

MESTRADO INTEGRADO EM MEDICINA

Approach to traveler's diarrhea and antibiotic resistance

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Artigo de revisão bibliográfica

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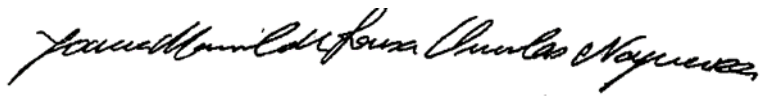
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À família e amigos, por nunca deixarem desvanecer o sonho e a vontade.

Abstract

Background: Traveler's diarrhea is the most common illness while traveling, especially to low income regions. It can be a source of great discomfort and interfere with planned activities. The substantial increase of antibiotic resistance in the past two decades, particularly to fluoroquinolones, resulted in a high spread of multi-drug resistant bacteria and calls the need for new alternatives and different approaches to this condition.

Objectives: Understanding the mechanisms of bacterial resistance and its impact on the management of traveler's diarrhea.

Methods: Research and review articles from the past ten years, including the MeSH terms "traveler's diarrhea/travellers' diarrhoea", "antibiotic resistance", "gram negative bacteria", "multi-drug resistant bacteria", "fluoroquinolones", "extended-spectrum β -lactamase" were collected from PubMed database. Only articles written in English were considered.

Development: Up to 40% of travelers experiences diarrhea. Traveling to low income areas with poor hygiene favors the ingestion of contaminated food and water, the route for developing traveler's diarrhea. While enterotoxigenic *E.coli* is the main cause around the world, *Campylobacter* spp is the most prevalent in Southeast Asia. Antibiotic therapy is not recommended in mild diarrhea. Fluoroquinolones, azithromycin and rifaximin can be used to treat moderate to severe diarrhea. Rifaximin cannot be used for invasive pathogens. In case of dysentery, only azithromycin is recommended. Loperamide or bismuth subsalicylate can be used for symptomatic relief in mild diarrhea. International travel, indiscriminate sell of antibiotics and its use in both humans and animals favors dissemination and perpetuation of multi-drug resistant bacteria. Chromosomal mutations alone or together with plasmid-mediated resistance genes are the main mechanisms of resistance. Taking antibiotics, independently of its class, facilitates the horizontal transmission of resistance genes between strains. Resistance to fluoroquinolones is worrying, however, resistance to both fluoroquinolones and azithromycin is increasing at a fast pace in some regions, seriously limiting treatment options. Prophylaxis is reserved for specific high-risk groups. There is no evidence for prevention with prebiotics and probiotics. Seeking pretravel advice should be reinforced.

Conclusion: The need to preserve antibiotic activity requires judicious use of antibiotics and preference for antimotility agents to treat milder forms of diarrhea, as well as strengthening prevention measures.

Resumo

Introdução: A diarreia do viajante é a patologia mais comum entre viajantes, sobretudo para regiões em desenvolvimento. Pode ser fonte de grande desconforto e interferir com as atividades planejadas. O aumento significativo da resistência antibiótica nas últimas duas décadas, particularmente às fluoroquinolonas, resultou numa grande propagação de bactérias multirresistentes e salienta a necessidade de novas alternativas e diferentes abordagens.

Objectives: Perceber os mecanismos de resistência bacteriana e o seu impacto na prevenção e tratamento da diarreia do viajante.

Methods: Artigos de investigação e de revisão dos últimos dez anos, incluindo os termos MeSH “traveler’s diarrhea/travellers’ diarrhoea”, “antibiotic resistance”, “gram negative bacteria”, “multi-drug resistant bacteria”, “fluoroquinolones”, “extended-spectrum β -lactamase”, foram selecionados da base de dados PubMed. Apenas foram considerados artigos em Inglês.

Development: Até 40% dos viajantes experiencia diarreia do viajante. Viajar para países em desenvolvimento com má higiene favorece a ingestão de comida e água contaminadas, a rota para desenvolvimento de diarreia do viajante. A *E.coli* enterotoxigénica é a principal causadora, no entanto a *Campylobacter* spp é a mais prevalente no Sudeste Asiático. A terapia antibiótica não está recomendada na diarreia leve. Fluoroquinolonas, azitromicina e rifaximina podem ser usadas no tratamento de diarreia moderada a severa. A rifaximina não pode ser usada contra patógenos invasivos. No caso de disenteria, apenas está recomendada azitromicina. Loperamida ou subsalicilato de bismuto podem ser usados para alívio sintomático na diarreia leve. Viagens internacionais, venda indiscriminada de antibióticos e o seu uso em animais e humanos favorecem a disseminação e perpetuação de bactérias multirresistentes. Mutações cromossómicas isoladas ou juntamente com plasmídeos portadores de genes resistentes constituem os principais mecanismos de resistência. A toma de antibióticos, independentemente da classe, facilita a transmissão horizontal de genes resistentes entre estirpes. A resistência às fluoroquinolonas é preocupante, no entanto,

resistência tanto às fluoroquinolonas como à azitromicina tem aumentado a um ritmo acelerado em determinadas regiões, limitando as opções de tratamento. A profilaxia está reservada para grupos específicos de alto risco. Não há evidência para recomendar prevenção com prebióticos e probióticos. A procura de consulta do viajante deve ser reforçada.

Conclusion: A necessidade de preservar a atividade antibiótica requer um uso criterioso dos antibióticos e preferência por agentes anti-motilidade no tratamento de formas leves de diarreia, assim como o reforço de medidas de prevenção.

List of Abbreviations

AB – antibiotics

ACG – American College of Gastroenterology

AZM – azithromycin

BSS - Bismuth subsalicylate

CDC – Centers for Disease Control and Prevention

CLSI - Clinical and Laboratory Standards Institute

EAEC – Enteraggregative *E.coli*

EPEC – Enteropathogenic *E. coli*

ESBL – extended-spectrum β -lactamase

ESBL-PE – extended-spectrum β -lactamase producing *Enterobacteriaceae*

ETEC – Enterotoxigenic *E.coli*

EU – European Union

FOS - fructooligosaccharides

FQ – fluoroquinolones

GOS – galactooligosaccharides

ISTM – International Society of Travel Medicine

LGG - *Lactobacillus rhamnosus* GG

LT – heat-labile toxin

MDR – multi-drug resistant

MIC – minimum inhibitory concentration

MRE – multi-drug resistant *Enterobacteriaceae*

NICE - UK National Institute of Health Care and Excellence

ORS – oral rehydration solution

PCR – polymerase chain reaction

SE – Southeast

ST – heat-stable toxin

TD – traveler’s diarrhea

UK – United Kingdom

USA – United States of America

UV – ultraviolet radiation

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Introduction

Traveler's diarrhea (TD) is the most frequent problem among travelers⁽¹⁾, especially those going from developed countries to undeveloped ones.⁽²⁾ A widely accepted definition describes it as the "passage of ≥ 3 unformed stools in 24 hours, accompanied by one additional gastrointestinal symptom, such as nausea, vomiting, abdominal cramps, fever, tenesmus, fecal urgency or presence of blood or mucus in the stools".⁽²⁻⁶⁾ Before the use of this definition, the severity of diarrhea was classified only according to the number of unformed stools passed in 24 hours. A functional impact-based classification was recently suggested by the expert panel of the International Society of Travel Medicine (ISTM), who established the following levels:

Mild (acute) corresponds to a diarrhea that is tolerable, is not distressing, and does not interfere with planned activities;

Moderate (acute) for a diarrhea that is distressing or interferes with planned activities;

Severe (acute) is a diarrhea that is incapacitating or completely restrains planned activities; note that all dysentery (passage of grossly bloody stools, frequently accompanied with fever) is considered severe;

