Research Open

Journal of Clinical Research and Medicine
Volume 4 Issue 1

Research Article

Travelers' Diarrhea in the Era of COVID-19

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Received: February 22, 2021; **Accepted:** February 26, 2021; **Published:** March 03, 2021

Abstract

The COVID 19 pandemic started as a cluster of unexplained pneumonia in Wuhan, China and till now more than 111 million cases have been reported. Due to stringent public health measures, including lockdown strategies, the international travels were tremendously reduced. Hopes rise for end of pandemic as Corona virus vaccinations proved to have high efficacy and the true real-world effectiveness is estimated to be very good. International travels will probably start and the many safety issues should be remembered and emphasized for all travelers and any destination. The most predictable and avoidable travel related illness is infectious diarrhea that may be reduced by simple measures as are hand hygiene, food and water safety and less by antibiotic use or other pharmacologic options.

Keywords: *Traveler's diarrhea, Guidelines, Antibiotics*

The COVID-19 pandemic forced tourism to shift from the global to an idyllic local pattern within country's borders but the Coronavirus vaccination strategies applied all over the world bring the expectation for less travel restrictions.

Travelers' diarrhea (TD) was the most predictable travel-related illness with rates (30-70%) depending on destination, season, adventurous eating or sexual practices and resulting in unpleasant holiday, hospitalization and eventually prolonged recovery mainly in immunosuppresed patients [1-3].

The etiology is dominated by bacteria (80%-90%), less by viruses and protozoa. Guidelines are published in the Yellow Book by CDC, the International Society of Travel Medicine, providing relevant data, clinical evidence and consensus statements [2,3]. Diarrhea often occurs abruptly and is accompanied by abdominal cramping, fever, nausea, or vomiting. The previous severity definitions based on the number of unformed stools per day were revised by using the relevant criteria of functional impact. This therapeutic approach depending on severity, safety and the effectiveness of treatment classifies TD in: mild (acute diarrhea that is tolerable, is not distressing, and does not interfere with planned activities), moderate (acute diarrhea that is distressing or interferes with planned activities) and severe (acute diarrhea that is incapacitating or completely prevents planned activities). Acute severe diarrhea also includes dysentery (grossly bloody stools) and persistent diarrhea (lasting>2 weeks) [3].

The main exposures, epidemiological entities and etiologies are expressed as:

- Foodborne outbreaks associated with many food items [noroviruses, nontyphoidal *Salmonella*, *Clostridium perfringens*, *Bacillus cereus*, *Staphylococcus aureus*, *Campylobacter* spp, *E. coli* pathotypes (enteroaggregative, enterotoxigenic, enteroinvasive), *Listeria*, *Shigella*, *Yersinia*, *Cyclospora cayetanensis*, *Cryptosporidium* spp, hepatitis A virus],
- Waterborne (drinking or swimming) - *Campylobacter*, *Cryptosporidium*, *Giardia*, *Shigella*, *Salmonella*, STEC, *Plesiomonas shigelloides*,
- Travel to resource-challenged countries - *E. coli* (enteroaggregative, enterotoxigenic, enteroinvasive), *Shigella*, Typhi and nontyphoidal *Salmonella*, *Campylobacter*, *Vibrio cholerae*, *Entamoeba histolytica*, *Giardia*, *Blastocystis*, *Cyclospora*, *Cystoisospora*, *Cryptosporidium)* [3,4].

Any traveler should be advised about the probable exposures, food, water safety and hygiene, and informed about individual and other population consequences related to the travel (dissemination of antimicrobial resistance), the self assessment of disease severity and treatment [3,5].

High-risk destinations (TD incidence >20%) include Africa (exception of South Africa), South and Central America, South and Southeast Asia, Mexico, Haiti, and the Dominican Republic, intermediate-risk destinations (TD incidence 8 to < 20%) include Southern and Eastern Europe, Central and East Asia (including China and Russia), the Middle East (including Israel), South Africa, and Caribbean Islands and low-risk destinations (TD incidence < 8%) include North America, Northern and Western Europe, Australia, New Zealand, Singapore, and Japan [1,6]. Foodborne outbreaks may occur in well developed countries affecting local population and travelers as it happened in Spain in 2019, *Listeria monocytogenes* was linked to the consumption of domestically produced chilled pork roast from a single manufacturer in the municipality of Sevilla [7].

