RESEARCH

Diarrhoeal episodes in travellers suffering from IBD

Pierre Ellul, Valerie Anne Fenech, Christine Azzopardi, Lara Callus, Nicholas Delicata, Jeffrey Muscat, Neville Azzopardi, Mario Vassallo

Gastroenterology Division, Mater Dei Hospital, Msida, Malta

Correspondence to

Dr Pierre Ellul, c/o Ms. Alessia Debattista, Gastroenterology Division, Mater Dei Hospital, 2nd Floor, Brown Block, msd2000 Msida, Malta; ellul.pierre@gmail.com

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ABSTRACT

Background and aims There is limited data on the risk of developing diarrhoea in travelling patients with inflammatory bowel disease (IBD). We analysed the rate of developing diarrhoea among travellers suffering from IBD and their healthy controls.

Methods We performed a retrospective case-controlled study among 78 patients with IBD and their healthy travelling companion controls, thus matching both groups to the same environmental conditions. Data was retrieved through a structured questionnaire, interview and clinical case notes review.

Results Sixteen (20.5%) patients with IBD developed diarrhoea while abroad ($p = 0.0001$) Statistical analysis using a χ^2 test for independence (with Yates Continuity Correction). Prior to travelling, they were in clinical remission. Only one healthy control (1.3%) developed diarrhoea while abroad. In 11 patients (14.1%), the duration of diarrhoea was 3 days or less, and resolved on its own without antibiotics, any increase in their IBD medications and without a medical consultation. The other five patients had a flare-up of their disease and needed medications to put them back into remission. There was no statistically significant difference between patients having immunomodulator medications versus those having aminosalicylates only in developing diarrhoea when abroad.

Conclusions Patients with IBD have a higher rate of developing diarrhoea compared with controls when travelling. Thus, such patients must always seek a pretravel medical consultation.

INTRODUCTION

Infectious agents are implicated in the aetiology, pathogenesis and clinical course of inflammatory bowel disease (IBD). While our understanding of this interplay is incomplete, it is clear that infections can initiate both the onset and

relapse of IBD.¹ The use of immunomodulator (IM) treatment in patients with IBD very often leads to clinical remission and improved quality of life (QOL). The use of IM therapy in the management of IBD may increase the risk of infectious complications. Furthermore, travellers being treated with IM could be at greater risk of acquiring food and waterborne infections.²

International travel has greatly increased both for work and leisure reasons. As the QOL of patients with IBD improves, so does their motivation for travelling abroad increase.³

Our primary aim was to determine if patients with IBD are at a higher risk of developing diarrhoea when abroad compared with healthy control subjects. Our secondary aim was to determine whether patients with IBD undergoing IM treatment are at a higher risk than patients having 5-aminosalicylate (ASA) medications.

METHOD

Study population

A retrospective study with matched controls was performed among patients with IBD who attended the gastroenterology clinics at Mater Dei Hospital, Malta. All patients were older than 18 years, had histological confirmation of IBD, and had travelled abroad in the previous 12 months with a healthy companion. Thus, the control group was comparable for travel destination, travel duration and exposure to infection.

Definitions and data collection

Immunosuppressive agents were defined as agents that completely or partly suppress one or more factors in the immune system based on the classification of

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WHO Collaborating Centre for Drug Statistics Methodology.⁴

Travel destination countries were classified according to the United Nations' Human Developmental Index (HDI) for the year 2011.⁵ Countries are classified as having a very high HDI, high, medium and low HDI.

Severe illness was defined as any health condition requiring hospitalisation, or cutting short the trip abroad so as to return for medical care at home. All other disease episodes were classified as mild.

A structured questionnaire was developed, and patients with IBD and their healthy travelling companions were interviewed by one of the authors. This investigated the demographics, medical history, medications, history of travelling abroad within the previous 12 months, clinical activity and symptoms (and change in symptoms) pertaining to the gastrointestinal tract.

All patients to be recruited had to be in clinical remission during the previous 3 months without any change in medication. Clinical remission was determined through the questionnaire and interview. This was defined as not having any change in stool frequency, no change in stool consistency, no change in the general well-being, no abdominal pain/discomfort, no recurrence of symptoms pertaining to active disease, no rectal bleeding, no extragastrointestinal manifestations, no changes to any medications, any visits to doctors regarding their IBD and through the hospital records.

Travel details included: pretravel advice from their general practitioner or gastroenterologist, immunisations prior to travel, prophylactic medications, country of destination, duration of travel and details about any illness experienced by the respondent during or within 30 days.

Furthermore, the medical notes of all patients with IBD participating in the study were retrieved and the clinical data was reviewed.

RESULTS

Characteristics of the study sample

Seventy-eight patients with IBD (mean age 42.2 years (17–68 years)) were recruited and were matched by 78 healthy controls who were their travelling companions.

