TRAVELERS' DIARRHEA: GASTROENTEROLOGICAL VIEW OF THE PROBLEM

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Key words: travelers' diarrhea, irritable bowel syndrome, therapy, rifaximin, probiotics

The number of journeys in the world, despite the economic crisis, had already reached 935 million by 2010 [56]. Place of rest is the most important factor determining the risk of traveler's diarrhea (TD). All the tourist areas of the world can be divided into three classes of TD risk: low, medium and high (Fig. 1) [8]. High risk exists in the Middle East, Latin America, Southeast Asia, Mexico and Africa — TD in these regions is found ranges from 20% to 90% during the 2-week stay. Medium-risk areas include Eastern Europe, South Africa and part of the Caribbean islands, where TD occurs approximately in 8-20% of cases. USA, Canada, Australia, New Zealand, Japan and Western Europe are the regions with the lowest risk of developing TD — less than 8% [51].

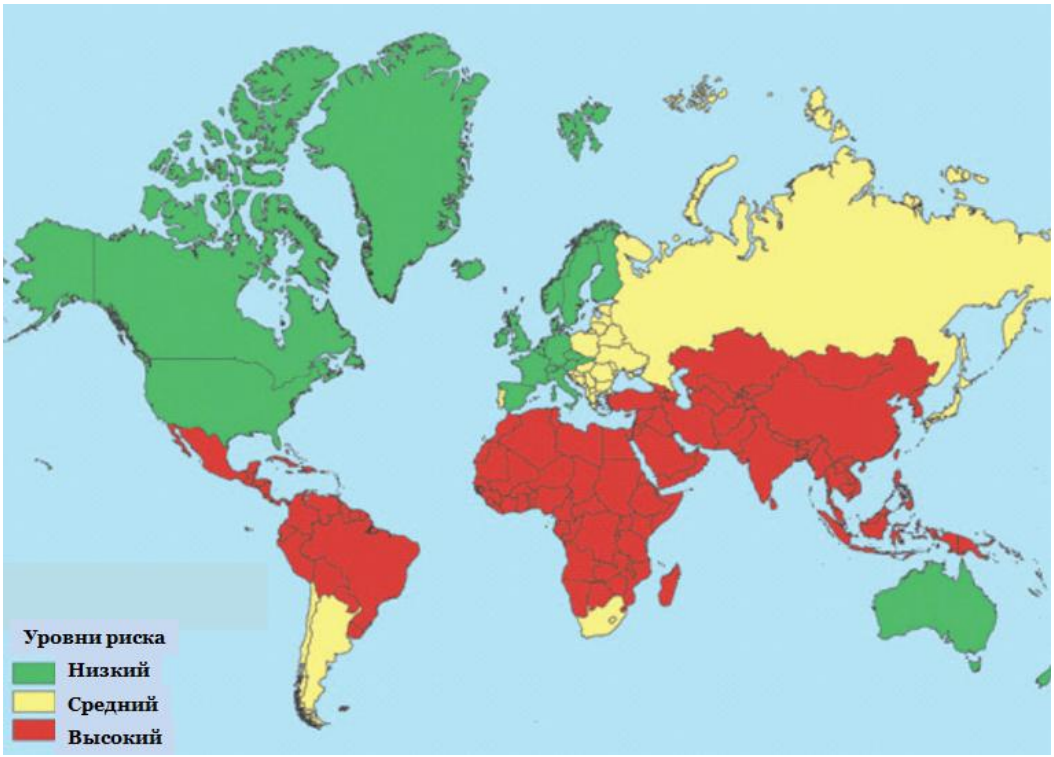

Fig. 1. Map of the world with the risk zones of developing TD.

Diarrhea is the most common problem of travelers in countries with hot climate, where it occurs with a frequency of 30 to 90% and has significant regional and seasonal variations [22, 25]. TD is a particularly serious problem for travelers from industrialized countries because they usually do not have immunity to pathogens encountered during travel. Following groups of people are subjected to the high risk of the disease:

- travelers from industrialized countries traveling to developing tropical or subtropical region;
- children or teenagers;
- tourists who come for the first time in developing regions (as opposed to tourists who often visit high-risk regions);
- lack of food guidelines (e.g., inability to exercise caution in choosing food and drink);
- undergone TD during previous trips (which indicates increased susceptibility);
- genetic risk factors for TD;
- daily use of proton pump inhibitors or other acid-supressive drugs;
- low-budget or extreme tour;
- need to live and work among the people of the region with a high risk of TD (e.g., Peace Corps volunteer or missionary) [6, 23, 48].