The incubation period is short for viruses and bacteria (6-72 hours) and much longer for intestinal parasites (1-3 weeks). Untreated bacterial diarrhea usually lasts 3-7 days, viral diarrhea 2-3 days and parasitic

enteritis lasts a couple of weeks. Usually, the microbiologic testing is not necessary except for persistent or severe diarrhea in returning travelers (strong recommendation, low/very low level of evidence). Molecular testing may confirm frequent or rare etiologies when needed [2-4]. Klem et al. found that the most frequent long term complication is postinfectious irritable bowel syndrome, 41.9% after enteritis caused by parasites and protozoa, and 13.8% after bacterial infection [8].

There were many studies and meta-analyses upon prophylaxis and treatment options in TD with the conclusion that antibiotics are not to be considered routinely in mild and moderate acute diarrhea [2,3]. No vaccines are available for common enteric pathogens causing TD, except for cholera and typhoid fever. Live attenuated cholera vaccines are recommended to adults, as a single dose given orally with a good efficacy (90% at 10 days and 80% at 3 months). The vaccines are not recommended to immunosuppressed patients, except for asplenic patients or those having chronic kidney disease. The commonly used typhoid fever vaccine is an inactivated Vi capsular polysaccharide vaccine given intramuscularly, in children ≥ 2 years and adults with an efficacy of 50-80%, the booster dose can be given after 2 years after primary vaccination. Both vaccines are recommended only for travelers to high risk regions, unconventional itineraries and housing (Table 1) [2].

Antibiotics in TD

- Azithromycin may be used to treat moderate TD and should be used in severe TD as a single dose regimen (1,000 mg) or two doses of 500 mg 12 hours apart (better tolerated) or 500 mg/day for 3 days (if no resolution in 24 hours). It is the preferred regimen for invasive and febrile diarrhea and in regions where there are suspected or demonstrated fluoroquinolone resistant *E. coli* pathotypes and *Campylobacter*. Can be given to pregnant women and children.
- Fluoroquinolones (orally) may be used in moderate noninvasive TD and less in severe TD (weak recommendation, moderate level of evidence). There is some evidence about the emergence of antimicrobial resistance and the risk of dysbiosis beyond the well-known musculoskeletal adverse events that makes the benefit/risk ratio doubtful. Levofloxacin may be used as a single dose of 500 mg or in a 3 day course, ciprofloxacin 750 mg as a single dose or 500 mg in a 3 day course and ofloxacin 400 mg as a single dose or in a 3 day course. The 3 day course is considered when symptoms persist > 24 hours [3,4].
- Rifaximin may be used in non-invasive moderate and severe TD (weak recommendation, moderate level of evidence). Rifaximin is not recommended in invasive TD (*Campylobacter, Salmonella, Shigella,* invasive *E. coli*). Since it is a non-absorbable oral antibiotic, the safety profile is excellent. In TD rifaximin is given as 200 mg three times daily for three days [9-12].

Antibiotic regimens may be combined with loperamide because the anti-motility action is the fastest then completed by the curative antibiotic treatment and there are no more adverse effects with the combined strategy [3,9]. Doxycycline might be recommended for malaria prophylaxis and was associated with lower TD risk, suggesting bacterial enteropathogen susceptibility similar to previous observations and additional benefit in infection prevention [13].

