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Traveller's Diarrhoea and Intestinal Protozoal Diarrhoeal Disease

Constantine M. Vassalos and Evdokia Vassalou
National School of Public Health, Athens
Greece

1. Introduction

Traveller's diarrhoea is usually a mild gastrointestinal disorder. It is generally acute and short-term, but in 10 percent of all cases symptoms last for more than a week. Bacterial and viral agents are responsible for more than 80 percent of cases of acute traveller's diarrhoea. Though incriminated in only one to three percent of cases of acute traveller's diarrhoea, parasites –mainly protozoa– account for about 30 percent of cases of persistent diarrhoea in travellers (Leder, 2009; Okhuysen, 2001). Recent acceleration and expansion of international travel for business, leisure, philanthropic or other purposes has contributed to an increase in cases of intestinal protozoal disease in the developed world (Topazian & Bia, 1994; Vassalou & Vassalos et al., 2010).

2. Traveller's diarrhoea

Since the 1950s, a decade which saw an increase in trips to exotic locales, the prospect of developing diarrhoea has been a major concern for foreign travellers. It is believed that traveller's diarrhoea is the most common health problem of people journeying abroad for education, research, business, or pleasure. Traveller's diarrhoea is classically defined as the passage of three or more unformed stools in a 24-hour period with or without mild gastrointestinal symptoms including cramps, nausea and mild fever (Steffen, 2005). More serious gastrointestinal symptoms, such as vomiting and dysentery with blood and/or mucus in the stool, are rare. Owing to the brief incubation period that ranges from hours to a few days, it is most likely that traveller's diarrhoea will develop on the third or fourth day of the travel. A second peak is observed around the 10th day, although some digestive problems may occur at any time (Cailhol & Bouchaud, 2007).

3. Aetiological agents

Many non-infectious phenomena, such as a change in lifestyle, climate or eating habits, consumption of spicy foods, and psychosomatic conditions, have been incriminated as causes of diarrhoea in the traveller. However, traveller's diarrhoea is generally of an infectious origin. Bacteria account for approximately 60 to 80 percent of all cases, whereas viral agents and parasites, mainly protozoa, are responsible for about 10 to 20 percent and 5 to 10 percent of the cases, respectively (Ericsson et al., 2008). There are differences in

causality among travel destinations, depending on the geographical distribution of pathogenic organisms. Enterotoxigenic *Escherichia coli*, or ETEC, is a major bacterial cause of traveller's diarrhoea worldwide. Several other bacteria, for instance *Shigella*, *Campylobacter*, *Salmonella*, *Aeromonas*, *Plesiomonas*, and non-cholera vibrio species, have also been involved (Shah, 2009). Rarely is *Vibrio cholerae* transmitted to western travellers. The risk of contracting cholera is estimated at one per 500,000 travellers to endemic areas (Synder & Blake, 1982). Enterotoxigenic *Bacteroides fragilis*, or ETBF, and *Arcobacter* strains including diarrhoeagenic *A. butzleri* as well as *A. cryaerophilus*, formerly considered non-pathogenic, have recently been shown to cause diarrhoea in those travelling to different parts of the Indian subcontinent and Latin America (Houf & Stephan, 2007; Jiang et al., 2010). In cruise ships and tourist resorts, there is high risk of acquiring viruses such as noroviruses (Domènech-Sánchez et al., 2009; Koo et al., 1996). Rotavirus, a common paediatric pathogen, has also been found in adults with traveller's diarrhoea (Anderson & Weber, 2004). *Giardia* is the most commonly encountered parasite among travellers with diarrhoea. *Cryptosporidium, Cyclospora, Isospora,* and microsporidia are emerging causes (Goodgame et al., 2005). Aetiological agents and their order of occurrence by different geographical regions are shown in Table 1.

Aetiological agents	Africa	Latin America	South Asia	Southeast Asia
Enterotoxigenic *Escherichia coli*	1	1	1	5
Enteroaggregative *E. coli*		2	2	
Enteropathogenic *E coli*	4	4		2
Campylobacter			4	1
Salmonella			5	3
Shigella	3		3	
Non-cholera vibrios				4
Norovirus	2	3		
Rotavirus	5	5		

Table 1. Traveller's diarrhoea: aetiological agents and their order of occurrence (from 1 to 5) among different geographical regions (adapted from Shah et al., 2009).

3.1 Pathogenicity

A variety of pathogens have been shown to contribute to traveller's diarrhoea. Based on the pathophysiological mechanism responsible for the diarrhoea, their pathogenicity can be divided into non-inflammatory, enteroinvasive, and inflammatory types. However, irrespective of the mechanism involved, the host defence system is evaded and modulated. Concerning traveller's diarrhoea of bacterial origin, the non-inflammatory diarrhoeas are due to enterotoxin-producing organisms, such as *Vibrio cholerae* and ETEC, which adhere to the mucosa and disrupt the absorptive and secretory functions of the enterocyte. In the case of viral traveller's diarrhoea, viruses such as rotaviruses disrupt the digestive and absorptive functions of the enterocyte: therefore the diarrhoea caused by the rotavirus is classified as osmotic. Enteroinvasive organisms such as *Salmonella*, *Shigella*, *Campylobacter*, or *Entamoeba histolytica* produce diarrhoea by invading intestinal mucosal barriers, followed by the initiation of acute inflammatory reaction through activation of cytokines and other

Localization	Enteropathogens	Virulence factors	Mechanisms
Small bowel	Enterotoxinogenic *E.coli* (ETEC)	Colonization factors (CFs) (adherence) Heat-labile toxin (LT), Heat-stable toxin (ST) (toxins)	Secretory (toxinogenic)
	Enteroaggregative *E.coli* (EAEC)	AAFs, dispersin (adherence) EAST1, Pet, Pic, ShET1 (toxins)	
	Vibrio cholerae	ACF, TCP (adherence) Ace, CT, RTX toxin, Zot (toxins)	
	Vibrio parahaemolyticus	Vp-TDH, Vp-TRH, Vp-TDH/1 (haemolysins)	
	Rotavirus	VP4 (adherence) NSP4 (toxin)	Osmotic Apoptosis of enterocytes Absorptive villus Architecture disruption
	Norovirus	VP1-P2 domain (adherence)	
	Giardia spp.	Variant-specific surface proteins (VSPs), arginine deiminase	
	Cryptosporidium spp.	Unknown	
	Cyclospora	Unknown	
Large bowel	*Entamoeba histolytica*	Gal-specific adhesin , cysteine proteinases, amoebapores Gal/GalNAc lectin, amoebapore and cystein proteases	Invasive
Small bowel and large bowel ileocolonic	*Campylobacter* spp.	CadF, JlpA, LOS, MOMP, PEB1 capsule (adherence) CiaB (invasion) CDT (toxin)	Inflammatory Invasive
	Shigella spp.	IcP, (SopA), Pic, SigA (protease) ShET1, ShET2, Shiga toxin (*S. dysenteriae*) (serotype 1 only) (toxin)	
	Salmonella spp.	AgF, LpF, MisL, Pef, RatB, ShdA, SinH, Type 1 fimbriae (adherence) Vi antigen (*S. enterica*) (serovar typhi) (immune evasion) CdtB (*S. enterica*) (serovar typhi), Spv (toxin)	
	Aeromonas hydrophila	Cytotonic Alt [heat-labile] and Ast [heat-stable], cytotoxic Act (enterotoxin) aerolysin (cytotoxin), hyl H (haemolysin).	
	Yersinia enterocolitica	Ail, Invasin (invasion) Yst (toxin)	

Table 2. Traveller's diarrhoea: localization, mechanisms and virulence factors of enteropathogens.

inflammatory mediators. In addition to enteroinvasive organisms, inflammatory diarrhoea can also be caused by cytotoxin-producing non-invasive bacteria, such as EAEC and *Clostridium difficile*, which adhere to the intestinal mucosa, activate cytokines and release inflammatory mediators (Navaneethan and Giannella, 2008).

3.1.1 Virulence factors

All the classical virulence factors including endotoxins, fimbriae and flagella, plasmids, apoptotic inducers, pathogenic islands and complete types I, II, and III secretion systems have been identified as being responsible for traveller's diarrhoea. Virulence factors in strains of *E. coli*, *Shigella*, *Salmonella*, *Vibrio*, *Campylobacter*, *Aeromonas*, *Yersinia*, *E. histolytica*, *Giardia*, and norovirus, as well as genes encoding virulence factors in these enteropathogens have been analysed. These factors are listed in Table 2. Research continues into candidate virulence factors of *Cryptosporidium* spp., while virulence factors of *Cyclospora* are yet to be defined.