Researchers have identified a genetic predisposition as the risk of TD, showing that the number of single nucleotide polymorphisms (SNP) is associated with increased risk of TD or diarrhea with a specific TD pathogen [16, 19, 49]. Genetic polymorphism of histocompatibility antigens with blood group AB0 type, secretory status and the presence of Lewis-antigen are associated with a higher susceptibility to infection with strains of norovirus. The presence of specific gene polymorphism markers of inflammation is associated with a high susceptibility to TD, including IL-8, IL-10, and lactoferrin osteoprotegerin [20, 29, 30, 31].

There are lots of TD pathogens worldwide: enterotoxigenic E. coli is the most common and widespread pathogen, some TD embodiments have defined

geographical risks (e.g., Campylobacter jejuni in Thailand), seasonality (e.g., Cyclospora during premonsoon dry season in Nepal), or epidemicity (e.g., norovirus outbreaks on cruise ships) [14].

Bacterial enteropathogens cause TD in about 80% of cases, viruses and protozoa make up most of the remaining cases. Microbial landscape of the intestine upon TD undergoes significant changes, which are presented in Fig. 2. The most common causative agents of TD are E. coli enterotoxigenic (20-75%), E. coli enteroinvasive (0-6%), Shigella spp. (2-30%), Salmonella spp. (0-33%), Campylobacter jejuni (3-17%), Vibrio parahemolyticus (0-31%), Aeromonas hydrophila (0-30%), Giardia lamblia (0->20%), Entameba histolytica (0-5%), Cryptosporidium sp. (0->20%), Rotavirus (0-36%), Norwalk virus (0-10%) [10]. The main route of transmission — fecal-oral, infection occurs through used products, water, unwashed hands.

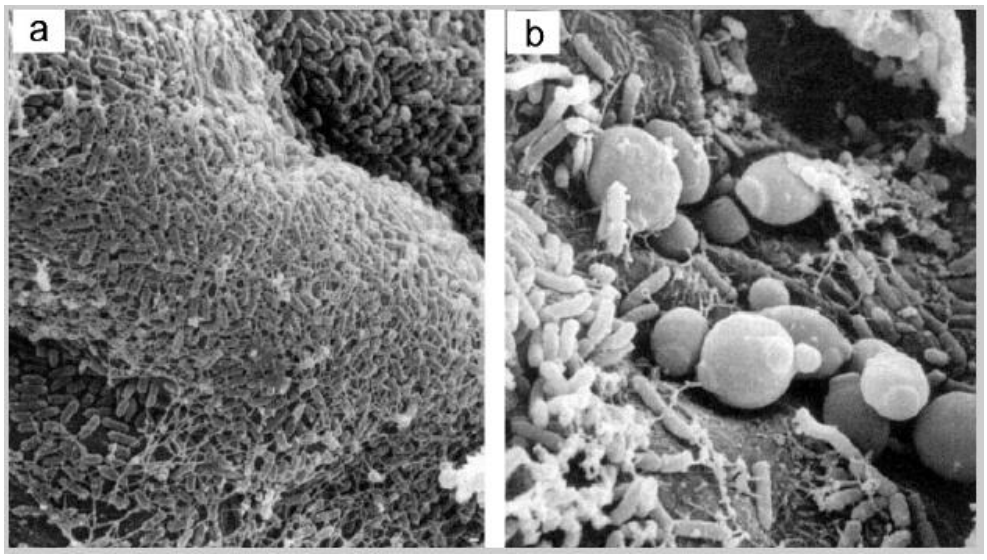

Fig. 2. Electron microscopy: a — microbial landscape of a healthy person, b — microbial landscape upon TD [26].

Watery diarrhea (toxigenic enterocolitis) is the most frequent clinical manifestation of TD and is associated with the risk of dehydration; body temperature normal, except in cases of severe dehydration. It occurs due to toxin of mucosa-colonizing intestinal pathogens, which increases adenylate cyclase activity, and stimulates secretion of water and electrolytes by enterocytes. Less frequent is invasive enterocolitis, which is caused by the direct invasion of bacteria to the

epithelial cells of the intestinal mucosa with consequent damage of the latter and the development of the inflammatory response, accompanied by fever, severe diarrhea, abdominal cramps and tenesmus, mucus and blood present in stool [24].

TD is seen as a clinical syndrome. Classic TD episode is triple or more frequent stool during the day, as well as one or more intestinal symptoms. TD start may be more acute if there were a big numbers of bacteria getting inside, while most of TD takes from 3 to 5 days. TD of viral etiology, which usually occurs on cruise ships and commercial airliners, such as norovirus, is followed by vomiting and has similar terms of duration [34, 44]. About 20% of the tourists are bedridden for 1-2 days, and 40% are forced to delay their planned activities. TD in most cases occurs within the first week and may be resolved within a few days without any treatment, but more than one TD episode in the same trip seems probable [32].

