TRAVELLERS' DIARRHOEA – PREVENTION, TRENDS AND ROLE OF MICROBIOME

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SUMMARY

Objectives: In this review, we present a contemporary look at the management of travellers' diarrhoea (TD), and we discuss the potential role of a microbiome as well as the administration of live microorganisms in order to prevent TD.

Methods: We performed a comprehensive search using the PubMed and Web of Science databases for the period 2014–2021, looking for original and review articles on travellers' diarrhoea.

Results: TD belongs among the most frequent illnesses experienced by travellers. For the most part, it is manifested as an acute yet self limiting condition, and only in a few cases proceeds to a prolonged form. Epidemiological analyses have shown that the majority of TD cases are caused by bacterial infections. In practice, pharmacological therapy is often used in the prevention and treatment of TD, since patients naturally seek preventive measures against the development of its severe course and its impact on planned activities. Bismuth salicylate is a strongly recommended TD prophylaxis but is not available on all European Union markets. Although the antibiotic prophylaxis is not generally recommended in guidelines, some antibiotic or chemotherapeutic agents are accessible over-the-counter in certain countries, and travellers are routinely encouraged to use them preventively. This routine can alter the microbiome of the traveller and promote the spread of drug resistant bacteria in their place of residence. Probiotic administration is considered safe, although the quality of evidence in favour of its prophylactic use in TD is currently low.

Conclusions: The challenge for public health authorities is to educate personnel that can directly influence the behaviour of travellers through safe and effective pharmacological alternatives to antibiotics. Manipulation of the gut microbiome using specific probiotic strains can represent a safe and promising intervention.

Key words: travellers' diarrhoea, prevention, prophylaxis, microbiome, probiotics

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INTRODUCTION

Diarrhoea is a common illness of travellers, particularly those, who are visiting developing countries. In 1963, Benjamin Kean described travellers' diarrhoea (TD) syndrome while studying travellers to Mexico (1). Several years later, he participated in the identification of a frequent cause of TD, the enterotoxigenic *E. coli* (ETEC) (2) and an appropriate therapy was developed shortly after ETEC identification (3). The incidence of TD remains in a range of between 10–40%, depending on traveller's characteristics and travel destination (4). More contemporary sources indicate that TD affects about 80 million travellers every year (5). TD occurs in 20–50% of travellers from developed countries travelling to developing countries for more than 2 weeks (6). Even when travelling in developed European countries, an inverse relationship has been observed between the level of per capita income and the incidence of TD (4). The incidence of TD is the same in men as in women, although women seek medical help more often (7). Travellers usually seek medical advice only after the onset of symptoms, what we find one of the problems that needs to be addressed to public health authorities. We reviewed the problematics of TD with an accent on effective preventive actions against its development.

MATERIALS AND METHODS

We performed a comprehensive search using the PubMed and Web of Science databases for the period 2014–2021, looking for original and review articles on travellers' diarrhoea. We established search terms prior to the comprehensive literature search as follows: (traveler* diarrhea OR traveller* diarrhoea) AND (microbiome OR probiotic*) AND (prevention OR prophylaxis). We restricted the language to English. We extracted the data (940 records) and moved to a reference manager. After removing duplicities, we screened abstracts whether they bring new information to the understanding of problematics. After discussion, we added yielded substantial articles (22 articles) to our existing database (13 articles). Further, we manually added additional 4 articles using Google Scholar.

RESULTS

Definition

TD can be defined as ≥ 3 liquid defecations over 24 hours and 3 degrees of severity are recognized. Mild TD is characterized as 3 unformed stools without the presence of other symptoms and

does not limit travellers in their planned activities. Moderate cases are defined as 3–5 or more unformed stools, without the presence of other symptoms. Severe TD manifests itself as > 5 unformed stools per day accompanied by symptoms, e.g., abdominal cramps, fever, vomiting, tenesmus and/or blood in faeces (6, 7). In rare cases (3%), patients develop TD with defecation frequency as high as ≥ 10 per day (8).

