Low risk of irritable bowel syndrome after *Clostridium difficile* infection

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OBJECTIVE: The incidence of postinfectious irritable bowel syndrome (IBS) ranges between 4% and 32% of individuals after bacterial or parasitic infection. This study analyzed IBS symptoms in hospitalized patients three months after a symptomatic *Clostridium difficile* infection.

PATIENTS AND METHODS: All patients with a proven, symptomatic C *difficile* infection identified in the department of bacteriology over a four-month period were considered for enrolment. Patients were excluded in cases of pre-existing IBS or other organic gastrointestinal diseases. Patients completed both modified Talley and Rome II questionnaires within five days of clinical improvement with metronidazole and at three months postinfection, when stools were cultured and C *difficile* toxins were examined to exclude ongoing infection.

RESULTS: Twenty-three patients were evaluated three months after infection with C *difficile*. Just after infection, 15 patients were symptom free, whereas eight patients exhibited symptoms suggestive of IBS. Three months after infection, 22 patients remained symptom free, whereas one patient presented with symptoms indicative of IBS. That female patient had a prolonged infection without vomiting.

CONCLUSIONS: We have shown that while transient functional bowel disorder occurred in 34.7% of patients (eight of 23 patients) recently infected with C *difficile*, only 4.3% of patients (one of 23 patients) had symptoms indicative of IBS after three months (ie, postinfectious IBS). Because an age-related reduction in immune responsiveness has been documented, it can be speculated that the low incidence of postinfectious IBS may be explained by the older age of the study population. Therefore, it cannot be excluded that the findings may be different in younger patients.

Key Words: Clostridium difficile; *Epidemiology; Postinfectious IBS*

Un faible risque de syndrome du côlon irritable après une infection par le *Clostridium difficile*

OBJECTIF : L'incidence de syndrome du côlon irritable (SCI) postinfectieux oscille entre 4 % et 32 % chez les personnes qui ont subi une infection bactérienne ou parasitaire. La présente étude contient l'analyse des symptômes de SCI chez des patients hospitalisés trois mois après une infection symptomatique par le *Clostridium difficile*.

PATIENTS ET MÉTHODOLOGIE : Tous les patients atteints d'une infection symptomatique et démontrée par le C *difficile* observés au département de bactériologie pendant une période de quatre mois étaient envisagés pour participer à l'étude. Les patients étaient exclus s'ils étaient déjà atteints du SCI ou d'une autre maladie gastro-intestinale organique. Les patients ont rempli à la fois le questionnaire Talley modifié et celui de Rome II dans les cinq jours suivant une amélioration clinique grâce au métronidazole et trois mois après l'infection, lorsqu'on procédait à une culture des selles et qu'on examinait les toxines du C *difficile* afin d'exclure une infection sortante.

RÉSULTATS : Vingt-trois patients ont été évalués trois mois après l'infection par le C *difficile*. Juste après l'infection, 15 patients ne présentaient aucuns symptômes, tandis que huit patients avaient des symptômes évocateurs du SCI. Trois mois après l'infection, 22 patients demeuraient sans symptômes, tandis qu'un patient avait des symptômes évocateurs du SCI. Cette femme a souffert d'une infection prolongée, non accompagnée de vomissements.

CONCLUSIONS : Nous avons démontré que même si un trouble intestinal fonctionnel transitoire se produit chez 34,7 % des patients (huit sur 23) récemment infectés par le C *difficile*, seulement 4,3 % (un sur 23) avaient des symptômes évocateurs du SCI au bout de trois mois (soit un SCI postinfectieux). Puisqu'on a documenté une réduction de la réponse immunitaire reliée à l'âge, on peut postuler que la faible incidence de SCI postinfectieux s'explique par l'âge avancé de la population à l'étude. Par conséquent, on ne peut pas exclure la possibilité d'autres résultats chez les jeunes patients.