Forty-four patients had Ulcerative Colitis (UC) and 34 patients had Crohn's Disease (CD). The travel duration abroad ranged from 3–60 days (mean 9.62 days). The countries they visited together with their respective United Nations HDI is shown in table 1. In terms of continents, Europe was visited by 88.5% of patients. The other continents where patients and their controls travelled to were North America (3.8%), Australia (1.3%) and Asia (6.4%).

The patients were asked if their travel was to a rural, urban area or both. Thirteen patients had been abroad to rural areas, 14 patients visited both urban

Table 1 Country and human development index

Country	Number of visits	Human development index
Russia	2	High
Italy	16	Very high
UK	23	Very high
USA	3	Very high
Thailand	2	Medium
Croatia	1	Very high
Germany	5	Very high
France	6	Very high
Austria	2	Very high
Slovenia	1	Very high
Switzerland	3	Very high
Greece	1	Very high
Australia	1	Very high
Portugal	1	Very high
Spain	1	Very high
Syria	1	Medium
Cyprus	2	Very high
Denmark	1	Very high
UAE	1	Very high
Holland	1	Very high
Israel	1	Very high
Belgium	1	Very high

and rural areas, while 51 patients had been to an urban area. The Montreal Classification was used for phenotypic determination of IBD (table 2).⁶

Surgical history

Seven patients with CD had had a right hemicolectomy. One patient with CD had a stricturoplasty. Three patients (two with CD and one with UC) had a cholecystectomy. Another two patients (one with CD and one with UC) had an appendectomy.

Table 2 Montreal classification

Montreal classification	Number of patients
Crohn's disease	
A1	3
A2	28
A3	3
B1	26
B2	8
B3	0
L1	8
L2	14
L3	11
Ulcerative colitis	
Proctitis	9
Left-sided	26
Pancolitis	9

Table 3 Features of patients with IBD who developed diarrhoea when abroad

Gender	
Female	12
Male	4
Medications	
ASA only	7
Infliximab	3
Azathioprine	5
Azathioprine+infliximab	1
Smoking status	
Non-smokers	15
Ex-smokers	1
Ulcerative colitis	
Proctitis	2
Left-sided	3
Pancolitis	4
Crohn's disease behaviour	
Inflammatory	6
Strictureing	1

ASA, aminosalicylate; IBD, inflammatory bowel disease.

Medications

All patients were receiving an ASA drug. Fifty-one patients (65.4%) were being administered an IM. These were azathioprine (38 patients), infliximab (11 patients), 6-mercaptopurine (1 patient) and methotrexate (1 patient). Six patients (7.7%) were undergoing dual IM treatment. No patients were taking any corticosteroids, and none of the patients had been prescribed corticosteroids in the previous 90 days.

With regards to treatment compliance while abroad, 11 patients were not compliant with their IBD medication. None of our patients had received any vaccinations prior to going abroad.

Symptoms while abroad

Sixteen (20.5%) patients suffering from IBD developed diarrhoea while abroad. Prior to leaving the country they were in clinical remission. Only one healthy control (1.3%) developed diarrhoea while abroad. The patient with IBD travelling with the latter was one of the patients who developed diarrhoea

while abroad. Their clinical features are shown in table 3.

Fourteen patients who developed symptoms travelled to areas classified as having a very high HDI. The other two patients had travelled to a country with high HDI, while one patient travelled to a country of medium HDI. Fourteen patients had travelled to urban areas, and two patients had travelled to rural areas.

In 11 patients (14.1%), the duration of diarrhoea was 3 days or less, and resolved on its own, without antibiotics, any increase in their IBD medications and without requiring a medical consultation.

None of the patients or controls developed any symptoms in the 30 days after returning from abroad.

Treatment and doctor consultation

Five patients (6.4%) (3 male) sought medical advice on returning. All had travelled to urban areas. All had clinical exacerbation of their disease. The rest did not consult any doctors due to their mild self-limiting symptoms. None of these patients (11) increased their IBD medications that they were taking, and they did not use any corticosteroids and/or antibiotics.

One patient who was travelling to a country of medium HDI cut short his holiday due to his symptoms. The other four patients were travelling to very high HDI countries.

Table 4 describes underlying types of IBD, medications they were taking prior to travelling abroad, the medications needed to obtain remission, results of stool samples (culture, ova cysts and parasites and *Clostridium difficile* toxin) and the final maintenance treatment of those patients who sought medical advice on returning.

Statistical analysis

Statistical analysis using a χ^2 test for independence (with Yates Continuity Correction) indicated that patients with IBD were more likely to develop diarrhoea when abroad than their controls. ($p=0.0001$).

