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TOPIC HIGHLIGHT

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Inflammatory bowel disease in travelers: Choosing the right vaccines and check-ups

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Abstract

The majority of patients with inflammatory bowel disease (IBD) achieve good control of the inflammatory activity using available therapies. When remission is achieved and quality of life recovered, a considerable proportion of IBD patients express their desire to travel abroad, be it for business, academic or leisure purposes. Their physicians should help and encourage them whenever possible. However, preventive measures are warranted to minimize the risk, since IBD patients are exposed to the same infections affecting the general population, plus opportunistic infections (OI) related to the immunosuppression. There are a large number of potential OI that might affect patients with IBD. The true prevalence of these infections is unknown, and can vary from country to country. Therefore, reactivation or *de novo* acquisition of infections such as tuberculosis, malaria, and viral hepatitis will be much more frequent in endemic areas. Therefore, physicians should be aware of these aspects when planning specific preventive measures for patients traveling to a particular country. This includes good control of environmental exposure, chemoprophylaxis when indicated, and the use of a specific vaccination program to prevent endemic infections. In addition, it should be noted that, though the risk of acquiring an infectious disease is probably greater for IBD patients traveling from a developed to a developing country, the inverse situation can also occur; it depends on the previous acquired immunity of the host against infections in any particular environment.

Key words: Inflammatory bowel disease; Vaccination; Opportunistic infections

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PREVENTIVE MEASURES AND CHECK-UPS BEFORE THE TRIP

Patients traveling abroad should adhere to a specific vaccination program depending on the country to which they are traveling. Specific advice by specialists in tropical medicine might be required at least 4-6 wk before the trip, to allow time for vaccines to take effect and to start taking chemoprophylaxis to prevent malaria when needed. Requirements for visiting/staying in any particu-

lar country can be found on the websites of the World Health Organization (WHO) (http://apps.who.int/tools/geoserver/www/ith/index.html) and of the Centers for Disease Control and Prevention (CDC) (http://wwwnc.cdc.gov/travel/destinations/list.aspx). An interactive map provides information on health risks for travelers to specific countries by clicking on any part of the country or a nearby country.

The vaccination status according to current recommended vaccination program for adult inflammatory bowel disease (IBD) patients[1-3] (Table 1) should be periodically monitored, particularly before the start of a trip. Concerns about the safety of live-attenuated vaccines in immunosuppressed patients have arisen due to the possibility of fatal reactivation of the infectious agent contained in the vaccine. However, there are no data regarding the required time free of immunomodulators for administering these vaccines with confidence. The risk of reactivation, which also occurs with opportunistic infections (OI), probably depends on the type, dose, and duration of immunosuppressants added to a particular host response, for example the existence or not of leucopenia and lymphopenia[4]. Thus, an immunosuppressant washing-out period of 2 mo before and after live attenuated vaccine administration seems to be prudent. Live attenuated vaccines include, among others, varicella and yellow fever vaccines (Tables 1 and 2). Additionally, there is limited information as to whether IBD patients, mainly those under immunosuppressants, acquire adequate levels of protection using the present recommended vaccination schedule. For example, in one study including adult patients with rheumatological diseases and Crohn's disease vaccinated against two strains of influenza (A/H3N3 and B), the majority achieved protective titers $\geqslant$ 40, irrespective of whether or not they were taking anti-tumor necrosis factor (TNF) therapy[5]. However, impaired response against a single dose of 23-valent pneumococcal polysaccharide vaccine[6] and against standard three doses of hepatitis B vaccine[7] was reported, mainly in those patients treated with combined immunosuppressants and biologics. Therefore, it remains to be established whether higher doses of vaccine and booster administration might afford better immunization against specific infections.

For IBD travelers coming from countries with well-developed immunization programs, vaccination against tetanus, diphtheria, and inactivated poliomyelitis should be administered every 10 years and a booster dose is recommended before traveling. A booster dose against pertussis is also advisable in combination with the former, as a resurgence of pertussis has been documented in many industrialized countries, such as the United States, Australia, and Canada. Estimating rates of pertussis in developing countries is difficult, because of a lack of access to diagnostic methods and under-reporting. However, epidemiologic estimates by the WHO from Asia, Africa, and South America demonstrate that these areas have the highest disease burden, and there is a public health problem in all age groups[8].