A typical example of TD manifestation is a diarrhoea caused by ETEC: intensive watery stool accompanied by abdominal cramps, nausea and malaise (9).

A post infectious irritable bowel syndrome develops in 3–17% of travellers. The predictors seem to be the severity of TD course, number of TD episodes, presence of diarrhoea prior to travelling, and infection caused by ETEC-producing heat-labile enterotoxin (10, 11).

Microorganisms Causing TD

The primary origin of TD relates to the ingestion of germs present in contaminated food and beverages (7). TD can be caused by bacteria, viruses, protozoa, and fungi. Generally, ETEC-producing heat-labile or heat-stable toxin is considered the most common cause. Further, TD could be caused also by enteroaggregative *E. coli* (EAEC), other *E. coli* pathotypes, noroviruses, rotaviruses, *Salmonella* spp., *Campylobacter jejuni*, and *Shigella* spp. Parasites and *Microsporidium* are rather of local importance in developing countries (7, 9), e.g., in the Sub-Saharan Africa region (12). According to recent publications it would appear that EAEC and enteropathogenic *E. coli* (EPEC) are more frequent in comparison to ETEC (5, 13).

Identifying pathogens from faeces using culturing methods is successful in only 15% of cases. In 2016, Lääveri et al. analysed TD-associated pathogens using polymerase chain reaction (PCR) methods with a focus on asymptomatic travellers and severity of symptoms. The travellers were not permitted to use antibiotic treatment. The faeces of 382 travellers were analysed before and after travelling. The analysis was designed to detect the following pathogens: *Salmonella*, *Yersinia*, *Campylobacter*, *Shigella*, *Vibrio cholerae*, and 5 pathogenic pathotypes of *E. coli* – EAEC, EPEC, ETEC, enterohemorrhagic (EHEC), and enteroinvasive (EIEC). The subjects were categorized by the presence or absence of TD during the journey and after return, and also by the severity of symptoms. A pathogen was identified in 61% of asymptomatic patients, in 83% of the patients who overcame TD, and in 83% of patients with ongoing TD. In these groups, 25%, 43% and 53% of the patients were hosting ≥2 pathogens, respectively. Of all identified pathogens, EPEC, EAEC, ETEC and *Campylobacter* were particularly associated with persistent symptoms of TD. Pathogens were found in the stool of a high percentage of travellers, both symptomatic and asymptomatic. The authors concluded that the modern methodology to a certain extent shifts the current opinion on detection of pathogens in faeces. The obtained data do not support the indication of antibiotic treatment based solely on the finding of a pathogen in the stool, since some pathogens do not evoke TD symptoms. Accordingly, antibiotic treatment is only rarely needed. In the future, analyses should always include a control group of asymptomatic patients (13).

Risk Factors

The risk of developing TD is significantly related to the level of hygiene and sanitation in the country of destination and is much greater in countries designated as "developing" or "Third World". These countries are characterized by low incomes, and this fact is related to a lower level of hygiene habits and sanitation (6, 7, 9, 14). It should be noted that more luxurious accommodation and catering facilities do not necessarily guarantee a reduction of the risk of developing TD (7).

Despite the fact that most episodes develop during the first week of a stay, with the peak 2–3 days after arrival at the destination (9), the duration of the visit is a further risk parameter. The first two weeks of visit seem to be crucial and determine the incidence of TD in defined region (7). In a study reported from Kenya, the risk of developing TD decreased with the duration of stay as follows: 1st week 36.7%, 2nd week 9.9% and 3rd week 3.3% (15). The overall risk of developing TD grows with increasing duration of visit, while the visits longer than 3 weeks are considered the riskiest (14). The risk of developing TD in a specified destination is regarded as high when the average incidence of TD is ≥20% during the first 2 weeks of the visit, and as intermediate when the incidence ranges from 8–20% (Fig. 1). We should recognize that the intermediate risk is reported in certain Southeast European countries and Russia.

