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Recent Advances in Travelers' Diarrhea: Epidemiology, Diagnosis, and Treatment

Jogendra Vijay Atluri[1*], B.R. Raghukumar[2] and Pavan Sreenath[3]

[1]Southwestern University, PHINMA, Cebu City, Philippines
[2]Kempegowda Institute of Medical Sciences, Bengaluru, Karnataka, India
[3]Andhra Medical College, Visakhapatnam, Andhra Pradesh, India

Abstract

Introduction: One of the most common clinical syndromes affecting travelers is travelers' diarrhea (TD). The purpose of this narrative review is to provide an overview of the key discoveries related to TD over the past two years, along with a list of future research topics.

Methods: A PubMed search was conducted to locate new data in TD research published between 2019 and 2023 compared with some reports published between 2000 - 2018. Contribution to epidemiology, etiology, diagnostics, management, and long-term consequences was also considered, along with public health, discovery, and clinical practice.

Results: A total of 218 articles were found during the initial search in the literature. We obtained 107 and examined 84 articles for potential inclusion. Despite this discovery, there is still a moderate risk of TD among students and military travelers, and it remains challenging to control food and water in large gatherings. The rise in culture-independent testing has resulted in the continuous identification of pathogens that were previously known, as well as a higher frequency of detecting norovirus. The resistance rates to fluoroquinolones are consistently increasing due to the escalation of multipathogen infections. This necessitates considering clinical, epidemiological, and diagnostic information. It is increasingly clear that non-absorbable antibiotics may offer an alternative to current recommendations (such as azithromycin and fluoroquinolones). However, they are not advised for febrile diarrhea, dysentery, or in regions/itineraries where invasive pathogens are likely to cause illness. Recent research has explored the connection between the microbiome and the prevention and consequences of TD. Although distinct characteristics have been identified, there is still a significant level of uncertainty. The acquisition and carriage of extended-spectrum beta-lactamase–producing Enterobacteriaceae (ESBL-PE) are on the rise. Lastly, ongoing research supports the post-infectious consequences, while further investigation is needed to understand the mechanisms behind reactive arthritis and post-infectious IBS.

Conclusion: The issue of TD remains an important travel health issue across the globe as we continue to learn more about it. More research is needed to mitigate risk factors associated with antibiotic use and its associated consequences.

Keywords: Antibiotics, Travelers' diarrhea, Irritable bowel syndrome, Reactive arthritis

[*]***Correspondence to*:** Jogendra Vijay Atluri, Southwestern University-Phinma, Cebu City, Philippines, E-mail: a.j.vijay97@gmail.com

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Introduction

Diarrhea is a change in normal bowel movements, characterized by an increase in the frequency, size, and water content of feces. It is typically clinically described as an increase in the number of liquid or semi-formed bowel movements to three or more within a 24-hour period. Acute diarrhea is commonly defined as diarrhea lasting for 14 days or less, while persistent diarrhea lasts for more than 14 days. Diarrhea lasting for over 30 days is often referred to as 'chronic' [1]. This analysis explores the impact of treatments for TD in adults. For the purpose of this analysis, TD is defined as diarrhea that occurs during or shortly after traveling in individuals who have crossed a national border from a wealthy country to a poor country [2-4].

Between 30% and 70% of individuals traveling internationally are likely to experience a diarrheal illness while they are traveling or shortly after. The occurrence of diarrhea among travelers is influenced by the time of year and the country they are visiting, with those going to Africa, Asia, Mexico, Central and South America, and the Middle East being at the greatest risk [5]. The precise epidemiology of TD is not well comprehended. The incidence is higher in individuals visiting countries with limited resources, but the specific rates vary depending on the location and time of year of travel [6]. The cause of diarrhea is determined by the geographical area, food hygiene standards, sanitation practices, water supply, and the season. In more than half of individuals with diarrhea, no specific pathogens are identified. When it comes to returning travelers, approximately 50% of cases are caused by bacteria such as enterotoxigenic *Escherichia coli*, *Salmonella*, *Shigella*, *Campylobacter*, *Vibrio*, *Yersinia*, and *Aeromonas* [7].

Methods

Comparing certain reports published between 2000 and 2018 containing the terms 'traveler's diarrhea' (including variations such as travelers and diarrhoea) either in the title or abstract sections, we conducted a PubMed literature search of articles written in English

between 2019 and 2023. The search method encompassed fresh information from observational studies and randomized controlled trials involving non-human subjects [8]. Articles were selected for inclusion based on their relevance to public health, discovery, and clinical practice related to TD [9]. The results were categorized according to epidemiology, etiology, diagnostics, management, and long-term effects.

Epidemiology

Incidence and risk factors

The occurrence and risk factors of TD vary depending on the type of traveler and the environment, as indicated by recent research findings. The TD affects not only tourists but also business travelers, military populations, and individuals staying in hotels or on cruise ships during outbreaks. In such cases, it is often possible to identify a single pathogen responsible for the outbreak. However, comparing data precisely can be challenging due to differences in how they are defined, such as attack rates per stay abroad or incidence rates per 1 or 2 weeks of stay [10-12]. Nonetheless, a general idea of the risk levels in different regions can be obtained. Figure 1 illustrates that developing countries are considered high-risk regions, with TD rates ranging from 20% to 90% for each 2-week stay. On the other hand, low-risk areas have an 8% occurrence of TD per 2-week stay. Intermediate-risk regions are defined as those with incidence rates between 18% and 20%.