Persistent when it lasts for more than 2 weeks.⁽⁷⁾

Even being usually self-limited (lasting 3-5 days), traveler's diarrhea can be a great source of discomfort, disrupting planned activities and, sometimes, even requiring a visit to the doctor, resulting in significative money and time losses.^(4, 5, 8) It should be noted the particular importance of this in business travellers, military, athletes or volunteers on mission, as their well-being and time is of great value. For that reason, prophylaxis can be considered in these classes.^(6, 9-11) And it is here where the pretravel consultation gets its role, by evaluating each case carefully and recommending the best practices and care to have abroad.⁽¹²⁾ The adhesion to this type of consultation is still low worldwide⁽¹²⁾, but its importance grows as international traveling keeps increasing year after year.⁽¹³⁾ Alongside with that, antimicrobial resistance has become a serious problem for the last two decades.⁽¹⁴⁾ Particularly, antibiotic resistance refers to the capacity of bacteria to change, adapt and grow, acquiring the capacity to withstand the effects of the antibiotics.⁽¹⁵⁾ In the case of enteropathogenic bacteria, they are showing a stronger resistance to first-line antibiotics, especially to fluoroquinolones.⁽¹⁴⁾ These two factors combined, the rise on both the international mobility and antibiotic resistance, allow humans to act as carriers, transporting the resistant bacteria back to their homelands.⁽¹⁶⁾ So, it works like a domino - poorly informed travelers^(17, 18) go to low income regions which are, by nature,

more propitious places for one to get a gut bacterial infection and this, pieced together with poor sanitary and hygienic conditions, precarious health services and indiscriminate selling of antibiotics, results in a wide spread of multi-drug resistant bacteria.⁽¹⁶⁾

Objectives

The main goal of this review is to perceive the extent of the problem of antibiotic resistance and its repercussions in the management of traveler's diarrhea, through exploration of the mechanisms of bacterial resistance and acknowledgment of the most effective measures for prevention and treatment of traveler's diarrhea, and also by raising awareness for the largely uncontrolled and unnecessary use of antibiotics.

Methods

The review was performed using PubMed database. Research and review articles including the following MeSH keywords – “traveler's diarrhea/travellers' diarrhoea”, “antibiotic resistance”, “gram negative bacteria”, “multi-drug resistant bacteria”, “fluoroquinolones”, “extended-spectrum β -lactamase” – and published in the last 10 years (from 2010 to 2019) were selected. Only articles written in English were considered. The articles were then reviewed manually and chosen according to their title and abstract. Those focusing on traveler's diarrhea epidemiology, etiology, treatment, prevention and antibiotic resistance were highlighted. Articles concerning antibiotic resistance in animals were excluded. Research studies on new vaccines whose use still lacks approval were excluded.

Epidemiology and Risk Factors

When comparing rates from two decades ago to current data, results show that incidence of traveler's diarrhea is declining⁽⁵⁾, nowadays affecting approximately 10 to 40% of travellers during a two week trip.^(2, 5) Traveller's destination, home country and journey duration, as well as travel style and host proper features, are factors that have influence on this rate.^(2, 19) Significant differences between genders were not found.^(2, 3) Regarding the visited countries, three levels of risk can be set (considering a two-week interval): high-risk destinations where

the disease's incidence is higher than 20%; intermediate risk corresponding to an incidence rate of 8 to 20% and, finally, low risk destinations with less than 8% risk.^(2, 5) Standing out the high-risk regions, such as Africa (excluding South Africa), South and Southeast Asia (with emphasis to India and Thailand), South, Central America and Mexico, as areas of poor income with precarious sanitary and hygienic conditions, they are areas of most concern to health practitioners.^(2, 3, 5, 20) The risk is higher for travelers going from a developed country to a developing one, most likely because people from less developed countries have already been exposed to the pathogens, therefore acquiring immunity and not manifesting the disease.⁽²⁾ Backpackers and adventure travellers have greater risk of suffering from acute diarrhea when compared with business travellers.^(2, 20, 21) This happens due to the likelihood of them buying food from street vendors allied with a low travel budget, which makes them have riskier behaviours.^(3, 5) In general, when it comes to this matter, hygienic conditions of food establishments appear to have more relevance than the rule "boil it, cook it, peel it, or forget it".^(3, 8, 19) Use of swimming pools or other recreational waters is a well-known predisposing factor for gastrointestinal infections.^(2, 5) Leaning over the patient factors, they include age, use of antacids (especially proton pump inhibitors) and previous conditions to be mentioned bellow.⁽²²⁾ Younger people are more propense to develop this disease - children because of their curiosity and tendency to grab objects and put them in their mouths and young adults because of their tendency to eat more.^(2, 5) The use of antiacids (especially proton pump inhibitors) and the occurrence of diarrhea two months before traveling also augments the risk for this disease. At last, inflammatory bowel disease is not only a risk factor for acquiring this disease, as well as it is for a longer duration of the diarrhea and presence of abdominal pain.⁽³⁾ Various genetic host factors have been associated with increased incidence of traveler's diarrhea^(5, 19), yet they haven't shown particular practical relevance, meaning they still don't interfere with health advice and care practises.⁽³⁾

Basically, the perfect set for developing TD is traveling to a low income country, especially in the warm and/or rainy season, with poor sanitation (which facilitates stool contamination and spread by vectors), conditions enhanced by ineffective refrigeration, lack of safe water and poorly hand hygiene habits, which all combined lead to food and beverages contamination.^{(2,}

23)

Etiopathogenesis

Fecal-oral transmission through the consumption of contaminated food or beverages or the contact with contaminated waters are the route for developing traveler's diarrhea.^(24, 25) Despite extensive search for the causative agent,^(2, 5, 11, 26) 40 to 50% of the times the cause is unknown.^(4, 11, 27, 28) The use of PCR techniques allows a wider pathogen identification, however, they are not routinely used in TD^(29, 30) and there is a lack of large epidemiologic studies resorting to this method.⁽¹¹⁾ Furthermore, for example, distinguishing *E.coli* strains from commensal ones can be challenging, as they have various biomarkers in common.⁽³⁰⁾

Gram negative bacteria represent 50 to 90% of identified microorganisms, being the main enteropathogens responsible for traveler's diarrhea both in children and adults,^(2, 11, 31-33) followed by virus which have a representation of about 5 to 20%^(2, 11, 26, 28, 32-34) and then parasites, the less common cause (4 to 10%), being *Giardia lamblia* the most frequent one within this class.^(2, 11, 28, 32, 34) In descending order, Enterotoxigenic (ETEC) and enteroaggregative (EAEC) *E.coli*, *Campylobacter spp.*, *Salmonella spp.* and *Shigella spp.* are the major bacterial causes.^(11, 28, 30, 33) ETEC is therefore the most frequent pathogen, representing 30 to 60% of traveler's diarrhea globally.^(2, 35) Norovirus, known as the "cruise ship virus",⁽²⁷⁾ and rotavirus account as the most frequent virologic agents^(26, 27, 30, 32, 34), and co-infection with other bacteria is commonly found.^(27, 35, 36) Actually, it is thought that multiple infections are more frequent than shown by routine methods^(26, 36). Identifying multiple pathogens can be a hard task - a patient can manifest typical bacterial traveler's diarrhea in his first week travelling and then have a "second wave" of diarrhea in the following week, parasite-related, and both of the episodes be linked to the same food he ate at the beginning of the journey.^(30, 34) Geographically speaking, these multiple etiology infections are often found in Southeast Asia.^(11, 37) Microorganisms prevalence also exhibits regional variability.^(4, 28) ETEC and EAEC together represent half of the cases in Latin America, Africa and South Asia.^(11, 27, 30) Oppositely, in Southeast Asia (specially Thailand), *Campylobacter* takes ETEC's place at the podium^(5, 30), followed by Enteropathogenic⁽³⁷⁾ *E.coli* (EPEC) and *Salmonella*.^(11, 27) Concerning the viruses, norovirus cases are of great importance in Latin America.^(11, 27, 31) When compared with other regions, Africa is linked to a higher risk of experiencing a gastrointestinal disease, but pathogen identification is harder due to the lack of resources⁽³⁶⁾ and there are less cases described because of not being such a trendy destination.⁽²⁴⁾ These geographic differences are extremely important for clinicians to adjust proper treatment and advice.⁽³⁷⁾ It is hard to discriminate the cause of TD based only on clinical presentation. However, as empirical treatment is frequently

started before performing or knowing the laboratory tests results, practitioners sometimes use time as a reference for treatment – when travelers experience the disease for more than 2 weeks, it is probable that they have a parasitic subjacent cause rather than a bacterial one, as its incubation period is longer (1-2 weeks comparing to 6-72 hours for bacteria).^(23, 38) Watery diarrhea associated with cramps is the classical presentation of ETEC, the most common agent.^(2, 39) A patient with abdominal cramps, fever and presence of blood in the stools (dysentery-like diarrhea) makes the doctors suspicious of *Campylobacter* or *Shigella* as the causative agent.⁽³⁹⁾ Virus usually present themselves with a short lasting diarrhea (2-3 days), frequently accompanied by vomiting and nausea.⁽³⁹⁾, while long-duration, greasy and frothy diarrhea strongly suggests *Giardia lamblia*, for example⁽²⁸⁾. Although these hints can't be followed linearly, they help guiding treatment decisions.