Irritable bowel syndrome (IBS) is a common disorder defined as a painful, chronic abdominal symptom complex usually associated with altered bowel habit, for which there is no discernible underlying structural abnormality (1). The relationship of IBS to previous infective gastroenteritis has long been recognized (2) and occurs in 4% to 32% of individuals recovering from enteric infection due to bacteria (3-5) or parasites (6). Indeed, bacterial gastroenteritis is now recognized to be the strongest risk factor identified for the development of IBS (7). Risk factors for the development of postinfectious IBS (PI-IBS) include the severity and duration of the initial illness, female sex, hypochondria and adverse life events in the previous 12 months (3,4,8). Recent studies suggest that genetic factors may predispose some IBS patients to a stronger inflammatory response (9), and this was reflected in a study of increased cytokine expression in PI-IBS patients (10). In contrast, the presence of vomiting and age older than 60 years may be protective (3,8). The infecting pathogen also influences the risk of PI-IBS. Indeed, Thornley et al (11) showed that the higher risk for reporting persistent altered bowel habits after

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Campylobacter species enteritis infection was associated with strains that caused the greatest toxicity to an epithelial cell line in vitro.

Clostridium difficile infection is responsible for virtually all cases of pseudomembranous colitis (12) and for up to 20% of cases of antibiotic-associated diarrhea without colitis (13,14). Today, broad-spectrum penicillins and cephalosporins are the most common antibiotics implicated in *C difficile* infection, which is a reflection of their widespread use. Pathogenic strains of *C difficile* produce diarrhea via several mechanisms, of which the most studied are enterotoxin (toxin A) and cytotoxin (toxin B). After binding to their receptors, both toxins enter the colonic cell, profoundly alter the cytoskeleton leading to cell rounding and activate the release of cytokines from human monocytes, thus inducing marked colonic inflammation (15). The current prospective study aimed to describe bowel habits of patients immediately and three months after a symptomatic *C difficile* infection, and to determine the incidence of symptoms indicative of IBS in the selected population.

METHODS

Protocol

All patients older than 18 years of age with symptomatic and culture-proven *C difficile* infection identified in the Department of Bacteriology (Hôpital de l'Archet II, Centre Hospitalier Universitaire de Nice, France) between November 2001 and February 2002 were considered for enrolment. The study was proposed to 58 patients with a proven symptomatic *C difficile* infection identified during the four-month recruitment period. Patients were not included if they used any medication known to affect bowel function, or had a documented history of functional or inflammatory bowel diseases, including microscopic colitis, celiac disease, lactose intolerance or a previously documented *C difficile* infection.

Patients were instructed to complete a series of standardized questionnaires evaluating demographic data and the severity of symptoms related to the gastroenteritis, the Hospital Anxiety and Depression Scale (HADS) (16) and the modified Talley bowel symptom questionnaire (17), evaluating the bowel habits of patients during the preceding two months (premorbid bowel habits) and their bowel habits immediately after the *C difficile* infection (baseline bowel habits).

The first set of questionnaires was administered when symptoms related to the acute infectious episode were improved (or cured) by metronidazole (eg, within five days after clinical improvement).

Three months after the acute illness, patients also completed the modified Talley bowel symptom questionnaire, and both stool culture and cytotoxin assays were performed to exclude recurrent or ongoing *C difficile* infection.

The local research ethics committee approved the protocol and all patients gave their written, informed consent.

