

Treatment of traveler's diarrhea - clinical review

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Summary:

Travelers' diarrhea is defined as the passage of three or more unformed stools per 24 hours plus at least one additional symptom such as nausea, vomiting, abdominal cramps, fever, blood/mucus in the stools, or fecal urgency that develop while abroad or within 14 days of returning from any resource-limited destinations.

The aim of this study was to show the methods of treatment of traveler's diarrhea. Our study material consisted of publications, which were found in PubMed, ResearchGate and Google Scholar databases. In order to find the proper publications, the search has been conducted with the use of a combination of key words like: " traveler's diarrhea", "travel", "diarrhea", "antibiotic". The first step was to find proper publications from the last 30 years. The second step was to carry out an overview of the found publications.

Major goals of treatment of the traveler's diarrhea are: to maintain optimal hydration level, to reduce the severity and duration of diarrhea and to eradicate pathogenic agents responsible for causing this disease. The choice of the best possible method of treatment of traveler's diarrhea depends on the patient's general condition, his medical history, severity and duration of diarrhea and the pathogenic agent that causes this disease.

Key words: traveler's diarrhea, travel, diarrhea, antibiotic

INTRODUCTION AND PURPOSE

Travelers' diarrhea is defined as the passage of three or more unformed stools per 24 hours plus at least one additional symptom such as nausea, vomiting, abdominal cramps, fever, blood/mucus in the stools, or fecal urgency that develop while abroad or within 14 days of returning from any resource-limited destinations [1]. It is the most common travel-related malady. Travelers' diarrhea affects 20–50% of international travellers [2]. High-risk areas include developing tropical and semi-tropical regions of South-East Asia, Sub-Saharan Africa and Latin America. Moderate-risk areas include South-East Asia, the Middle East, Oceania and the Caribbean [3]. Pathogenic agents cause roughly 85% of cases of traveler's diarrhea, of which 30-60% cause enterotoxigenic *Escherichia coli*. Other bacteria responsible for causing this disease include: enteroaggregative *Escherichia coli*, enteroinvasive *Escherichia coli*, diffusely adherent *Escherichia coli*, *Salmonella* spp, *Shigella* spp, *Campylobacter* spp, and *Yersinia enterocolitica*. Viruses such as norovirus, rotavirus, astrovirus, enteric adenovirus or protozoal parasites such as *Giardia lamblia*, *Entamoeba histolytica*, *Cyclospora cayetanensis*, *Dientamoeba fragilis*, *Cystoisospora belli* cause about 10% of cases of traveler's diarrhea [1].

The aim of this study was to show the methods of treatment of traveler's diarrhea. Our study material consisted of publications, which were found in PubMed, ResearchGate and Google Scholar databases. In order to find the proper publications, the search has been conducted with the use of a combination of key words like: " traveler's diarrhea,", "travel", "diarrhea", "antibiotic". The first step was to find proper publications from the last 30 years .The second step was to carry out an overview of the found publications.

DESCRIPTION OF THE STATE OF KNOWLEDGE

In accordance with the guidelines of International Society of Travel Medicine mild traveler's diarrhea is tolerable, is not distressing, and does not interfere with planned activities. Moderate traveler's diarrhea is distressing or interferes with planned activities. Severe traveler's diarrhea is incapacitating or completely prevents planned activities; all dysentery is considered severe [4]. Major goals of treatment of the traveler's diarrhea are: to maintain optimal hydration level, to reduce the severity and duration of diarrhea and to eradicate pathogenic agents responsible for causing this disease. The choice of the best possible method of treatment of traveler's diarrhea depends on the patient's general condition, his medical history, severity and duration of diarrhea and the pathogenic agent that causes this disease [1,2,4,5,].