There is no significant impact of seasonal variations on the prevalence of TD. A British tourist visiting Monastir, Tunisia, experienced traveler's diarrhea between May and July, which increased to 20% - 23% in August and October. Similarly, Jamaica and other places experienced high rates of both total and classic TD between June and October [13]. However, upon comparing the rates over time, it becomes clear that there has been a noteworthy decrease in TD rates in southern Europe. Additionally, it appears that Tunisia and Jamaica have effectively minimized the risk of illness through the coordinated efforts of their authorities, particularly the ministries of health and tourism [14]. In contrast, most other destinations have shown minimal to zero reduction in risk in recent decades, despite our group's investigation using identical questionnaires.

There are notable variations in the occurrence rates of TD for

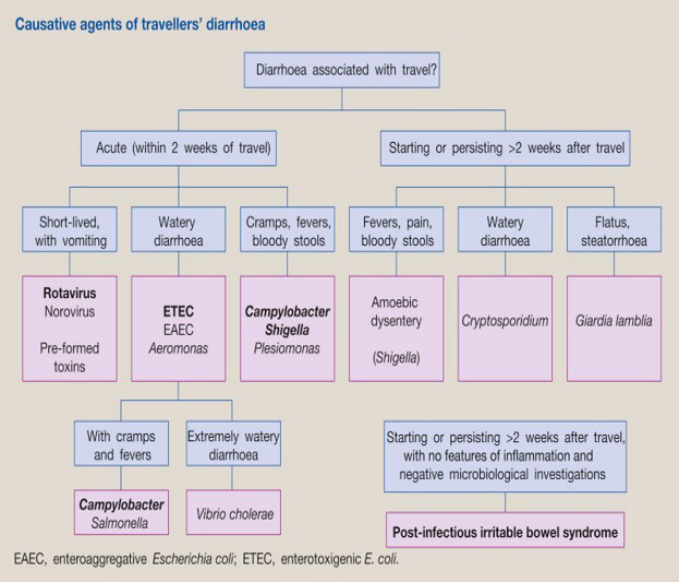

Figure 1: Causative agents of TD [25].

different risk groups, even within a single location. The primary determinant appears to be the choice of accommodation. As evidenced in Jamaica, the occurrence rates for traveler's diarrhea ranged from 0% to 33% among 18 hotels that were visited by a minimum of 40 guests for a week [15]. Experts acknowledge that the occurrence rates of TD reflect the level of hygiene maintained at the visited places. It is also expected that the duration of exposure plays a role. Previous research has shown that 5-star hotels tend to have a slightly higher occurrence rate of TD compared to many 3- or 4-star hotels. This finding is logical, given that higher-end hotels often rely more on manual food preparation. The nature of travel is another determining factor: beach vacations in resorts have lower incident rates (28%), while tours have slightly higher rates (31% for group tours and 32% for individual tours), and adventure tours have the highest rates (34%). "All-inclusive" tours are typically associated with higher incident rates, which can be hypothetically explained by increased consumption of alcoholic beverages by travelers on such tours [16-18]. Secondly, the traveler's country of origin is the most relevant host factor. It has long been observed that individuals from developing countries have a very low occurrence rate of TD (2% - 8%) when visiting other developing countries. This phenomenon has been demonstrated among convention delegates, students, and military populations. Similarly, multiple studies have found that travelers who have recently visited tropical regions have a reduced occurrence rate of TD, likely due to the development of some form of immunity [19].

Several studies have indicated that younger individuals are more susceptible to TD. Infants, toddlers, and young adults between the ages of 15 and 30 are particularly at risk of developing TD. It can be hypothesized that small children are especially vulnerable to this condition because they come into contact with contaminated surfaces and objects and then often lick their fingers. On the other hand, young adults may be more prone to consuming a larger number of pathogens due to their increased appetite. Sex does not seem to have a significant impact on the incidence rates of TD, as most studies do not show a noticeable difference. The higher risk among young adults cannot be solely attributed to their more adventurous travel style, as even when the population is divided by hotel and only travelers on all-inclusive tours who do not eat outside are considered, a significant difference is still observed. Recent research has also shown that there is a genetic predisposition to TD [20]. In individuals with the AA genotype 251, there is a significantly higher occurrence of diarrhea caused by enteroaggregative *E. coli* compared to those with the T genotype or even the TT genotype. Whether the increased incidence of TD among British travelers is linked to genetic variations or different dietary habits remains unknown. Furthermore, a lack of gastric acidity, which can occur due to surgery or the use of medications like omeprazole or magnesium and aluminum hydroxide (e.g., Maalox; Novartis), has been identified as a risk factor for TD [21].

Pathophysiology

The main way that TD is commonly spread is through the transmission of the causative microorganism (causative agents are mentioned in the table below) via the fecal-oral route, usually by consuming food or water that has been contaminated. The time it takes for symptoms to appear varies depending on the specific microorganism involved, with viruses and bacteria taking between 6 and 24 hours, and intestinal parasites requiring 1 to 3 weeks [22-24]. The pathophysiology of TD differs depending on the causative agent and can be categorized into two pathways: non-inflammatory and inflammatory. Non-inflammatory agents reduce the absorptive capacity of the intestinal lining, leading to increased output from the gastrointestinal tract. Inflammatory agents, in contrast, cause damage to the intestinal lining either through the release of cytotoxins or direct invasion. This loss of

surface area leads to a decrease in absorption and an increase in bowel movements (Figure 1) [25].