4. Epidemiological data

Each year 100 million people from industrialized countries travel to areas of high risk for contracting traveller's diarrhoea, the majority of which are in the developing world. And up to 40 million cases of diarrhoea are reported among such travellers. Approximately 15 to 50 percent of travellers to tropical and subtropical areas in Africa, the Caribbean and Latin America, or in South Asia may develop diarrhoea (Steffen, 2005). Traveller's diarhoea can affect men and women equally. It is rare in travellers over the age of 55, while it is more frequent in children and in young adults under the age of 30 (Pitzinger et al, 1991). A Geosentinel study indicated that in more than 17,000 international travellers acute and chronic diarrhoea were the most common syndromes —at a rate of 335 diarrhoeal cases per 1,000 returned travellers (Freedman et al., 2006). Travellers to South Central Asia are at the greatest risk of contracting acute diarrhoea. On the other hand, the highest rates of chronic diarrhoea were reported after a journey to West Africa and East Asia (Sanders et al., 2008). ETEC is the main causal agent of traveller's diarrhoea in Africa, Latin America, and South Asia, followed by enteroaggregative *E. coli*, or EAEC, in Latin America and South Asia, whereas *Campylobacter* predominates in Southeast Asia (Hill & Beeching, 2010). Of the viral agents, noroviruses were found in mixed infections with bacteria such as ETEC in one-third of diarrhoea cases among those travelling to Latin America (Chapin et al., 2005). Rotaviruses are also frequent causes of traveller's diarrhoea in Mexico and Jamaica (Steffen et al., 1999; Vollet e al., 1979,). Considering parasites, *Giardia* has been mostly found after travel to central parts of South Asia (Freedman et al., 2006). *E. histolytica*, like other parasites, is frequently encountered among travellers returning from Asia, however seldom found after a short stay in Mexico (Frachtman et al., 1982; Freedman et al., 2006). Study groups in Nepal, Haiti and Peru have shown that *Cyclospora* is endemic in the regions of South Asia, the Caribbean and Latin America, respectively (Yates, 2005). In most cases, traveller's diarrhoea is quite mild, benign, and lasts for a short period of time (Hill, 2000). However, in 40 percent of the cases, digestive disturbances may lead to a change in travel plan with a potential for serious negative impact on the travel objective, for instance that of a business traveller. In 20 to 30 percent of cases, travellers may be confined to bed for a period of time, while in some (<1%) hospitalization is required.

5. Sources and modes of transmission

Traveller's diarrhoea is most commonly contracted by ingesting food and/or beverage contaminated with faecal material of human or animal origin. Despite the popular belief that drinking water posed the most significant risk for traveller's diarrhoea, unsafe/contaminated food was shown to be the major vehicle for infection. Raw or rare meat, poultry and seafood, and also the fruit and vegetables eaten raw are the more likely vehicles to spread the pathogens. Direct contact with contaminated, unwashed hands and indirect transmission by non-biting flies, such as the house fly, play only secondary roles in the transmission of diarrhoea to the traveller.

6. Risk factors

There are a variety of environmental and host-related factors that can predispose travellers to diarrhoeal illness. These risk factors include those that are associated with travel destination, planning, or seasonality and those in relation with the traveller's age, eating habits, or susceptibility.

Environment has been considered to have an impact on traveller's diarrhoea. The wider hygiene gap between the country of origin with a higher level and that of the destination may put a traveller at greater risk of contracting traveller's diarrhoea. Travel destinations are classified into three groups according to their hygiene level. Group I includes developed countries such as the United States, Canada, Australia, New Zealand, Japan, and the North and Western European countries with high level of hygiene and consequent low risk for acquiring diarrhoea by travellers to those countries (at a rate less than eight percent). Group II consists of areas of intermediate risk (at a rate of eight to 20 percent): such as Eastern European countries, South Africa, tourist places in Thailand, the Caribbean, and the Mediterranean. Areas of low hygiene level and high risk (at a rate more than 20 percent), such as the most part of Asia, the Middle East, Africa, and Central and South America, belong to group III. Furthermore, individuals travelling to temperate regions in winter are less at risk: for instance, the rate for *Campylobacter* infection was 58 percent in autumn, while it was only eight percent in the wintertime (Mattila et al., 1992). A recent study indicated that the rate for both enteroaggregative and enteropathogenic *Escherichia coli* infections among visitors to Mexico in winter was similar to that recorded in summer, whereas the rate of ETEC traveller's diarrhoea increased by seven percent for each degree centigrade increase in weekly ambient temperature (Paredes-Paredes et al., 2011). In travellers to the Tropics, however, the occurrence of diarrhoea does not seem to follow a clear seasonal pattern: EAEC, *Shigella*, and rotavirus are mostly found during the dry season. And those travelling during the rainy season or post-moonson are at a high risk for acquiring traveller's diarrhoea due to ETEC or *Giardia*, but not viral diarrhoea. (Taylor & Echeverria, 1986). The effect of the El Niño/Southern Oscillation, or ENSO, climate phenomenon should also be considered: the rise in average annual temperatures related with ENSO event has been positively associated with risk of diarrhoeal disease (Lauerman, 2001; Lama et al., 2004; Sari Kovats et al., 2003).

Travel plans and itineraries are also related to the possibility of exposure. Campers and backpackers, people who have more contact with the rural population, are at a higher risk than are business travellers (Piyaphanee et al., 2011). Being busy and often confined to

their hotel rooms, business travellers dine in their hotels. Organized travelling and planned itineraries may be considered safer. However, unforeseen situations may arise (Vassalos & Vassalou et al., 2011). For instance, travellers may end up eating food that has been on display for several hours or may try food from street vendors and local popular restaurants (Tjoa et al.,1977; Adachi, 2002). In the latter case, inadequate water supplies can lead to incorrect dish washing. Improper storage of food may also result from limited access to electricity. Recently, it has been shown that food contamination is widespread in developing countries despite the fact that food is cooked and served hot (Koo et al., 2008). Also, the individual traveller may or may not practise sound eating habits regarding consumption of food and/or water. Travellers visiting areas with access to clean drinking water and food are at lower risk for diarrhoea. In addition to all the foregoing, overcrowded areas such as campgrounds, military camps and cruise ships are particularly prone to diarrhoeal disease.

Besides environmental factors, host-related factors, viz personal factors and host genetic background, may also contribute to traveller's diarrhoea risk. Traveller's diarrhoea usually develops at the beginning of the tour. A longer stay may, however, increase the possibility of the occurrence of a gastrointestinal disorder (Piyaphanee et al., 2011). Young people are the ones most likely to develop diarrhoeal disease because of their keenness to explore the local flavours. Elderly travellers are less liable to contract diarrhoea, since they are more cautious about what they eat and drink (Alon et al., 2010). But they are also more likely to suffer complications because of their immunocompromised status from having debilitating, underlying medical conditions, such as diabetes, renal failure or hypochlorhydria induced by taking antacids. Rehydration therapy is important for the very young, elderly and those in cardiac glycosides or diuretics (DuPont & Khan, 1994). In contrast, healthy travellers visiting areas of low hygienic level may only experience mild gastrointestinal symptoms. The development of natural immunity plays a role in the lower rates of diarrhoeal disease among the locals in destination countries with relatively lower levels of socio-economic development. Similarly, earlier travel to an area of low hygienic level would also reduce the possibility of acquiring traveller's diarrhoea due to the immunity acquired from previous exposure to pathogens prevalent in such areas (DuPont et al., 1986). That is particularly important for travellers with high socio-economic status, who are less likely to develop protective immunity in their countries of origin.

Persons with blood type O are susceptible to developing cholera, whereas individuals with blood type A are more likely to get giardiasis (Harris et al., 2005; El- Ganayni et al., 1994). Differences in ABO, Lewis, secretor phenotypes seem to be associated with differences in susceptibility to infection caused by norovirus strains (Huang et al., 2002; Hutson et al., 2002; Marionneau et al., 2005). Several single nucleotide polymorphisms, or SNPs, have been investigated for possible association with traveller's diarrhoea. It was found that travellers with the T/T genotype in position codon 632 of the lactoferrin gene were more likely to develop traveller's diarrhoea (Mohamed et al., 2007). Polymorphism in the interleukin (IL)-8 promoter appears to be associated with susceptibility to EAEC (Jiang et al., 2003), whereas polymorphism in IL-10 promoter is likely to be associated with traveller's diarrohea due to ETEC (Flores et al., 2008). Osteoprotegerin, or OPG, is an immunoregulatory member of the tumour necrosis factor receptor superfamily. Polymorphism in the OPG gene has been found to be associated with increased susceptibility to traveller's diarrhoea (Mohamed et al., 2009).

7. Diagnostic approach

In a returned traveller with diarrhoea, a history of events is required to be established post-travel; a questionnaire concerning travel destination and conditions, eating habits, antimalarial chemoprophylaxis, onset of symptoms and other matters is suggested. In post-travel febrile diarrhoea, the traveller should be tested for malaria, given that malarial gastrointestinal manifestations are quite common. Once malaria is excluded, further work up should include routine haematological and biochemical testing, transabdominal ultrasound scan, stool culture and microscopy for cells, ova and parasites. For the isolation of *Escherichia coli, Campylobacter*, *Salmonella*, *Shigella*, *Aeromonas*, *Plesiomonas*, *Vibrio* and *Yersinia*, standard microbiological procedures are used. ETBF culture is carried out under anaerobic conditions. In the past, an aetiological agent remained unidentified in about 40 percent of such cases. Improved modern techniques have proven helpful in increasing the rate of identification of the cause of diarrhoea (Shah et al., 2009). The possibility of detecting *Shigella*, *Salmonella* or *Campylobacter* has increased substantially by using polymerase-chain-reaction (PCR)-based methods. Molecular techniques are used to detect the heat-labile and the heat-stable toxins of ETEC, aggR gene of EAEC , ipaH and invE genes of EIEC, and the genes of *B. fragilis* toxin of ETBF. To detect noroviruses, immunochromatography and reverse transcriptase PCR are employed. Diagnostic approach of traveller's diarrhoea is demonstrated in Figure 1.