Antibodies against hepatitis B should be checked when planning a trip to high prevalence areas (China, Southeast Asia, and tropical Africa) or intermediate prevalence areas (Eastern Europe, the Mediterranean, Russia, and Central and South America). For immunocompromised patients, regular testing and booster administrations, when anti-HBs antibody levels fall below 10 mIU/mL, are recommended[9]. This is important because not only can the response to standard dose of vaccination be impaired, but antibody titters can decrease with time in immunosuppressed patients who have achieved an adequate previous immunization. There is a combined Hepatitis A inactivated and hepatitis B recombinant vaccine for the immunization of adults. The effect of hepatitis A immunization in IBD patients is not known, but it seems to be severely impaired in immunosuppressed patients for other disease conditions[4].

Influenza viruses change rapidly from season to season, consequently Influenza vaccine must be manufactured and administered every year. This vaccine includes the three strains that cause the most illness in the upcoming season based on virus samples and patterns collected from around the world. Influenza viruses circulate worldwide and IBD travelers should be aware of the outbreaks of specific influenza viruses when they plan a trip to a particular country. They should be vaccinated for the specific strain affecting this particular area at a given moment. In this sense, the pandemic caused by the H1N1 swine-derived influenza strain, or the previously emerged avian influenza strains still circulating, constitute good examples of the need for specific protection[10].

One of the biggest problems for IBD patients traveling to tropical areas of South America and Sub-Saharan Africa is how to prevent yellow fever. It is caused by an RNA hepatotropic virus that causes a pansystemic disease, with fever, hepatic, renal and myocardial injury, hemorrhage, shock, and mortality as high as 50%. Vaccination against yellow fever is mandatory when visiting 16 countries and strongly recommended for all endemic countries. Although limited studies indicate that vaccine immunity lasts for at least 45 years, the WHO requires booster immunizations every 10 years to maintain adequate protection. The yellow fever vaccine 17D contains live attenuated virus and is contraindicated for IBD patients who cannot stop immunosuppressants for at least 4 mo. Hence, traveling to endemic areas should be discouraged for patients requiring continuous immunosuppression to keep their IBD under control. However, the long-lasting immunization effect of yellow fever vaccine allows its administration at any time that is convenient for immunosuppressant discontinuation when a trip to endemic areas is expected in the future. Risk of serious adverse events following yellow fever vaccination is very low, but increases with age (4 per 100 000 doses for people aged 60-69 and 7.5 per 100 000 doses for people 70 and older)[11].

Neisseria meningitidis causes endemic meningococcal disease worldwide, with a specific serotype distribution

Table 1 Current recommended vaccination program for adult inflammatory bowel disease patients[1-3]

Illness	Vaccine	Recommendation	Schedule
Tetanus Diphteria	Purified anatoxin	Recommended	Every 10 yr
Poliomyelitis	Injectable: inactivated	Recommended	Every 10 yr
Pertussis	Acellular antigen	Authorized	Every 10 yr
Hepatitis B	Recombinant peptide	Recommended	Single/double doses? Booster?
Pneumococcal disease	23-valent purified antigen	Recommended	Every 5 yr Single/double doses? Booster?
Influenza	Inactivated virus	Recommended	Annually
Human papillomavirus infection	Recombinant L1 protein	Authorized	??
Measles,mumps and rubella	Live attenuated	Contraindicated during immunosuppression	??
Varicella	Live attenuated	Contraindicated during immunosuppression	Double dose (4 wk interval)
Haemophilus influenzae B disease	Conjugated capsular polyosidique antigen	Authorized	Single dose

Table 2 World distribution of travel-related preventable illnesses and current recommended vaccination program for adult inflammatory bowel disease patients

Illness	Regions with high and intermediate endemicity	Vaccine/schedule	Recommendation
Hepatitis A	High: Africa South America, Middle East Southeast Asia, China Intermediate: Southern and Eastern Europe	Inactivated virus (every 10 yr)	Authorized
Yellow fever	Africa: Sub-Saharan Africa America: Central and South America	Live attenuated (every 10 yr) 17D strain (17D-204 /17DD)	Contraindicated during immunosuppression
Meningococcal disease	Europe: Serogroups B, C Americas: Serogroups B, C, Y Africa and Asia: serogroups A, C, W135	Conjugate polysaccharide C Polysaccharide combined A+C Polysaccharide combined A+C+W+Y (single dose among persons aged 11-55)	Authorized Authorized Authorized
Typhoid	High: Southern Africa Western, Eastern South central and Southeastern Asia Intermediate: Eastern, Middle and Northern Africa, Western Asia, Latin America/Caribbean, Oceania	Vi Capsular polysaccharide (single dose IM. Booster dose every 2-3 yr for those at risk)	Authorized
Cholera	Africa: Congo, Kenya, Mozambique, Uganda, Tanzania and West Africa	Oral Killed (2 doses at 1-6 wk interval with a buffer to protect the B-subunit against stomach acidity)	Authorized
	South and Central America: Peru, Ecuador, Guatemala, Nicaragua Asia: Afghanistan, India, Cambodia, Malaysia, Nepal, Sri Lanka	Oral live	Contraindicated during immunosuppression
Rabies	High: Africa, Asia, parts of Central and South America Intermediate: Eastern Europe, parts of central and South America (Chile, Argentina)	Cell culture-derived vaccine (travellers, not handling animals: 2 doses, at days 0-28. If risk continues booster dose at 6-12 mo)	Authorized
Japanese encephalitis	Southeast Asia Far East	Cell culture-derived vaccine (2 doses, at days 0-28 booster dose?)	Authorized
Tick-borne encephalitis	Europe: Central and Eastern Europe, Russia Asia: China, Siberia, Russian Fareast	Inactivated virus (3 doses at 0,1 and 12 mo)	Use with caution

