. This chronic sequela should be considered during active management and follow up of patients with CDI.

Keywords

gastrointestinal infections; functional gastrointestinal disorders

INTRODUCTION

Irritable bowel syndrome (IBS) is one of the most prevalent gastrointestinal disorders, affecting 15% of the U.S. population.¹ The role of infectious enteritis in development of IBS was first described in the early 1960s,² and since then, there has been growing epidemiological evidence supporting the association between gastrointestinal infections and subsequent development of IBS.^{3–5} Different microorganism types have been associated with post-infectious IBS (PI-IBS) including bacteria,^{6–7} viruses,⁸ and protozoa.⁹ It has been shown that 4–36% of individuals with infectious enteritis develop PI-IBS,⁴ and symptoms persist for 10 years in some cases.¹⁰

The incidence of *Clostridium difficile* infection (CDI) has risen over the last decade and it has become a significant source of mortality, morbidity and a major health care burden.^{11–12} The main risk factors for CDI are advanced age (>65 years), antibiotic treatment and hospitalization.^{13–14} However, CDI is now being increasingly recognized as a cause of diarrhea in the community, and community acquired CDI accounts for 20–40% of all CDI cases.¹⁵ These patients are younger and often lack the above mentioned risk factors for CDI.^{16–18} The median risk for at least one recurrence following an index episode of CDI is 22%,¹⁹ and patients who experience a first recurrence are at a higher risk for subsequent recurrences.²⁰ There is some evidence that patients get diagnosed with “recurrent CDI” based on clinical suspicion alone,²¹ with some being re-treated without laboratory confirmation. *C. difficile* PI-IBS can theoretically mimic symptoms of a recurrence, resulting in unnecessary antibiotic treatment. Systemic antibiotic use in turn can increase the recurrent CDI.²²

The risk of PI-IBS following CDI has been studied but the data available is scarce.^{23–24} Two small studies have shown that 4–12% of individuals may have PI-IBS symptoms following CDI. Another recent retrospective cohort study among military personnel showed an incidence of IBS of 5–9/100,000 person years following CDI.²⁵ None of these studies have examined host- or infection-related risk factors for development of PI-IBS following CDI.

Our aim was to determine the incidence and risk factors for new-onset PI-IBS development among laboratory-confirmed cases of CDI from a large community-based cohort who did not have IBS prior to the infection. We hypothesized that CDI is associated with PI-IBS development and that specific host- and infection-related factors predict development of PI-IBS following an episode of CDI.

METHODS

Patients (>18 years) with positive *C. difficile* PCR from September 2012–November 2013 were identified using the microbiology laboratory database at Mayo Clinic. Clinical notes and laboratory results were reviewed to confirm CDI diagnoses. A diagnosis of CDI required the presence of diarrhea (three or more watery stools per day, not on laxatives or with an alternative explanation for diarrhea) in addition to the positive stool PCR. A total of 684 CDI cases identified over this time frame were eligible to be contacted. A standardized questionnaire was mailed to these participants 6 months following the CDI (supplementary material). Another mailing was made one month later for the passive non-responders. For non-responders to two postal mailing attempts, telephone calls were made to ensure they had received the survey and to allow completion of the survey over the phone, if needed. A maximum 3-month period was allowed for survey completion by each participant (6–9 months from the CDI episode). The survey consisted of a brief demographic questionnaire, Rome III diagnostic criteria for IBS (for current and pre-CDI gastrointestinal symptoms), IBS symptom severity score (IBS-SSS), and the hospital anxiety and depression scale (HADS). IBS phenotype was defined using the Rome III criteria as well. The Mayo Clinic Survey Research Center conducted the survey. Electronic medical records were reviewed to rule out alternate diagnoses that may cause symptoms mimicking IBS. Additionally, patients with recurrent episodes of CDI after the index episode were identified and excluded. The electronic medical records were also reviewed to determine diagnosis of anxiety and depression prior to the infection using ICD codes and clinician documentation. The study was approved by the Mayo Clinic Institutional Review Board.

Statistical Analysis

Means and standard errors are reported for continuous variables, while frequencies and percentages are reported for categorical variables. Univariate logistic regression models were used to measure the association between potential risk factors and the outcome of new-onset PI-IBS 6 months or more following the CDI. Based on the number of patients with *C. difficile* PI-IBS (n=52) and the 10 events per variable rule-of-thumb, a logistic model having no more than about 5 variables was used to prevent over fitting. Based on prior research, age at CDI and gender were forced into the multivariable model regardless of statistical significance and all other variables were candidates for inclusion into the final model. Forward and stepwise variable selection using a type I error of 0.10 was utilized. In addition, best subsets selection using the score statistic was also used with a maximum of 7 variables included. All techniques supported the same multivariable model which is the one presented. A complete case analysis was used for all models.