Evaluation and management of *C difficile* infection

The diagnosis of *C difficile* infection was confirmed when both stool culture and the detection of toxins A and B by rapid immunoassays were positive (18). The severity of the acute illness was evaluated using both medical records and a questionnaire assessing the presence and duration of digestive symptoms, including diarrhea, abdominal pain, fever, bleeding, passed mucous, amount of weight loss and vomiting. Diarrhea was the predominant symptom of *C difficile* infection (eg, unformed stool for two or more days with no other cause such as other pathogens, medication side effects or other gastrointestinal conditions). The evaluation also included a physical examination, complete blood count, serum chemistries, and when appropriate, colonoscopy and abdominal ultrasound or tomodensitometry examinations. All patients included in the evaluation received metronidazole for seven days. Bacteriological examinations were repeated at the end of treatment, to ensure the absence of contagion, and at three months post-treatment, to exclude recurrent or ongoing infection. A resolution of *C difficile* infection was considered to have occurred when bacterial eradication (eg, negative stool culture and toxin assays) was obtained after the end of treatment and persisted three months post-treatment, whatever the presence of symptoms indicative of IBS were.

Diagnosis of IBS

The presence or absence of symptoms suggestive of IBS was determined within five days of improvement (or cure) of symptoms related to the *C difficile* infection (baseline bowel habits) and three months later, using the Rome II criteria (19). After the initial visit, patients were classified into two groups: patients with or patients without IBS-like symptoms (eg, patients whose symptoms met the Rome II criteria except for duration). Patients were identified as having PI-IBS when symptoms persisted three months after the resolution of the acute illness and with proven eradication of the *C difficile* infection.

Statistical analysis

Data were entered into Microsoft Access 98 (Microsoft Corporation, USA) and analyzed using SPSS/PC 11.1 (SPSS Inc, USA) for Windows XP (Microsoft Corporation, USA). Data are presented as the mean ± SD. Comparisons between parametric data were made using the nonparametric Mann-Whitney U test. Associations between categorical data were assessed using the χ^2 test.

RESULTS

Response rate and study population

The study was proposed to 58 patients with a proven symptomatic *C difficile* infection identified during the recruitment period (eg, four months). Fifteen outpatients (25.8%) were admitted to the hospital because of diarrhea due to *C difficile* after a course of antibiotics. Forty-three patients (74.1%) were previously hospitalized for other comorbid conditions, and 35 of those patients (81.3%) acquired *C difficile* after receiving antibiotics. Nineteen patients were not enrolled – 13 were unable to complete the initial questionnaire and six refused to participate. The remaining 39 patients met the inclusion criteria and were included in the baseline evaluation (Figure 1).

Baseline evaluation

Among 39 patients with a proven symptomatic *C difficile* infection, four met the Rome II criteria for IBS, based on the premorbid modified Talley bowel symptom questionnaire at the initial visit, and were classified as having pre-existing IBS. Those patients were not aware of their diagnosis before the study, although a careful screening of medical records was performed during their hospitalization. One patient developed inflammatory bowel disease after the colitis and was excluded

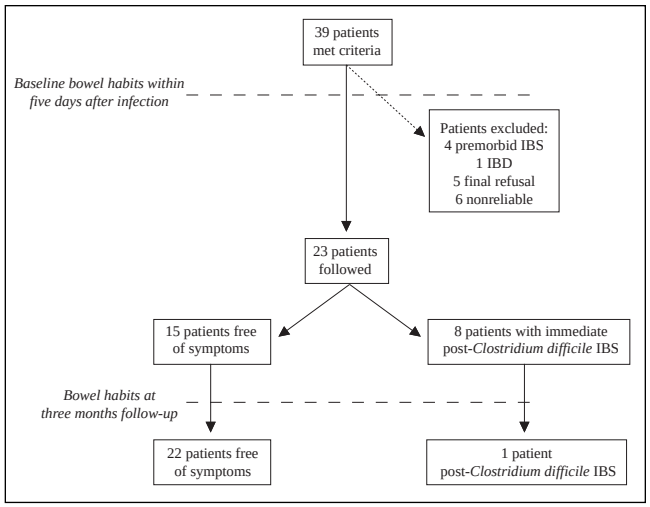

Figure 1) *A flow chart of the protocol of the present study. The number of patients with* Clostridium difficile *infection who were enrolled in the study and followed up for three months is described. IBD Inflammatory bowel disease; IBS Irritable bowel syndrome.*

from the study. Although careful screening was performed, five individuals refused to participate at the time of baseline evaluation, and six individuals were considered incompetent to complete the questionnaires.