8. Prevention

8.1 Hygiene measures

Traveller's diarrhoea is associated with inadequate sanitation and hygiene in countries being toured. Occurrence of traveller's diarrhoea is also related to the hygienic standards practised at the food preparation level. The challenge is to avoid faecal contamination of food and water. Furthermore, there is a need to minimize the burden of pathogen in the food and/or water just before consumption (Bandres et al., 1988). It has been shown that consumption of cold foods stored at a temperature that allows microorganisms to grow and produce toxins is responsible for small clusters of sickness even in luxury hotels.

The old adage 'boil it, cook it, peel it, or forget it' remains valid at the individual level. A traveller often wants to taste a local cuisine or to try vendor food, or a traveller may be forced to consume water of suspect quality. Table 3 shows a list of some foods and beverages that could be consumed safely during travel, and some others that are best avoided. Practical methods for water disinfection are: boiling for 1 min (or for 3 min at altitudes above 2, 000 m/6, 562 ft), or filtering through a 0.10 to 0.30 μm membrane in order to remove bacteria and protozoan parasites followed by chlorination or iodination to kill viruses. Travellers should remember to wash their hands with soap and running water or to use alcohol-based gels or solutions for a thorough hand-rub after going to the bathroom and before eating. In the case of infants, the best prevention measure is breastfeeding. Alternatively, infant formula should be prepared by using boiling hot water. Traveller's diarrhoea is also related to leisure activities such as swimming and diving in lakes or rivers, which are contaminated with human sewage or animal faeces. Consequently, travellers should choose to swim or dive in swimming-pools, which are kept properly sanitised and are regularly checked, even though protozoal cysts and viruses are resistant to usual levels of chlorination.

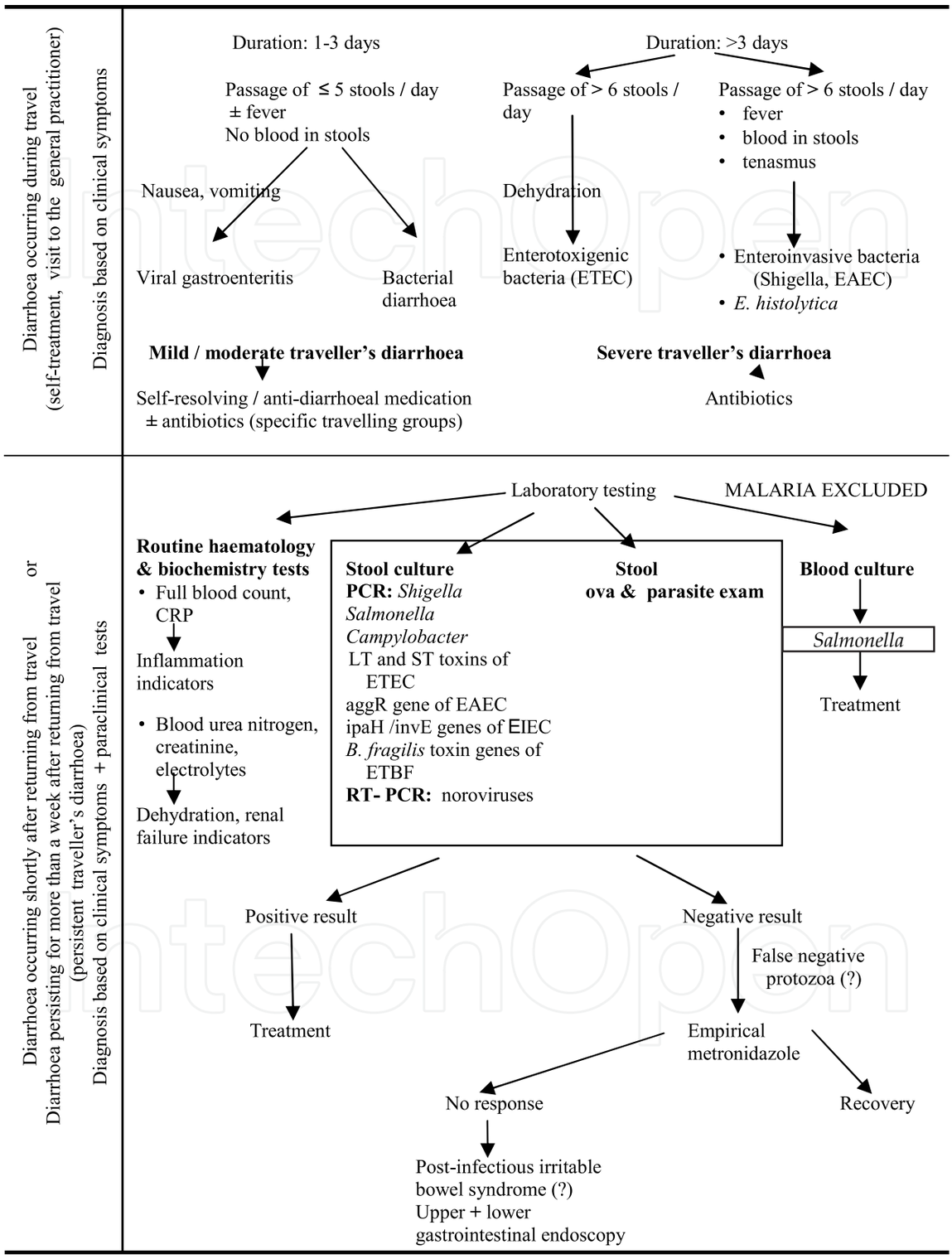


Fig. 1. Diagnostic approach and management of traveller's diarrhoea.

Foods and beverages that can be consumed	Foods and beverages that would be better avoided
Dry items such as bread, biscuits, or dry foods Syrups, jellies, jams, honey Any foods carefully prepared in one's own apartment or hotel Cooked foods consumed hot Beverages served steaming hot Decontaminated water (through filtration, chlorination or iodination) Bottled water with intact seal apparent on opening Bottled carbonated drinks including soft drinks and beer Fruits peeled by the traveller	Moist foods served at room temperature including vegetables and meats Underdone meat and fish Hot sauces on tabletop Seafood Ice-creams Salads Milk and dairy products Prepared foods eaten cold Any food served buffet-style maintained at room temperature Hamburgers not served hot or at fast food service restaurants with rapid turnover of prepared hamburgers (hamburger toppings are a major concern in these areas) Tap water even in hotels claiming filtration systems Large quantities of ice Non-bottled drinks Fruits and vegetables with intact skins: berries, tomatoes Pre-peeled fruit

Table 3. Examples of foods and beverages that can be consumed and the ones better avoided.

8.2 Chemoprophylaxis

8.2.1 Non-antimicrobial agents

Bismuth subsalicylate has been shown to provide a 65 percent protection rate in cases of traveller's diarrhoea, when the typical dosage of 525 mg is orally given four times daily. Bismuth subsalicylate cannot be used for a period more than three weeks. Bismuth subsalicylate should be avoided in travelling children and in travellers on anticoagulants owing to the activity of the salicylate ions (Diemert, 2006; Ericsson, 2005)

8.2.2 Probiotics

Probiotics, such as *Lactobacillus rhamnosum* strain GG, *L. acidophilus*, *L. bulgaricus*, and *Saccharomyces boulardii*, are live microorganisms capable of colonizing the intestine, and thus competing with enteric pathogenic microorganisms. These strains may secrete antimicrobial agents, induce the production of mucin or modulate immune response. Use of probiotics can be considered an alternative prophylaxis against traveller's diarrhoea, even though the protection provided by them is still quite low with a rate of only 47 percent (Hilton et al., 1997; McFarland, 2007). No side effects were observed; yet in elderly or immunocompromised travellers and in travellers with an underlying condition, probiotcs should be prescribed with caution (DuPont, 2008).

8.2.3 Antibiotics

Pre-travel medical consultation should make the decision regarding the need and modality of antibiotic prophylaxis. The doctor and traveller should first discuss the plan and duration of the journey. Antibiotic prophylactic is only recommended for a select group of travellers (DuPont & Ericsson, 1993). Such a group comprises those with immunodeficiency, including travellers with AIDS or neoplasia, travellers undergoing treatment with immunosuppressants, travellers with an underlying condition, i.e. diabetes, that could be worsened by the diarrhoeal illness, and those with achlorhydria or hypochlorhydria due to gastrectomy, administration of a H_2 receptor blocker or a proton pump inhibitor.