History and physical

Symptoms typically manifest 1 to 2 weeks after reaching a destination with limited resources, although symptoms can appear at any time during the stay or shortly after arrival. The TD is defined as experiencing three or more loose bowel movements within 24 h, or a twofold increase from one's usual bowel habits [26]. Diarrhea usually occurs suddenly and is accompanied by abdominal cramps, fever, nausea, or vomiting. Patients should be questioned about the presence of blood in their stool, any fevers, or other related symptoms. A comprehensive travel history should be gathered, including details about the timeline and itinerary, dietary and water intake at the destination, illnesses among fellow travelers, and potential sexual exposures [27, 28].

Physical examination in self-limited cases may indicate mild diffuse abdominal tenderness on palpation. Dehydration should be assessed through skin turgor and capillary refill [29]. A patient may experience severe abdominal pain, a high fever, and hypovolemia (tachycardia and hypotension) in more severe cases.

Etiology

Etiologic investigation into the causes of TD has continued to shed light on patterns and geographical differences in the pathogens associated with this condition. Recently, 19 articles were published that examined the prevalence of pathogens causing travel-related diarrhea (Figure 2). These recent studies have confirmed that the primary cause of TD is bacterial in nature. Consistent with previous research, enterotoxigenic *E. coli* (ETEC) remains one of the most commonly identified pathogens globally, with particularly high prevalence in Latin America and African countries, but lower prevalence in Southeast Asia. Separate studies have also focused on ETEC toxins [30]. While a study in Thailand found no difference in the distribution of the heat-labile (LT) and heat-stable (ST) toxins between symptomatic and asymptomatic travelers, a study of Finnish travelers in various low- and middle-income countries found that moderate/severe TD was associated with the STh (human) subtype, and that LT was the most frequently identified toxin. Despite being commonly isolated pathogens, both enteroaggregative *E. coli* (EAEC) and enteropathogenic *E. coli* (EPEC) have been questioned in terms of their pathogenic significance due to their high prevalence in asymptomatic travelers [31]. Given the significant burden of TD and the potential for long-term complications, it is important to understand the range of possible causative pathogens. In the past, stool culture and microscopy were the mainstays of microbiological diagnostics; however, these methods have limited sensitivity. The proportions of enteropathogens causing TD to vary significantly between different travel destinations, but ETEC (5 - ≥35%), appear to be the most common, followed by EAEC (<5 - 35%), *Campylobacter* spp. (<5 - 35%), and *Salmonella* spp. (<5 - 35%). More recently, PCR-based (multiplex) approaches have increased the detection rates of enteric pathogens. However, the detection of multiple pathogens in a single TD patient and the high proportion of asymptomatic controls with a positive assay (44.4%) challenge the clinical interpretation of test results. Currently, only a limited number of studies have included a control group or analyzed samples obtained during travel rather than after return to assess the performance of multiplex approaches in TD [32-36].

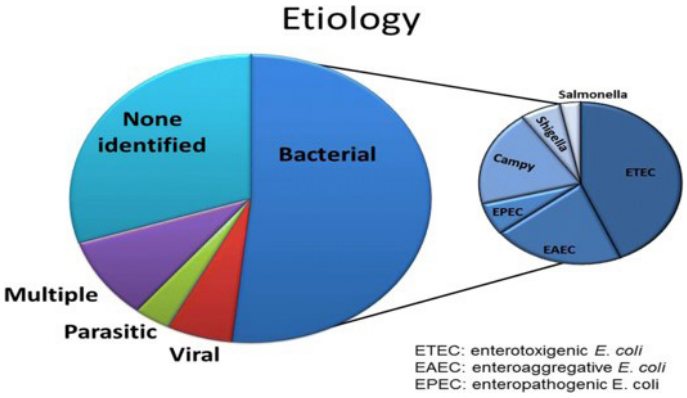

Figure 2: Pathogen prevalence of diarrheal illness among long term travelers [37].

Etiologic investigation continued to highlight patterns and regional discrepancies in the microorganisms linked to TD. Recent studies, comprising of eight articles, have examined the prevalence of pathogens causing travel-related diarrhea. These recent investigations have corroborated that the main cause of TD is predominantly bacterial [38]. In accordance with previous research, ETEC remains one of the most prevalent microorganisms globally, with a particularly high occurrence in Latin America and African nations, but a lower prevalence in Southeast Asia. Distinct research studies have also delved into ETEC toxins. Although an Asian case-control study found no disparity in the distribution of heat-labile (LT) and heat-stabile (ST) toxins between symptomatic and asymptomatic travelers, a prospective study involving Finnish travelers in different low- and middle-income countries discovered that moderate/severe TD was associated with the STh (human) subtype, with LT being the most commonly identified toxin. Despite being commonly found pathogens, recent findings and previous studies have raised doubts about the pathogenic significance of EAEC and EPEC due to their high prevalence among asymptomatic travelers. A case-control study conducted in Nepal showed no significant difference for either pathogen (EAEC $p = 0.560$; EPEC $p = 0.370$). Similarly, in Thailand, the frequency of EPEC isolation was equal in both cases and controls (5%; $p = 0.860$), with no testing conducted for EAEC. In a supplemental nested case–control study involving stool samples collected during global travel, the isolation of EPEC was found to be significantly associated with TD ($p = 0.01$), whereas EAEC showed no such association ($p = 0.08$). Moreover, among 59 children who had returned from traveling to tropical and subtropical countries, EAEC was consistently detected as a co-infection. However, previous research has reported a higher frequency of EAEC and EPEC isolation in current TD cases compared to resolved cases, which supports their role in pathogenesis. Furthermore, recent research on EAEC has continued to support its pathogenic nature by identifying specific genetic and virulence profiles that are associated with disease and disease severity, thereby suggesting that heterogeneity contributes to variations in clinical presentation [39,40]. There is currently limited evidence available for EPEC. Consequently, further investigation is necessary to explore the significant genetic and virulent characteristics of both pathogens. Another notable observation was the increased frequency of norovirus detection compared to other pathogens. Despite concerns that norovirus may not be the sole cause of illness due to its tendency to persist in pediatric diarrheal studies, it was identified as the only pathogen in 81% of cases where norovirus was detected. Similarly, even in Asia, norovirus was found in a considerably higher number of cases than controls, strongly indicating its association with the disease [41]. Like other enteropathogens, accurately quantifying the number of pathogens detected will likely play a crucial role in determining the attribution of the disease.