per continent (Table 2). Polysaccharide vaccines against meningococcal serogroups A, C, Y, and W135 have been available for several decades, but have been little used due to poor immunogenicity and minimal effects on nasopharyngeal carriage. The recent advent of a quadrivalent conjugate vaccine including A, C, Y, and W135 ensures a broad coverage for travelers and should always be considered before the polysaccharide vaccine[12]. However, effective global prevention of meningococcal disease will not be achievable without the availability of a vaccine against Group B meningitis (predominant in Europe and America), for which outer membrane protein vaccines are under development[13].

Travel to the Indian subcontinent is associated with the highest risk of contracting enteric fever. There are two available vaccines against *S. typhi*: the live attenuated oral vaccine containing the *S. typhi* strain Ty21a (Ty21a vaccine) and the parenteral capsular polysaccharide vaccine based on the *S. typhi* Vi antigen (Vi vaccine). Thus, the Vi vaccine is recommended for IBD patients. It is

available for children ⩾ 2 years old, conferring protection 7 d after injection with a maximum neutralizing antibody concentration demonstrated 28 d after vaccination[14]. Percentages of efficacy in immunocompetent individuals range from 55% to 72%, but the figure is unknown for IBD patients taking immunosuppressants. The gastroenterologist should discuss with the patient the efficacy of the vaccine and reinforce the necessity of strict food and water precautions. The same control measures are required to prevent cholera and all diarrheal illnesses. However, when access to clean water and sanitation are not guaranteed, cholera vaccine should be administered, conferring 85% short-term protection, and 60% protection up to 3 years following vaccination. IBD patients taking immunosuppressants should receive the oral-killed vaccine licensed in more than 20 countries, including the European Union (Dukoral®). Another available oral-killed vaccine (Vabiotech, ORC-Vax®) was initially licensed only in Vietnam[15].

Rabies is a viral zoonosis, almost invariably fatal in humans. Rabies is widely distributed throughout the world and present in all continents. However, the probability of rabies exposure is directly related to the incidence of rabies in the area and the probability of contact with infected animals. In areas of high-risk exposure, such as most parts of Africa, Asia, and Latin America, human rabies occurs from the bite of domestic and stray dogs and cats without owners. By contrast, in low-risk areas (North America, southern Africa, parts of the Caribbean, and Europe), the principal mammalian reservoir species are wild carnivores[16]. Currently, cell-culture derived vaccines are used, and these are authorized for use by IBD patients traveling to high risk areas, particularly where there is limited access to medical care[1,3].

Japanese encephalitis (JE) is a leading cause of viral meningoencephalitis transmitted by *Aedes* mosquitoes in large parts of Asia. It is mainly a problem in rural rice growing and pig farming regions, but can also be found at the outskirts of cities. It occurs more commonly in the rainy season (roughly May-September), when the mosquitoes are most active[17]. Individuals under chronic conditions and under anti-TNF therapy are particularly considered candidates for JE vaccine[18]. A novel inactivated cell culture-derived vaccine (IXIARO®) has recently been licensed in the United States and Europe and can be safely administered to IBD patients.

Tick-borne encephalitis (TBE) is a disease of the central nervous system caused by a tick-borne viral infection. A recent systematic review has demonstrated that the three currently licensed TBE vaccines (Encepur children®, Encepur Adults®, and FSME-IMMUN"new"®) gave seroconversion rates of over 87%[19]. However, the relationship between seroconversion and clinical protection has not been established. As all the vaccines may produce commonly but generally mild adverse effects, their use in IBD patients is authorized with caution. In addition, the TBE vaccine has been suspected of causing an exacerbation of autoimmune diseases, but a cause-and-effect relationship has not been confirmed. Taking all these factors together, risk-benefit should be weighed and vaccine administered to those patients traveling to high-risk rural or forested areas, especially in the spring or summer.