Antibiotic prophylaxis may also be recommended for certain important business travels of short duration. Situations where such a use can be justified are: travel for negotiating and signing important business deals, politicians gathering for summits, athletes participating in international meetings, speakers making presentations at international conferences, or students travelling for a short duration to appear in an examination or any other similar situation. Antibiotic prophylaxis can induce a false sense of security in a traveller who may consequently relax the adherence to hygiene and other precautions. This raises the possibility of infection by resistant organisms and worse outcomes. Hypersensitivity to the prescribed antibiotic can be a serious problem during travel. Vaginal candidiasis is not uncommon in such cases and pseudomembranous colitis due to *Clostridium difficile* can be a serious illness (DuPont et al., 2009). Antibiotic prophylaxis should be taken with caution and the administration should never exceed a period of two to three weeks. Although small, the risk of emerging resistant strains should also be taken into account, since the antibiotics used for traveller's diarrhoea prophylaxis and treatment are the same. Fluoroquinolones provide up to 90 percent protection. The oral administration of ciprofloxacin, 500 mg once a day, or norfloxacin, 400 mg once a day, starts upon arrival at travel destination and continues for 24 to 48 hours after departure from areas of elevated risk of traveller's diarrhoea. With fluoroquinolones taken as a short-term prophylaxis, the risk of side effects is small. Yet the emergence of resistance not just for Enterobacteriaceae strains such as *Campylobacter* spp. as found in Southeast Asia, but also for strains of *Salmonella* spp. and *Shigella* spp. is a major concern. Such an occurrence could reverse the progress made so far in the prevention and management of traveller's diarrhoea (Kuschner et al., 1998; Lindgren et al., 2009; Mensa et al., 2008). This has not been a concern when using rifaximin in a dose of 200 mg orally twice a day. Rifaximin given orally is poorly absorbed (Koo et al., 2010). It offers a 58 to 77 percent protection rate and does not affect intestinal flora even after continuous administration for a period of two weeks (DuPont et al., 2005). Also, it can be used to prevent traveller's diarrhoea in children who are at least 12 years old.

8.3 Immunoprophylaxis and vaccines

Although diarrhoea due to heat-labile toxin (LT) producing ETEC is more frequent in travellers, the development of vaccines that protect against more than one pathogenic strain is challenging. Today, oral, inactivated vaccine against cholera, which consists of killed whole cell, or WC, *Vibrio cholerae* and the non-toxic, recombinant cholera toxin B-subunit, or BS, is the only vaccine proven to fight a form of traveller's diarrhoea. But it is only administered to specific travelling groups such as people involved in humanitarian aid and military personnel deployed overseas, if travelling to an area where they are going to be at unavoidable risk of exposure to cholera. Nevertheless, the amino acid sequences of cholera

toxin B subunit and LT toxin of ETEC share approximately 80 percent homology, thus implying that the WS/BS vaccine may also offer some protection against traveller's diarrhoea caused by enterotoxigenic *E. coli* (Hill et al., 2006). Unfortunately, since the temporary protection provided is moderate at a rate of only seven percent, the use of WC/BS vaccine against cholera is therefore not routinely recommended for the majority of travellers (Hill et al., 2006). Transcutaneous vaccine, comprising purified LT toxin of ETEC, does not appear to offer either statistically significant protection against ETEC or any in general protection against traveller's diarrhoea (Frech et al., 2008).

9. Treatment

Traveller's diarrhoea treatment includes rehydration, diet, antisecretory agents, antimotility drugs, and antibiotics.

9.1 Rehydration

Traveller's diarrhoea does not usually cause dehydration. If patients are otherwise healthy and are not dehydrated, they can drink water *ad libitum*. They can rehydrate by taking frequent, small sips of bottled/boiled water or a rehydration drink. Until diarrhoea subsides, patients should avoid consuming beverages with high osmolality or caffeine content. These drinks can aggravate diarrhoea (Ericsson et al., 2008). Fluid replacement with oral rehydration solution is necessary for the very young and the elderly travellers, since they are vulnerable to the effects of dehydration (Rose et al., 2010). Further, in potentially dehydrating diarrhoea cases, oral rehydration solution should be used by all age groups: excessive fluid loss is not a rare event among adult travellers to the developing countries, especially in South Asia, where enterotoxigenic *E. coli* is the predominant cause of traveller's diarrhoea (Table 1). In an attempt to maintain a good state of hydration, vigorous treatment of traveller's diarrhoea should start as soon as the diarrhoea begins (Ericsson et al., 2008; Rose et al., 2010).

9.2 Diet

Complete abstention from food is neither required nor recommended, since foods providing calories are necessary to facilitate renewal of mucosal cells lining the intestine (Lever & Soffer, 2009). Dietary restriction, on the whole, has been questioned lately except for food or drinks with high content of simple carbohydrates. Patients with traveller's diarrhoea have been advised to restrict lactose containing foods after correcting dehydration because of transient lactase deficiency (Ericsson et al., 2008). But no hard evidence has yet surfaced to support that dietary restriction benefits those travelling to developing countries (Gottlieb & Heather, 2011; Huang et al., 2004). Instead, frequent small meals, incorporating well cooked complex carbohydrates/starch such as mashed potatoes, rice or other cereals, are being generally encouraged. This may not be important for a well nourished adult traveller from a developed country but would be an important consideration in travellers, whose nutritional status is borderline and may be further affected by the loss of appetite (Ericsson et al., 2008).

9.3 Non-antimicrobial agents

Non-antimicrobial agents can be used in cases of travellers with mild to moderate diarrhoea. Bismuth subsalicylate is composed of a bismuth oxide core structure with salicylate ions

attached to the surface. It exerts antisecretory, antimicrobial and adsorbent effects to control diarrhoea, even though its exact mechanism still remains unknown. It was shown that bismuth subsalicylate can alleviate non-specific symptoms such as nausea in patients with traveller's diarrhoea (Hill & Beeching, 2011). The dosage of 525 mg is orally given every half hour eight times daily. In travellers with acquired immunodeficiency syndrome or with chronic enteric disease, bismuth absorption may occur across the damaged mucosa (DuPont et al., 2009b). Serious neurotoxic and nephrotoxic adverse events may be attributable to the use of bismuth (Bao, 2006). The highest concentrations of absorbed bismuth are found in the kidneys and liver (Fowler & Sexton, 2007). Bismuth subsalicylate should not be used by travellers with renal or hepatic impairment. Antisecretory racecadotril, 100 mg after the first loose stool followed by 100 mg three times daily up to seven days, which acts as a peripherally acting enkephlalinase inhibitor, is prescribed in patients with traveller's diarrhoea. In pediatric patients, it is given as an adjunct to oral rehydration therapy. Antimotility agents may be good for relieving the symptoms of traveller's diarrhoea and used as adjuncts to antibiotic treatment. Loperamide, the most widely used antimotility drug, is an opioid-receptors agonist, which does not affect the central nervous system, acts on the opioid receptors of the myenteric plexus of the large intestine and decreases intestinal movements. Two capsules are recommended as the initial dose and subsequently one capsule is given after each unformed stool, with clinical improvement being seen within 48 hours. Although it may trap pathogens in the intestine, loperamide may help travellers who cannot afford to have diarrhoea during a short-term trip of critical importance. It should not be given in the presence of mucus or blood in the stool with or without fever, which represents diarrhoea due to enteroinvasive bacteria. Loperamide may cause narcotic intoxication and ileus in young children and be responsible for severe constipation in the elderly (Galleli et al., 2010; Li et al., 2007). The use of antimotility agents by the pediatric and geriatric population is not always without risk and should perhaps be avoided.

9.4 Antibiotics

Antibiotics are used in moderate and severe traveller's diarrhoea. Such antimicrobial agents are fluoroquinolones, azithromycin and rifaximin (Table 4).

Fluoroquinolones, which are synthetic broad spectrum antibiotics, are active against invasive bacteria including *Shigella*, even though, mainly in Southeast Asia, resistance of *Campylobacter* to fluoroquinolones has emerged. In the latter case, azithromycin, which is a subclass of macrolide antibiotics, is recommended; it has high intracellular concentrations and serum-based definition of resistance does not necessarily apply to controlling the disease in a clinical situation. If the traveller wishes for a prompt relief from afebrile, gastrointestinal symptoms, loperamide can be taken in combination with one of the antibiotics mentioned above. Among travellers visiting Mexico, loperamide combined with azithromycin was shown to reduce the time from the last unformed stool when compared to those who were administered only azithromycin (Ericsson et al., 2007). Rifaximin, a novel semi-synthetic derivative of rifamycin, is active against ETEC but not against invasive bacteria (Taylor et al., 2008).

9.5 Self evaluation and treatment

Traveller's diarrhoea usually develops shortly after arrival at the travel destination. Study indicates that 80 percent of patients with traveller's diarrhoea choose to treat themselves

Antibiotic per os[a]	Adults' dosage (normal renal function)	Children's dosage (normal renal function)[b]
Fluoroquinolones		
Norfloxacin	800 mg once or 400 mg b.i.d. for 1-5 days	-
Levofloxacin	500 mg once or 500 mg q.d. for 1-5 days	-
Ofloxacin	400 mg once or 200 mg b.i.d. for 1-5 days	-
Ciprofloxacin	750 mg once or 500 mg b.i.d for 1-5 days	10-15 mg kg^{-1} b.i.d. for 3 days
Macrolide		
Azithromycin	500-1000 mg [c] once or 500mg q.d. for 3 days	20 mg kg^{-1} q.d. for 3 days
Rifamycin derivate		
Rifaximin	200 mg t.i.d.[d]	-

[a] Antibiotics taking should be interrupted in case of improvement
[b] Children's dose should not exceed adult dose
[c] 1000 mg azithromycin dose can cause nausea
[d] Rifaximin should not be administered in bloody diarrhoea

Table 4. Antibiotics dosage for moderate or severe traveller's diarrhoea.

irrespective of the illness being mild or more severe (Hill, 2000). For that reason, during pre-travel consultation, travellers should be given information about the problem and importance of traveller's diarrhoea and instructed on how to proceed with self-evaluation. Local medical help should be sought if diarrhoea lasts for more than 48 hours or in case of fever, blood or mucus in the stool. Otherwise, travellers could replace lost fluids and electrolytes and take non-antimicrobial agents in their possession. In high risk areas with difficult access to medical services, travellers should promptly start taking antibiotics (immediately after the symptoms appear, and before they get worse). The choice of antibiotic should be determined by the locally prevalent predominant organisms and their sensitivity pattern. Fluoroquinolones are usually recommended for most travel destinations excepting South and Southeast Asia, where azithromycin can be a better choice because of prevalence of fluoroquinolones-resistant *Campylobacter* (Table 1). For self-treatment, a single dose of antibiotics can be given. If there is no improvement, administration can continue for three days (Tribble et al., 2007). An otherwise healthy adult can take the antibiotics in combination with loperamide to achieve a faster improvement of diarrhoea (Ericsson et al., 2007).