In a simplified way, traveler's diarrhea occurs through increased intestinal secretion and decreased absorption, leading to watery diarrhea.⁽⁴⁰⁾ Enterotoxin and cytotoxin production, epithelial adherence and invasion of the mucosa are the essential mechanisms of virulence. Enterotoxins (such LT and ST, produced by ETEC), through different pathways, favor chloride secretion and decreased sodium absorption, turning out in this non-inflammatory watery diarrhea mentioned above.⁽⁴¹⁾ *Shigella* acts through cytotoxin release and mucosal invasion, which gives origin to an invasive inflammatory diarrhea, resulting in more severe symptoms. Some bacteria like *Campylobacter* or *Salmonella* act through both secretory and inflammatory mechanisms. This explains why these agents are frequently associated with the occurrence of fever or blood in the stools.⁽²⁾

Treatment

Based on guidelines proposed by the panel of experts of the International Society of Travel Medicine (ISTM), adequate therapy for traveler's diarrhea is given according to its functional classification in mild, moderate or severe. That said, for a mild impact diarrhea, antibiotic treatment is not recommended and loperamide or bismuth subsalicylate (BSS), when available, can be considered. When confronted with a moderate TD, recommendations state that antibiotics may be used, as well as loperamide (monotherapy or as adjunctive therapy). Warnings are made for the use of fluoroquinolones (FQ) because of increasing resistance and its side effects, and for both fluoroquinolones and rifaximin in determined regions – use of FQ is not recommended in Southeast Asia and using rifaximin is not advisable in areas where there is a known risk of infection with an invasive pathogen. At last, guidance says that

treatment with antibiotics, preferentially azithromycin, should be used in severe TD. Fluoroquinolones and rifaximin may be used, except in the case of dysenteric diarrhea. Single-dose antibiotics can be used whether in moderate or severe diarrhea. Additional advices state that evidence is lacking for the recommendation of prebiotics or probiotics.⁽⁷⁾ USA, UK, Canadian and Australian guidelines are practically in total agreement concerning treatment advice, therefore TD management presented bellow was based on their recommendations.^(7, 23, 33, 40, 42-45)

A. Antibiotics (AB)

Antibiotics have proven to be effective in reducing TD duration in approximately one and a half days and even less when loperamide is added to the therapeutic scheme. They are also responsible for changing the course of the disease by turning it less severe.⁽⁷⁾ The efficacy of an antibiotic depends on both etiologic agent and antibiotic susceptibility.⁽²³⁾ Fluoroquinolones, azithromycin and rifaximin are currently recommended for TD treatment. Its use and prescription, however, must be judiciously weighted and reserved for severe cases or for travelers to regions with poor healthcare access.⁽⁴³⁾

A.1. Fluoroquinolones (FQ)

FQ are broad spectrum antibiotics, traditionally and widely prescribed for the treatment of traveler's diarrhea as first-line agents.^(22, 40)

Single-dose therapy (levofloxacin 500 mg or ciprofloxacin 750 mg) can be prescribed to patients presenting with moderate or severe TD, sparing the need of carrying out a 3-day therapy with these drugs, as its efficacy for noninvasive pathogens is similar. It is important to keep in mind that if symptoms remain after 24h, 3-day therapy should be completed.⁽⁴⁰⁾ Guidelines are discordant here – ISTM experts advise against the use of FQ if dysentery is present (because of the possibility of infection with fluoroquinolone resistant *Campylobacter* or *Shigella* species)⁽⁷⁾, while ACG (American College of Gastroenterology) clinical guidelines for acute diarrheal infection recommend 3-day treatment with levofloxacin 500 mg or ciprofloxacin 500 mg daily in these cases.⁽⁴⁰⁾

Although FQ remain effective in a wide number of TD cases, documented resistance to *Campylobacter* and increasing resistance to other enteric pathogens (*Shigella* and *Salmonella*)

explains its contraindication when travelling to Southeast Asia (where both fluoroquinolone resistance and *Campylobacter* are strongly prevalent).⁽²³⁾ Despite being well tolerated, these antimicrobial agents are not free from adverse effects, of which Achilles tendon rupture (black box warning issued by US FDA) and risk for *Clostridium difficile* infection should be highlighted.^(7, 40) Warnings were made by the European Medicines Agency (EMA) Committee of Medicinal Products for Human Use (CHMP), for the risk of tendon injury in the elderly, chronic renal disease, organ transplantation and patients under corticotherapy.^(46, 47) Prolongation of QT interval, possibly leading to fatal dysrhythmias, aortic aneurysm and dissection are rare consequences from the use of FQ in the elderly.^(22, 43) Nevertheless, TD therapy is so short (maximum of 3 days) that these side effects appear of low relevance.⁽²³⁾ On the contrary, alterations in gut microbiota and acquisition of multidrug resistant (MDR) bacteria are now “breaking points” to take into account when balancing whether FQ should be or not prescribed.^(7, 42) It is noteworthy to mention that English Public Health does not recommend fluoroquinolones for severe TD treatment.⁽⁴⁴⁾ Fluoroquinolones are not recommended for children under 18, except when other alternatives are unavailable and its use seems to be beneficial.⁽⁴²⁾

A.2. Azithromycin (AZM)

The continuous increase of FQ resistance worldwide made azithromycin a reliable alternative for traveler’s diarrhea treatment.⁽²³⁾ Studies comparing both fluoroquinolones and azithromycin showed that azithromycin was similar or even better in reducing TD duration.^(40, 42) In fact, this macrolide is recommended as the first-line agent for dysentery or severe diarrhea with or without fever or blood in the stools.^(7, 45) AZM proved its efficacy in treating fluoroquinolone-resistant *Campylobacter* in Thailand, whether using single-dose (1g/day) or 3-day (500mg/day) course treatment.^(40, 44) It also showed effectiveness in treating diarrhea caused by *Shigella spp* and *Salmonella spp*⁽⁷⁾, although a 5 day course therapy seems to overcome single-dose or a 3 day course therapy if *Shigella dysenteriae* is the agent.⁽⁴⁰⁾ These bacteria are frequently responsible for severe, invasive, dysenteric diarrhea, which explains why AZM is recommended in this kind of presentation, regardless of the region of the world.⁽²²⁾

AZM is normally well tolerated, meaning its use is not related to any known serious side effect.^(42, 45) However, gastrointestinal complaints, such as nausea and vomiting⁽⁴²⁾, have been reported, especially associated with single-dose therapy. It is suggested that splitting the 1g single dose in two doses of 500 mg during the first day might show identical results with less

adverse effects.^(7, 23) Pregnant women and children may use azithromycin to treat severe illness⁽²²⁾, but the UK National Institute of Health Care and Excellence (NICE) recommends that, when there are children in risk of severe TD, practitioners advice must be sought.⁽⁴⁵⁾