Travel style is one of the determining factors. Backpackers often choose street food which may contain a significantly greater pathogen load in comparison with meals prepared by professional staff in restaurants (7–9). Cruise travellers report fewer episodes of gastrointestinal problems, although in the case of an outbreak (most often caused by a norovirus), it is difficult to limit the spread of infection. Younger travellers tend to choose more sophistically prepared dishes, consuming larger portions of food, leading to ingestion of higher pathogen inoculum (7). Infants and toddlers have usually more intensive course of TD, often resulting in a need for medical assistance (19).

Protective Factor

A previous visit to high-risk destination is considered a protective factor against the development of TD (20).

DISCUSSION

The general issue of this problematics is a lack of epidemiological information limiting the ability of formulation the recommendations. Most TD has a mild course, a short duration, and does not require any causal treatment (6). Only in 10% of cases does TD persist for more than 7 days, in 5% longer than 14 days and in 1% longer than a month (16). Symptomatic treatment of manifestations, such as rapid passage, abdominal cramps and nausea, may be advised (7). In practice, pharmacological therapy is often used in the prevention and treatment of TD, since patients naturally seek preventive measures against the development of its severe course and its impact on planned activities.

Non-pharmacologic Prevention

Even though the prevention measures for TD are widely known within the healthcare professional community, travellers do ask for advice only rarely. They usually learn from non-medical sources that present unprofessional, scientifically unsound principles which claim to reduce the risk of developing TD.

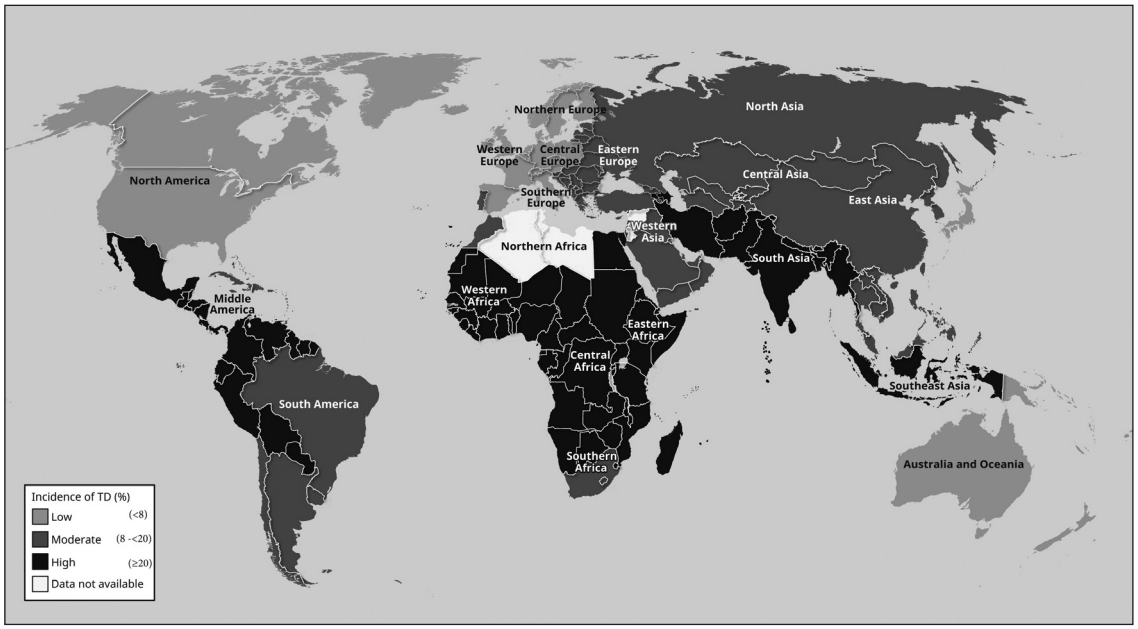

Fig. 1. *Incidence of travellers' diarrhoea among residents of industrialized countries during the first two weeks in different regions of the world in 1996–2008.*
Adapted from studies by Steffen et al. (7), Soonawala et al. (8), Pitzurra et al. (16), Belderok et al. (17), Mues et al. (18)