Epidemiology of Antimicrobial Resistance

It is crucial to monitor the emergence of antimicrobial resistance (AMR) in pathogens causing TD in order to track global infectious

disease risks. The surveillance of enteric pathogens and their associated AMR heavily relies on the availability and accessibility of microbiological diagnosis. In countries with high disease burden, where laboratory diagnostics might not always be accessible, the causes of most acute diarrheal episodes and enteric illnesses often remain unknown. However, there is now a potential to improve access to affordable pathogen-specific rapid diagnostic assays at primary care facilities, especially with the development of accurate antigen detection tests for V cholerae. Recent studies, such as the work by Murphy et al., have reported changes in AMR among TD-related pathogens in Nepal. Notably, near complete resistance to fluoroquinolones was observed among *Campylobacter* and *Shigella* isolates, with resistance rates of 97% and 78% respectively. ETEC also showed resistance at a rate of 23%. Additionally, among the 47 cases that were willing to follow-up, 7 experienced persistent symptoms. Possible explanations for this included treatment failure, drug-bug mismatch, or irritable bowel syndrome. These findings underscore the importance of ongoing monitoring for the emergence of treatment failure. In line with recent guidelines, fluoroquinolones are not recommended for the treatment of moderate to severe TD in Southeast Asia specifically, although they remain an option globally. Furthermore, an increase in AMR to azithromycin was also observed [42-44]. Between 2012 and 2014, a study observed an 8% increase in *Campylobacter* azithromycin-resistant isolates in Nepal, compared to a previous report from 2001 to 2003 where no such isolates were detected. Additionally, there was an increase in azithromycin resistance among ETEC and *Shigella* (ETEC complete resistance ranged from 0% to 10% and *Shigella* intermediate susceptibility ranged from 35% to 39%). These trends align with the growing resistance of *Shigella* spp. and *E. coli* in Asia/India against macrolides and fluoroquinolones. These findings are concerning as azithromycin is the recommended treatment for TD in Southeast Asia and globally. Further research should focus on monitoring the resistance to azithromycin and the occurrence of clinical resistance. In a related study, Grass et al. investigated the susceptibility of enteric bacterial infections to quinolones among individuals in the United States (US) by linking data from the US Antimicrobial Resistance Monitoring System to enteric infections reported to Foodborne Diseases Active Surveillance Network. The study found that international travel was associated with over a tenfold increase in the likelihood of acquiring isolates that were not susceptible to quinolones [45]. These findings support previous research that has shown high rates of fluoroquinolone resistance in diarrheal patients who have traveled to industrialized countries. While previous studies suggest that patients infected with drug-resistant pathogens may experience more severe illness, hospitalizations, or even death, further research is needed to fully understand the implications of quinolone nonsusceptibility on patient outcomes in TD. It is clear that continuous monitoring of AMR trends among TD pathogens and evidence of treatment failure are crucial, given the ongoing research that supports the trajectory of resistance [46].

Diagnostics

TD may improve on its own without any treatment. However, while you wait, it's crucial to stay hydrated by consuming safe fluids like bottled water or water infused with electrolytes such as an oral rehydration solution. If you're not experiencing quick improvement, there are several medications available to help alleviate symptoms. Nevertheless, the enhanced sensitivity of PCR and its capacity to identify more pathogens in comparison to stool culture diagnostic methods have consistently been reaffirmed. This change in diagnostics is transforming our comprehension of epidemiologic patterns. For example, the viral contribution to the cause of TD, previously believed to be primarily bacterial, coincided with the adoption of molecular techniques for viral detection. Nonetheless, this prospective transformation in diagnostics underscores the difficulties in identifying disease-causing pathogens and determining the clinical usefulness of these tests [47].

An average of 41.2% of TD cases resulted in multipathogen detection using a variety of diagnostic methods, as determined by recent reports considered in this review. Moreover, data from case-control studies in this review showed an average of 44% of asymptomatic controls demonstrated pathogen detection [48]. It is important to understand detected microbes better in light of their pathological significance.

In general, the consensus on the clinical usefulness of PCR remained varied. One study showed that only EPEC and ETEC were identified as significant pathogens associated with TD symptoms through PCR. *Campylobacter*, *Salmonella*, and norovirus GI/GII were exclusively found in TD cases, but their statistical significance was limited due to a small sample size. Another study revealed that the implementation of multiplex-PCR in an emergency department had no impact on the time for disposition or the use of empirical antibiotics for diarrhea cases [49]. However, it did significantly reduce the length of hospital stay and the time for optimal antibiotic treatment. Moreover, fewer patients were discharged with antibiotics after the introduction of PCR. Although this study did not specifically focus on TD, similar research analyzing the cost-effectiveness of PCR in the context of returning travelers would be valuable [50].