A.3. Rifaximin and Rifamycin SV MMX

Rifaximin is a non-absorbable rifamycin derived antibiotic⁽²²⁾ that emerged as a “game changer”, respecting its safety profile when compared with the previous antimicrobial agents.^(7, 48) Its efficacy against the most prevalent TD agent, noninvasive *E. coli*, has been proven⁽⁴⁹⁾ – rifaximin was superior to placebo in terms of number of cured travelers⁽⁴⁰⁾ and studies comparing its efficacy with fluoroquinolones, showed no significative difference between the proportion of patients achieving clinical cure.⁽⁴²⁾ The recommended dose is 200mg three times a day (600mg/day) in a three day course treatment for moderate or severe nondysenteric TD.^(7, 40) One study suggested that a single-dose treatment with 1650mg of rifaximin might be as effective as single-dose therapy with other agents such as levofloxacin, although this has not been put into practice⁽⁵⁰⁾. However, rifaximin has shown to be less effective against invasive pathogens.⁽⁴⁰⁾ Having this into account and knowing that the number of subjects affected by invasive species of *Campylobacter*, *Salmonella* and *Shigella* is not negligible, rifaximin cannot be prescribed to a traveler going to regions like South and Southeast Asia, where these invasive pathogens are known to be prevalent,^(51, 52) neither in cases of dysentery.⁽⁷⁾ The real advantage of using rifaximin is the absence of side effects.⁽⁴²⁾ In fact, it is so well tolerated that can be compared to a placebo in this matter. As a non-absorbable agent, its action is confined to the gastrointestinal (GI) tract, achieving particularly high concentrations in the small intestine and having a nonsignificant systemic absorption.^(53, 54) Furthermore, unlike other antibiotics, rifaximin does not interfere with bacterial microbiome composition, having an eubiotic favorable effect on the gut.⁽⁵⁵⁾

Rifamycin SV-MMX is another nonabsorbable agent, assigned by FDA since 2018 as a treatment for traveler’s diarrhea caused by noninvasive strains of *E.coli*.⁽²³⁾ Contrary to rifaximin, rifamycin SV acts both in the distal small bowel and colon.⁽⁵⁴⁾ Its anti-bacterial activity is superior to placebo and comparable to fluoroquinolones on a three day course treatment of 800 mg per day (400+400mg).⁽⁵⁶⁾ Once again, as a nonabsorbable agent, its use is related to a low rate of side effects and drug interactions.⁽⁵⁷⁾ Other advantage conferred to this drugs is the lower associated risk of acquiring multiple drug-resistant-(MDR) microorganisms,⁽⁵⁸⁾ a subject to be discussed through the next chapter.

Conclusively, there are a few things that must be taken into account. The majority of patients experience watery non dysenteric diarrhea. Then, the exception are the ones who experience dysenteric TD with fever and blood in the stools. On the other hand, it is known that invasive pathogens responsible for this severe TD are rarely behind afebrile non dysenteric disease.⁽⁵⁸⁾ That said, the vast majority of cases would benefit from treatment with these poorly absorbable antibiotics that show a safe profile acting specifically on the lumen of the GI tract, preserving other AB that would be more suitable for other types of infections.⁽⁵⁶⁾ Nevertheless, it is not acceptable to acquire two different types of antibiotics in order to have full coverage of both watery and dysenteric TD taking into account the cost, complex dosage and clinical sense in deciding which one to take (distinguishing invasive from noninvasive diarrhea should not be the patient's responsibility).⁽⁵⁴⁾ Recently, two authors suggested that a non-absorbable agent should be selected for a "travel kit" and that patients should seek expert advice or buy a systemic antibiotic (such as azithromycin) in a pharmacy abroad (over-the-counter drugs) in the case of severe diarrhea. They also suggest that when traveling to areas where medical facilities are difficult to reach or nonexistent, travelers should carry azithromycin as a second line option.⁽⁵⁸⁾ These last statements contradict the guidelines, whose recommendations of taking a fluoroquinolone or azithromycin (when not contraindicated) are the ones followed in practice.^(7, 23)

B. Antimotility and antisecretory agents (BSS – antisecretory; Loperamide – antimotility and antisecretory)

Antimotility and antisecretory agents are recommended for mild traveler's diarrhea, as they provide symptom relief and help reducing disease duration and intensity, allowing people to accomplish their planned schedule.⁽⁷⁾

Loperamide – Imodium® is a synthetic opioid-like agent that has both antimotility and antisecretory properties.⁽⁵⁹⁾ For lower doses, it has a potent antisecretory effect, creating also an antimotility effect when administered in higher doses.⁽²²⁾ Patients should take an initial dose of 2 tablets (4 mg) and then do additional doses of 2 mg after each following diarrheal episode, respecting a maximum dose of 16 mg within 24 hours.⁽⁷⁾ (some guidelines suggest a maximum of 12mg, it varies with country licensing).⁽⁴⁰⁾ It takes 1 to 2 hours to show a therapeutic effect, a fact that travelers should be aware in order to avoid iatrogenic constipation.⁽²²⁾ If the patients start to manifest symptoms such as severe abdominal pain, fever or blood in the stools, antibiotic therapy should be taken.⁽⁷⁾ Loperamide can be useful as an adjunctive therapy with

antibiotics for moderate to severe diarrhea because while the antimicrobial acts on the infection, loperamide acts through reducing motility, providing quicker relief and recovery.^(40, 42) Yet, it must not be forgotten that antimotility agents are not recommended as single-therapy in patients with inflammatory bowel disease or presenting with dysentery or any invasive symptoms⁽⁴³⁾ – it is suggested that it may interfere with the mechanism by which microorganisms are eliminated.⁽⁵⁹⁾ Although age restrictions for children vary through different guidelines,^(22, 23, 43) these agents are absolutely contraindicated for children under 2 years old.⁽⁴²⁾

Bismuth subsalicylate (BSS) - PeptoBismol® is an antisecretory drug that may be considered when treating mild forms of TD.⁽⁷⁾ Its salicylate component has anti-diarrheal characteristics⁽⁴⁰⁾ but it also enhances salicylate toxicity when the patient already taking aspirin or salicylates.⁽²²⁾ Doses of two chewable tablets (263 mg each) every 30-60 minutes with a maximum of 8 doses in 24 hours are recommended for acute mild diarrhea.⁽⁴⁰⁾ Travelers should be warned that it can cause black tongue and darkening of the stools.⁽⁴⁵⁾ It is contraindicated in patients with aspirin allergy, renal insufficiency, gout, those under therapy with anticoagulants, probenecid and methotrexate, as well as pregnant women.⁽²³⁾ It should not be used in children under 12 years old in USA⁽²³⁾ and under 16 years old in UK because of the risk of developing Reye's syndrome.⁽⁴⁵⁾ It is also not recommended when severe or dysenteric diarrhea is present.⁽⁴⁵⁾ This drug not available in Portugal.

Racecadotril is another antisecretory drug that is not commonly used in TD, but was approved in the UK and licensed in Europe with the purpose of treating acute diarrhea in children >3 months.⁽²²⁾

There are other antidiarrheal agents such as diphenoxylate - Lomotil®, zaldaride maleate and crofelemer, but they are not by far as effective as loperamide has shown to be for traveler's diarrhea management and control.⁽⁴⁰⁾ In fact, loperamide is the first line therapy for rapid symptom control⁽⁴⁵⁾ and it has shown to be more effective than BSS.⁽⁷⁾ Its use alongside with antibiotics should be reserved for cases of moderate-severe diarrhea or when failure with one of the agents alone occurs.⁽⁴²⁾

C. Oral Rehydration Therapy

Oral rehydration solution (ORS), a glucose-based solution, saved millions of lives in developing countries. Although there are no studies documenting its effectiveness in TD, this condition causes great loss of fluids and electrolytes, making its replacement crucial, mostly in

vulnerable groups such as elderly and children.⁽⁶⁰⁾ So, CDC recommends drinking fluids in case of diarrhea, as long as they are purified. The standard World Health Organization oral rehydration solution (WHO ORS, 311 mOsm/L) and similar oral solutions should be used in cases of severe diarrhea accompanied or not with vomiting.⁽²³⁾

Antibiotic Resistance

Antibiotic resistance happens when bacteria develop mechanisms to overcome the effects of a previous effective drug.⁽⁶¹⁾ Despite being a natural consequence, overuse and improper use of antibiotics leads to quicker dissemination of resistant strains.⁽⁶²⁾ This problem emerged as a public health matter in the beginning of the millennium with the emergence of extended-spectrum β -lactamases (ESBL) and FQ resistance, and later with resistance to other antibiotic classes.⁽⁶³⁾