Current evidence shows that avoidance of certain foods and beverages provides only mild protective effects. Washing hands and using antibacterial gels seem to be the most effective precautions (7, 9). However, even these measures are not effective in all situations, since pathogenic microorganisms have been detected in sauces, raw fruits and vegetables, or ice cubes for beverages (7). Discussed principles that a traveller may benefit from are summed up in the following points (6):

- Wash hands thoroughly with an antibacterial soap before each meal.
- Choose food that is thoroughly cooked and served hot.
- Avoid elaborately prepared local specialities.
- Avoid foods that are stored for extended periods at room temperatures, reheated foods, or foods that may have come in contact with insects or animals.
- Avoid eating seafood, oysters and clams, shellfish, mussels.
- Consume only self-peeled fruits and vegetables (e.g., banana, papaya, citruses), avoid raw salads and leafy vegetables.
- Boil or filter tap water.
- Avoid mixed drinks and drinks with ice, ice cream, milk, and dairy products made from uncooked or unpasteurized milk (including cheese).
- Dry foods such as bread can generally be considered safe.

Pharmacologic Prophylaxis

Bismuth salicylate is strongly recommended in the prophylaxis of TD (21), however, it is not available on all markets within European Union.

Routine preventive use of systemic antimicrobial therapy is not recommended except for patients with a potential serious health risk in case of the development of TD (21), including patients with malignancies, undergoing immunosuppressive therapy, HIV patients, or patients with nonspecific inflammatory diseases (Crohn's disease, ulcerative colitis) (9). If prophylactic antibiotic treatment is indicated, rifaximin is the agent of choice. Ciprofloxacin and levofloxacin are not recommended in the prophylaxis of TD (21). Nifuroxazide, a broad-spectrum locally acting chemotherapeutic agent is often being proposed and sold to travellers as an over-the-counter drug for prophylactic use in developing countries such as Egypt, yet little is known about its efficacy and adverse effects including the possible disruption of the gut microbiome of the host.

The role of microbiome in TD development remains elusive. There is little empirical research dealing with microbiome changes in travellers (22). In 2015, Youmans et al. compared gut microbiomes of travellers with TD caused by ETEC/noroviruses/multiple pathogens/unidentified pathogen with the microbiomes of healthy travellers. A pattern of a "dysbiotic" microbiome was profiled from these observations. The ratio of phyla Firmicutes to Bacteroidetes was higher in favour of Firmicutes for travellers with TD (regardless of its aetiology or the presence of the pathogen). When travellers with TD and travellers without TD were compared, both had approximately the same α-diversity (number of bacterial species) but differed significantly in β-diversity (distribution of various bacterial species) (23). Stamps et al. reported that in the studied group of warfighters there were few apparent differences in subject microbiomes before and after deployment. The data suggest that despite high incidence of TD while on deployment most subjects had few changes in their gut microbiome that persisted after deployment was complete (24).

Only partial successes have been achieved in the effort to define a "protective" and a "risk" microbiome. Even in the future, it may be extremely difficult to draw clear conclusions from clinical observations of microbiome changes during travelling due to various factors including asymptomatic pathogen carriage, dose of the pathogen, host microbiome before infections, and the time taken to visit a medical facility. Microbiomes are inherently dynamic and therefore it is necessary to distinguish between the factors that are of significance and factors that are irrelevant. Each of the

researched factors, as well as many currently unknown factors, will undoubtedly influence the handling of the obtained data (25). Manipulating the microbiome with interventions such as probiotic and/or prebiotic administration or faecal transplants is considered a promising intervention in the field of TD, but still insufficiently investigated. Nowadays, there is low quality evidence in favour of prophylactic supplementation with probiotics, and therefore this approach has not yet been recommended (6, 7, 9, 21, 22).