Updates in diagnostics

Future research should consider using predetermined intervals for PCR testing and monitoring symptoms to gain a better understanding of how pathogens persist after treatment and symptom resolution. It has also been proposed that quantitative PCR could be useful in distinguishing between colonization and infection. A study examined the possibility of using biorepositories of diarrheal and non-diarrheal samples to investigate this further [51]. Additionally, the development and validation of self-collected stool samples, such as filter paper stool cards, could be an important tool in advancing our knowledge of epidemiology and supporting field trials for new vaccines and therapeutics. Finally, more research is needed to fully comprehend the co-pathogen issue.

It is crucial to consider the clinical presentation of TD cases and the identified pathogens when deciding on treatment. Ongoing research is necessary to determine the true pathogenic significance of various etiologic agents. A key aspect is gaining a better understanding of how the timing of testing in relation to the onset of diarrhea affects the detection of pathogens [52-53]. Additionally, studying the duration of pathogen shedding will aid in distinguishing between previous or asymptomatic colonization and current infections. Collaboration between etiologic and diagnostic research is essential to develop diagnostic methods and protocols that can effectively differentiate disease-causing pathogens from non-causative ones while maximizing the sensitivity of modern testing.

Treatment

Anti-motility agents

There are several medicines that provide quick but temporary relief, including loperamide and drugs that contain diphenoxylate.

- They reduce muscle spasms in your gastrointestinal tract.
- Slows down the transit time through your digestive system.
- Allows more time for absorption.

Avoid giving anti-motility drugs to infants or individuals with a high body temperature or bloody stools. This is because they can hinder the elimination of harmful microorganisms and exacerbate the condition. Furthermore, discontinue the use of anti-motility medications after 48 h if you experience abdominal discomfort or if your symptoms worsen and your diarrhea persists. In these instances, it is advisable to consult a physician. You may require blood or stool examinations and treatment involving antibiotics [54].

Bismuth subsalicylate

In addition to reducing the frequency of your stools, this nonprescription medicine can shorten the length of your illness. Children, pregnant women, and people allergic to aspirin should not take it.

Antibiotics

A doctor may prescribe antibiotics if you have more than four loose stools a day or severe symptoms, such as a fever or blood or pus in your stools (Figure 3).

Avoiding dehydration

To avoid dehydration, it is crucial to maintain proper hydration when suffering from traveler's diarrhea. The most effective way to replenish lost fluids is by consuming an oral rehydration salts solution. These solutions are composed of water and salts in precise proportions, which help restore both fluids and electrolytes. Additionally, they contain glucose to facilitate absorption in the intestinal tract [54-55]. Bottled oral rehydration products can be found in well-developed areas at pharmacies, while various pharmacies offer their own brands. In most countries, you can purchase packets of powdered oral rehydration salts labeled as World Health Organization- oral rehydration salts from stores, pharmacies, and health agencies. Simply follow the instructions on the package to reconstitute the powder using bottled or boiled water.

If these products are unavailable, you can prepare your own rehydrating solution in an emergency by mixing together:

- 3/4 teaspoon table salt.
- 2 tablespoons sugar.
- 1 quart uncontaminated bottled or boiled water.
- Sugar-free flavor powder, such as crystal light (optional).

Throughout the day, you or your child can consume the solution in small quantities as an addition to solid foods or formula, as long as dehydration continues. Consuming small amounts decreases the chances of vomiting. Breastfed babies can also consume the solution but should still nurse as needed. If symptoms of dehydration, such as a dry mouth, intense thirst, decreased or no urination, dizziness, or extreme fatigue, do not improve, it is important to immediately seek medical attention. Oral rehydration solutions are specifically designed for urgent, temporary use only [56].

Antibiotics

Antibiotic use is currently the primary treatment for moderate and severe TD. However, the decision to use antibiotics is still a topic of debate due to the balance between immediate clinical relief and the risk of AMR colonization. Rifamycin has recently emerged as a potential treatment alongside rifaximin for non-invasive pathogens, which are the main cause of TD. These antibiotics specifically target the colon or small intestine, making them highly attractive for treatment purposes. The efficacy of rifamycin in treating non-invasive pathogens has been found to be comparable to ciprofloxacin. However, a trial conducted by Steffen et al. did not show a significant difference in the time it took for the last unformed stool to occur between ciprofloxacin and rifamycin, with both antibiotics having an average duration of around 55 h [57].

An appealing characteristic of rifamycin SV MMX (and possibly rifaximin) in the context of TD treatment is the potential to cause less microbiome disturbance and a resultant decrease in acquisition of multidrug resistant (MDR) organisms during travel. There was no significant difference in acquisition of MDR organisms in stool after treatment with azithromycin vs rifamycin SV MMX, but there was shown to be significantly less acquisition of MDR organisms in stool after treatment with rifamycin SV MMX when compared with ciprofloxacin [58]. A decrease in MDR organisms after treatment with rifamycin SV MMX could potentially reduce complications post-infection, and further studies on this topic are recommended. Further research is needed to evaluate the potential benefits of these nonabsorbable on their reduction of post-antibiotic consequences, balanced with their apparent decreased efficacy against severe and invasive disease. Furthermore, while the eubiotic effects of rifaximin have been detailed in a number of clinical contexts, such effects have not been directly shown in the context of TD. Finally, the combination of these non-absorbable antibiotics with loperamide and in single-dose regimens, which also appear to have a decreased risk of MDRO acquisition, is needed in comparison with the current first-line agent, azithromycin [59-60].