RESULTS

Survey Response Rate

The overall response rate was 46.1% (315/684). One hundred and three patients actively refused to participate in the study, while 197 patients did not respond (passive non-responders). Fifteen patients were deceased, 20 patients were physically or mentally unable to participate in the study. Twenty eight patients did not participate due to other exclusions. Six patients returned partially completed questionnaire and were lost to follow up for subsequent contact.

Study Population

Of the 315 responders, 74 were excluded for meeting Rome III criteria for IBS prior to the CDI episode based on Rome III survey responses for pre-CDI IBS or documentation in the electronic medical record. Thirty were excluded due to alternate diagnoses, such as inflammatory bowel disease, microscopic colitis or celiac disease. Six were excluded due to missing data. Thus, 205 of the 315 responders were defined as at-risk for *C. difficile* PI-IBS development (Figure 1). Responders (without prior IBS) were more likely to be older (mean 57.6 years vs 45.8 years) but had similar gender distribution (43.4% vs 39.1%) and BMI (mean 27.3 kg/m² vs 27.8 kg/m²) as non-responders.

Incidence of PI-IBS following CDI

Of the 205 at-risk patients, 57 met Rome III IBS criteria for ongoing gastrointestinal symptoms 6 months following the CDI episode. Five of these were considered not to have IBS since they had at least one additional episode of CDI following the index episode. Overall, 52/205 (25.4%) patients were defined as having PI-IBS following the CDI episode. Of these, 27 (52%) were IBS-M (IBS-mixed), 21 (40%) were IBS-D (IBS-diarrhea predominant), 2 (4%) were IBS-C (IBS-constipation predominant), and 2 (4%) were IBS-U (IBS-undifferentiated). The mean (SEM) IBS symptom severity score (IBS-SSS) was 238 (14) on a scale of 0–500 with 500 being the most severe symptoms. Of the 52 PI-IBS patients, 44 were tested for recurrence and were found to be negative for *C. difficile*.

Demographic Characteristics

The mean (SEM) age was similar for the *C. difficile* PI-IBS and non PI-IBS groups [56 (2.4) years vs 58 (1.5) years]. The distribution of gender was also similar, with 38% males in the *C. difficile* PI-IBS cohort and 45% males in the non PI-IBS group. Patients with *C. difficile* PI-IBS had a higher mean BMI compared to the non PI-IBS group (29 kg/m² vs 27 kg/m², $p=0.06$). Patients with *C. difficile* PI-IBS had a higher mean (SEM) HADS anxiety score of 9.8 (0.4) as compared to 8.1 (0.2) ($p<0.0001$) for individuals without PI-IBS. The HADS depression score was not different among the two groups. The prevalence of anxiety prior to infection was similar in the PI-IBS (13.5%) and non PI-IBS group (6.5%). Additionally, the prevalence of depression prior to infection was similar in the PI-IBS (7.7%) and non PI-IBS group (11.8%). Distribution summaries of these and other demographic variables among *C. difficile* PI-IBS and non PI-IBS cohorts are shown in Table 1.

Clinical Characteristics during CDI Episode

A higher proportion of patients in the *C. difficile* PI-IBS cohort reported a >7 day duration of CDI symptoms as compared to the control group (79% vs 61%, $p=0.02$). During the CDI episode, a higher percentage of patients who later developed PI-IBS reported nausea (69% vs 43%, $p=0.002$), vomiting (32% vs 16%, $p=0.02$) and abdominal pain (86% vs 68%, $p=0.02$). Distribution summaries of these and other infection-related variables among *C. difficile* PI-IBS and non PI-IBS cohorts are shown in Table 1 along with univariate odds ratios.

Logistic Regression Model for Variables Associated with *C. difficile* PI-IBS

In a multivariable model, CDI symptom duration >7 days was independently associated with an increased risk of PI-IBS diagnosis with an OR (95% CI) of 3.0 (1.24 – 7.10). The current anxiety score from the HADS and BMI were associated with an increased risk of PI-IBS diagnosis following the CDI episode with ORs (95% CI) of 1.33 (1.16 – 1.53) and 1.08 (1.02 – 1.14), respectively. Reporting of blood in stool was associated with lower odds of *C. difficile* PI-IBS diagnosis with an OR of 0.44 (0.19– 1.02). Variables included in the multivariable logistic regression model are listed in Table 2.

