ORIGINAL ARTICLE

Pretravel Preparation and Travel-related Morbidity in Patients with Inflammatory Bowel Disease

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Background: There are no published data on health preparation and travel-related morbidity in patients with inflammatory bowel disease (IBD).

Methods: A retrospective web-based questionnaire study on past travel experiences with more detailed questions concerning the most recent journey. Participants were recruited from the IBD outpatient clinic and via the website of the Dutch patient organization.

Results: In all, 277 patients who had traveled abroad during the past 5 years (172 Crohn's disease, 105 ulcerative colitis) filled out the questionnaire. The majority (62%) answered that IBD limited their choice of travel destinations. Forty-three percent traveled to resource-limited destinations and 76% thereof obtained pretravel advice. Only 48% were prescribed an antibiotic for self-treatment in case of infectious diarrhea, and 23% were not protected against hepatitis A. Fecal urgency and incontinence were the main IBD-related inconveniences. Thirty-two percent reported a new episode of diarrhea and 28% thereof attributed it to an enteric infection. In total, 15/277 (5%) consulted a foreign physician, of whom five were admitted to hospital. Fifty-four (19%) had a self-reported exacerbation of IBD within 2 months following travel and 24% thereof attributed it to the recent travel. The Mantel–Haenszel odds ratio for an exacerbation within a 2-month period after travel was 1.1 (95% confidence interval [CI] 0.7–1.8) when the number of self-reported exacerbations in a 5-year period was used as reference and 1.5 (95% CI 0.9–2.6) when the year 2008 was used as reference.

Conclusions: Pretravel advice for IBD patients was often deficient. There was a considerable amount of travel-related morbidity and inconvenience.

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Key Words: inflammatory bowel disease, travel, vaccination

Travelers with inflammatory bowel disease (IBD) are at a greater risk of travel-related morbidity. First, use of immunosuppressive therapy increases susceptibility to and severity of infections,[1–6] attenuates the immune response to vaccination,[4,7,8] and increases the chance of morbidity after vaccination with live attenuated vaccines such as yellow fever vaccine.[9,10] Second, in long-standing IBD functional asplenia may occur, which increases the chance of fulminant infections with polysaccharide encapsulated bacteria and *Plasmodium falciparum*.[11,12] Third, an episode of gastroenteritis, which is the most common travel-related illness, is regarded as a risk factor for an exacerbation of IBD and may influence drug absorption and elimination.[4,13] Use of inactivated carbon to treat diarrhea also influences drug absorption.[14] It stands to reason that pretravel preparation reduces the risk of morbidity.[15] The European Crohn's and Colitis Organization and the Dutch national guideline for pretravel advice offer specific recommendations for (immunocompromised) travelers with IBD[4,16]: 1) An antibiotic should be prescribed for self use in case of gastroenteritis (Evidence Level (EL) 5, Recommendation Grade (RG) D).[17] 2) Acquisition of immunity should be monitored after administering certain vaccines (EL 2a, RG B). 3) Travel to areas where yellow fever is endemic is discouraged if vaccination with live attenuated vaccines is contraindicated (EL 5, RG D). Of note, an inactivated yellow fever vaccine is being developed.[27] 4) Individuals with functional asplenia should be informed of the extra risk associated with malaria and should be vaccinated for *Streptococcus pneumoniae, Haemophilus influenzae*, and *Neisseria meningitides* and should carry an antibiotic for self use in case of fever (EL 5, RG D). 5) As immunosuppressants and in particular tumor necrosis factor alpha (TNF-α) inhibitors increase the risk of tuberculosis, certain high-risk travelers should be screened for tuberculosis before and after travel (EL5, RG D). The rate of *Mycobacterium tuberculosis* infection is of similar magnitude to that of the local population.[18]

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No prior studies have reported on health preparation and travel-related morbidity in patients with IBD. In order to evaluate and improve the quality of pretravel advice we performed a web-based questionnaire study on past travel experience and investigated pretravel preparation of Dutch IBD patients and the quality of pretravel advice. We also surveyed health problems encountered during travel and investigated whether travel increased the risk of an exacerbation of IBD.