Several new therapeutics have been developed, including phages, and engineered bacteriocins. A phage called PDX has been shown to kill EAEC in human feces and in mice, suggesting a non-traditional antibiotic therapy against EAEC. Human feces and mouse feces show that PDX kills EAEC in vitro and *in vivo*.

Chemoprophylaxis

Despite TD typically being a mild and self-restricting condition, there continues to be a necessity for reliable and efficient methods of prevention. Since contaminated edibles or drinks serve as the primary means of transmitting all TD-causing pathogens, precautions concerning dietary practices (adhering to the principle of "boil it, cook

Agent	Dosage	Comments
	PROPHYLAXIS[a]	
Bismuth subsalicylate preparations[b]	2 tablets (chewed) 4 times daily	Avoid in travelers taking chronic salicylates or warfarin
Ciprofloxacin[c]	500 mg po daily	Reserve for high-risk travelers
Rifaximin	200 mg po 1-2 times daily	Reserve for high-risk travelers
	TREATMENT[d]	
ORS or purified liquids	Until thirst is quenched	Maintain hydration in all forms of diarrhea
Loperamide	4 mg po, then 2 mg after each loose stool; max 16 mg daily	Do not use when traveler has fever or bloody stools
Bismuth subsalicylate preparations[b]	525 mg (1 oz.) every 30 min, for total of 8 doses	Avoid in travelers taking chronic salicylates or warfarin
Ciprofloxacin[e]	500 mg po 2 times daily	Drug of choice where resistant *Campylobacter* is not prevalent (e.g., Mexico, Central America, sub-Saharan Africa)
Levofloxacin[e]	500 mg po once daily	Drug of choice where resistant *Campylobacter* is not prevalent (e.g., Mexico, Central America, sub-Saharan Africa)
Azithromycin[e]	1,000 mg po once or 500 mg daily	Drug of choice in children and travelers to South and Southeast Asia where *Campylobacter* is prevalent; 1,000-mg dose can cause nausea
Rifaximin[e]	200 mg po 3 times daily	Not effective for invasive forms of diarrhea, especially those involving bloody stools or fever

[a] Not indicated for most travelers.
[b] Bismuth subsalicylate liquid dosages expressed in mL of 262 mg/15 mL concentration.
[c] Other fluoroquinolones likely are effective, but have not been studied for TD prophylaxis.
[d] Seek medical care if traveler has severe dehydration, persistent illness despite treatment, severe abdominal pain, fever, or bloody stools.
[e] A single dose may be given initially. If diarrhea improves, antibiotic may be continued for up to 3 days.
max: maximum; ORS: oral rehydration salts; TD: traveler's diarrhea.
Source: References 9, 13.

Figure 3: Prophylaxis and treatment options for TD [54].

it, peel it, or disregard it!") continue to serve as the foundation for prevention [61-62]. Nevertheless, the effectiveness of pretravel health guidance in reducing the occurrence of TD remains unsatisfactory, primarily due to challenges in motivating travelers to take necessary precautions regarding their food and beverage consumption.

Travel-associated gastrointestinal disorders have been the subject of extensive research since the late 1970s. To prevent TD, different types of drugs can be considered, including nonantibiotic agents and prophylactic antibiotics.

Despite the high level of protection offered by antibiotics, it is currently not recommended to give preventive antimicrobial drugs to healthy travelers who simply wish to avoid getting TD. In 1985, a Consensus Conference held at the National Institute of Health confirmed that antibiotics can effectively prevent TD but cautioned against the general use of TD prophylaxis due to the potential for drug-related adverse reactions. One of the first antibiotics to be studied was doxycycline (100 mg/d), which proved to be effective due to its wide coverage of TD-causing pathogens. Unfortunately, doxycycline-resistant strains emerged in many popular tourist destinations, limiting their usefulness in TD treatment and prevention [63]. In the early 1980s, other systemic antimicrobials, like trimethoprim-sulfamethoxazole, were also successfully used until rising drug resistance restricted their use to specific regions and seasons, such as inland Mexico during the summer [64].

Over the past decade, significant attention has been given to 4-fluoroquinolones (such as norfloxacin, ciprofloxacin, fleroxacin, ofloxacin, and levofloxacin) due to their outstanding safety record and broad coverage against enteropathogenic agents. Studies have demonstrated that taking a daily dose of a single low dose, such as 400 mg of norfloxacin or 250 mg of ciprofloxacin, can provide up to 90% protection against TD, assuming the enteropathogens in the study area are susceptible to the medication. While there is currently insufficient data to recommend lower doses, it is possible that these doses could be effective [65]. However, it is important to limit the duration of intake to no more than 3 weeks, as the long-term adverse reactions and potential for AMR are still unknown.

Until now, fluoroquinolones have shown impressive effectiveness in the laboratory against the majority of bacterial causes of TD. However, the growing resistance and emergence of quinolone-resistant *C. jejuni* in Thailand and Southeast Asia is a cause for serious alarm [66]. Prior to 1990, the occurrence of quinolone-resistant *E. coli* strains was infrequent; however, since then, the use of quinolones for treatment has become widespread. Regrettably, the circumstances are changing, and resistant strains are being more frequently isolated, particularly in Asia [67].

Up to this point, quinolones continue to be the preferred medications when chemoprophylaxis is required for individuals with significant underlying illness. Nevertheless, adverse reactions have been noted, such as dermatitis, vaginal yeast infection, central nervous system responses, sensitivity to light, and digestive issues; and, uncommonly, there have been grave incidents, including severe allergic reactions [68]. Additionally, there may be uncertainty in terms of how to handle a condition that arises despite the patient being prescribed antibiotic prophylaxis. Quinolones are not authorized for prophylactic use in pediatric patients and expectant mothers.