DISCUSSION

In this study of 205 CDI patients without prior IBS, we demonstrate that a quarter of patients report symptoms consistent with IBS 6 months following their CDI episode. This is significant considering the progressively increasing burden of CDI. Previous studies have shown a wide range of PI-IBS incidence, from 4–36% following gastrointestinal infections, however, most of the studies report a 10–15% incidence.^{4,26} The incidence of *C. difficile* PI-IBS in our study is also higher than the previously reported incidence. One of these studies showed a incidence of 4% but that study only had 3 months of follow-up and a sample size of 23 patients, of which one reported *C. difficile* PI-IBS.²³ The CDI diagnosis in this study was made using both culture and by detection of toxins by rapid immunoassay. Another small study of 94 CDI patients showed an incidence of 12% and over 50% were lost to follow-up, leaving 41 CDI patients available for analysis.²⁴ None of the controls (non-infected) in this study developed IBS over the duration of follow-up.

Several studies have looked at risk factors for PI-IBS development following gastrointestinal infections but this is the first to determine risk factors associated with PI-IBS development following CDI in those without prior IBS. Severity of initial illness has been proposed as risk factor for PI-IBS following bacterial enteritis,^{27–29} but no evidence is available for patients following CDI. We showed that patients with prolonged symptom duration (i.e., >7 days) have an increased likelihood of developing PI-IBS following CDI. We also found that patients reporting nausea, vomiting and abdominal pain had higher odds of PI-IBS development following CDI on univariate analysis. On multivariable analysis, however, only duration of CDI symptoms (>7 days) was found to be significantly associated. Blood in the stool, which can be perceived as a marker for severe disease was not associated with *C. difficile* PI-IBS diagnosis on univariate analysis and was found to be protective against PI-IBS on multivariable analysis. Previous studies have found mixed results as pertains to

association between bloody diarrhea and PI-IBS development.^{30–31} Our patient population was specifically asked about “blood in the stool” and not bloody diarrhea in the survey which could have led to inaccurate responses or this could be due to recall bias.

Previous studies have shown that psychological factors such as anxiety and depression at the time of enteritis may increase the risk of PI-IBS.^{32–34} We found that current anxiety was associated with a diagnosis of PI-IBS following CDI. We did not find any association between depression and PI-IBS. It is possible that PI-IBS is making individuals more anxious since anxiety and depression prior to infection were not associated with PI-IBS development.

Age has been proposed as a risk factor with individuals less than 60 years at a higher risk for PI-IBS,^{4,27} however, we did not find any significant correlation with age. This could be due to over representation of the elderly in our responder population. Additionally, there have been other studies which found no effect of age in increasing the risk of PI-IBS.^{35–36} There is conflicting data regarding gender as a risk factor for PI-IBS. We didn't find an association between gender and PI-IBS in contrast to previous studies.^{30,37–38} However female patients have a higher incidence of psychological disorders, including anxiety and depression,⁴ and in two studies, the association of gender was not observed after multivariate analysis despite being significant in univariate analysis, thereby supporting the above argument.^{33,39} A relationship between obesity and IBS has been studied in the past.⁴⁰ We found patients with a higher BMI to be at an increased risk for *C. difficile* PI-IBS, although there is much to be explored in this area in order to understand the mechanism involved in obesity increasing the risk of IBS. Changes in gut microbiota have been proposed as one mechanism and have been observed in obese patients,⁴¹ and IBS,⁴² separately. Interestingly, fecal microbiota diversity was found to be reduced in PI-IBS which inversely correlated with lamina propria lymphocytes and psychological scores suggesting a possible link between dysbiosis, inflammation and stress in PI-IBS.⁴³