MATERIALS AND METHODS

Design and Study Population

Between April 2009 and April 2010 we performed a retrospective web-based questionnaire study on travel experiences in the past 5 years with more detailed questions regarding the most recent journey abroad. Dutch-speaking IBD patients at the outpatient clinic of the Leiden University Medical Center (LUMC) in the Netherlands received an informative letter in the waiting room inviting them to participate in a survey. Patients who provided informed consent were sent a web-based questionnaire via e-mail. LUMC is a tertiary referral center for IBD. To obtain a representative sample of IBD patients' travel experiences we also recruited participants by posting information and a link to the questionnaire on the website of the Dutch IBD patient organization.[19] The study protocol was approved by the Medical Ethics Committee at LUMC.

Definitions

Travel destination was categorized into two groups: 1) countries where hepatitis A is endemic, meaning that vaccination is recommended according to the national guideline (VAC+ countries), and 2) countries where hepatitis A is not endemic (VAC− countries).[16] Drug use was divided into four categories: i) none, or loperamide or mebeverine only; ii) 5-aminosalicylate or topical steroids only; iii) glucocorticoids or immunomodulators (azathioprine, 6-mercaptopurine, methotrexate); iv) TNF-α inhibitors. As specified in the guideline,[16] we defined those who should have been screened for tuberculosis as those who had traveled to high-risk countries for at least 8 weeks, and those who traveled to high-risk countries for less than 8 weeks, but more than 2 weeks and whose travel was characterized by at least two of the following factors: very frequent use of public transportation in resource-limited countries, lodging with local population under resource-limited circumstances or intense (medical) professional contact with the local population.

Questionnaire

All participants filled out questions on disease characteristics. Those who had only traveled to VAC− countries in the past 5 years reported the number of journeys abroad in the past 5 years and answered questions regarding the most recent travel: questions regarding the bowel disease, pretravel preparation, health-related issues while abroad, and travel-related illness upon return. Participants who had traveled to a VAC+ country in the past 5 years answered additional questions on pretravel vaccination for hepatitis A and yellow fever and questions designed to estimate the risk of latent tuberculosis. We piloted the questionnaire among IBD patients and staff of the department of Clinical Epidemiology at our center. A question on the nature of inconvenience due to IBD during travel was added at a later stage and was completed by half of all respondents.

Statistical Analysis

We investigated whether travel abroad was associated with an increased risk of an exacerbation of IBD. For each traveler the expected risk of an exacerbation within any 2-month period was compared with the observed risk of an exacerbation within the first 2 months after returning home from travel. The expected risk of an exacerbation within any 2-month period was calculated by dividing the number of self-reported exacerbations in the past 5 years by 30 (5 years multiplied by 12 months, divided by 2 months). If this fraction exceeded 1, the risk was defined as 1. The observed risk of an exacerbation within 2 months following travel was either 1 or 0, depending on whether such an exacerbation had or had not occurred. Using the observed and expected risk of an exacerbation per traveler we calculated the Mantel–Haenszel overall odds ratio (MH-OR) for the risk of an exacerbation within a 2-month period after travel. Because the number of self-reported exacerbations in the past 5 years may not reflect the current rate of exacerbations per year, a sensitivity analysis was performed which was limited to those who had traveled after 2008 and in which the number of exacerbations in 2008 was used as reference.

All participants were asked whether IBD did or did not influence their choice of travel destinations. In a prediction model we explored which factors influenced respondents' answers to this question. The following variables were analyzed with χ^2-tests for categorical variables and *t*-tests for continuous variables: "gender," "age," "type of bowel disease (Crohn's disease or ulcerative colitis)," "Montreal classification of disease activity and extent,"[20] "time since diagnosis," "past bowel surgery," "type of medication," "work disability due to IBD," and "the average number of exacerbations of IBD over the past 5 years in categories (0 exacerbations per year, up to 1 exacerbation per year, 1 to 2 exacerbations per year, more than 2 exacerbations per year)." Variables with *P*-values < 0.2 were entered in a multiple logistic regression model based on maximum likelihood estimation. Interaction terms were not entered in the model to prevent overfitting. Variables with *P*-values < 0.2 in the final model were reported. Cook's distance values, leverage values, and standardized residuals were examined to detect cases that might be influencing the model disproportionately. Variance inflation factors were examined to test whether any covariates were highly collinear.