Severe forms of TD, which last more than 14 days, may continue after returning from a trip [36]. TD of protozoal aetiology occurs with delayed onset of symptoms and may persist for several weeks. Coinfection of Clostridium difficile may occur in patients who had already taken antibiotics for the prevention of malaria or postinfectious irritable bowel syndrome (PI-IBS), when fever and vomiting are cut off, but diarrhea and abdominal pain are present, decreasing after defecation [9, 13].

Patients are forced to seek medical care during the trip or upon having returned home. After returning to the country of residence, patients with TD may still complain about numerous persistent or recurrent gastrointestinal symptoms such as diarrhea, constipation, discomfort or pain in the abdomen, bloating [11]. 5-10% of travelers with TD later begin to suffer from IBS in severe form [21, 35]. This variant is called PI-IBS [3]. It is characterized by the presence of a bacterial infection in the gut, a genetic predisposition to chronic inflammation of the intestine, the violation of intestinal motility, bacterial overgrowth syndrome in the small intestine and the violation of intestinal permeability [50]. The risk of developing PI-IBS is 5 times higher in people who had TD than in those tourists who did not suffer from diarrhea while traveling [21]. Duration of PI-IBS course has been evaluated in several studies — in more than half of the cases the disease has been persisted for more than 5 years

[15, 28]. Independent risk factors for chronic PI-IBS include female gender, young age, high levels of anxiety or depression, fever or weight loss during acute intestinal diseases and contamination of Campylobacter toxigenic strains [45, 55]. In US hospitals among patients with IBS about 10% traveled 6 months prior to the beginning of the disease, suggesting a possible link between TD and the development of PI-IBS [53]. In our practice, we often encounter such patients, while real better feeling comes only upon complex treatment, which includes not only antispasmodics, antibiotics, probiotics, but also psychotropic drugs.

TD immunization has been known for over 60 years, it is carried out for people who are moving out of the zone of low risk to the areas of high risk, it reduces the severity of TD, indicating the effectiveness of immunization against common pathogens [7].

Recommendations for treatment. Travelers with mild diarrhea, that does not violate the quality of life, can restore the electrolyte loss by the intake of clean water in combination with saltine crackers, canned fruit juices and salty broth. Dairy products can worsen symptoms, caffeine can enhance the secretion of the gastro-intestinal tract and thus lead to increased fluid loss.

Severe diarrhea, especially in children and pregnant women, requires a careful restoration of lost fluid. It is recommended to use preparations for oral rehydration containing glucose (or complex sugar) and sodium chloride [27]. If preparations for oral rehydration are unavailable, solution can be prepared by adding one teaspoon of salt and eight teaspoons of sugar per liter of purified water.

All persons with a high risk of TD must have antibiotics, probiotics, sorbents for self-treatment while traveling. Admission of loperamide upon TD can lead to severe intoxication, significantly impair the patient's condition and prognosis. The author observed during a trip to China infectious-toxic shock in the Russian tourist, who "treated" TD by loperamide for several days. The loperamide may be used only in conjunction with an antibiotic [33, 54].

In 70-80-ies three antibiotics were successfully used for the TD treatment and prevention — fluoroquinolones (ciprofloxacin or levofloxacin), rifaximin and

azithromycin [40, 46]. In 1985, at the Consensus Development Conference in the US, travel medicine specialists voted against the use of system (suction) antibiotics for the prevention of TD because of the fear of side effects and development of resistance extraintestinal bacteria [18]. These problems that systemic antibiotics have, rifaximin does not. Rifaximin has been made in Italy since 1987 and is approved in 33 countries, including the US and Russia for adults and children older than 12 years. The drug has a broad spectrum of antimicrobial activity, comprising the majority of Gram positive and Gram negative aerobic and anaerobic bacteria causing gastrointestinal infections, including TD [47]. Two published studies demonstrated the efficacy of rifaximin for TD prevention among young people of the US who had traveled to Mexico [39, 43]. Rifaximin was superior to 58-77% compared to placebo in preventing the development of TD. Use of rifaximin for 1 or 2 weeks to prevent TD demonstrated minimal effects on the normal flora of the large intestine [43]. A. W. Armstrong et al. evaluated the efficacy of rifaximin in a randomized, double-blind, placebo-controlled clinical studies involving 100 volunteers at the air base in Incirlik (Turkey). In conclusions of the study rifaximin was recommended for the prevention of TD for servicemen in regions with a high risk of TD [42]. Rifaximin (Alpha Normiks, Alfa Wassermann, Italy) is a highly effective drug with uncomplicated watery diarrhea, which occurs in 95% of cases of TD, acquired while traveling in Latin America or Africa, and in 90% of cases while traveling in Southeast Asia and India. Rifaximin is a non-resorptive antibiotic and therefore has fewer systemic side effects and does not cause the resistance of abenteric flora. Fluoroquinolones are more effective than rifaximin for the treatment of inflammatory diarrhea caused by strains of Shigella [1]. According to a multicenter, double-blind, placebo-controlled study, involving 3380 patients who had an acute infectious diarrhea during a trip to Mexico, Guatemala and Kenya, its duration after administration of rifaximin at doses of 600 and 1200 mg per day amounted to 32.5 hours and 32.9 hours correspondingly, while the placebo — 60 hours [52]. The use of rifaximin not only prevents TD, but has a prophylaxis effect on the development PI-IBS [12]. Antibiotic treatment is recommended in the all cases