TD-causing pathogens are not adequately covered by ampicillin, like most other penicillin, as a therapeutic or prophylactic agent [69]. The spectrum of mecillinam just like another penicillin, includes mainly gram-negative aerobic microorganisms, but mecillinam lacks effectiveness against such pathogens as enterococci because it shows selection of resistant pathogens in fecal flora [70].

A number of macrolides, including clarithromycin, have been found to significantly impair oropharyngeal and intestinal microflora by inducing a significant overgrowth of enterobacteria and selecting highly resistant isolates when used for prolonged periods, making them unsuitable for long-term prophylactic use.

Due to the increase in resistance to quinolones, there is a significant interest in the development of new antimicrobial medications that have minimal absorption in the intestines. This would allow for high levels of the medication in the intestines while avoiding the rare but serious toxicity of systemic drugs used in treatment and prevention. Recent research has shown promising results for rifaximin, a broad-spectrum antibacterial drug derived from rifamycin. It has been effective and safe in treating patients with bacterial infectious diarrhea who have traveled to Mexico, Guatemala, and Kenya. This medication, currently used in Italy to treat enteric bacterial infections, should be considered as a potential candidate for prophylaxis against traveler's diarrhea and warrants further evaluation.

Bismuth subsalicylate

Several studies have verified that the protective effectiveness of bismuth subsalicylate (BSS) is as high as 65%. This compound has been demonstrated to possess a temporary intraluminal antibacterial action in the prevention of TD. The most favorable rates of protection were documented when the substance was administered as 2 tablets taken 4 times daily (2.1 g/day) for a maximum duration of 3 weeks, as it appears that the simultaneous consumption of contaminated food and BSS provides the optimal antibacterial impact. Anecdotally, wine is said to have some form of preventative effect, but research has shown that it has a comparable effect to BSS in reducing the number of viable organisms; however, the clinical significance of these findings remains uncertain [71].

There were a number of adverse reactions reported with BSS, including transient blackening of the tongue and stools, constipation, tinnitus, and nausea. When considering malaria prophylaxis with doxycycline, it is important to note that BSS may reduce doxycycline absorption, resulting in lower levels of circulating doxycycline. Despite the high level of compliance, BBS is only rewarded with moderate protection, making it unattractive for travelers.

Probiotics

An alternative approach to preventing TD involves the utilization of probiotics, which are appealing due to their non-toxicity and lack of interactions with medication. Mechanisms that may provide protection and contribute to the effectiveness of these treatments include the production of acidic compounds, hydrogen peroxide, or substances that fight against microbes [72]. Additionally, probiotics can compete for nutrients or adhesion receptors, neutralize toxins, and stimulate the immune system. Numerous assertions have been made about the health benefits of probiotics, particularly in relation to their ability to prevent and treat intestinal disturbances. However, only a limited number of probiotic agents have demonstrated efficacy in controlled trials.

According to Oksanen et al., administration of Lactobacillus GG as a preventive measure for tourists visiting Turkey resulted in a 12% decrease in TD. However, this effect was statistically significant only for one specific destination. In a separate study that was double-blind, randomized, and controlled, American travelers who received Lactobacillus GG (at a dosage of 2 x 10^9) had a TD risk of 4%, whereas the control group had a risk of 7%, indicating a minimal yet significant

level of protection. Other lactobacilli, such as *Lactobacillus fermentum* and *Lactobacillus acidophilus*, did not show any protective effect, possibly due to variations in their ability to colonize the intestine [73].

These findings support the notion that nonpathogenic bacteria can provide protection against TD. Therefore, it is worthwhile to further investigate probiotics, as they are cost-effective, have a high safety profile, and are widely accepted. This makes them an ideal choice for self-medication by tourists, especially those in high-risk groups like children and pregnant women.

Long-term Consequences

Microbiome changes

When considering TD and its long-lasting impacts, recent research has commenced investigating the role of the microbiome. A recent study conducted by Leo et al. revealed that, in comparison to individuals who did not encounter TD (n = 34) while traveling abroad, there was a decline in diversity among all individuals who did (n = 9). The individuals who experienced TD observed heightened levels of the phyla Proteobacteria and Bacteroidetes, alongside reduced levels of the phylum Firmicutes. Nonetheless, all travelers, regardless of TD infection, experienced an increase in the family Enterobacteriaceae. Travelers who encountered TD but did not take antibiotics (n = 17) had their microbiota return to pre-travel levels within the initial month after returning from their trip. These findings substantiate the potential for further comprehension of colonization resistance in the context of travelers, which refers to the ability of the intestinal microbiota to resist the long-term establishment of foreign bacteria. Another study conducted by Walters et al. also explored the link between the microbiome and travel. Among deployed military personnel with TD, they observed an elevation in the relative abundance of the specific families Lachnospiraceae and Verrucomicrobia [74]. Studies consistently discover alterations in microbiome composition among travelers with TD, although these compositions are not necessarily consistent between different populations or destinations. Additional research is required to fully grasp the relationship between the two, particularly regarding the mechanisms of colonization resistance and the potential to prevent infection through various approaches.