TABLE 1. Demographic and Disease Characteristics of 277 Dutch Patients with Inflammatory Bowel Disease (IBD) Who Filled Out a Web-based Questionnaire on Pretravel Preparation and Travel-related Morbidity

Characteristic	Crohn's disease $n = 172$	Ulcerative colitis $n = 105$	All $n = 277$
Mean age, years (SE)	42 (1.0)	43 (1.2)	43 (0.8)
Gender, female *n* (%)	127 (74)	71 (68)	198 (71)
Median time since diagnosis, years (IQR)	13 (8–20)	12 (6–17)	13 (7–19)
Location of disease activity *n* (%)[a]			
Ileum only	45 (26)	—	—
Colon only	48 (28)	—	—
Ileocolon	69 (40)		
Any localization and jejunum or stomach	10 (6)	—	—
Fistulas	66 (38)	—	—
Strictures	74 (43)	—	—
No strictures or fistulas	53 (31)	—	—
Proctitis only	—	11 (10)	—
Left hemicolon only	—	24 (23)	—
Pancolonic	—	60 (57)	—
Unknown	—	10 (10)	—
Past bowel surgery *n* (%)[b]	90 (52)	22 (21)	112 (40)
Colostoma	6 (4)	1 (1)	7 (3)
Ileostoma	14 (8)	8 (8)	22 (8)
Ileorectal anastomosis	4 (2)	1 (1)	5 (2)
Pouch	2 (1)	10 (10)	12 (4)
Current medication for IBD *n* (%)			
None / loperamide / mebeverine only	28 (16)	17 (16)	45 (16)
5-aminosalicylate / topical steroid only	31 (18)	41 (39)	72 (26)
Systemic immunosuppressant	78 (45)	43 (41)	121 (44)
TNF-α inhibitor	60 (35)	13 (12)	73 (26)
Work-disabled (complete or in part) *n* (%)	65 (38)	31 (30)	96 (35)
Comorbidity requiring medication *n* (%)[c]	33/87 (38)	22/60 (37)	55/147 (37)
Admitted to hospital for an exacerbation of IBD in the past 5 years *n* (%)	76 (44)	35 (33)	111 (40)

SE: standard error of the mean; IQR: interquartile range.
[a]Montreal classification of IBD.[20]
[b]i.e., part of the bowel was removed.
[c]Denominator is different due to missing data.

RESULTS

Study Population

In all, 277 IBD patients who had traveled abroad during the past 5 years (172 Crohn's disease, 105 ulcerative colitis) filled out the questionnaire. The response rate at the outpatient clinic was 70%. Respondents' mean age was 43 years, median duration of IBD 13 years, and 40% underwent bowel surgery in the past. At the time of the survey 44% used a glucocorticoid or an immunomodulator, mostly azathioprine, and 26% a TNF-α inhibitor (10% infliximab, 16% adalimumab) (Table 1). None of the participants had been diagnosed with functional asplenia. Fifty-five percent (153/277) had been recruited at the outpatient clinic at LUMC. Use of glucocorticoids or an immunomodulator (73/153, 48%) and of a TNF-α inhibitor (49/153, 32%) was more common in this group than in participants who had been recruited via the website of the IBD patient organization (48/124, 39%, and 24/124, 19%, respectively), reflecting the fact that LUMC is a tertiary referral center for IBD.

Factors Influencing the Choice of Travel Destinations

The majority (171/277, 62%) answered that IBD limited their choice of a travel destination. This was significantly more so for those on a TNF-α inhibitor (odds ratio [OR] 2.2, 95% confidence interval [CI] 1.2–4.3), for those

TABLE 2. Travel Characteristics of 277 Dutch Patients with Inflammatory Bowel Disease Regarding the Most Recent Travel Abroad

Characteristic	All $n = 277$
Destination, *n* (%)	
Countries not endemic for hepatitis A, *n* (%)*	157/277 (57)
Countries endemic for hepatitis A, *n* (%)	120/277 (43)
Eastern Europe	9
Central America	21
South America	28
North Africa	31
South Africa	6
Africa remaining	14
Middle-East	20
Central and Eastern Asia	14
Indian subcontinent	2
South-East Asia	24
Median travel duration, weeks (IQR)	2 (1–3)
Main travel purpose, *n* (%)	
Tourism	216/277 (78)
Visit friends/relatives	39/277 (14)
Business/professional/study/volunteer work	22/277 (8)
Medication for IBD at the time of travel, *n* (%)	
None / loperamide / mebeverine only	38/277 (14)
5-aminosalicylate / topical steroid only	97/277 (35)
Systemic immunosuppressant	123/277 (44)
TNF-α inhibitor	45/277 (16)