Our study has limitations. It was a cross-sectional study with patients contacted via a survey which makes it prone to recall and survey response bias. Additionally, a control group without CDI derived from the same population would have been helpful in defining risk-ratios. A number of epidemiological studies in PI-IBS^{7,29} including ours are prone to recall bias for pre-infection IBS symptoms. The CDI diagnosis was made on the basis of a positive PCR and presence of 3 watery stools/day and it is possible that some of the patients had a false positive diagnosis. We demonstrate that 25% of CDI patients without prior IBS develop PI-IBS at least 6 months after CDI which is higher than the median PI-IBS incidence following infection from other pathogens. This makes it important to consider the possibility of PI-IBS when patients with a history of CDI present with ongoing gastrointestinal symptoms. Such patients may be inappropriately re-treated for CDI. Ongoing anxiety and higher BMI independently increase the odds of PI-IBS diagnosis following CDI. Additionally, longer duration of CDI symptoms is also moderately associated. Considering the significant incidence of *C. difficile* PI-IBS, retreatment for recurrence should only be offered after laboratory confirmation of the diagnosis. The risk factors for *C. difficile* PI-IBS can also be potentially modified to help reduce the incidence of PI-IBS following CDI. A potential implication is that a more prompt diagnosis and treatment for CDI does not only

have implications for treating the acute infection but also on the delayed sequela of PI-IBS. A prospective cohort study with assessment of prior IBS symptoms at the time of infection and with a control group will be needed to define the incidence and the risk factors for PI-IBS with a clearer perspective during the course of the disease and help determine the sequelae. Additionally, mechanistic studies to determine the pathophysiology of *C. difficile* PI-IBS will be helpful in understanding this entity and probably IBS in general. These include the role of gut microbiota and ascertaining changes over a longer period among CDI patients who resolve their symptoms and those that go on to develop PI-IBS.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

CDI	<i>Clostridium difficile</i> infection
PI-IBS	post-infectious irritable bowel syndrome

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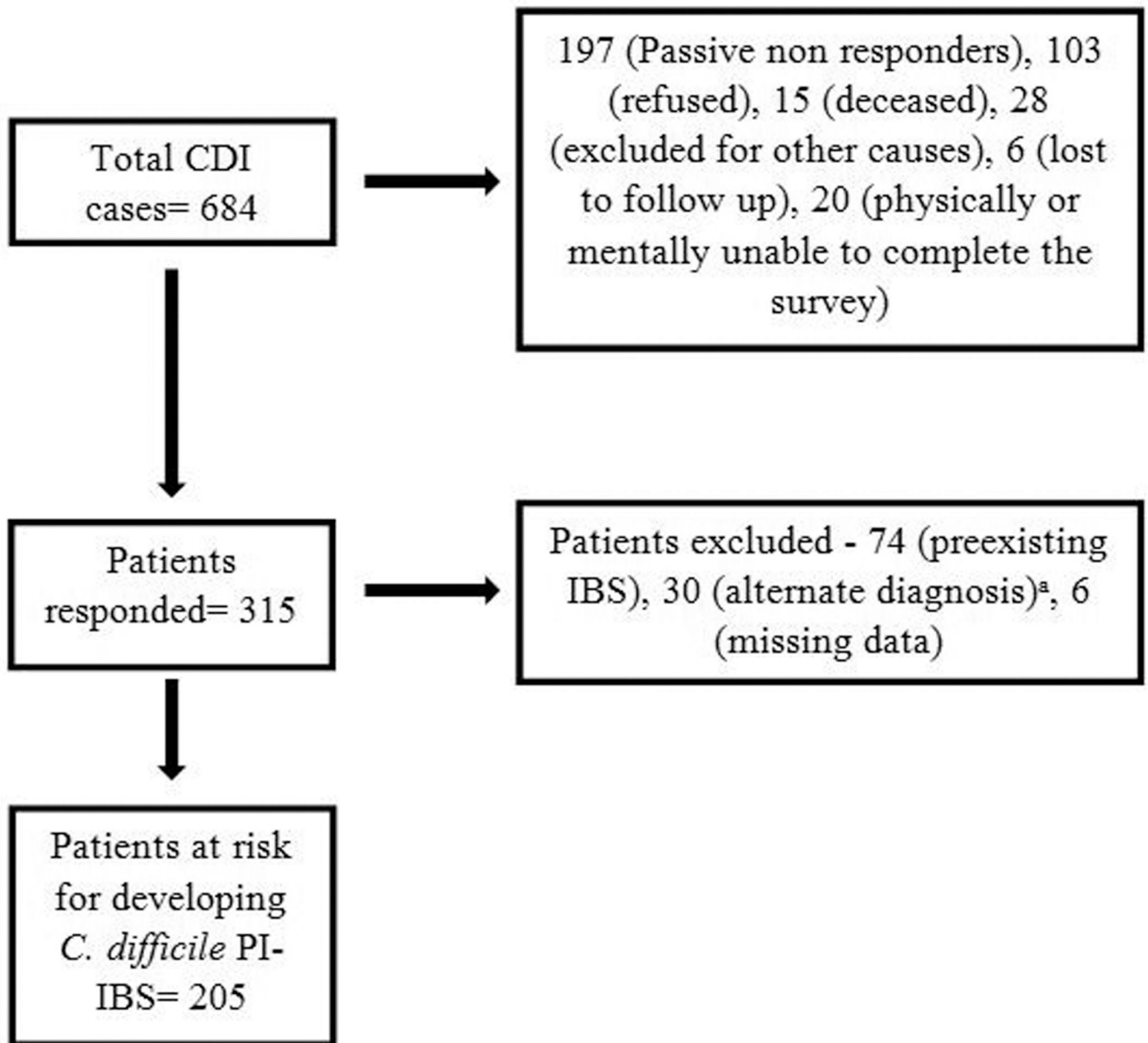