Antibiotic therapy is highly effective in eradication of pathogenic agents responsible for causing traveler's diarrhea. The choice of the antibiotic depends on type of pathogen that causes traveler's diarrhea and its antibiotic resistance. Fluoroquinolones, azithromycin, and rifaximin are being used in the treatment of traveler's diarrhea due to their high effectiveness. Fluoroquinolones such as ciprofloxacin, levofloxacin, and ofloxacin are highly effective in eradication of broad spectrum of bacteria [1,2,5]. This antibiotics act by inhibiting topoisomerase II and topoisomerase IV, thus disrupting DNA replication. Thanks to that fluoroquinolones could induce the death of bacteria [5]. In accordance with the guidelines of International Society of Travel Medicine the recommended dose of ciprofloxacin for adults is 750 mg taken orally as a single dose. If symptoms are not resolved after 24 hours, it is necessary to continue dosing 750 mg/day taken orally for the next 3 days. The recommended

dose of levofloxacin for adults is 500 mg taken orally as a single dose. If symptoms are not resolved after 24 hours, it is necessary to continue dosing 500 mg/day taken orally for the next 3 days. The recommended dose of ofloxacin for adults is 400 mg taken orally as a single dose. If symptoms are not resolved after 24 hours, it is necessary to continue dosing 400 mg/day taken orally for the next 3 days [4]. Fluoroquinolones do not cause serious side effects. Their most common adverse reactions are: nausea, dyspepsia, vomiting, dizziness, insomnia and headache. Fluoroquinolones are contraindicated in children under 8 years of age and pregnant women [1,2,5]. Azithromycin is a macrolide antibiotic, that binds to the 50S subunit of the bacterial ribosome, thus disrupting translation of mRNA. This results inhibition of protein synthesis. Thanks to that azithromycin could stop the growth of bacteria [5]. In accordance with the guidelines of International Society of Travel Medicine the recommended dose of azithromycin for adults is 1000 mg taken orally as a single dose. If symptoms are not resolved after 24 hours, it is necessary to continue dosing 1000 mg/day taken orally for the next 3 days [4]. Fluoroquinolones have similar effectiveness in eradication of bacteria and reduction of symptoms of traveler's diarrhea like azithromycin [6]. The antibiotic is safe to use in children and pregnant women [1,2,5]. Rifaximin is a semisynthetic antibiotic, that binds to the β -subunit of bacterial RNA polymerase, thus disrupting transcription. This results inhibition of protein synthesis. Thanks to that rifaximin could stop the growth of bacteria [5]. In accordance with the guidelines of International Society of Travel Medicine the recommended dose of rifaximin for adults is 200 mg taken orally 3 times a day for 3 days [4].

Loperamide is most commonly used medication in the symptomatic treatment of mild and moderate traveler's diarrhea. It is highly effective in reduction of severity and duration of diarrhea [1,2]. Loperamide is an opioid-receptor agonist, that causes antimotility effect. It acts by binding to the μ -opioid receptors in the myenteric plexus of the large intestine, thus decreasing its activity. Lääveri et al. and Riddle et al. proved in their systematic reviews, in which they analysed in total 28 studies, that adding loperamide to antibiotic therapy may hasten resolution of traveler's diarrhea with no or minimal adverse reactions compared to antibiotic therapy alone [7,8]. In accordance with the guidelines of International Society of Travel Medicine the recommended loading dose of loperamide for individuals above 12 years of age is 4 mg taken orally, then 2 mg taken orally after each episode of diarrhea (maximum dose - 16 mg/day). For children 6-11 years of age, the recommended loading dose is 2 mg taken orally, then 1 mg taken orally after each episode of diarrhea (maximum dose - 6 mg/day) and that for children 2-5 years of age, the recommended loading dose is 1 mg taken orally, then 1 mg taken orally after each episode of diarrhea (maximum dose - 3 mg/day) [4]. This medication should not be given to children under 2 years of age due to the risks of respiratory depression and serious cardiac adverse reactions. Most common side effects of loperamide are: constipation, dizziness, nausea, and abdominal cramps. Less common but far more serious side effects are: toxic megacolon, paralytic ileus, angioedema, anaphylaxis/allergic reactions, toxic epidermal necrolysis, Stevens-Johnson syndrome, erythema multiforme, urinary retention, and heat stroke. The symptoms of overdosing are: drowsiness, vomiting, and abdominal pain, and burning. The contraindications to the use of loperamide are: known hypersensitivity, high fever, overt bloody diarrhea, infection with *Clostridium difficile* [1,2]. Another medication with antimotility effect that could be used in the symptomatic treatment of mild and moderate traveler's diarrhea is diphenoxylate. It is only available as a combination