Some studies showed higher rates of extended-spectrum β-lactamase producing Enterobacteriaceae (ESBL-E) if combined therapy (loperamide and antibiotic) was used in TD [3,14]. Arcilla et al. found that the most important predictors for the acquisition of ESBL-E during international travel were: antibiotic use during travel (adjusted odds ratio 2.69, 95% CI 1.79-4.05), persistent TD after return (2.31, 1.42-3.76), and pre-existing chronic bowel disease (2.10, 1.13-3.90) [5]. Ghandi et al. evaluated the patterns of empiric antibiotic self-treatment in international travelers from US using 31 Global TravEpiNet (GTEN) sites (Centers for Disease Control and Prevention sponsored consortium of clinics that provide pretravel health consultations). Between 2009 and 2018 the rate of antibiotic prescription declined steadily from >75%, mainly for fluoroquinolones showing that doctors and travelers are less prone to antibiotic treatment or prevention [15].

TD Prevention

Beyond hand hygiene, sanitation and food safety recommendations, antimicrobial prophylaxis is not routinely considered in international travelers (strong recommendation, low/very low level of evidence) being prescribed only for travelers at high risk of health-related complications of TD (strong recommendation, low/very low level of evidence). The most commonly recommended antibiotic is rifaximin which has an excellent safety profile [3,4,12].

Table 1: Treatment options in TD diarrhea [2,3].

	Treatment	Grade Practice Recommendation/Level of Evidence
Acute mild diarrhea	1. Oral rehydration (sealed beverages). 2. Antibiotics are not recommended. 3. Self treatment may be considered with Loperamide* or bismuth subsalicylate (BSS)**.	2, 3. Strong recommendation, moderate level of evidence
Acute moderate diarrhea	1. Oral rehydration [sealed beverages, oral rehydration solution (ORS) if dehydration is severe]. 2. Loperamide may be considered for use as monotherapy or adjunctive therapy. 3. Antibiotics may be used: azithromycin, fluoroquinolones, rifaximin.	2. Strong recommendation, high level of evidence. 3. Weak recommendation, moderate level of evidence.
Acute severe diarrhea	1. Oral or parenteral rehydration. 2. Antibiotics should be used. 3. Azithromycin is preferred. 4. Fluoroquinolones or rifaximin may be used.	2. Strong recommendation, high level of evidence. 3. Strong recommendation, moderate level of evidence. 4. Weak recommendation, moderate level of evidence.

*Loperamide, 4 mg (2 mg/tb), as soon as possible then 2 mg after each lost stool, maximum 12 mg/day. Not recommended for children <12 years, in febrile or bloody diarrhea [9].
**BSS 524 mg (262 mg/tb) every 30 minutes to 1 hour as needed (maximum of 8 doses/24 hours). Not recommended for children <12 years, pregnant women, travelers taking aspirine or methotrexate [10,11].

BSS (two tabs 4 times a day) may be used for prophylaxis and can reduce the incidence of travelers' diarrhea by almost half, though it should be avoided in children and pregnant women due salicylate side effects (strong recommendation, high level of evidence) [3,10,11]. Regarding probiotics and prebiotics there is insufficient evidence to recommend their use as preventive or treatment measure in TD. A recent systematic Cochrane review found that probiotics may not affect the duration of diarrhea [16].

Foodborne and waterborne infections, may be severe in immunocompromised people. Travelers with liver disease should avoid direct exposure to salt water that may expose them to *Vibrio* spp., and all immunocompromised hosts should avoid raw seafood. Drug interactions should be evaluated before considering antibiotic prophylaxis or self treatment. Fluoroquinolones and rifaximin have significant interactions with antiviral HIV treatment. Macrolides may have significant interactions with antiviral HIV medication and transplant-related immunosuppressive drugs. Fluoroquinolones and azithromycin in combination with calcineurin inhibitors and mTor inhibitors (tacrolimus, cyclosporine, sirolimus, everolimus) may cause prolonged QT interval [2].

With or without COVID-19 vaccine passports, probably more and more people will travel all over the world in the next years needing protection for the most frequent unpleasant event during the travel, TD. Somehow, a blessing in disguise, the COVID-19 pandemic imposed the highest hygiene rules and probably lower rates of infectious diarrhea in international travelers will be observed.