IQR: interquartile range;
*Defined as countries for which vaccination against hepatitis A is recommended according to the national guideline for travel medicine.

who underwent bowel surgery in the past (OR 1.5, 95% CI 0.9–2.6), for those who were work-disabled due to IBD (OR 2.2, 95% CI 1.2–3.9), and for those who reported a larger average number of exacerbations of IBD over the past 5 years (reference category 0 exacerbations OR 1.0, up to 1 exacerbation per year OR 2.9 (95% CI 1.3–6.4), 1 to 2 exacerbations per year OR 2.2 (95% CI 0.8–5.6), more than 2 exacerbations per year OR 4.8 (95% CI 1.7–13).

Pretravel Advice and Vaccination

Forty-three percent (120/277) had traveled to countries where hepatitis A is endemic (VAC+), often while on a glucocorticoid or an immunomodulator (58/120, 48%) or a TNF-α inhibitor (20/120, 17%) (Table 2). Of those who traveled to VAC+ countries 76% (91/120) obtained pretravel advice from a qualified source. Fewer men (22/37, 59%) than women (69/83, 83%) obtained pretravel advice. Forty-eight percent (44/91) received a prescription for an antibiotic for self-treatment in case of infectious diarrhea. Travelers to VAC+ countries who underwent bowel surgery in the past may be at a greater risk of dehydration. Therefore, this group in particular should carry an antibiotic to treat infectious diarrhea. Only 53% (17/32) were advised to do so. At the time of travel 23% (27/120) were not protected against hepatitis A (i.e., they had never been vaccinated for hepatitis A and had never been infected with hepatitis A). Guidelines stipulate that the antibody response to inactivated hepatitis A vaccine should be checked in vaccinees on immunosuppressant drugs and that nonresponders should receive passive immunization. Antibody titers were checked in less than half (10/26; 38%) of those in whom the response should have been checked. Regarding vaccination for yellow fever, three of 11 participants (27%) who received the live attenuated vaccine should not have been vaccinated, as two used azathioprine and one a TNF-α inhibitor. All three were vaccinated at specialized travel clinics. Three travelers who visited countries for which yellow fever vaccination is required had never been vaccinated. Two of these travelers visited countries where no cases of yellow fever have been reported in recent years (Kenya and Tanzania), and for which travelers with a contraindication for vaccination are routinely exempted. The other traveled to Uganda and used prednisolone and azathioprine.

Travel-related Morbidity

Fecal urgency and incontinence were mentioned most frequently as the main IBD-related inconveniences during travel (36%). Abdominal discomfort (10%) and fatigue or joint or muscle pain (9%) were also common hindrances. Onset of a new episode of diarrhea was reported by 32% (90/277) and more so by those with Crohn's disease than by those with ulcerative colitis. Past bowel surgery, Montreal Classification of disease activity, and extent and type of medication were not associated with the onset of a new episode of diarrhea (data not shown). Twenty-eight percent (25/90) thought that the diarrheal episode was due to an enteric infection, of which 56% (14/25) used an antimicrobial agent. In total 15/277 (5%) consulted a foreign physician, of whom five were admitted to hospital. Three of those who were admitted had undergone bowel surgery in the past, one of whom had a pouch. Details are specified in Table 3.