The administration of probiotic microorganisms is considered safe (14, 22). It should be noted that probiotics are effective in preventing antibiotic-associated diarrhoea and in treating acute diarrhoea in children, which has been positively evaluated in recent years by evidence-based medicine (26, 27). Unfortunately, only 3% of clinical trials of probiotic microorganisms focus on TD prevention (28).

Recently, it has been emphasized that the beneficial effects of live microorganisms are strain-specific and specific to the indication (29). Therefore, any conclusion on the efficacy of live microorganisms in individual cases should be drawn based on a subgroup analysis of the specific strain or specific mixture of strains (30). The selection of an appropriate strain appears to be crucial in the prevention of TD. Recent meta-analyses have shown that from all the studied strains, only *Saccharomyces boulardii* HANSEN CBS 5926 (synonymous with CNCM I-745) has proved to be significantly effective in reducing the risk of TD, with its greatest effect on travellers visiting North Africa and Turkey (14, 22).

Vaccination

Nowadays, there is no licensed vaccine providing a solid protection against the development of TD. Although vaccines against *Salmonella* Typhi, *Vibrio cholerae* and rotavirus have been developed, none of these microorganisms is the major cause of TD (9). Dukoral, the cholera vaccine, simultaneously provides protection against one of the most common TD pathogens, the heat-labile toxin producing ETEC, but has a limited efficacy of 60% (6). A vaccine against ETEC was developed several years ago, however, it was found ineffective and had a number of adverse effects (31).

Therapy

Oral solution with reduced osmolarity is considered an ideal rehydration option and in most cases yields satisfactory results. The composition of the solution is presented in Table 1 (32, 33). Adult patients can also be hydrated with clear broth, mineral water, or (diluted) fruit juice (9).

Loperamide (or diphenoxylate) is used in the symptomatic treatment of mild TD. Loperamide acts on gastrointestinal opioid receptors, supressing the motility of intestines and prolonging the passage. Its use is indicated especially when the rapid ceasing of symptoms such as persistent watery stool is needed. In the treatment of moderate TD, loperamide may be used as a monotherapy or an auxiliary treatment to antibiotic therapy, especially if the prompt suppression of symptoms is required (6, 7, 21). Loperamide should not be used where signs of an invasive pathogen are present – fever, faecal occult blood and abdominal pain (9).

Some publications recommend the use of bismuth salicylate, which reduces the severity and frequency of defecation, yet it seems less effective when compared to loperamide (7, 9).

When visiting the (sub)tropics, 5–30% of patients use an antibiotic therapy (34). Although antibiotic treatment may reduce the duration of TD by 36 h (7), it may also lead to the acquisition of multidrug resistant pathogenic strains (6, 34–36). In 2018, Lääveri et al. reported how many of 456 travellers used/did not use antibiotics and whether they developed/did not develop diarrhoea during the travel and used quantitative PCR for stool pathogens examination; 16% of travellers used antibiotics, 89% of which were used due to TD. The pathogen was identified more frequently in patients who did not take antibiotics (83% vs. 50%). Surprisingly, pathogenic bacteria (Shigella, EIEC) were detected in the faeces of travellers who have been using antibiotics during the travel; up to 50% of treated patients were carriers of a TD-causing pathogen, which may indicate resistance or reinfection/recolonization after the treatment (34). Acquired multi-resistant bacteria can persist in the gastrointestinal tract in 50% of returnees for 1 month, in 10% up to 1 year, and meanwhile may be transmitted to approximately 10% of the household population (6).