PREVENTIVE MEASURES DURING THE TRIP

Though vaccination or chemoprophylaxis remains the most effective means of traveler infection prevention, some additional measures upon exposure to environmental factors during the trip should be taken. These include the avoidance of insect bites and the ingestion of safe foods and beverages. Insects are vectors of infections such as malaria, dengue, filariasis, Chagas, leishmaniasis, onchocerciasis, and trypanosomiasis, among others. At the WHO and CDC websites there is updated information about diseases that should be prevented per country, the type of insect vector, and the best means of prevention. Some of these diseases may be partly prevented by the application of insect repellents. However, the ideal mosquito repellent remains to be identified. It should repel multiple species of arthropods, have long-lasting effect, cause no local or systemic toxicity, be resistant to abrasion and rub-off, and be greaseless and odorless. DEET (N,N-diethyl-m-toluamide) remains the gold standard of currently available insect repellents[19]. Used at variable concentrations ranging from 10% to 75%, it is considered that a concentration higher than 50% offers no additional benefit. Other measures, such as avoidance of outdoor exposure during the period of maximum insect activity (for example crepuscular periods for malaria mosquitoes), and wearing long-sleeved shirts, long pants, and a hat outdoors, are also advisable.

It is important to prevent animal bites and scratches to avoid rabies. If suspected exposure to rabies occurs, prompt and thorough cleansing of the wound, together with administration of immunoglobulin added to immunization with the above-mentioned vaccine starting immediately after exposure, virtually guarantees complete protection[16].

IBD patients should pay particular attention to preventing traveler's diarrhea (TD), as there is evidence showing that intestinal infections can trigger the disease[20] or induce relapses[21]. However, infection by enteropathogenic bacteria does not appear to be associated with a poorer clinical outcome of the IBD flare[21]. There is no evidence supporting the need for chemoprophylaxis for IBD travelers to prevent diarrhea, and the majority of specialists prefer not to recommend it to travelers[22]. However, a recent expert review included IBD patients as potential candidates for chemoprophylaxis[22]. An intermediate and very reasonable position might be early self-treatment when a gastrointestinal infection is suspected[4,23]. Fluoroquinolones are the drugs of choice in IBD, followed by azithromycin in patients who take fluoroquinolone as a part of their treatment[4]. The efficacy of Rifaximin against enteroinvasive bacteria (*Campilobacter*,

Table 3 Preventive measures for inflammatory bowel disease patients coming from developing countries (mainly while taking immunosuppressants or before starting)

	South America	Maghreb and Western Orient	Sub-Saharan Africa	Southeast Asia and India	Other
Thick drop	Consider	No	Always	Consider	No
Stool parasite	Always	Consider	Always	Always	No
Urine parasite	No	No	Always		No
Strongyloides (culture, serology)	Always	Consider	Always	Always	No[1]
Trypanosoma (serology)	Always	No	No	No	No
Histoplasma (serology)	Always	No	Always	No	No
HBV and HCV (serology)	Always	Always	Always	Always	Always
Tuberculin skin test or IGRA	Always	Always	Always	Always	Always

[1]Consider in case of Chinese individuals with eosinophilia. HBV: Hepatitis B virus; HCV: Hepatitis C virus.

Shigella, and *Salmonella*) has never been proved and consequently it is not an appropriate drug for IBD patients with bloody diarrhea and fever[4,22].

The evidence for the use of vaccines against enterotoxigenic *Escherichia coli* (ETEC) is scarce and it cannot be recommended at the present time for TD prevention. In addition, studies should be performed to demonstrate which foods and beverages have the lowest and the highest risk for TD. Though firm evidence is lacking demonstrating the value of dietary and beverage selection in the prevention of TD, uncooked fruits and vegetables and untreated drinking water are considered to hold the highest risk[22].

PREVENTIVE MEASURES AND CHECK-UPS TO DETECT INFECTIONS HARBORED DURING THE TRIP

Patients with IBD are likely to be treated with steroids, immunomodulators, or biologicals. It has been reported that these therapies can increase the risk of severe infections[24] or OI[25], especially when administered in combination, and even more so in the elderly or when narcotics are also prescribed. Thus, those patients on maintenance therapy with these drugs who travel to developing countries are, at least hypothetically, at increased risk for OI. Of course, the time spent in those countries may be one of the most decisive factors in increasing the risk of such infections, and it should be always taken into account when evaluating these patients. Most OI will present as acute manifestations soon after (or even while) the patient returns home. However, some parasitic or protozoal infections can remain latent for years (e.g. strongyloidosis, Chagas' disease, or histoplasmosis); we must remember this especially in patients who stay for a long period of time in developing countries or, even more importantly, for individuals coming from developing countries who are diagnosed with IBD once in a developed country.