10. Clinical course

All patients suffering from traveller's diarrhoea develop similar symptoms, regardless of the causal agent. It usually occurs within the first week of travel and resolves upon returning to the country of origin. The onset of traveller's diarrhoea is usually sudden, although abdominal pain, anorexia, and malaise may sometimes occur before the diarrhoea begins. Other manifestations such as nausea and vomiting in 10 to 25 percent, mild fever in up to 30

percent, and blood in stool in one to 10 percent of the cases may accompany diarrhoea. Average duration is approximately four days. Fifty percent of patients begin to recover within 48 hours (Steffen et al., 1983).

Irrespective of the aetiology, mild traveller's diarrhoea is generally short-term: this is not the case with more severe attacks (Hill, 2000). It is estimated that up to 25 percent of the cases of traveller's diarrhoea have more than five bowel movements in a day, and 30 to 45 percent of the cases may have their trip interrupted or travel plan altered for at least 12 to 24 hours (Steffen et al., 1987). Some patients with traveller's diarrhoea need to seek medical help while travelling or upon returning to the country of origin.

10.1 Viral gastroenteritis

Viral gastroenteritis is an intestinal infection caused by a variety of viruses resulting in mild, short-term diarrhoea, with vomiting being a prominent feature. It is often clinically undistiguishable from bacterial acute diarrhoea. In popular travel destinations, however, viruses have been shown to be responsible for up to 10 percent of cases of traveller's diarrhoea (Apelt et al., 2010). Viruses, mostly incriminated in cases of gastroenteritis, include GI and GII norovirus strains (Ajami et al., 2010) and rotaviruses belonging to groups A and C (Peñaranda et al., 1989; Sheridan et al, 1981). Enteric adenoviruses type 40 and 41 as well as astroviruses, though being an important cause of acute infantile gastroenteritis, do not appear to be a major health problem in travellers. Viruses can be transmitted from person to person or through contaminated food and water. Outbreaks of norovirus gastroenteritis have occurred in case of travellers co-existing in relatively confined spaces, such as aboard cruise ships and in tourist resorts, thus being in close contact with other passengers and tourists, relatively (Widdowson et al., 2002; Kornylo et al., 2009) Noroviruses cause transient malabsorption of D-xylose and fat, while rotaviruses cause malabsorption of glucose through the mechanism of cAMP protein kinase (Karst et al., 2010; Lorrot & Vasseur, 2007). Antibiotics do not work on viral gastroenteritis. Notwithstanding this, non-antimicrobial agents have been found effective in the treatment of intestinal viral infection associated with traveller's diarrhoea. Studies have shown that mixed viral and bacterial infections are common in gastroenteritis (Marshall, 2002). Thus, combination therapy with loperamide plus antibiotic is given empirically for traveller's diarrhoea (Ostrosky-Zeichner & Ericsson, 2001).

10.2 Persistent traveller's diarrhoea

Traveller's diarrhoea generally resolves even without treatment. However, in 10 percent of cases, digestive disturbances tend to persist for more than two weeks after the onset of the diarrhoea. In persistent cases, the patient continues to complain of intermittent or continuous gastrointestinal symptoms, such as loose stools, abdominal pain, bloating or other non-specific symptoms. Continued intestinal infection, post-infectious mucosal damage, or chronic gastrointestinal functional disorder may be responsible for persistent traveller's diarrhoea. In most of these cases, tests for the presence of pathogens may fail if sampling is delayed for a period of time after the onset (Connor, 2011).

10.2.1 Functional disorders

Similar to any acute inflammatory process, traveller's diarrhoea may disrupt the brush border microvilli of intestinal epithelial cells where disaccharidases reside. Consequently, a

transient lactose intolerance may occur. Likewise, transient malabsorption of xylose, folate and vitamin B12 may also occur (Lindenbaum, 1965). Another post-infectious sequela is the development of irritable bowel syndrome, or IBS. Among sufferers, five to 10 percent are likely to experience non-specific gastrointestinal symptoms that are compatible with those of irritable bowel syndrome. Also, it has been found that 10 percent of patients with irritable bowel syndrome have reported travelling abroad before the onset of their symptoms (DuPont et al., 2010). Travellers experiencing diarrhoea during their trip were five times more likely than travellers without to develop post-infectious irritable bowel syndrome, or PI-IBS (Stermer et al., 2006). In 15 percent of travellers, traveller's diarrhoea with serious symptoms can lead to post-infectious irritable bowel syndrome within a six month period (Okhyusen et al., 2004). Risk factors for developing post-infectious irritable bowel syndrome include female gender, young age, pre-existing anxiety or depression, fever or weight loss, and infection due to strains of *Campylobacter* with toxigenic properties (de la Cabada Bauche & DuPont, 2011). Following traveller's diarrhoea, transient changes in intestinal motility should may lead to stasis and small intestinal bacterial overgrowth. This can cause secondary diarrhoea, and other non-specific symptoms that resemble those of irritable bowel syndrome (Attar et al., 1999; Tureja et al., 2008).

10.2.2 Persistent intestinal infection

In acute traveller's diarrhoea, parasites account for only a small percentage of the cases. In persistent traveller's diarrhoea, by contrast, intestinal protozoa are the most frequently encountered aetiological agents. Where travellers develop persistent diarrhoea, the most commonly detected enteric protozoa are *Giardia, Cryptosporidium*, and *Entamoeba histolytica,* followed by a small percentage of cases caused by *Isospora belli* and microsporidia. In returning traveller patients, *Cyclospora cayetanensis* has also been suggested to cause diarrhoea that continues after travel. Risk factors that are associated with contracting intestinal protozoal infections while travelling abroad are quite well known: longer duration of stay, and the low level of hygiene and socio-economic development in the country travelled (Kansouzidou et al., 2004; Müller et al., 2001; Okhyunsen et al., 2001; Taylor et al., 1988).

11. Intestinal protozoal diarrhoeal disease

11.1 Giardiasis

Giardiasis is a disease of the small intestine caused by *Giardia*; it has recently been included in the World Health Organization 'Neglected Disease Initiative'. Clinical spectrum of *Giardia* infection may vary from asymptomatic carriage to acute and chronic diarrhoea with abdominal pain. *G. intestinalis* is a cosmopolitan flagellated protozoan of humans and other animals. Molecular analysis has demonstrated that *Giardia* isolates can be separated into at least eight genotypes or assemblages, namely A to H, that may show host preference (Lasek-Nesselquist et al., 2010). Humans are mostly infected by assemblages A and B. Genomic difference may underlie the often distinct difference in biology and clinical manifestations observed between the two assemblages. This implies that *Giardia* assemblage A and assemblage B may represent two distinct species (Franzén et al., 2009). *Giardia* infection is usually transmitted by ingesting cysts found in contaminated water or food, but human-to-human transmission has also been reported in situations of poor faecal–oral hygiene. Giardial encystation (when trophozoites pass through the small intestine to the colon) is

successful only if *Giardia* cysts are able to excyst after ingestion and entry into the small intestine (Lauwaet et al., 2007).

11.2 Amoebiasis

Amoebic colitis is characterized by gradual onset and symptoms present over a period of one to two weeks. It can thus be distinguished from bacterial dysentery. The protozoan may be responsible for various symptoms such as bloody diarrhoea and non-specific symptoms i.e. weight loss, fatigue, and abdominal pain. Also, it may cause fulminating dysentery. *Entamoeba,* whose habitat is the large intestine, is one of the most commonly detected enteric protozoans worldwide. It has been demonstrated that it comprises two species, *E. histolytica* and *E. dispar* and these cannot be morphologically differentiated from each other under the light microscope (Clark, 2004). However, these two species can be differentiated by using zymodeme patterns, monoclonal antibodies, or DNA probes (Stanley, 2003). Most recently, *E. histolytica* genome sequence has been re-annotated and re-assembled and data have been compared to closely related organisms (Lorenzi et al., 2010). Infection with *E. histolytica* is considered more prevalent in developing countries. It is transmitted by contaminated water and/or food or by the faecal-oral route. Immunocompromised persons as well as persons with a mental illness housed in institutional settings are at high risk for acquisition of amoebiasis. *Entamoeba* has two stages in its life cycle: active and motile trophozoite and the dormant cystic form. Trophozoite or the trophic form can be detected in the fresh unformed stool from a host. By contrast, cysts can survive outside the host, in the environment i.e. in water, in soils, or in food. *E. histolytica* is considered to be pathogenic, as opposed to the non-pathogenic *E. dispar*. Since *E. dispar* is regarded as non-pathogenic and commensal, infections with *E. dispar* are characteristically asymptomatic. Recently, however, there have been reports of patients infected with *E. dispar* experiencing gastrointestinal symptoms (Fotedar et al., 2007).