Antibiotic agents should be chosen on the basis of destination (7). First-line antibiotics include azithromycin and fluoroquinolones (ciprofloxacin, levofloxacin) (6, 7, 21). The non-absorbable antibiotic rifaximin is effective against non-invasive pathogens (7). At this point, it should be emphasized that TD symptoms can persist in up to 20% of patients after successful eradication of the pathogen. This state is known as post-infection irritable bowel syndrome and may develop due to microbiome disruption as a result of previous infection and/or antibiotic treatment (6). The authors Ericsson and Riddle discuss the option of carrying antibiotic medication in reserve instead of seeking medical help in the destination. The reason is the nature of care that might be provided (e.g., unnecessary hospitalization, intravenous fluids, polypharmacy, or wrong antibiotics) and inconvenience (37). Nevertheless, recently obtained data revealed that only less than half of those travellers with TD justifying antibiotic treatment had in fact used antibiotics. It demonstrates that most cases meeting the current criteria for using antibiotics recover without antimicrobial treatment. The data suggest that treatment guidelines should be revised and a stricter definition of cases indicating antibiotic treatment should be introduced (38).

The role of probiotics in TD therapy remains unexplored. Although the therapeutic effect (shortening of duration and reducing the frequency of defecation) of certain probiotics (*S. boulardii*) in

Table 1. *Oral rehydration solutions with reduced osmolarity*

	WHO	**ESPGHAN/ NASPGHAN**
Glucose	75 mmol/L	74–111 mmol/L
Sodium	75 mmol/L	60 mmol/L
Chloride	65 mmol/L	N/A
Potassium	20 mmol/L	20 mmol/L
Citrate	10 mmol/L	10 mmol/L
Osmolarity	245 mOsm/L	200–250 mOsm/L

Source: Behrens et al. (31), Booth et al. (32)
WHO – World Health Organization; ESPGHAN – European Society for Paediatric Gastroenterology Hepatology and Nutrition; NASPGHAN – North American Society for Pediatric Gastroenterology, Hepatology and Nutrition

acute infectious gastroenteritis has been demonstrated (39), there is a high degree of heterogeneity between studies (6). Currently, scientific societies do not recommend using probiotics as a TD treatment strategy due to a lack of evidence (impossibility of issuing recommendations according to the principles of evidence-based medicine) (21).

CONCLUSIONS

The research and validation of effective and safe measures to prevent TD represent a challenge for the future, in particular because the aetiology of TD is diverse. Regarding the prophylaxis of TD, commonly used hygiene measures have failed to be sufficiently effective in practice. This can be attributed to the fact that travelling abroad is associated with exploring and tasting local cuisines, which leads tourists to ignore hygiene recommendations. From a hygienic point of view, emphasis should be placed on regular hand washing and/or the use of antibacterial gels, even though robust data to suggest this is effective in preventing TD are lacking. Vaccines targeting the most common cause of TD (*E. coli*) with promising clinical profile are in the process of development but are yet not commercially available. There are new developments in progress proven to be effective in animal models encompassing phage therapy and microcins, but none of which with sufficient data from human studies. A recent guideline generally supports the use of bismuth salicylate, while strongly recommends against the routine use of antibiotics (21).

The unrestricted availability of diverse antimicrobial agents in pharmacies in developing countries has led to their routine use, which may contribute to the emergence of multidrug-resistant bacteria. Thus, non-prescription antimicrobial use promotes inaccurate drug choices, dosages and therapy durations. Therefore, effective strategies leading to the reduction of antibiotic usage and its accompanying consequences are warranted.

Travellers are often being instructed (by non-clinical sources, e.g., travel agency employees) to use antimicrobial agents prophylactically. Since travellers usually seek medical attention only after the onset of symptoms, one of the issues that needs to be addressed to public health authorities is how to educate and train travel agents and delegates to directly influence the behaviour of travellers prior to travel. Moreover, public health authorities are increasingly adopting the use of social media to communicate with the public; hence educational programmes should also be developed in this area.

In this context, manipulation of the gut microbiome achieved by use of targeted probiotics represents a promising and safe intervention, although its role in the prevention of TD development needs to be better understood. One of the possible strategies for the beneficial gut microbiota modulation is the administration of the probiotic yeast *S. boulardii* HANSEN CBS 5926 (CNCM I-745), which has been proven to be safe and concurrently the most effective among the probiotic options (14).

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Conflict of Interests

RD and MW declare no conflict of interest at the time of submission of the manuscript. RD is an employee of S&D Pharma.

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