drug with a subtherapeutic dose of atropine to prevent abuse and overdose. Diphenoxylate has a similar action to loperamide, thus decreasing motility of gastrointestinal track [1,2]. The recommended dosage is 5 mg of diphenoxylate/0.5mg of atropine every 6 hours for 2 days [4]. Many studies proved that this medication is far less effective and causes more side effects than loperamide. Diphenoxylate is contraindicated in children and pregnant women [1,2]. Bismuth subsalicylate is the other medication with antisecretory effect that could be used in the treatment of mild traveler's diarrhea. This drug acts by stimulation of absorption of fluids and electrolytes by the intestinal wall. The recommended dosage of this drug is 524 mg orally every 30 to 60 minutes until the diarrhea resolve. It should be remembered to not exceed 8 doses/day [4].

International Society of Travel Medicine has made the recommendations for the treatment of traveler's diarrhea depending on its severity. Most of the cases of traveler's diarrhea are mild, self-limited and do not require treatment with antibiotics or antimotility agents. Special attention should be paid to the appearance of alarm symptoms like dehydration, bloody diarrhea, intractable vomiting, severe abdominal pain, and high fever. If required the use of bismuth subsalicylate or loperamide should be considered for treatment of mild traveler's diarrhea. The use of antibiotic is not recommended. Treatment of moderate to severe traveler's diarrhea requires the use of antibiotics such as fluoroquinolones, azithromycin, and rifaximin. Azithromycin could also be used for the treatment of dysentery. Loperamide may be used for the treatment of moderate to severe traveler's diarrhea as monotherapy or adjunctive therapy [4]. In accordance with the recommendations of International Society of Travel Medicine the traveler should be informed that if the illness does not impact his or her travel, he or she should keep up on fluids and consider taking loperamide. If the traveler's illness is having some impact but is tolerable, they should be instructed to start loperamide and consider taking a single dose antibiotic for expeditious resolution of symptoms, while understanding the benefits and risk of antibiotics for moderate disease. If the traveler's illness is keeping them in bed or confined to their room, they should be informed to start antibiotics and add loperamide if expeditious relief is desired. The traveler should be advised that if symptoms do not begin to improve within 24 – 36 hours despite self-treatment, it may be necessary to seek medical attention. In accordance with the guidelines of International Society of Travel Medicine it is not recommended to use probiotics in the treatment of travelers' diarrhea [4]. Bae in his meta-analysis and Pinos et al. in their systematic review proved that probiotics such as *Lactobacillus rhamnosus* GG, *Lactobacillus acidophilus*, *Lactobacillus casei*, *Bifidobacterium lactis*, and *Saccharomyces boulardii* could also be used in the treatment of traveler's diarrhea due to their inhibitory effect on pathogenic agents resulting from stimulating the growth of gastrointestinal microbiota [9,10]. Microbiologic testing is recommended in returning travelers with severe or persistent symptoms or in those who fail empiric therapy. Molecular testing, aimed at a broad range of clinically relevant pathogens, is preferred when rapid results are clinically important or non-molecular tests have failed to establish a diagnosis. Prophylaxis should be considered only in high risk groups with rifaximin being the first choice and bismuth subsalicylate as second option [4].

CONCLUSIONS

1. Most of the cases of traveler's diarrhea are mild, self-limited and do not require treatment with antibiotics or antimotility agents.
2. If required the use of bismuth subsalicylate or loperamide should be considered for treatment of mild traveler's diarrhea. The use of antibiotic is not recommended.
3. Treatment of moderate to severe traveler's diarrhea requires the use of antibiotics like fluoroquinolones, azithromycin, and rifaximin. Azithromycin could also be used for the treatment of dysentery Loperamide may be used for the treatment of moderate to severe traveler's diarrhea as monotherapy or adjunctive therapy.

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