All of the 23 remaining patients acquired C *difficile* after a course of antibiotics. Fifteen of the 23 patients (65%) were previously hospitalized for a comorbid condition (cancer, chronic renal failure, malnutrition), whereas eight of the 23 patients (34.7%) were outpatients who received antibiotics for a benign cause without any significant comorbidity. Endoscopy was performed in all 23 patients, and showed predominant patchy colonic erythema with no or small adherent yellow plaques (stage I colitis) in nine of the 23 patients (39.1%) and typical adherent pseudomembranes of 2 mm to 10 mm in diameter covering a hyperhemic colonic mucosa (stage II colitis) in 14 of the 23 patients (60.8%). Colitis was mainly localized in the left colon and rectum without any severe lesions (eg, large ulcerations, confluence of lesions, pancolitis).

Patients were classified into two groups according to the baseline modified Talley bowel symptom questionnaire: eight patients developed IBS-like symptoms, whereas 15 patients remained symptom free (Figure 1). The mean age (67.7±11.5 years) of eight patients who met the Rome II criteria was similar to that of the 15 patients who were symptom free (65.4±16.9 years; not significant). There were more women in the group of patients who met the Rome II criteria than in the group of patients who were symptom free (75% versus 60%; P=0.08). The mean HADS scores were not different between patients with and without IBS-like symptoms, both for anxiety (5.6±3.7 versus 5.2±3.5, respectively; not significant) and for depression (4.2±3.8 versus 6.2±4.6, respectively; not significant). The demographic data and characteristics of C *difficile* infection in both groups are indicated in Table 1. The C *difficile* infection was more severe in patients with IBS-like symptoms, with a significantly longer duration of abdominal pain, passed mucous and less vomiting. No difference was seen according to the severity of colitis at endoscopy.

TABLE 1
Demographic data and characteristics of *Clostridium difficile* infection in patients with symptoms indicative of irritable bowel syndrome (IBS) (as determined by the Rome II criteria) and symptom-free patients at the time of baseline evaluation

Characteristic	Symptom free patients, n=15	Patients with IBS, n=8	P
Sex (female:male), n	9:6	6:2	0.08
Age, years*	65.4±16.9	67.7±11.5	NS
Stage of colitis, n			
I (erythema)	4	5	NS
II (typical pseudomembranes)	9	5	
III (severe lesions [large ulcerations or confluence of lesions])	0	0	
Duration of abdominal pain, days*	1.4±0.5	6.0±3.6	<0.01
Diarrhea*			
Duration, days	13.0±5.5	9.2±3.5	NS
Bowel movements, n/day	6.3±2.1	7.5±2.5	NS
Duration of fever, days*	2.0±1.1	2.0±2.6	NS
Duration of bleeding, days*	1.2±1.1	0.8±0.8	NS
Duration of vomiting, days*	2.5±1.1	0.5±1.0	<0.01
Weight loss, kg*	8.0±2.6	7.7±1.6	NS
Duration of mucous passed, days*	7.0±2.1	9.0±2.3	0.04

**Data are presented as the mean ± SD. NS Not significant*

Follow-up evaluation three months after infection with C *difficile* (Table 2)

The bowel habit of four pre-existing IBS patients was unchanged three months after infection, and the diagnosis of IBS was maintained because they fulfilled the Rome II criteria. The 15 patients without any digestive complaints remained completely symptom free. The mean HADS scores of the 22 symptom-free patients after three months (5.6±3.3 for anxiety and 5.7±4.4 for depression) were not statistically different from the scores of those identified symptom free with IBS-like symptoms at the time of the initial evaluation. Among eight patients who developed IBS-like symptoms after the infection, one of them fulfilled the Rome II criteria and was considered PI-IBS after three months (Figure 1). The female patient identified with PI-IBS was older (68 years) than the mean age of the 22 patients who were completely symptom free (66.6±15.2 years). She had a prolonged duration of infection, especially for abdominal pain and passed mucous associated with the absence of vomiting. The HADS scores reached 6 for anxiety and 7 for depression.