11.3 Cryptosporidiosis

In cryptosporidiosis caused by *Cryptosporidium*, immunocompetent individuals experience acute watery diarrhoea, which is usually self-limited and accompanied by non-specific symptoms such as abdominal pain, nausea and fatigue. In immunocompromised hosts, however, clinical manifestations of cryptosporidiosis vary with the level of immunosuppression. For instance, in case of low levels of CD4 helper T cells, immunocompromised patients could have persistent diarrhoea due to cryptosporidiosis (Brink et al., 2002). *Cryptosporidium* is an apicomplexan protozoan affecting humans and many animals. Molecular divergence between the two *C. parvum* variants, which were shown to have differences in epidemiological and clinical features, was discovered by using numerous techniques. These variants are now known as *C. parvum* in humans and in animals, and *C. hominis* in humans (Morgan-Ryan et al., 2002). A further important advance in the understanding of this protozoan is the publication of the *C. parvum* and *C. hominis* genome sequences. However, it has been suggested that there exist differences in the genetic make-up of *Cryptosporidium* populations, indicating variation in their infectivity for humans (Jex et al., 2008). In addition to genotypic differences, phenotypic differences have also been demonstrated suggesting that additional genetic pleomorphisms within the known genotypes exist. Monoxenous life cycle has an asexual stage, or sporozoites, and a sexual stage, or oocysts, and is completed within the small intestine. Sporulated thin-walled

oocysts are autoinfective. Thick-walled oocysts that transmit the cryptosporidial infection from one host to another are resistant forms, even in chlorinated water, upon being excreted (Currrent and Garcia, 1991). Cryptosporidial oocysts can be excreted for weeks after the diarrhoea subsides. *Cryptosporidium* can survive in source waters for a long period of time. Cryptosporidial infection is transmitted by drinking contaminated water or eating contaminated food, and by animal-to-human or faecal-oral routes. The infective dose is low. In healthy, immunocompetent people, ingestion of as few as up to 30 *Cryptosporidium* oocysts can cause infection, whereas in immunocompromised patients even fewer oocysts are required (DuPont et al., 1995).

11.4 Isosporiasis

Isosporiasis, a diarrhoeal illness that is caused by *Isospora belli,* generally causes watery diarrhoea and non-specific gastrointestinal symptoms such as cramps and abdominal pain. In immunocompetent individuals, isosporiasis is usually transient; however, immunocompromised patients can experience persistent diarrhoea resembling the cryptosporidial diarrhoea mentioned above (Mudholar & Namey, 2010). *I. belli* is a coccidian protozoan. Although ubiquitous, *I. belli* is more frequently encountered in the tropical and subtropical countries. Humans are the sole identified reservoir for *I. belli* infection. Transmission has not yet been elucidated, even though *I. belli* has been suggested to be transmitted through contaminated water. Similar to *Cryptosporidium*, the *I. belli* life cycle has an asexual stage and a sexual stage in the intestine. Oocysts are immature and incapable of infecting the human host after excretion. The large oocysts mature outside the body and become sporulated and infective within a two to three day period.

11.5 Cyclosporiasis

Cyclosporiasis, a diarrhoeal disease caused by *Cyclospora*, is generally the cause of self-limited diarrhoea accompanied by cramping, abdominal pain, nausea and other non-specific symptoms (Türk et al., 2004). Immunocompromised hosts, however, may experience prolonged diarrhoea that may become quite serious if left untreated (Türk et al., 2004). *C. cayetanensis* is a coccidian protozoan that has been associated with diarrhoea in the developing world. It is considered an obligatory intracellular parasite found in jejunum. *Cyclospora* reservoirs are yet to be defined, even though humans appear to be the only reservoir for *Cyclospora*, similar to *I. belli* (Ortega & Sanchez, 2010). It has been proposed that this coccidian protozoan parasite may be transmitted via contaminated water and food. In order to become infective, very large *Cyclospora* oocysts, which resemble those of *Cryptosporidium* but are roughly twice the size, need sporulation outside the body, in the environment: in this they are dissimilar to *Cryptosporidium* but similar to *I. belli*.

11.6 Microsporidiosis

Microsporidiosis is commonly found in immunosuppressed individuals (Matthis et al., 2005). Among the numerous microsporidian species, only *Enterocytozoon bieneusi* and *Encephalitozoon intestinalis* are associated with intestinal infection in humans worldwide. Therefore, infection with *E. bieneusi* or *E. intestinalis* should be considered in cases of chronic diarrhoea. Microsporidia are small, obligatory, intracellular organisms that infect vertebrate and invertebrate hosts. Although it has been proposed that they belong to the protist group of archezoa, microsporidia have molecularly been re-classified from protozoa to fungi or a

sister group of fungi (Parfrey et al., 2006). Microsporidia have specialized polar tubes, asexually reproduce within the cell, and form thick-walled spores that are capable of surviving in the environment for a long period of time.

11.7 Dientamoebiasis

Recently, *Dientamoeba fragilis* has been regarded as a pathogenic organism (Katz & Taylor, 2001). Most patients with dientamoebiasis report frequent unformed stools and abdominal pain. Mucus in the stool is sporadically observed. In about 30 percent of patients with dientamoebiasis, diarrhoea is persistent and may turn into the chronic form, which lasts more than four weeks, with abdominal pain being the predominant symptom (Stark et al., 2005). *D. fragilis* is one of the smaller parasites that can live in the human large intestine. Unlike other intestinal protozoa that are mainly detected in the developing world, *D. fragilis* is often seen in developed countries with high levels of hygiene. Once classified as an amoeba, it has been demonstrated to be a close relative of the trichomonads (Johnson et al., 2004). It is considered to be a non-flagellated trichomonad. It is worthwhile mentioning that *D. fragilis* has no apparent cyst-like forms (in this it is dissimilar to other intestinal protozoa). Although it still remains unclear (Barratt et al., 2011), it has been proposed that infection between humans occurs during the trophozoite stage. Our as-yet-unpublished results corroborate the possibility of intrafamily transmission (Stark et al., 2009).

11.8 Blastocystosis

Once thought to be a harmless inhabitant of the human gut, *Blastocystis* is now considered a potential pathogen. Immunocompromised or debilitated individuals seem more prone to getting a diarrhoea attributable to blastocystosis (Vassalos et al., 2008). *Blastocystis* sp. is a ubiquitous anaerobic protozoan parasite that lives in the intestine of humans, other animals and arthropods. *Blastocystis* isolates have been separated into at least 10 subtypes according to phylogenetic trees that have been constructed from sequences of the small subunit ribosomal RNA (Stensvold et al., 2009). Subtype 3 has been found to be the most common genotype (Tan, 2008). The protozoan is more frequently encountered in tropical and subtropical countries. *Blastocystis* is polymorphic. It has various morphological forms, including vacuolar, granular, amoeboid, cyst, multivacuolar and avacuolar forms, with the vacuolar form being the most commonly detected in stool examination. Amoeboid forms are predominantly seen in isolates from symptomatic patients (Tan, 2008). *Blastocystis* vacuolar forms could transit to *Blastocystis* cysts and vice versa. Thus, faecal–oral transmission has been proposed. Also, it is transmitted by contaminated water or by human-to human and animal-to-human routes.

11.9 Mechanisms of diarrhoea production

Diarrhoea caused by *Giardia* is mediated by increased rates of transit of small intestine origin as well as enhanced chloride secretion (Cotton et al., 2011). Yet the mechanisms of pathogenesis are poorly understood (Buret, 2007). However, host and parasite factors seem to contribute to the pathogenesis of *Giardia* infection. Increase in rates of enterocyte apoptosis and disruption of epithelial tight junctions lead to dysfunction in the small intestinal barrier resulting in activation of CD8 cytotoxic T-lymphocytes. CD8 lymphocytes may induce brush border microvilli injury and enterocyte malfunction that leads to malabsorption and maldigestion of small intestine origin (Buret, 2005). *Cryptosporidium* is

localized within a unique intracellular but extracytoplasmic niche (Tzipori & Ward, 2002). The coccidian parasite is found attached to brush border microvilli of epithelial cells of the small intestine where it can cause damage that leads to the death of enterocytes. To replace the damaged cells, cell division is triggered in the crypt region resulting for instance in hyperplasia. The absorptive function of the villar tips is impaired and chloride secretion by the crypt cells increases, thus leading to an overall enhancement of intestinal secretion. Under this proposed mechanism, *Cryptosporidium*-induced diarrhoea is classified as osmotic (Sears & Guerrant, 1994). The host immune system is likely to reduce the number of thin-walled oocysts in an attempt to prevent autoinfection, which tends to perpetuate cryptosporidial infection in the host. In principle, the mechanism of diarrhoea production appears to follow the same pattern as seen in isosporiasis and cyclosporiasis.