In the process of the emerging resistance to ampicillin, doxycycline and trimethoprim-sulfamethoxazole, fluoroquinolones, azithromycin and rifaximin came to substitute these drugs in TD therapy. However, resistance to these antibiotics, based on CLSI breakpoints, is also increasing.^(64, 65) CLSI breakpoints are based on drug concentration in the serum. It is difficult to assess if this method accurately translates clinical outcome because both ciprofloxacin and azithromycin reach high fecal and tissue levels.^(14, 64) Rifaximin, being a non-absorbable agent, achieves higher levels in the feces and is reserved for noninvasive diarrhea.⁽¹⁴⁾ Regardless of this, the real problem stands on the lack of new alternative agents for treating TD. Currently there is a gap between the emergence of MDR bacteria and pharmaceutical companies response capacity.⁽⁶⁶⁻⁶⁸⁾

Sales over-the-counter, as well as self-medication without medical authorization and the use of counterfeit drugs are very common in developing countries.⁽⁶⁹⁾ Furthermore, even when medical care is sought, overprescription is also a phenomenon.⁽⁶⁹⁻⁷¹⁾ In fact, in countries like Nepal, ciprofloxacin is the most frequently prescribed drug, often used as a prophylactic measure.⁽⁷¹⁾ On the other side, unavailability of appropriate antibiotherapy when necessary worsens the problem.⁽⁷⁰⁾ Although policies that regulate these practices exist, they are not currently applied in low income regions.⁽⁷²⁾ The use for veterinary purposes and farming was limited/banned in high income countries such as USA and Australia.⁽⁷³⁾ Even though data of antibiotic importation exists, regulation and extent of its use is not controlled in

underdeveloped regions.⁽⁶⁹⁾ FQ used for growth incitement in animal husbandry stimulate selection of resistant clones, which is responsible for resistant infections and poor therapeutic outcome in humans.⁽⁷³⁾ Despite all this, lack of basic hygiene and sanitation, food safety and access to potable water remain on the basis of the problem, enhancing dissemination and perpetuation of resistance strains in the environment.^(70, 72)

On the other hand, international travel favors acquisition, colonization and spread of resistant bacteria.⁽⁶³⁾ Geographical areas visited are the major risk factor,⁽⁷⁴⁾ followed by the occurrence of traveler's diarrhea and the consumption of antibiotics during travel.⁽⁷⁵⁾ Traveling to some regions, namely North Africa, India and Southeast Asia induce greater risk of acquiring TD and multi-drug resistant *Enterobacteriaceae* (MRE). These risks are evidently associated with high population density and absence of basic infrastructure.⁽⁶⁷⁾ Traveler's diarrhea and use of antibiotics disrupt the intestinal flora compromising its "barrier" effect.⁽⁷⁶⁾ TD interferes with the intestinal microbiota by giving space for bacterial species to flourish, while antibiotic intake appears to induce selection of strains that are resistant to the used drug.⁽⁷⁷⁾ Moreover, as co-resistance to other antibiotics is common, travelers are often colonized with multi-drug resistant bacteria (MDR).⁽⁷⁸⁾ Of these, multi-drug resistant *Enterobacteriaceae*, especially those producing ESBL, are the most prevalent.⁽⁷⁹⁾ MRE acquisition rates ranged approximately from 20% to 50% depending on geographic region visited, reaching rates of 80% in Asia.^(65-67, 80)

A. Extended-spectrum β -lactamase-producing *Enterobacteriaceae* (ESBL-PE)

Extended-spectrum β -lactamase (ESBL) have been reported since the 1980s, at first related to hospital-acquired infections.⁽⁸¹⁾ However, it was in the late 90s that they widely appeared among community-acquired *E.coli* strains and ever since the CTX-M family became the most prevalent around the world.⁽⁸²⁾ These enzymes have the ability to hydrolyze penicillins, expanded-spectrum cephalosporins and monobactams (aztreonam), while susceptibility to carbapenems is maintained.⁽⁷⁵⁾ CTX-M-15, followed by CTX-M-14, are two alleles belonging to the blaCTX-M gene family that dominate the ESBL pandemic.^(83, 84) Although CTX-M-15 is the most prevalent around the world, there is some regionality seen by the predominance of CTX-M-14 in the Western Pacific region.^(82, 84) These genes are supposed to be extensively present in the community and travel favors its dissemination.⁽⁷²⁾ ESBL-PE resistance mechanisms are spread both through clonal expansion and carriage in mobile genetic elements called plasmids, which allow horizontal gene transfer (HGT) between these strains and other pathogenic or

commensal strains present in the gut.⁽⁸³⁾ In fact, gut microbiota acts as a reservoir for genetic material that confers antimicrobial resistance, constituting the “gut resistome”.⁽⁸⁵⁾

ESBLs can be produced by all Gram-negative bacilli belonging to the *Enterobacteriaceae* family, including *E.coli*, *Klebsiella* species, *Enterobacter* species and *Salmonella* species.^(86, 87) However, among several studies, 88 to 100% of ESBL-PE correspond to *E.coli* strains.^(63, 80) Within these, the presence of *E.coli* clone ST131, a common producer of CTX-M-15 enzyme, was described worldwide, reinforcing the role of international travel and ingestion of contaminated food on the spread of resistant strains.^(82, 88)

High ESBLs carriage rate among developing regions explains traveler’s acquisition rates.⁽⁸²⁾ While in Europe and North America, the rate is increasing through the years, but still remains below 10%^(84, 86, 89, 90), in tropical and subtropical regions, rates are higher and have been increasing at a faster pace.⁽⁹¹⁾ In fact, an average carriage of 20-40% in healthy people⁽⁶³⁾ and prevalence reaching almost 70% in some Asian communities, makes developing regions endemic for EBSL-PE.^(80, 82)

A considerable proportion of travelers gets colonized with ESBL-PE when traveling abroad, resulting in a rate of ESBL acquisition of approximately 30%.^(74, 77, 84, 86, 89, 90) Once again, there are important regional differences and traveling to India comes with an increased risk of returning colonized with these enzymes.^(91, 92) Acquisition rates range from 29 to 88% in the Indian subcontinent, 18 to 67% in China and Southeast Asia, and 13 to 53% in the Middle East, being slightly lower and ranging from 0 to 57% in Northern Africa and 0 to 49% in Central and South America.^(63, 77, 84, 86, 90, 93) There are limited data concerning central and eastern Africa.⁽⁷⁷⁾ Apparently, neither the duration of the stay nor the type of travel (backpacking, for example) interfere with these statistics, suggesting that colonization can happen right on the first days traveling or in a short duration journey.^(74, 94)

As expected, colonization rates were higher when more than one risk factor was present. A study showed that 11% of travelers who did not suffer traveler’s diarrhea neither took antibiotics (AB) were colonized with ESBL-PE, 21% of those who had TD but did not take AB and finally 37% of those positive for both risk factors. These numbers increased consistently for travelers to Southeast Asia and even more when the destination was South Asia. A striking rate of 80% was hit when three risk factors were present – occurrence of TD, taking AB and traveling to South Asia.⁽⁷⁶⁾ In a subsequent study, they tested the interference of loperamide in this scenario, concluding that in the group of people with TD, taking loperamide alone is not a risk factor for acquiring ESBL-PE.⁽⁹⁵⁾ However, when taken together with AB, loperamide

antimotility effect allows a prolonged contact of antibiotics with the gut mucosa, favoring AB capacity of selecting resistant strains.⁽⁹⁵⁾

Oppositely to the rate of acquisition, ESBL-PE duration of carriage varies significantly between studies.⁽⁷⁷⁾ It is important to retain that this carriage is transient and has an average duration of 30 days.^(66, 77, 87) In most of the cases, it does not last for more than 3 to 6 months after return,^(66, 75, 84, 89, 93, 96) however, some studies showed persistence up to 12 months after returning.^(87, 97) This prolonged carriage is more common among travelers with comorbidities and those traveling to South and Southeast Asia and taking antibiotics, as well as carriers of the CTM-X-9 strain.^(63, 67, 75, 84, 93) Nevertheless, the probability of developing an infection caused by an ESBL-PE strain seems very low and decreases over time.^(86, 96) There is a 12% estimated probability of transmission to household members, though this value may be overestimated.^(63, 67, 77) This risk should not be neglected and hygiene measures, such as hand washing, should be reinforced, especially for those living with vulnerable individuals, as elderly or people with known comorbidities.^(67, 75, 77, 86)