Of the 11 patients with IBD who had self-limiting diarrhoea of less than 3 days, eight patients were receiving IM medications (15.7% of patients on IM treatment). The other three patients were taking ASA medications (11.1% of patients having only ASA

Table 4 Features of patients who sought medical advice

		Medications before leaving abroad	Use of medications to obtain remission	Stool culture, ova, cysts and parasites, <i>Clostridium difficile</i> toxin	Maintenance treatment while in remission
Patient 1	UC	ASA	Corticosteroids+AZA	Normal	ASA+AZA
Patient 2	UC	ASA	AZA+infliximab	Normal	ASA+AZA+infliximab
Patient 3	UC	ASA+AZA	Corticosteroids	Normal	ASA+AZA
Patient 4	UC	ASA	Increase dose of ASA	Normal	ASA
Patient 5	CD	ASA	Corticosteroids	Normal	ASA

ASA, aminosalicylate; AZA, Azathioprine.

medications). There was no statistically significant difference between patients taking IM medications versus those taking ASAs only in developing diarrhoea when abroad.

DISCUSSION

International travel is important both for work and QOL purposes. The primary aim of our study was to evaluate the risk of patients with IBD to develop diarrhoea when travelling abroad. Our case-controlled study demonstrated that patients with IBD were more likely than healthy controls to develop diarrhoea when abroad ($p=0.0001$). It is important to note that 20.5% of patients with IBD developed diarrhoea while abroad. If one compares self-limiting diarrhoea between the two groups, patients with IBD were still more likely to develop diarrhoea than their healthy controls ($p=0.002$). Statistical analysis using a χ^2 test for independence (with Yates Continuity Correction).

Our other hypothesis was that patients receiving IM treatment would develop diarrhoea more often than those patients who are not being administered these drugs. However, our data demonstrated that patients who were receiving IM treatment did not have an increased risk of developing diarrhoea while abroad. Nevertheless, our findings may represent immunocompromised persons who were well and confident enough to travel. This data is supported by two different recent studies.^{7,8} A study by Ben-Horin *et al* showed that IM medications in IBD are not associated with any risk of travel-related illness.⁷ Baaten *et al*⁸ demonstrated that with the exception of travel-related skin infections, patients with IBD receiving IM medications do not have symptomatic infectious diseases more often or longer than non-immunocompromised travellers.⁸

As with any retrospective study, recollection bias could skew the results in unpredictable directions. However, we attempted to limit this bias by restricting the study to trips taken within the last 12 months, and we interviewed both the patient with IBD and the control. Case-note review also helped to decrease recall bias in terms of medications and reported events.

The median travel duration of 9.6 days corresponded well with the median travel duration of an average traveller (7–10 days).³

It is interesting to note that 68.75% of the patients who developed diarrhoea had symptoms that resolved within 72 h without any medications. The only control who developed diarrhoea was travelling with one of the patients with IBD. Thus, were these episodes of self-limiting diarrhoea or traveller's diarrhoea (TD) related to dietary change? This would pose the question if TD is more common among patients with IBD.^{9–12} We think it is unlikely to be secondary to dietary change, as 93.6% travelled to areas with a cuisine similar to the Maltese.

All five patients who definitely had a disease flare had travelled to urban areas with four patients travelling to countries of very high HDI, and the other patient travelled to a country of medium HDI. For those with self-limiting diarrhoea, 10 patients had travelled to countries with a high HDI, and one to a country classified as high HDI. Nine of these patients had travelled to urban areas. An important question arises regarding the latter group. Were these episodes of self-limiting diarrhoea minimal disease flare-ups? It has been suggested⁷ that most illnesses in developed countries are the result of disease flares and not enteric infections. However, one of the healthy travellers (control) also reported diarrhoeal symptoms while travelling with a patient who had IBD. Thus, could patients with IBD be more susceptible to enteric pathogens than healthy controls, which results in TD? Or could an infection by an enteropathogen provoke a relapse of quiescent IBD? An answer to the exact cause of the diarrhoea of very short duration, as in the above cases, is currently difficult to provide. Thus, this reinforces the fact that prior to travel, patients with IBD should have a pretravel medical consultation. The pretravel preparation of patients with IBD, especially those being administered immune suppression medications, must address the following:

1. Is the traveller's underlying IBD stable?
2. Immunisation against travel-associated vaccine-preventable diseases
3. Advice regarding waterborne infections that might result from swallowing water during recreational activities, attention to hand hygiene, safe food and beverage precautions
4. Advice regarding the possibility of TD (within the context of IBD).^{13,14}

In conclusion, travellers with IBD have an increased risk of developing diarrhoea when travelling abroad. However, patients on IM treatment are not at an increased risk. This risk of diarrhoea must not be underestimated, as 20.5% of patients with IBD developed symptoms. A pretravel medical consultation should be a must in all patients with IBD.

Key messages

- ▶ International Travel has been on the increase. Thus, patients with IBD may be required to travel both for work and pleasure purposes.
- ▶ Our case-controlled study demonstrated that patients with IBD were more likely than healthy controls to develop diarrhoea when abroad.
- ▶ Self-limiting diarrhoea was more likely to develop in IBD patients than their healthy controls.
- ▶ Patients who were receiving IM treatment did not have an increased risk of developing diarrhoea while abroad.

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