E. histolytica has been suggested to produce several potential virulence factors such as adhesins that enable adherence to the host cell, amoebapores that are capable of forming a hole in a target cell; and cysteine proteinases that can degrade extracellular matrix components. Intestinal inflamation, killing of mucosal cells and invasion of protozoan are the combined effects of these virulence factors (Padilla-Vaca & Anaya-Velázquez, 2010). Lysis of host neutrophils may also contribute to the cell damage. In a host-parasite interplay, however, it is quite possible that the virulence may reflect how much control the host is capable of exercising over invasion and replication of *Entamoeba* trophozoites (Galván-Moroyoqui et al., 2008). Invasion of intestinal epithelium by *Entamoeba* trophozoites can result in the development of dysentery, ulcers, or an amoeboma (Suriptiastuti, 2010). Dysenteric syndrome is characterized by the production of small volumes of bloody, mucoid stools without faecal leukocytes. Amoebic 'flask-shaped' ulcers can be observed in sections of the gastrointestinal tract. Amoeboma is the formation of amoebic granuloma in the intestinal wall. If entroinvasive illness turns into chronic amoebic colitis, the disease mimics inflammatory bowel disease. *D. fragilis* is considered to cause non-invasive, superficial irritation of the colonic mucosa, along with an eosinophilic inflammatory response (Johnson et al., 2004). *Blastocystis* is also considered to be the cause of non-invasive mucosal inflammation. Our published results have shown that *Blastocystis* subtype 3 might be pathogenic, only when amoeboid forms of *Blastocystis* are present (Katsarou-Katsari et al, 2008), and suggest that there are intra-specific differences within *Blastocystis* subtypes that contribute to the protozoan parasite's pathogenicity (Vassalos et al., 2010). The host immune status seems to play some role on the development of blastocystosis. Immunocompromised patients will suffer from diarrhoeal disease as the potential pathogenic forms of *Blastocystis* thrive when host defences are weakened. Interplay with intestinal microbiota may differ between pathogenic and non-pathogenic forms of *Blastocystis* (Vassalos et al., 2008). *E. bieneusi* clusters have been found in intestinal and biliary tract cells, whereas *E. intestinalis* infects the intestinal tract and may also disseminate to the mesenteric nodes and kidney. In the context of host-parasite relationship, microsporidia seem to be highly sophisticated parasites. Not only is proteome complexity reduced in the microsporidia but also several eukaryotic pathways are pared down to what appears to be minimal functional units so that host cell manipulation can be achieved (Williams, 2009).

11.10 Routine diagnostic arsenal

The challenge is to identify the likely intestinal protozoal agent involved in diarrhoeal disease as fast and accurately as possible so that therapeutic management can start.

Conventional ova and parasite testing that involves light microscopic examination of stool samples is employed for the low cost detection of intestinal protozoal diarrhoeal disease. The method, however, is a labour intensive and time consuming process, and requires an experienced microscopist. On the other hand, antigen detection assays are considered to be rapid and reliable methods for detecting enteric protozoan parasites, without the need for skilled microscopy. Direct fluorescent antibody, enzyme-linked immunosorbent assay (ELISA), and rapid dipstick-like tests are the diagnostic procedures in use for antigen detection in diagnosis of protozoa of the intestine.

Giardial infection can be diagnosed by identification of cysts and trophozoites in the stool; wet mount preparations and trichrome stained smears of stool specimens are the recommended procedures. *Entamoeba* cysts and trophozoites can also be observed by examining a fresh stool and by using trichrome stain. *Cryptosporidium* oocysts can be visualized with a modified acid fast stain. Similarly, identification of *Isospora* oocysts requires acid fast staining. To detect *Cyclospora*, however, Safranin stain is used. *Cyclospora* can also be identified in stool samples, since the protozoan is able to autofluoresce at 330 to 380 nm under ultraviolet microscopy. Microsporidial infection can be diagnosed by identification of free and intracytoplasmic spores with Giemsa and modified trichrome, or with fluorochrome stains such as calcofluor and Uvitex 2B, stains that have an affinity for chitin. Morphological differences between *E. bieneusi* and *E. intestinalis* can be made out in small intestine biopsy specimens by electron microscopy.

It is possible to detect *Giardia* by using direct immunofluorescence or ELISA. *Cryptosporidium* oocysts can be detected by using monoclonal antibody-based direct immunofluorescence assay or ELISA. Newly developed stool antigen detection methods, i.e. ELISA, capable of discriminating between *E. histolytica* and *E. dispar* may also prove particularly useful. For laboratory diagnosis of the enteric protozoans *G. intestinalis*, *E. histolytica*, and *Cryptosporidium* spp., diagnostic kits using immunochromatography are now commercially available. To detect microsporidia, free and intracytoplasmic spores can be examined using an indirect immunofluorescent assay with monoclonal antibodies.

PCR-based methods are also increasingly used for the detection of intestinal protozoa in case of diarrhoea. Inexpensive in-house PCR protocols can be adapted to detect intestinal protozoa. Furthermore, the trend has been moving from the detection of a single intestinal protozoal agent involved in diarrhoeal disease to a multiplex approach, thus allowing simultaneous identification of multiple protozoan parasites in order not to loose valuable time (Stark et al., 2011). In our laboratory, nested multiplex PCR is routinely used to differentiate *E. histolytica* from the non-pathogenic *E. dispar* (Evangelopoulos et al., 2000). As for the differentiation of intestinal protozoa other than *Entamoeba* spp. at the inter- or intra-specific level, further refinements are required in PCR-based methods. Thus, outbreaks of intestinal protozoal diarrhoeal disease could be readily investigated and research in molecular epidemiology could be made possible. Polymerase chain reaction techniques, such as real time PCR based on SYBR-Green fluorescence, can also be used to simultaneousley identify microsporidial species (Polley et al. 2011). In diarrhoeal patients with dientamoebiasis, highly variable intermittent shedding of *D. fragilis* trophozoites has been shown to confound diagnosis when methods such as microscopy, culture or conventional PCR are used to detect the protozoan. However, intermittent shedding does not seem to interfere with the diagnosis of dientamoebiasis in cases where real time PCR, which demonstrates high sensitivity, is employed. This is thus being seen as the method of choice (Stark et al., 2010).

11.11 Treatment and management

The agents that are used for the treatment of intestinal protozoal diarrhoeal diseases are set out in Table 5. Concerning the treatment of giardiasis, there are several drugs including the 5-nitroimidazole and benzimidazole derivatives, quinacrine, furazolidone, paromomycin, and nitazoxanide that have been proved effective and approved. Metronidazole is considered the antiprotozoal agent of choice for the treatment of giardial infection; however, decreased susceptibility to metronidazole has been reported. Therefore, albendazole can alternatively be administered. Combination therapy may also be used when first line drugs fail, nitazoxanide is not available, or co-infection with other parasites occurs (Lopez-Velez et al., 2010).

Where cysts are detected in an asymptomatic *Entamoeba* carrier, a luminal agent, such as diloxanide or paromomycin, should be given to treat intraluminal infection and clear amoebic cysts (Stanley, 2003). In enteroinvasive disease, i.e. severe colitis due to *E. histolytica,* tissue penetrating metronidazole should be administered against invasive trophozoites and then a luminal amoebicide should be given to kill any remaining cysts. Using *in vivo* models, metronidazole was found to be the most effective (Becker et al., 2011). However, if metronidazole tolerance occurs, tinidazole may alternatively be used (Gonzales et al., 2009). Cryptosporidial infection is self-limited and immunocompetent hosts may only need to be treated supportively. In immunocompromised patients with cryptosporidiosis, the most commonly used agents are paromomycin, and azithromycin, which are partially effective. Nitazoxanide, a thiazoline compound, has been shown to be effective in immunocompetent individuals. However, nitazoxanide could be effective in case immune response is appropriate (Gargala, 2008). Consequently, in immunocompromised patients, it is necessary to combine treatment against cryptosporidial infection with a therapy for restoring immunity (Cabada & White, 2010).

In cases of symptomatic *Isospora* or *Cyclospora* infections, trimethoprim-sulfamethoxazole, a sulfonamid antibiotic, is administered. In immunocompromised patients experiencing recurrent diarrhoeal disease, secondary prophylaxis with trimethoprim-sulfamethoxazole attempts to treat *Isospora* or *Cyclospora* infection, and thus prevent relapses. Nitazoxanide is also in use for the treatment of isosporiasis and cyclosporiasis in patients with sulfa allergy (Zimmer et al., 2007).

Microsporidial infection of immunocompetent individuals is self-limited and does not require antiparasite treatment. Many agents have been tested in the treatment of microsporidia infection. However, the results have shown variable therapeutic success in the treatment of microsporidiosis in humans. Albendazole has been demonstrated to be effective against *Encephalitozoon* spp. such as *E. intestinalis* but not against *Enterocytozoon bieneusi*. Fumagillin, an irreversible inhibitor of methionine aminopeptidase-2, has been demonstrated to be effective for eradicating *E. bieneusi,* despite its side effects. In renal transplant recipients, fumagillin shows acceptable safety when monitoring immunosuppressive therapy (Champion et al., 2010).

Currently, there is no consensus for the treatment of symptomatic dientamoebiasis (Johnson et al., 2004). The therapeutic agents commonly used to treat *D. fragilis* infection are metronidazole, paromomycin, newer nitroimidazole derivatives such as secnidazole and ornidazole, tetracycline, or a combination therapy.