of moderate and severe TD, when abdominal pain, cramping and diarrhea are present, and especially if there is a fever or dysentery.

Among non-antibiotic antimicrobials, the most effective is bismuth subsalicylate (De-Nol, Astellas Pharma Europe B.V., the Netherlands). The studies have shown that it possesses mild antimicrobial activity, antisecretory and anti-inflammatory properties. Upon receiving 262 mg of bismuth subsalicylate for 4 times a day with meals, the level of TD occurrence decreased from 40% to 14% as compared to placebo [37, 38].

For the prevention and treatment of TD drugs which regulate the balance of intestinal flora (probiotics) are recommended in addition to antibiotics. Analysis of the effectiveness of probiotics [17], which used the levels of evidence in the treatment/prevention developed by the Oxford Centre for Evidence-Based Medicine, identified the current state of knowledge on the use of results of clinical studies of probiotics: TD prevention — evidence level 2b.

Linex® can serve as an example of a probiotic product that meets modern requirements. Its composition includes L. acidophilus, B. infantis, Ent. faecium, the content of which is not less than 10^7 of microbial bodies. Microorganisms belonging to the drug are enclosed in a capsule which is disclosed in the stomach. However, due to the high acid resistance of all the formulation components, bacteria are not destroyed in the stomach, and the drug is able to exert a probiotic effect at all levels of the gastro-intestinal tract. The combination of lactobacilli and bifidobacteria in the preparation with proven probiotic properties provides a symbiotic effect in colonizing the colon, while the presence of aerobic microorganism — Enterococcus — facilitates active immunomodulating and bactericidal action of the preparation at the level of the stomach and small intestine. Linex® microbes are resistant to most of the antibiotics, which allows using the drug on the background of antibiotic therapy. Resistance of derived strains retained after repeated inoculation for 30 generations and in vivo. Linex® studies show that transfer of resistance to other microorganisms does not happen [5]. If necessary, Linex® can be used simultaneously with antibacterial and chemotherapeutic agents.

Efficacy of Linex® components, combinations thereof, and the preparation itself is directly proved by clinical trials in various gastrointestinal diseases [1, 2, 4].

Approximately 3% of tourists may have diarrhea, which persists for more than two weeks, despite standard antimicrobial therapy. This can be explained by infection with antibiotic-resistant bacteria, as well as invasive parasites, such as Giardia lamblia, C. parvum and C. cayetanensis. Noninfectious etiology is also possible, such as inflammatory bowel disease, disaccharidase deficiency, IBS and cancer.

Unfortunately, when the tourists are planning a trip and, along packing their bags, they pack a set of "travel kits", at best, upon consulting at the pharmacy. It is difficult to consult with your doctor for a recommendation, if it is a polyclinics, or expensive, if it is a private medical center. The media often insincere when it comes to the prevention and treatment of diseases of the digestive organs, recommending pancreatin for "stomach" or claiming that all the toxins in diarrhea are allegedly "evacuated at first diarrheal stool". As a result, when there is a health problem in a foreign country where drugs are available only upon prescription, our tourists are beginning self-medication, which can only reduce the quality of life and prognosis of the disease, and the trip itself turns into the hard test. Active medical disease prevention, including TD, is necessary when traveling, particularly in people with a high risk of its development. Standardized guidelines for tourists traveling abroad should be elaborated, and "travel kits" should be formed with affordable and full instructions for use of each of the component.

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Travelers' diarrhea: gastroenterological view of the problem

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Key words: travelers' diarrhea, irritable bowel syndrome, therapy, rifaximin, probiotics

The tourists go on vacation abroad to the countries with a high risk of traveler's diarrhea every year. This disease has an infectious etiology, its severity depending on several factors — predominantly, on the pathogen. Some patients who have suffered from traveler's diarrhea may have such complications as postinfectious irritable bowel syndrome, which is very difficult to be treated. Non-drug and drug therapy is used for the prevention and treatment of traveler's diarrhea, which includes antibacterials, probiotics, sorbents. The article presents the results of current research, as well as international standards and guidelines for choosing the best preparations that are recommended for the treatment of traveler's diarrhea.