What is disturbing is that ESBL-PE often shows multiple co-resistance to other largely used antibiotics,^(72, 92) such as cotrimoxazole, ciprofloxacin and aminoglycosides (gentamicin).⁽⁶⁵⁾ One explanation for this is the presence of various resistance genes within the same plasmid.^(85, 98) So, taking one of this drugs predisposes colonization with ESBL-PE resistant to the taken drug, favoring the emergence of MDR pathogen, which complicates treatment and prophylactic measures.⁽⁷²⁾

B. Resistance to fluoroquinolones (FQ)

The WHO highlighted FQ resistance as a public health threat.⁽⁶¹⁾ The first quinolone – nalidixic acid - was the base molecule for synthesizing the well-known FQ.⁽⁷⁰⁾ At the beginning, FQ appeared as a safe alternative, as they were well-tolerated and active against a wide range of gram positive and gram-negative bacteria,⁽⁷³⁾ soon becoming the drug of choice for treating traveler's diarrhea.⁽⁹⁹⁾ Its broad spectrum activity and stability, however, led to extensive misuse and overuse both in humans and animals, which then led to the development of a growing and worrying resistance worldwide.⁽⁷³⁾

FQ inhibit bacterial DNA synthesis and replication through the inhibition of two enzymes – DNA gyrase (encoded by *gyrA* and *gyrB*) and topoisomerase IV (encoded by *parC* and *parE*).⁽¹⁰⁰⁾ Basically, FQ resistance can be acquired through two different pathways – chromosome or

plasmid-mediated.⁽¹⁰⁰⁾ In the chromosomal pathway, there can be inactivation of the FQ target through mutations in *gyrA* and *parC* genes, an overexpression of efflux pumps or a decreased outer membrane permeability.^(69, 73) There are three known genes involved in plasmid-mediated quinolone resistance (PMQR). The *qnr* genes protect DNA gyrase and topoisomerase IV from binding to quinolones,⁽¹⁰¹⁾ being responsible for nalidixic acid resistance and decreased susceptibility to FQ. They are commonly associated with ESBL-PE. In fact, the three major groups – *qnrA*, *qnrB* and *qnrS* genes – are commonly found within the same plasmids as genes that confer resistance to β -lactams or aminoglycoside antibiotics.⁽⁹⁹⁾ Secondly, the *aac(6=)-Ib-cr* gene encodes an aminoglycoside acetyltransferase, prompting acetylation and decreasing activity in both drug classes. It is capable of acetylating ciprofloxacin and norfloxacin.⁽¹⁰⁰⁾ At last, *qepA* or *opxAB* genes encode for efflux pumps, conferring a significative increase in MIC (minimum inhibitory concentration) of hydrophilic molecules such as ciprofloxacin and norfloxacin.⁽⁹⁹⁾ So, enteropathogens can develop resistance to FQ through several mechanisms, from accumulation of multiple chromosomal mutations to the carriage of more than one PMQR gene.⁽⁷⁰⁾ *qnr* genes alone, for instance, do not generate high level resistance to quinolones. Instead, they act as facilitators of that process.⁽⁸⁵⁾ Moreover, plasmids carrying resistance genes for more than one antibiotic class explain why dissemination and maintenance of FQ resistant strains occurs without previous exposure to the drug.⁽⁹⁹⁾ Taking ciprofloxacin while traveling favors horizontal dissemination of PMQR genes between species.⁽⁹⁰⁾ However, FQ resistance genes are perpetuated through other antibiotic classes, which explains the growing number of MDR clones.⁽⁷⁰⁾

Mechanisms as well as rates of resistance to FQ, vary accordingly with the pathogen involved.⁽¹⁴⁾ While a single mutation in a determined point of the *gyrA* gene confers resistance to nalidixic acid and FQ in *Campylobacter* species, cumulative mutations are needed for *E.coli*, *Salmonella* and *Shigella* to acquire such high level resistance.⁽⁷³⁾ Plasmid-mediated resistance is frequent among these enteropathogens.⁽⁹⁹⁾ In fact, simultaneity of *blaCTX-M* and *qnr* genes in the same plasmid has been documented.^(78, 85) As with CTX-M enzymes, international travel favors *qnr* genes acquisition, and travelling to Southeast Asia is associated with increased probability of acquiring *qnrS*, whereas *qnrA* and *qnrB* are not associated with any particular region.⁽⁸⁵⁾

Once again, traveling to South and Southeast Asia, as well as treating traveler's diarrhea with antibiotics, are major risk factors for colonization with FQ-resistant *Enterobacteriaceae*.⁽⁹⁰⁾ Despite this, the greatest risk of infection with quinolone-resistant strains goes for travelers to Africa, though these cases are less reported.⁽¹⁰²⁾ Unregulated use of antibiotics in developing

countries, as well as its use in farming, have a huge impact on fluoroquinolone resistance. Besides, FQ are frequently the drug of choice for treating urinary tract infections, upper respiratory or even other enteric infections.⁽⁶⁴⁾ Bacteria resistance patterns reflect the antibiotic consumption habits in each region, giving us information on different mechanisms of resistance in TD causing microbials.⁽¹⁰³⁾

The mutation Ser83Leu and double mutation Ser83Leu/Asp87Asn in the *gyrA* gene are the most found through quinolone resistant ETEC, the main causative agent of traveler's diarrhea.⁽¹⁰⁴⁾ However, for both ETEC and EAEC, mutations in *gyrA* and *parC* are usual.⁽¹⁰⁵⁾ In fact, it has been noticed that a single mutation in *gyrA* confers them resistance to nalidixic acid, while resistance to fluoroquinolones usually requires the occurrence of double mutation in *gyrA* or *parC* genes, associated or not with the presence of PMQR genes.⁽¹⁰⁰⁾ In general, it appears that EAEC strains are more resistant to fluoroquinolones than ETEC ones,⁽⁶⁴⁾ although rates of more than 40% were estimated for both in Southeast Asia and India.⁽¹⁰⁰⁾ In Latin America, EAEC is more prevalent than ETEC.⁽⁶⁴⁾ That said, steadily increasing rates of fluoroquinolone resistant EAEC were detected in those areas, though the majority is still susceptible.^(14, 100) Lastly, a recent study concluded that, given these increasing resistance rates, ciprofloxacin should no longer be recommended for treating TD caused by EAEC, especially in Asia and Africa.⁽¹⁰⁶⁾

Increases in resistance to FQ and ESBL production have been seen in typhoidal and nontyphoidal *Salmonella*.⁽⁶³⁾ In nontyphoidal *Salmonella* species, the ones causing foodborne TD, resistance has been increasing through the last 15 years, mostly in India and other Asian countries.⁽⁶³⁾ Although it is true, decreased susceptibility to ciprofloxacin is still much more common than complete resistance to the drug.⁽¹⁰⁷⁾ The growing number of fluoroquinolone resistant *Salmonella* reported in industrialized countries and linked to foreign travel exposes the probability of experiencing TD caused by a resistant strain in developing regions.⁽¹⁴⁾

Fortunately, since 2007, the number of TD cases due to *Shigella* is decreasing.⁽¹⁰³⁾ However, it is still one of the main causes of diarrhea in travelers, mainly those traveling to Africa and to the Indian subcontinent. Thus, fluoroquinolone resistance rates are also higher in these areas (~30%).^(103, 108) It is important to take into account that clinical response to ciprofloxacin varies according to specific serogroup. For instance, non-dysenteriae subtypes respond better than *Shigella dysenteriae* type 1.⁽¹⁴⁾ As with other *Enterobacteriaceae*, ESBL-producing *Shigella* show significantly higher ciprofloxacin resistance rates than non-producing strains.⁽⁹⁸⁾ Although FQ resistance is controlled in developed countries,⁽¹⁰⁸⁾ the worrying rates in South Asia made the

Indian Government propose treatment with third generation cephalosporins in cases of dysentery due to *Shigella* to their citizens, but that may also apply to travelers.⁽⁹⁸⁾