Concerning *Blastocystis* infections, the treating agents that are currently in use have been considered to be generally effective. However, decreased susceptibility to metronidazole has

Protozoa	Drug(s) of choice	Alternative drug(s)
Giardia intestinalis	Metronidazole 250 mg t.i.d. × 5 days Tinidazole 2 g × 1 day	Albendazole 400 mg q.d. × 5 days Quinacrine 100 mg t.i.d. × 5 days Paromomycin 25 – 30 mg kg^{-1} per day in 3 doses × 7 days
Entamoeba histolytica	*Asymptomatic carriers (cysts)* Paromomycin 500 mg t.i.d. × 10 days Diloxanide furoate 500 mg t.i.d. × 10 days *Symptomatic patients (trophozoites)* Metronidazole 750 mg t.i.d. × 5 days or Tinidazole 2 g × 3 days followed by paromomycin 500 mg t.i.d. × 10 days or diloxanide furoate 500 mg t.i.d. × 10 days	Diloxanide furoate 500 mg t.i.d. × 10 days plus Tetracycline 250 mg q.i.d. × 10 days followed Chloroquine 500 mg q.i.d. × 7 days
Cryptosporidium.	Nitazoxanide 500 mg b.i.d. × 3- 14 days	Albendazole 400 mg b.i.d.x 7-14 days Paromomycin 500 mg t.i.d. × 14 days
Isospora belli	Trimethoprim- Sulfamethoxazole (160mg/800mg) b.i.d. × 10days	Ciprofloxacin 500mg b.i.d. × 7 days Pyrimethamine 75 mg q.d. plus folinic acid 10 mg q.d. × 10 days
Cyclospora cayatensis	Trimethoprim- Sulfamethoxazole (160mg/800mg) q.i.d. ×10days	Nitazoxanide 500 mg b.i.d. × 3- 14 days
Encephalitozoon intestinalis	Albendazole 400 mg b.i.d. × 14-28 days	
Enterocytozoon bieneusi	Albendazole 400 mg b.i.d. × 28 days	Fumagillin 60 mg q.d. × 14 days
Dientamoeba fragilis	Tetracycline 500 mf q.i.d. × 10 days	Paromomycin 25 – 30 mg kg^{-1} per day in 3 doses × 7 days Metronidazole 750 mg t.i.d. × 5- 10 days
Blastocystis sp.	Nitazoxanide 500 mg b.i.d. × 3 days	Metronidazole 750 mg t.i.d. × 5- 10 days Trimethoprim- Sulfamethoxazole (160mg/800mg) b.i.d. × 7 days

Table 5. Treatment of diarrhoeal disease due to intestinal protozoa: drugs of choice and alternative drugs.

been described. An asymptomatic *Blastocystis* carrier should be followed up so that a thorough examination could be ordered in case symptoms become evident. The use of broad spectrum antimicrobial should be restrained, being used only in cases of symptomatic *Blastocystis* infections. Thus, the emergence of resistant *Blastocystis* strains should be prevented (Vassalos et al., 2008).

12. Conclusion

Since the mid-1950s when the term 'emporiatrics' was coined by Waters and Kean, substantial progress has been made in dealing with traveller's diarrhoea. Rather than being seen as an unavoidable scourge for the hapless tourist, traveller's diarrhoea has been considered an illness that requires further investigation and fuller action. Currently, an increasing number of pathogens likely to be responsible for traveller's diarrhoea have been identified (Jiang et al., 2010). Concerning classical enteropathogens, such as ETEC, the mode of action and regulation by host factors is known. Also, progress in prophylaxis has been dramatic. Old, but still good, advice for sound eating and drinking habits can now be coupled with drug administration.

When taking only chemoprophylaxis, travellers may be at a lower risk of contracting traveller's diarrhoea but they are not 100 percent immune from a variety of pathogens likely to be responsible for the illness. Travellers would be thus in error if they assume that they are safe and pay no attention to hygiene and sanitation rules (Wagner & Wiedermann, 2009). There has been sustained research effort for a vaccine that would be effective against ETEC, the leading cause of traveller's diarrhoea, and reduce the duration and severity of the symptoms. A vaccine, which combines cholera toxin subunit B with killed whole cell (W/rBS), is currently being assessed in clinical trials (Svennerholm, 2010).

Concerning traveller's diarrhoea treatment, the emergence of resistance against antibiotics has led to research for novel drugs or therapeutic regimens. In the United States, rifaximin has now been approved for the treatment of traveller's diarrhoea attributable to non-invasive *E. coli*. Rifaximin is still being evaluated for the prevention of traveller's diarrhoea (Armstrong et al., 2010).

In any such cases, prompt management is currently recommended, since it has been proved that induced intestinal irritation may lead to temporary or prolonged functional disorders, as is the case with persistent traveller's diarrhoea that is mainly of parasitic origin (Connor, 2011). Intestinal protozoa found in travellers complaining of persistent diarrhoea upon their return home from exotic destinations have practically been the sole enteric protozoa detected in the industrialized countries. Owing to high levels of hygiene and food safety, there has been a dramatic decline in infections caused by intestinal protozoa in the developed countries. In the last decades, however, intestinal infections due to opportunistic protozoa have emerged because of a marked increase in the number of immunocompromised individuals from a range of causes. Also, immigration from and adventurous travel to developing tropical countries with low hygienic level and a high prevalence of ubiquitous enteric protozoa have recently increased. Therefore, lately, cases of intestinal protozoal diarrhoeal disease have been increasing in the developed world.

This re-emergence has rekindled interest in research on intestinal protozoa. Inter- or intra-specific genotype differences may help explain variations in phenotypic features, various pathogenic mechanisms, and the presence of virulence factors of enteric protozoa. For *E. histolytica*, the parasite lifestyle was examined at the whole-genome level so that new genes

encoding virulence factors along with signaling pathways and processes could be identified (Lorenzi et al. 2010; Weedal & Neil Hall, 2011). Ongoing research on host and parasite factors likely to contribute to the pathogenesis of giardiasis may elucidate assemblage-specific pathogenic mechanisms (Cotton et al., 2011). New potential drug targets have been discovered in an attempt to develop the next generation of antiprotozoals. Researchers test novel promising drugs that target unique proteins and metabolic pathways of the protozoan *G. intestinalis* (Lale et al. 2010). Others continue to attempt to develop an antiprotozoal agent that would be effective against the coccidian *Cryptosporidium*. Nitazoxanide, which was discovered in the 1980s, has routinely been considered an alternative treatment option in case of diarrhoeal disease due to *Giardia*, *Entamoeba*, *Isospora* and *Cyclospora*. In immunocompromised hosts, however, nitazoxanide fails to treat cryptosporidiosis unless it is combined with antiretroviral therapy, perhaps because of partial antiparasitic effect of protease inhibitors (Cabada & White, 2010). Despite its side effects, fumagillin is used for treating microsporidia infections. Fumagillin analogs have recently been shown to be active against *E. histolytica* (Arico-Muendel et al., 2009). Concerning dientamoebiasis and blastocystosis, the ambiguity that surrounds the mode of transmission of *D. fragilis* (Barratt et al., 2011) and the pathogenic stage of *Blastocystis* (Vassalos et al., 2008; Tan, 2008) complicates the management of these intestinal infections. Likewise, the role of interplay between host defence mechanisms and intestinal protozoan survival strategies is complex. Further investigation of host-parasite relationship is of critical importance in the design and implementation of new vaccines and candidate drugs.

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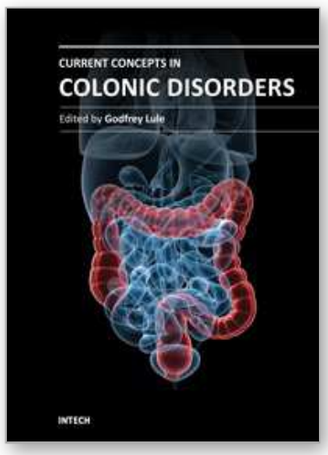
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Current Concepts in Colonic Disorders
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The 21st Century has seen a resurgence of research of the gastrointestinal tract, especially since it was established that it plays a central role as an immune system organ and consequentially has a huge impact on causation, impact and transmission of most human ailments. New diseases such as the Acquired Immunodeficiency Syndrome, hepatitis and tumours of the gastrointestinal tract have emerged and they are currently subjects of intensive research and topics of scientific papers published worldwide. Old diseases like diarrhea have become extremely complex to diagnose with new and old pathogens, drugs, tumours and malabsorptive disorders accounting for the confusion. This book has set out algorithms on how to approach such conditions in a systematic way both to reach a diagnosis and to make patient management cheaper and more efficient. "Current Concepts in Colonic Disorders" attempts to put all the new information into proper perspective with emphasis on aetiopathogenesis and providing rational approach to management of various old and new diseases. As the book editor, I have found this first edition extremely interesting and easy to understand. Comments on how to improve the content and manner of presentation for future editions are extremely welcome.

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University Campus STeP Ri
Slavka Krautzeka 83/A
51000 Rijeka, Croatia
Phone: +385 (51) 770 447
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www.intechopen.com

InTech China
Unit 405, Office Block, Hotel Equatorial Shanghai
No.65, Yan An Road (West), Shanghai, 200040, China
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元
Phone: +86-21-62489820
Fax: +86-21-62489821

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