Posttravel Screening and Posttravel Morbidity

According to the national guideline, 11 travelers should have been screened for tuberculosis after travel by way of a Tuberculin Skin Test (TST). The guideline is based on travel destination, duration, and intensity of contact with the local population. Nine of these 11 travelers used an immunosuppressant at the time of travel, but none used a TNF-α inhibitor. Three travelers were actually

TABLE 3. Travel-related Morbidity For 277 Dutch Patients with Inflammatory Bowel Disease

Characteristic	Crohn's Disease $n = 172$		Colitis Ulcerosa $n = 105$		All $n = 277$
	VAC− $n = 99$	VAC+ $n = 73$	VAC− $n = 58$	VAC+ $n = 47$	
Any illness while abroad, *n* (%)	55/99 (56)	39/73 (53)	22/58 (38)	18/47 (38)	134 (48)
Onset of a new episode of diarrhea, *n* (%)	37/99 (37)	31/73 (43)	7/58 (13)	14/47 (30)	89 (32)
Duration, *n* (%)					
1-3 days	20/37 (54)	17/31 (55)	5/7 (71)	7/14 (50)	49/89 (55)
3-7 days	12/37 (32)	8/31 (26)	1/7 (14)	4/14 (29)	25/89 (28)
1-3 weeks	2/37 (5)	2/31 (6)	—	2/14 (14)	6/89 (7)
More than 3 weeks	3/37 (8)	2/31 (6)	1/7 (14)	1/14 (7)	7/89 (8)
Does not remember	—	2/31 (6)	—	—	2/89 (1)
Symptoms, *n* (%)					
Vomiting	1/37 (3)	—	1/7 (14)	3/14 (21)	5/89 (6)
Fever	3/37 (8)	—	1/7 (14)	2/14 (14)	6/89 (7)
Treatment, *n* (%)					
None	20/37 (54)	10/31 (32)	5/7 (71)	4/14 (29)	39/89 (44)
Loperamide / activated carbon	13/37 (35)	12/31(39)	1/7 (14)	6/14 (43)	32/89 (13)
Antimicrobial agent	1/37 (3)	7/31 (23)	2/7 (29)	4/14 (29)	14/89 (16)
Oral rehydration solution	—	4/31 (13)	1/7 (14)	2/14 (14)	7/89 (8)
Extra prednisolone	2/37 (5)	1/31 (3)	1/7 (14)	—	4/89 (1)
5-aminosalicylate	1/37 (3)	—	—	—	1/89 (1)
Cause of diarrheal episode (participants' opinion), *n* (%)					
IBD	32/37 (86)	11/31 (35)	3/7 (43)	6/14 (43)	52/89 (58)
Infection	3/37 (8)	12/31 (39)	3/7 (43)	7/14 (50)	25/89 (28)
Does not know	2/37 (5)	8/31 (26)	1/7 (14)	1/14 (7)	12/89 (13)
Consulted a physician while abroad, *n* (%)	5/99 (5)	6/73 (8)	3/58 (5)	1/47 (2)	15 (5)[a]
Admitted to hospital	1/99 (1)	2/73 (3)	1/58 (2)	1/47 (2)	5 (2)[b]
Journey interrupted, returned home	1/99 (1)	—	—	—	1 (0.4)

VAC-: traveled to countries that are not endemic for hepatitis A; VAC+: traveled to countries that are endemic for hepatitis A.
[a]Reasons for consulting a physician while abroad: gastrointestinal complaints/dehydration ($n = 6$, of whom 4 had a history of bowel surgery), joint/muscle pain or trauma ($n = 3$), upper airway tract infection ($n = 2$), uveitis ($n = 1$), altitude sickness ($n = 1$), itch ($n = 1$), hot flushes ($n = 1$).
[b]Details for those who were admitted to hospital: cholangitis/dehydration, South Africa; gastro-enteritis with dehydration due to *Salmonella enteritidis*, admitted in The Netherlands upon return from Tunesia; vomiting/dehydration, Europe; infectious diarrhea/exacerbation colitis ulcerosa, Europe; enteritis, central Asia.

screened before and 8 weeks after travel (3/11, 27%); eight were not, of whom six used an immunosuppressant.

Nineteen percent (54/277) reported an exacerbation of IBD within 2 months following travel; 24% (13/54) attributed the onset to the recent travel. The OR for an exacerbation within a 2-month period after travel, using the number of self-reported exacerbations in a 5-year period as reference, was not increased (MH-OR 1.1, 95% CI 0.7–1.8). Using 2008 as reference, the MH-OR was higher (1.5, 95% CI 0.9–2.6).