Campylobacter spp, namely the most reported species *C. jejuni* and *C. coli*, are food-borne pathogens capable of causing very limiting diarrhea in travelers.⁽⁶⁹⁾ Campylobacteriosis is a zoonotic disease and has been linked with poultry, its major reservoir.⁽¹⁰⁹⁾ The Thr-86-Ile gyrA mutation alone or together with the chromosomally encoded CmeABC efflux pump are the main mechanisms for FQ resistance in *Campylobacter*, conferring high-level resistance.^(70, 73, 109, 110) Resistance emerged early in the 90s and increased at a fast pace, oppositely to what happened with the previous pathogens.⁽¹⁴⁾ Even though resistance rates have been increasing both in developed and developing countries, rates of approximately 90% were reached in Nepal, Thailand and other SE Asia countries, comparing with 30-40% in USA and UK.^(63, 71, 72, 111) A study in Peru showed resistance rates in some cities similar to those in Thailand, which is worrying considering that FQ are the first recommended drug for treating TD in South America.⁽⁶⁹⁾ It is sometimes difficult to correlate FQ resistance with clinical failure. However, a study showed clinical failure in 6 out of 18 patients treated with FQ in southern Asia when *Campylobacter* was implied.⁽¹¹²⁾ Anyhow, campylobacteriosis is not distinguishable from other enteric infections and so fluoroquinolones are frequently used to treat it, enhancing resistance in this pathogen.⁽⁷³⁾ The presented rates are attributed to uncontrolled sell and prescription of antibiotics in developing countries, but also to fluoroquinolone use in animals.⁽¹⁰⁹⁾ Human to human transmission is rare, which leaves us with food chain transmission, especially through chicken meat.⁽⁶⁹⁾ Although WHO has warned for limited use of FQ in the food animal industry, the use of enrofloxacin and norfloxacin in low-income regions is still unsupervised.^(69, 71)

C. Resistance to macrolides (azithromycin)

Azithromycin has great intracellular penetration and is the macrolide of choice for treating TD in areas where FQ resistance is highly prevalent.⁽¹⁰³⁾ Its reversible bondage to the P site on the ribosomal 50 subunit of ribosomes inhibits protein synthesis.⁽⁷³⁾ Resistance to macrolides happens through modification of target, efflux pumps and changes in membrane permeability.⁽⁷³⁾ The most important, however, involves mutations on domain V in the 23S rRNA gene, mainly the 2075 substitution.^(109, 113) The efflux pump CmeABC, as in fluoroquinolones, acts synergistically with chromosomal mutations, conferring high macrolide resistance.⁽⁷³⁾ The number of gene copies mutated is proportional to MIC levels (minimum

inhibitory concentration).⁽¹¹³⁾ For instance, *Campylobacter* species have three 23s rRNA copies. In order to achieve high level resistance, mutation in those three is generally required. When two copies are mutated, it results in decreased susceptibility to macrolides only.⁽⁷³⁾ Therefore, low spontaneous mutation rate and the need for a long drug exposure time in order to achieve resistance, result in low macrolide resistance worldwide, especially when comparing to fluoroquinolones.⁽⁶⁹⁾

For ETEC and EAEC, resistance to azithromycin, as well as with other antibiotics, is more common in South and Southeast Asia.⁽¹¹¹⁾ Resistance rates of approximately 30% were found for both species in those regions. Nevertheless, AZM concentration in the gut is still higher than the MIC for resistant bacteria, which means that clinical failure to macrolides might not correlate to resistance rates.^(64, 100)

A study in Nepal reported high MIC for azithromycin in *Salmonella* infections, as well as clinical failure.⁽⁷¹⁾ However, there are not many data on macrolide resistance concerning this pathogen. A 2011 study found good in vitro activity against nontyphoidal *Salmonella enterica*, being effective against strains showing decreased susceptibility to fluoroquinolones.⁽¹¹⁴⁾ Though reduced susceptibility to AZM seems to be more frequent than complete resistance, consensus on CLSI breakpoints is needed.⁽¹¹⁵⁻¹¹⁷⁾

High drug concentration in the feces and susceptibility to azithromycin were shown in patients with shigellosis infection.⁽¹⁴⁾ In fact, a study recommended AZM to treat shigellosis in children and to anyone traveling to South America.⁽¹⁰³⁾ Despite that, clinical failure rates of 29% were found in *S. dysenteriae* type 1⁽⁷²⁾ and five extremely drug resistant strains – showing resistance to a great number of antibiotics including fluoroquinolones, and with high azithromycin MIC - were acknowledged by CDC (USA).⁽⁹⁸⁾

Most of the data on azithromycin resistance in TD are related to *Campylobacter* spp. Given the extensive fluoroquinolone resistance in Southeast Asia, mainly in Thailand, azithromycin is the recommended drug when traveling there.^(72, 109) In the beginning of the millennium, AZM was very effective in treating campylobacteriosis and treatment failure was uncommon and usually related to *C. coli*.⁽¹¹¹⁾ A posterior study in Peru, however, registered a surprising prevalence of 17% of resistance in *Campylobacter*. Fortunately, macrolide resistance is more frequent among non-jejuni strains.⁽⁶⁹⁾ It has been hypothesized that the use of macrolides in the animal industry might correlate to the emergence of resistance in humans, drawing again attention for unrestricted use of antibiotics in low-income regions.^(69, 73) At last, a recent study reported a case of a heteroresistant *Campylobacter jejuni* isolate. This clone presented

subpopulations with different susceptibilities to azithromycin which is worrying because it can favor resistant strains and compromise treatment outcome.⁽¹¹³⁾

All these data are a reminder of the increasing azithromycin resistance. However, when treatment with one of the drugs (fluoroquinolones and macrolides) fails, it is unlikely to fail using the other drug afterwards.^(71, 102) Nevertheless, in the case of Nepal, for example, the need for new drugs is eminent, as well as improvement of sanitary conditions.⁽⁷¹⁾

D. Resistance to rifaximin

Rifaximin is a good alternative to ciprofloxacin and azithromycin, but it cannot be used in cases of febrile invasive diarrhea.⁽¹⁴⁾ Rifaximin suppresses replication through bondage to the β -subunit of RNA polymerase (encoded in the *rpoB* gene).⁽¹¹⁸⁾ The main mechanisms of resistance rely on mutations in the *rpoB* gene and overexpression of efflux-pumps.⁽¹¹⁹⁾ The number of travelers suffering from campylobacteriosis and shigellosis in South and Southeast Asia make it infeasible to use rifaximin there.⁽⁷¹⁾ Although increasing MICs for ETEC and EAEC were observed,⁽⁶⁴⁾ rifaximin remains effective and can be used against these pathogens,⁽¹⁰⁰⁾ probably due to high concentrations reached in the gut.⁽¹¹⁹⁾ It seems that rifaximin is also capable of co-selecting resistant strains, but not as much as fluoroquinolones and macrolides.⁽⁹⁶⁾

Prevention

According to the guidelines of the ISTM's panel of experts, chemoprophylaxis is reserved for travelers at serious risk of morbidity caused by TD, such as dehydration and bacteremia.⁽⁷⁾ These travelers are essentially patients with chronic illnesses, immunocompromised patients and individuals with history of complications after an enteric infection.⁽¹²⁰⁾ Chemoprophylaxis is not recommended for other individuals, given the risk of colonization with a MDR microorganism.^(7, 23, 42, 45) In the specific subgroup of travelers that includes athletes, musicians, politicians and so on, chemoprophylaxis, although uncommon, might be considered after discussion with the health practitioner.⁽¹²¹⁾ Bismuth subsalicylate (BSS) may be chosen for prophylaxis, though is not available in several countries. Rifaximin is the drug of choice when

considering antibiotic prophylaxis, while using fluoroquinolones is discouraged in most cases.^(122, 123) However, it is important to bear in mind resistance patterns and common causative agents in the destination before prescribing therapy.⁽¹²⁴⁻¹²⁶⁾