In summary, we have shown that while transient functional bowel disorder occurred in eight of 23 patients recently infected with C *difficile*, only one had PI-IBS after three months.

DISCUSSION

In the present prospective study, we showed that the development of symptoms indicative of IBS three months after a symptomatic C *difficile* infection was uncommon (4.3%). This low incidence may be explained by the relatively old age of the study population.

Previous studies (3,4,8,20,21) have shown that the incidence of PI-IBS ranges between 4% and 32%. Although the

TABLE 2
Demographic data and characteristics of *Clostridium difficile* infection for patients identified with postinfectious inflammatory bowel syndrome (PI-IBS) and patients identified as being symptom free after three months

Characteristic	Symptom-free patients, n=22	PI-IBS patients, n=1
Sex (female:male), n	14:8	1:0
Age, years*	66.6±15.2	68
Stage of left colitis, n		
I (erythema)	8	1
II (typical pseudomembranes)	14	0
III (severe lesions [large ulcerations or confluence of lesions])	0	0
Duration of abdominal pain, days*	3.7±2.8	6
Diarrhea*		
Duration, days	12.0±4.8	18
Bowel movements, n/day	7.2±2.0	8
Duration of fever, days*	2.0±1.7	2
Duration of bleeding, days*	1.5±1.1	0
Duration of vomiting, days*	1.9±1.4	0
Weight loss, kg*	7.7±2.2	6
Duration of mucous passed, days*	8.0±2.0	9

**Data are presented as mean ± SD*

pathogenesis of PI-IBS remains unclear, this subgroup of patients constitutes a part of the IBS population with evidence of low-grade inflammation (22,23) and altered intestinal permeability (24-26). The value of making the diagnosis of PI-IBS is that it provides patients with an explanation for their condition and may lead to new treatment options in high-risk selected patients (for review [27,28]). For example, certain probiotics may lead to symptomatic improvement in phenotypically similar IBS patients with diarrhea predominance (29). Risk factors for PI-IBS identified previously have included female sex, psychological profile, the duration of the initial illness and microbial virulence factors (3,4,8,11). To date, the occurrence of IBS soon after the recovery from a *C difficile* infection has never been investigated. In the present study, only one of 23 patients (4.3%) developed symptoms suggestive of IBS three months after a symptomatic *C difficile* infection.

Several factors may explain this low incidence. First, the age of patients studied (median age of 64.5 years) was older than that of previous studies. Indeed, the female PI-IBS patient was 68 years old, while the median age of eight patients with transient bowel dysfunction was 64.5 years. In contrast, in a study by Spiller et al (24), the median age of patients with postdysenteric IBS caused by *Campylobacter* species enteritis was 44 years. Similarly, in a study by Gwee et al (10), patients with acute gastroenteritis who went on to develop IBS were younger (44±6.8 years) than infected patients who did not develop IBS (48±5.2 years). In a postal survey (3) of patients six months after bacterial gastroenteritis, the adjusted RR for age of self-reported changes in bowel habits was lower in patients older than 60 years of age (RR=0.36; 95% CI 0.1 to 0.9) than in patients between the ages of 30 and 44 years (RR=1.75; 95% CI 1.1 to 2.7). From a theoretical point of view, the protective role of age older than 60 years may be related to an age-related reduction in immune responsiveness. From animal studies (25), it is evident that a major determinant of postinfective gut dysfunction is the adaptive immune response to the infection and that maintenance of this dysfunction requires ongoing immune activity. It is possible that the immune response to *C difficile* is either substantially different from that of enteritis due to *Salmonella* species and *Campylobacter* species, or more likely, that the immune response of the older population of this study was insufficient to generate or sustain a state of persistent gut dysfunction. Thus, while 34.7% of our patients presented with symptoms indicative of IBS immediately after the infection, a much smaller number (one of 23, or 4.3%) had persistent symptoms after three months. Indeed, recent data suggest the existence of an age-related decline in rectal mucosal lymphocytes and mast cells (22,30), which may explain, at least partially, the low rate of PI-IBS after *C difficile* infection in our population-based study of patients older than 60 years of age. In addition, 65% of patients in the present study were hospitalized for other conditions and developed *C difficile* after receiving antibiotics. This comorbidity may also have attenuated the immune response to *C difficile* and thus the subsequent development of PI-IBS.