DISCUSSION

In this study on past travel experiences among 277 Dutch patients with IBD, we found that more than half of the patients traveled while using systemic immunosuppressive therapy, that 40% traveled to resource-limited destinations, and that one in four failed to obtain pretravel advice and vaccinations for these medically more hazardous destinations. The pretravel consult was deficient in some respects. There was considerable travel-related morbidity and IBD caused much inconvenience and limited the choice of travel destinations. The risk of an exacerbation of IBD after travel was increased, but the increase was not statistically significant.

This is the first survey on pretravel preparation and travel-related morbidity in patients with IBD. Apart from a number of useful websites with advice for travelers with IBD[21–23] and apart from guidelines, review articles, and expert opinion,[4,11,16,24,25] we know of only one cohort study that examined morbidity in travelers with IBD. In

that study few of the 71 IBD patients used systemic immunosuppressive therapy and travel-related morbidity was not significantly higher in patients than in controls.[26] In another study among Dutch renal transplant recipients, a comparable proportion of transplant recipients failed to obtain pretravel advice and a comparable proportion was not protected against hepatitis A. Hospitalization for travel-related morbidity was higher in transplant patients.[13]

Regarding the deficiencies in the pretravel consult, one should take into account that guidelines on travel medicine are based on consensus and that there may be valid reasons not to follow a guideline. First, although IBD patients with a shorter bowel are at increased risk of dehydration and although immunosuppressive drugs increase the risk of severe salmonellosis[6] there are no compelling reasons for all travelers with IBD to carry an antibiotic for self-treatment in case of diarrhea. Opponents may argue that distinguishing infectious diarrhea from IBD activity is very difficult and that unnecessary use of antibiotics may aggravate IBD. Second, our finding that many travelers were not screened for latent tuberculosis can be commented upon. We did not have detailed information on the circumstances under which respondents came in contact with the local population. Therefore, based on our definition, we may have over- or underestimated the "true" proportion that should have been screened for tuberculosis. Furthermore, a TST has reduced sensitivity in IBD patients in general and in those on systemic immunosuppressive therapy in particular.[28,29] An interferon gamma release assay (IGRA) increases sensitivity of screening for tuberculosis. Because IGRA is costly, TST is still used in most travel clinics.

Although we did not find that travel increased the risk of an exacerbation of IBD within a 2-month period after travel, one should realize that there may be inaccuracies in patients' self-reported number of exacerbations and that patients may be more inclined to travel when their disease is in a stable phase. Therefore, the individual's self-reported number of exacerbations over the past 5 years may not be a valid marker for the expected incidence of an exacerbation following travel. In this respect it is interesting that the MH-OR was higher in the sensitivity analysis in which the number of exacerbations in 2008 was used as reference, which may be a better estimate of the expected incidence of an exacerbation after travel. It should be noted that we inquired about exacerbations of IBD within a 2-month period after travel and did not account for the incubation period of travel-related infectious diarrhea. Therefore, it is possible that some self-reported exacerbations were actually episodes of travel-related infectious diarrhea. Such bias may have increased the MH-OR.

This study has a number of limitations. First, it was designed as a questionnaire study taken after the fact. This allowed us to survey a larger number of patients in a shorter time-frame than a study in which participants are recruited before travel. The downside is an increase in the chance of recall bias among respondents and an increase in the chance of preferentially selecting travelers with more severe travel-related morbidity who may be more inclined to respond to a questionnaire taken after the fact. Second, we could not determine the response rate for those who were recruited via the website of the IBD patient organization. Third, besides enteric symptoms the survey only contained a general question on any additional travel-related morbidity. Morbidity that travelers deemed less relevant may not have been mentioned. Last, although we piloted the questionnaire among patients and epidemiologists, questions could have been misinterpreted.

Based on our study, we make the following recommendations: 1) The physician caring for patients with IBD is best positioned to raise awareness of the risks associated with travel and to refer patients to a travel medicine clinic. 2) Travel clinics should check serology after hepatitis A vaccination in those who use systemic immunosuppressants. Even if seroprotection is not attained after one dose, a second dose is often effective, as has been shown in organ transplant recipients.[30] 3) Continued vigilance is needed when prescribing live attenuated vaccines such as yellow fever vaccine. 4) Fecal urgency and incontinence are major sources of inconvenience and should be addressed by IBD physicians and healthcare workers at travel clinics.

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