Figure 1. Study population flow for determination of *C. difficile* PI-IBS cases and controls
CDI, *C. difficile* infection; IBD, inflammatory bowel disease; IBS- irritable bowel syndrome, PI-IBS, post-infectious IBS
a. IBD, microscopic colitis, celiac disease

Table 1
Distribution of demographic, infection-related and psychological variables among *C. difficile* IBS patients and controls

Variable	<i>C. difficile</i> PI-IBS (N=52)	No PI-IBS (N=153)	No. of Missing values	Univariate PI-IBS OR (95% CI)	P value
Demographic and psychological					
Age, mean (SEM)	55.7 (2.4)	58.3 (1.5)	0	0.99 (0.98–1.01)	0.39
Male gender, n (%)	20 (38.5%)	69 (45.1%)	0	0.76 (0.40–1.45)	0.40
Current Smoker, n (%)	8 (15.7%)	13 (8.6%)	3	1.97 (0.77–5.08)	0.16
Caucasian, n (%)	51 (98.1%)	142 (93.4%)	1	3.59 (0.45–28.71)	0.23
BMI, mean (SEM)	28.8 (1.2)	26.8 (0.5)	1	1.04 (0.998–1.094)	0.06
HADS anxiety score, mean (SEM)	9.8 (0.4)	8.1 (0.2)	2	1.27 (1.13–1.43)	<0.0001
HADS depression score, mean (SEM)	8.5 (0.2)	8.5 (0.1)	3	1.03 (0.83–1.29)	0.78
Pre-CDI anxiety diagnosis, n (%)	7 (13.5%)	10 (6.5%)	0	2.22 (0.80–6.18)	0.12
Pre-CDI depression diagnosis, n (%)	4 (7.7%)	18 (11.8%)	0	0.62 (0.20–1.94)	0.41
CDI episode-related					
Nausea, n (%)	33 (68.8%)	60 (42.9%)	17	2.93 (1.46–5.88)	0.002
Vomiting, n (%)	15 (31.9%)	22 (16.2%)	22	2.43 (1.13–5.22)	0.02
Diarrhea, n (%)	49 (94.2%)	138 (91.4%)	2	1.54(0.42–5.62)	0.51
Abdominal pain, n (%)	43 (86.0%)	95 (67.9%)	15	2.91 (1.21–6.97)	0.02
Fever, n (%)	13 (26%)	52 (38.5%)	20	0.56 (0.27–1.15)	0.12
Blood in stool, n (%)	11 (22.4%)	46 (32.9%)	16	0.59 (0.28–1.26)	0.17
Duration of CDI symptoms >7 days, n (%)	41 (78.8%)	90 (60.4%)	4	2.44 (1.16–5.13)	0.02
Hospitalized during CDI, n (%)	31 (59.6%)	88 (57.9%)	1	1.07 (0.57–2.04)	0.83

Table 2Multivariable model for new-onset IBS following *C. difficile* infection (N=183)

Variable	<i>C. difficile</i> PI-IBS OR (95% CI)	P value
Male gender	0.62 (0.28–1.34)	0.22
Age at CDI	1.00 (0.98– 1.02)	0.97
BMI	1.08 (1.02– 1.14)	0.004
HADS anxiety score	1.33 (1.16– 1.53)	<0.0001
Blood in stool during CDI	0.44 (0.19– 1.02)	0.06
Duration of CDI >7 days	2.96 (1.24– 7.10)	0.01

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