The severity of the initial illness, in particular, a prolonged duration, has been shown to influence the development of PI-IBS (8,11). In a community-based study (3) in Nottingham, United Kingdom, of 357 individuals with gastroenteritis, the duration of diarrhea was the strongest predictor of developing PI-IBS, with an adjusted RR of 11.4 when diarrhea lasted longer than 22 days. Moreover, the relatively low incidence of PI-IBS (7%) may be explained by the milder nature of the initial illness, because only one in 10 patients were hospitalized. In the present study, the severity of the disease was mainly based on medical records rather than on endoscopic findings. Although the inclusion of nonsymptomatic patients would have carried the possibility of increasing the sample size, the focus on symptomatic patients allowed a more rigorous study design, with a clear beginning of infection and a subsequent follow-up examination after three months. We observed that individuals classified with IBS after the initial visit were more frequently female with a more prolonged duration of abdominal pain and passed mucous, and the rarity of vomiting. This was also seen in the female patient who demonstrated symptoms of PI-IBS at the three-month follow-up examination. However, we found no association between the stage of colitis and the subsequent development of IBS symptoms. In fact, all patients were managed at the hospital for nonsevere *C difficile*-associated colitis, mainly localized to the left colon and rectum without profound ulceration or confluence (eg, stage I and stage II colitis). Accordingly, a larger study is required to assess the relationship between the severity of macroscopic inflammation and the occurrence of IBS.

We did not find anxiety to be a risk factor for developing PI-IBS, although such a small sample size does not allow us to make any statements about this, because others have observed that emotional stress predisposes a patient to PI-IBS (4). Nevertheless, the HADS scores of individuals with symptoms indicative of IBS or PI-IBS were not statistically different from those of patients without any digestive complaints.

Our study had several limitations. A control group may have been helpful to define the normal incidence of new IBS in the absence of infection. However, we assumed that this 4.3% incidence was lower than previously reported in controlled (or uncontrolled) studies of PI-IBS (3,8,20,31,32) and fairly similar to the known prevalence (4.7%) of IBS

(eg, non-PI-IBS) in the French general population (33). Although the diagnosis of IBS may have been ascertained by a more prolonged observation of symptoms, we deliberately limited the follow-up examination to three months postinfection, considering the poor compliance of our population. Although the incidence of *C difficile* infection appears to be increasing in our society (34), it remains a condition that is seen predominantly in older patients. Patients in this age group may be less compliant with instruction, and in our particular population, a substantial number were unable to meaningfully complete the questionnaires, thus reducing our study population. Indeed, 13 patients were unable to complete the initial questionnaire. Moreover, among the 39 patients who were convened to our centre for the baseline evaluation, six (15.3%) were considered to be insufficiently reliable to complete the questionnaires. These observations underscore the difficulty of studying the incidence of PI-IBS after *C difficile* infection using an older hospitalized patient population.

CONCLUSIONS

We showed that symptoms indicative of IBS occurred in 4.3% of patients three months after a symptomatic *C difficile* infection. The old age of the study population may explain this low incidence. The results are of practical use in the management of symptomatic patients recovering from *C difficile* colitis; the low probability of PI-IBS identified in this study should prompt investigations of an alternative etiology of their symptoms.

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