Another important factor is familiarizing oneself with the endemic infections affecting countries from which the patients are returning (Table 3). Depending on the geographic area, our investigations should be directed towards some infective agents or others. However, no specific recommendations are yet available for returning travelers; of course, there is no definition for "long-term" travel or stay in developing countries. Therefore, in this section the authors will try to draw a modest picture of which infections should be investigated, and how.

The most common clinical setting should be that of a patient returning from a short stay in a developing country who presents with diarrhea[26]. In this case, stool samples for microbiological evaluation using conventional cultures (mainly to detect enteric pathogens) should be taken and examination for fecal parasite detection should be carried out. It is important to collect at least three samples from different bowel movements (preferably from different days). If infestation by *Giardia lamblia* or *Criptosporidium parvum* is suspected, immunofluorescence is necessary. The presence of fecal *Entamoeba* cysts must be corroborated by serology; if positive, combined therapy with metronidazole and paromomycin should be started. However, in seronegative patients, paromomycin alone might be sufficient[27].

Among chronic infections, strongyloidosis might reactivate in case of immunosuppression[28]. Infection by *Strongyloides stercolaris* is endemic in tropical and subtropical regions, and it can be also seen anecdotally in Europe, the United States, Japan, and Australia. Evaluation of stool samples remains of paramount importance, although with limited diagnostic yield because of the intermittent presence of ova and larva in feces. Collection of repeated stool samples is strongly warranted, as is the use of concentration techniques or specific cultures that can achieve 80% sensitivity. Although serologic tests are highly sensitive, they do not differentiate past from current infection. Strongyloidosis might present not only by diarrhea, but also by abdominal pain or rectal bleeding. It should be especially suspected in patients coming from endemic areas, with a compatible clinical picture and peripheral eosinophilia[29]. Similarly, schistosomiasis is a prevalent chronic infestation in tropical and subtropical regions. Diagnosis is based in the visualization of ova in urine samples. Chagas' disease, or American trypanosomiasis, is a zoonosis found all over South America. The infection can remain latent for 10 to 30 years, and 30%-40% of individuals will then develop a chronic disease[30]. Interestingly, clinical symptoms will be those

related to the development of visceral involvement; in the case of the GI tract, dysphagia due to megaesophagus and constipation, abdominal pain and bloating due to megacolon make up the most common clinical picture[31]. Parasitological studies are of low diagnostic yield, and serological tests (indirect hemaglutination, indirect immunofluorescence, and ELISA) are preferred; in fact, two positive serological tests are necessary to establish the diagnosis[32]. Although digestive involvement is not usually life threatening, cardiac involvement can result in a fatal outcome.

Malaria and tuberculosis are the most common infectious diseases. *Plasmodium falciparum* can persist as a latent infection for 1 to 5 years, *P. ovale* and *P. vivax* for 3 to 5 years, and *P. malariae* for up to 40 years. Thick drop test in peripheral blood remains the diagnostic test of choice, although PCR tests can be useful in cases of low parasitemia[33,34].

Tuberculosis is nowadays systematically ruled out in patients who might be treated with anti-TNF agents. However, this diagnosis should always be taken into account in IBD patients returning from or coming from developing countries. Tuberculin skin tests and interferon gamma assays can be used for the diagnosis of latent or active TB, as recently stated in the European Crohn's and Colitis consensus[4,35]. Finally, histoplasmosis is widely distributed, although predominantly in America and Africa. Primoinfection is often subclinical, but reactivation can be life threatening. Diagnosis is based on direct observation on microscopy, and it is corroborated by a positive culture of biological samples (sputum, skin lesions, liver biopsy, or bone marrow aspiration). Antigenuria is useful to monitor therapeutic response[36,37].

CONCLUSION

In summary, patients with IBD on immunosuppressanttherapy (including steroids) must be carefully evaluated in case of fever, diarrhea, abdominal pain, or rectal bleeding when returning from or coming from developing countries. Learning about the geographical area and time spent in the area are of paramount importance in identifying one or another OI and appropriately targeting the diagnostic tests. In addition, an accurate medical history, as well as a complete physical examination, will be of great value.

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