Author Contributions

Concept and writing of the manuscript (A.R.). The author approved the final version of the manuscript.

Funding

No external financial support was received.

Conflict of Interest

Nothing to declare for the author.

References

1. Steffen R, Hill DR, DuPont HL (2015) Traveler's diarrhea: a clinical review. *JAMA* 313(1):71-80. [crossref]
2. Centers for Disease Control and Prevention. CDC Yellow Book 2020: Health Information for International Travel. New York: Oxford University Press.
3. Riddle MS, Connor BA, Beeching NJ, DuPont HL, Hamer DH, et al. (2017) Guidelines for the prevention and treatment of travelers' diarrhea: a graded expert panel report. *J Travel Med* 24(suppl_1):S57-S74. [crossref]
4. Shane AL, Mody RK, Crump JA, et al. (2017) Infectious Diseases Society of America Clinical Practice Guidelines for the Diagnosis and Management of Infectious Diarrhea. *Clin Infect Dis* 65(12):1963-1973. [crossref]
5. Arcilla MS, van Hattem JM, Haverkate MR, Bootsma MCJ, van Genderen PJJ, et al. (2017) Import and spread of extended-spectrum β-lactamase-producing Enterobacteriaceae by international travellers (COMBAT study): a prospective, multicentre cohort study. *Lancet Infect Dis* 17(1):78-85. [crossref]
6. LaRocque R, Harris J.B. Travelers' diarrhea: Microbiology, epidemiology, and prevention.
7. European Centre for Disease Prevention and Control, European Food Safety Authority, 2019. Multi-country outbreak of Listeria monocytogenes sequence type 6 infections linked to ready-to-eat meat products – 25 November 2019.
8. Klem F, Wadhwa A, Prokop LJ, Sundt WJ, Farrugia G, et al. (2017) Prevalence, Risk Factors, and Outcomes of Irritable Bowel Syndrome After Infectious Enteritis: A Systematic Review and Meta-analysis. *Gastroenterology* 152:1042–1054. [crossref]
9. Dunn N., Chika N. Okafor. Travelers Diarrhea. [crossref]
10. Brum JM, Gibb RD, Ramsey DL, Balan G, Yacyshyn BR (2020) Systematic Review and Meta-Analyses Assessment of the Clinical Efficacy of Bismuth Subsalicylate for Prevention and Treatment of Infectious Diarrhea. *Dig Dis Sci,* [crossref]
11. Budisak P, Abbas M (2020) Bismuth Subsalicylate. *StatPearls Publishing,* [crossref]
12. Robertson KD, Nagalli S (2020) Rifaximin. *StatPearls Publishing,* [crossref]
13. Lago K, Telu K, Tribble D, Ganesan A, Kunz A, et al. (2020) For The Infectious Disease Clinical Research Program TravMil Study Group. Doxycycline Malaria Prophylaxis Impact on Risk of Travelers' Diarrhea among International Travelers. *Am J Trop Med Hyg* 103(5):1864-1870. [crossref]
14. Kantele A, Mero S, Kirveskari J, Lääveri T (2016) Increased Risk for ESBL-Producing Bacteria from Co-administration of Loperamide and Antimicrobial Drugs for Travelers' Diarrhea. *Emerg Infect Dis* 22(1):117-120. [crossref]
15. Gandhi AR, Rao SR, Chen LH, Nelson MD, Ryan ET, et al. (2020) Prescribing Patterns of Antibiotics for the Self-Treatment of Travelers' Diarrhea in Global TravEpiNet, 2009–2018, *Open Forum Infectious Diseases,* [crossref]
16. Collinson S, Deans A, Padua-Zamora A, Gregorio GV, Li C, et al. (2020) Probiotics for treating acute infectious diarrhoea. *Cochrane Database of Systematic Reviews,* Art. No.: CD003048. [crossref]

Citation:

Amanda Radulescu (2021) Travelers' Diarrhea in the Era of COVID-19. *J Clin Res Med* Volume 4(1): 1-3.