Since antibiotics have the capacity of changing the gut microbiome and causing dysbiosis,⁽¹²⁷⁾ and both international travel and antimicrobial resistance keep increasing, alternatives are needed.⁽¹²⁸⁾ It is known that bacterial pathogenicity is not the only factor responsible for developing TD. The host immune system and the status of the gut microbiota must also be taken into account.⁽¹²⁹⁾ A healthy intestinal microbiome helps providing resistance to pathogen colonization and growth.^(130, 131) There are not enough data to recommend the use of pre and probiotics yet, but there is a growing interest on these therapies.⁽¹³²⁾ Prebiotics, such as fructo-oligosaccharides (FOS) and galacto-oligosaccharides (GOS), are non-digestible dietary ingredients capable of selectively stimulating the growth or activity of bacterial microbiota. They stimulate the immune system and prevent attachment of pathogenic bacteria to the gut.⁽¹³³⁾ Probiotics, on the other hand, are defined as “live microorganisms that, when administered in adequate amounts, confer a health benefit to the host”.⁽¹³⁴⁾ *Lactobacillus* and *Bifidobacterium*, as well as *Saccharomyces* yeasts, are the most common. They prevent bacterial adhesion, increase the immune response and re-establish the microbiota balance through alteration in pH and reinforcement of the epithelial barrier, for example.⁽⁴¹⁾ Synbiotics are products containing both probiotics and prebiotics.⁽¹³⁵⁾ Prebiotics show more stability than probiotics, but while probiotics take action in the small intestine (where infectious pathogens attack), prebiotics act in the large intestine.⁽¹²⁷⁾ One research on the effect of B-GOS, a novel GOS mixture with apparent role on bacterial adhesion in the small intestine, showed statistically significant results on reducing diarrhea and abdominal pain in travelers.⁽¹²⁷⁾ A further study, however, concluded that this mixture was effective in preventing only 1-day self-limiting TD and that there was no proven efficacy for more severe cases. Furthermore, the prebiotic should be started one week before traveling.⁽¹³⁶⁾ A synbiotic was tested in a 2013 study, but showed no favorable results on TD prevention.⁽¹²⁸⁾ As for probiotics, *Lactobacillus* and *Saccharomyces boulardii* are the most explored for TD prevention.⁽¹³⁷⁾ There is also some interest on their efficacy preventing one of the possible consequences of TD, the irritable bowel syndrome (IBS).⁽⁶⁰⁾ The only probiotic with some efficacy in preventing TD so far is *S. boulardii*.^(138, 139) An interesting study explored the ability of a probiotic, *Lactobacillus rhamnosus* GG (LGG), preventing colonization with ESBL-PE in travelers to India, but did not find any correlation.⁽¹⁴⁰⁾ Probiotics, as they contain live microorganisms, must be carefully used

in immunocompromised patients, or else they may cause infection.⁽¹²⁷⁾ Further consistent research on these therapies is needed to establish concise recommendation.⁽¹⁴¹⁾

The variety of pathogens causing TD, as well as serological heterogeneity between strains, are obstacles for the development of a vaccine.⁽¹³⁶⁾ Given some similarities between *Vibrio cholerae* and ETEC, Dukoral® may protect against LT toxin of ETEC. However, this vaccine is only prescribed for cholera in EU and Australia.⁽⁴¹⁾ Research is being done for vaccines directed against ETEC and the other major bacteria causing TD, though high costs of each vaccine program limit the progress.⁽¹⁴²⁾

Although preventive hygiene measures and advices exist and are important, they are rarely strictly followed.⁽¹³⁹⁾ The saying “Boil it, cook it, peel it or forget it... easy to remember, impossible to do” accurately describes the scenario.⁽³³⁾ Regardless of no evidence supporting caution with food and beverages, cooking food thoroughly, eating it while steaming hot and avoiding raw and undercooked ingredients is highly recommended.^(33, 143, 144) Where people eat seems to have more impact than what people eat, and that is why street vendors should be avoided.⁽³³⁾ Ideally, only bottled beverages should be consumed, including water for teeth brushing. In the absence of safe drinking water, water must be purified through boiling, filtering, halogenation (with chlorine or iodine) or exposure to UV light.^(132, 144, 145) Hand washing with soap and water or sanitizers is mandatory before eating. This proved to be effective in reducing TD risk, therefore travelers should carry a bottle of alcohol-based hand sanitizer with them.^(143, 146, 147) Finally, people traveling to developing countries should seek pretravel advice, especially immunosuppressed patients, pregnant woman, humanitarian volunteers and other people with important chronic illnesses. Consultation with a travel medicine expert should be considered.⁽¹⁴⁴⁾ However, 20 to 80% of travelers does not book a pretravel consultation.⁽¹⁴⁸⁾ In general, people are not aware of the risks of taking antibiotics and the high probability of returning colonized with MDR *Enterobacteriaceae* when traveling, highlighting the importance of expertise pretravel advice to fill this gap.^(18, 149) It is fundamental to prevent the unnecessary use of AB by clarifying the traveler and reinforcing that TD is usually mild, transitory and mostly does not require the use of AB, explaining and encouraging the use of other options for symptomatic relief such as loperamide.^(150, 151)

Conclusion

Antibiotic resistance has become a serious problem in the last two decades. When it comes to traveler's diarrhea, resistance to the recommended antibiotics, mainly fluoroquinolones, is increasing at a significant rate, compromising TD treatment and its use for other pathologies. Efforts are needed to minimize the use of AB while new alternatives are not available. Despite this, further studies are needed to assess if the currently used MIC of FQ and AZM for the most prevalent pathogens correlates well with clinical failure to the drug. Furthermore, it would be interesting to compare single dose vs prolonged course treatment in terms of resistance and colonization with resistant strains and effects on the gut microbiota. It has been estimated that single dose treatment is equally effective in most cases of TD, but there is still no evidence associating the duration of the treatment with reduced probability of colonization with MDR strains. Overall, more studies on antibiotic resistance correlating the specific drug (FQ, AZM or rifaximin) and its effect on each enteropathogen in different countries are important to assess the evolution of resistance patterns in each region and to become aware of situations similar to the one in Nepal, where resistance keeps increasing and the treatment options are limited. Besides, antibiotic practices in developed and developing countries should be regulated for both humans and animals, to avoid indiscriminate use.

International travel itself is responsible for alterations in the microbiome. Adding antibiotics to the equation may favor dysbiosis which can last up to one year. Although there are several studies on the gut microbiome, more research is needed for better understanding the changes the intestine undergoes while traveling and taking AB. Although the microbiome is a complex system, an integrated and diverse microbiota is more protective and resistant to colonization with pathogens and resistant species than a damaged one. A thorough study of the microbiome may facilitate the development of new prebiotics and probiotics useful for TD prevention, strengthening travelers with a stronger barrier to bacterial infection.

It is known that the aspect with most impact on preventing TD is the improvement of hygienic and sanitary conditions in low income regions. However, implementing these measures is a slow process that is not expected nor foreseeable in the future. Moreover, although several studies are being conducted, there is still no licensed vaccine. In the meanwhile, the constant update of guidelines and recommendations, such as the ones elaborated by the ISTH consensus group, are of great value to standardize information and guidance.

Most people do not seek pretravel advice and those who do often show poor adhesion to the recommendations given. The pretravel consultation is not mandatory and sometimes neither reinforced by the travel industry, even when the destination is a developing country. Raising awareness of the importance of pretravel advice would be essential to increase adhesion. Regarding the consultation itself, the practitioner must highlight some things about TD - firstly, that it is a highly prevalent disease while traveling; secondly, explaining that most cases are mild, self-limited and do not require AB treatment; at third, offering alternatives for symptomatic relief (such as loperamide); lastly, informing of the risk of colonization with MDR bacteria that can be carried back to their home country. Even knowing that general safety measures are usually not strictly followed, advice on food and beverages must be made, as well as hand hygiene. The physician may prescribe AB and recommend their carriage on the “travel kit” (because of the risk of buying counterfeit or poorly conserved drugs in the destination), but always emphasizing its use only for more severe diarrhea that does not improve with loperamide or when blood or mucus are present in the stools. Increasing fluid intake in case of diarrhea must also be supported.

Facing this imbalance between the rise on antibiotic resistance and the lack of new drugs, there is the need to preserve the AB activity for the future generations. Raising awareness on this matter and convincing travelers to use antisecretory drugs instead of resorting directly to AB is urgent.

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