Reactive arthritis

The development of reactive arthritis and other types of arthritis that may be linked to infection is an increasingly important area of interest when considering the long-term effects of TD. In 2020, Tuompo et al. conducted the initial prospective study on the association between musculoskeletal symptoms and the acquisition of diarrhoeagenic *E. coli*, particularly EAEC and EPEC [75-78]. This study included 224 volunteers out of the initial 526 contacted, who completed three questionnaires (pre-travel, post-travel, and 3-week follow-up) and provided pre-travel and post-travel stool specimens. Out of these volunteers, 155 reported experiencing TD during their travels, while 69 did not. Through a multivariate analysis, the researchers discovered that 18.7% of those with TD and 13.0% of those without TD reported musculoskeletal symptoms (95% CI 0.7-3.4; p = 0.3). Although the musculoskeletal symptoms were generally mild, they typically appeared 21.5 days (SD 23.5, range 0 - 56) after TD and lasted for an average of 82.8 days (SD 92.9, range 2 - 300). The researchers also found that the acquisition of diarrhoeagenic *E. coli* was associated with an increased risk of developing musculoskeletal symptoms, regardless of the severity of TD symptoms. Additionally, the study revealed that among travelers who exhibited reactive musculoskeletal symptoms and had diarrhoeagenic *E. coli* present in their post-travel stool samples, none of these bacteria were detected in their pre-travel stool samples [79,80]. This suggests that the diarrhoeagenic *E. coli* was acquired during travel. Overall, further investigation is needed to gain a better understanding of this topic, and larger studies should be conducted to determine the incidence of musculoskeletal symptoms and reactive arthritis among travelers with TD caused by diarrhoeagenic *E. coli*.

Post-infectious Chronic Gastrointestinal Disorders

Despite the established link between TD and post-infectious IBS (PIIBS), recent studies have shed light on its prevalence and potential mechanism involving the continuous activation of the immune system in PI-IBS and other persistent non-IBS abdominal issues (PI-AC). In a prospective study conducted in 2018, a group of 101 participants were surveyed regarding their gastrointestinal symptoms before and after traveling, with follow-up intervals at 2 weeks, 6 months, and 1 year [81]. While the overall rates of PI-IBS and PI-AC were relatively low, individuals who experienced TD had a higher incidence of PI-AC (though not PI-IBS) compared to those who did not. Further investigation into the underlying mechanisms revealed that psychological factors prior to infection and the severity of TD symptoms (rather than immunological or gene expression differences) were associated with the development of PI-AC. Additional research is necessary to better understand the role of TD in the development of PIIBS and other PI-AC, as well as to explore potential interventions to mitigate these effects [82].

Antibiotic resistance and extended-spectrum beta-lactamase–producing Enterobacteriaceae

Ongoing research is continuously enhancing our comprehension of the risk involved in acquiring antibiotic-resistant bacteria and Enterobacteriaceae that produce ESBL-PE. Furthermore, researchers are uncovering potential underlying mechanisms. In a cohort study conducted from 2016 to 2017, involving 230 German volunteers who primarily traveled to Southeastern Asia (26%), South America (23%), and Eastern Africa (23%), it was found that 36% of the travelers reported symptoms of TD, and 23% tested positive for ESBL-PE upon their return [83]. The researchers conducted multivariate analyses and discovered that age, type of accommodation, and travel to Asia were linked to ESBL-PE colonization. Out of the 53 travelers who tested positive for ESBL-PE after their journey, 42 were re-examined after 6 months, and 7 of them still tested positive for ESBL-PE. Numerous additional studies have been published regarding the epidemiology of ESBL-PE. Ljungquist et al. conducted a study to determine the prevalence of ESBL-PE carriage among Swedish patients who experienced TD after traveling internationally. They reported a prevalence rate of 28%, which showed no significant increase compared to a similar study conducted a decade earlier, despite the doubling of international travel in the past ten years and the rising prevalence of ESBL-PE. The prevalence of ESBL-PE was highest among travelers from Africa (54%), Asia (45%), and North America and the Caribbean (22%).

Regarding the comprehension of mechanisms and elucidation of the variability observed in the acquisition of ESBL-PE, Leo et al. examined the host microbiome and its correlation with ESBL-PE acquisition. They discovered that the acquisition of ESBL-PE was not connected to a particular microbiome before or after traveling. Furthermore, there was no notable effect on the microbiota when untreated MREs were acquired. Nevertheless, the investigation of MRE acquisition and carriage still requires additional examination and research in a broader scope [84, 85] (Table 1).

Research examining the long-term consequences of TD infection on the microbiome has found that TD infection increases Proteobacteria,

Table 1: Advantage and disadvantages of treatment options for travelers' diarrhea.

Drug	Dose	Advantage	Disadvantage
Ciprofloxacin	500 mg b.d.x 3 days*	Generic drug (less expensive)	Rarely tendonitis and rupture, Clostridium difficile colitis, Campylobacter strains are often resistant
Levofloxacin	500 mg q.d.s.x 3 days	Helps treating bacterial respiratory tract infection	Similar side effect and susceptibility patterns as of ciprofloxacin
Rifaximin	200 mg t.d.s. x 3 days	Excellent safety profile	Not effective against invasive forms of TD, especially associated with passage of bloody stools or presence of fever
Azithromycin	1000 mg in single dose	Broad activity against all bacterial forms of TD	Nausea, it is the most effective drug against febrile or dysenteric TD

Bacteroidetes, and Firmicutes levels, as well as decreasing overall diversity. It is still necessary to investigate the role of microbiome in reactive arthritis and post-infectious IBS, as well as the development and mechanisms of these conditions.

Conclusion

We continue to make progress in our understanding of TD globally. To reduce antibiotic usage and its associated consequences, more research is needed to mitigate risk factors where possible..

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Conflict of Interest

None.

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