

# Traveller's diarrhoea

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This review covers the most important aspects of traveller's diarrhea, including epidemiology, clinical features, microbiology, recommended treatment and prevention measures. Frequently traveller's diarrhea is due to bacterial infection. At present this condition is very common but its incidence can be reduced with a few simple measures. While fluoroquinolones are considered the treatment of choice, azithromycin and rifamixin are also good alternatives. Nowadays there is no prevention of traveller's diarrhea except for a recently developed vaccine against cholera and a specific strain of enterotoxigenic *E. coli*. [Emergencias 2008;20:260-268]

**Key words:** Diarrhea. Penid therapy. Loperamide. Macrolides. Quinolones. Travel.

## Introduction

Traveller's diarrhoea is defined as the presence of three or more soft depositions within 24 hours which initiates during or shortly after a journey and is usually accompanied by other symptoms such as nausea, vomiting, abdominal pain, fever, faecal urgency, tenesmus, and blood or mucous in the stools.

Although the intestinal pathogens causing this disease are known, the predominant microorganisms vary according to the season of the year and the country of destination. The population is increasingly at risk, partly due to the increase in exotic travel destinations<sup>1-3</sup>. The prevalence of traveller's diarrhoea is 20% to 50% and it has been estimated that this disease affects at least 11 million people annually<sup>4</sup>. Although the picture is benign, it may have a great impact on the patient.

## Epidemiology

Numerous epidemiologic studies have established that the probability of developing this disease depends on several factors:

1. Where the person is: the country of origin is a determinant of risk since travellers from developed countries have a greater incidence. In addition,

some nationalities are more susceptible than others when visiting the same places, although the origin of these differences is unknown<sup>5</sup>. Moreover, most studies have reported that children and young adults have a greater risk than other age groups although differences as per sex do not seem to influence.

2. Where the person goes: some studies have suggested that the country of destination constitutes an isolated factor which best predicts the risk of developing traveller's diarrhoea<sup>6,7</sup>. Thus, three areas have been defined according to the level of risk: low risk area 5% (North and centre of Europe, USA, Canada, Japan and Australia); intermediate risk 15%-20% (Southern and Eastern Europe, Russia, China, Israel, Caribbean Islands and South Africa); and high risk area 20%-60% (Middle East, South and South-East Asia, South America and Central Africa).

3. When the person travels: the incidence is higher in the summer months particularly in countries with a subtropical climate<sup>8</sup>.

4. Where the person stays: the hygienic characteristics of the accommodation are important as is the choice of the type and place where meals are taken<sup>5,7-10</sup>.

5. What the person does: request medical advice before travelling and meticulous travel preparations reduce the risk of traveller's diarrhoea<sup>11,12</sup>.

6. What the person eats or drinks: foods such as raw or little cooked seafood contain a high number of bacterial and viral pathogens and should therefore be avoided.

7. The characteristics of the host: these depend on the genetic susceptibility of each individual. Thus, an association has been reported with the polymorphism of the interleukin-8 promoter gene and diarrhoea produced by enteroinvasive *Escherichia coli*<sup>13</sup>. Likewise, the presence of gastric hypochlorhydria may increase the risk of developing traveller's diarrhoea since high pH levels favour infection by *Salmonella* or *Campylobacter*<sup>9</sup>. Similarly, immunosuppressive states such as in HIV and AIDS, immunosuppressive therapy, and an IgA deficiency also predispose infection by *Salmonella* and by protozoa (*Isospora*, *Cryptosporidium*)<sup>14</sup>.

## Clinical characteristics

Symptoms begin the second or third day of stay and in more than 90% of the cases during the first 2 weeks. It has been estimated that nearly 20% of the patients require bed rest for 1-2 days, 40% are obliged to modify their travel itinerary and up to 1% require hospital admission. The symptoms usually last 3-5 days except in 5% to 10% of the patients, in whom these may last up to 2 weeks or more<sup>15</sup>.

Three clinical syndromes may be differentiated:

- Mild watery diarrhoea of brief duration, with or without fever the risk of which minimises with the journey stay.

- Dysentery which is more prolonged and may be accompanied by fever and stools with blood (may be invasive when leucocytes are found in the stools).

- Chronic diarrhoea which lasts more than 1 month and affects from 1% to 3% of the travellers with diarrhoea and is usually caused by protozoa.

If severe, diarrhoea may lead to important electrolyte loss producing renal damage and altering the absorption of some medications (warfarin, anticonvulsants, oral contraceptives).

## Microbiology

The causal pathogen may be identified in 40-60% of the cases, 85% of which correspond to bacteria, although notable variations have been described according to the region visited and the season of the year<sup>16</sup> (Table 1).

In general, enteroaggregative *E. coli* is the bacteria most frequently isolated<sup>17</sup>. These bacteria

**Table 1.** World distribution of the pathogens which most frequently cause traveller's diarrhoea<sup>3</sup>

|                                | Asia  | South America | Africa |
|--------------------------------|-------|---------------|--------|
| <b>Bacterial cause</b>         |       |               |        |
| Enterotoxigenic <i>E. coli</i> | 6-37% | 17-70%        | 8-42%  |
| Other <i>E. coli</i>           | 3-4%  | 7-22%         | 2-9%   |
| <i>Campylobacter jejuni</i>    | 9-39% | 1-5%          | 1-2%   |
| <i>Salmonella</i>              | 1-33% | 1-16%         | 4-25%  |
| <i>Shigella</i>                | 0-17% | 2-30%         | 0-9%   |
| <i>Plesimonas higelloides</i>  | 3-13% | 0-6%          | 3-5%   |
| <i>Aeromonas</i>               | 1-57% | 1-5%          | 0-9%   |
| <b>Viral cause</b>             |       |               |        |
| Rotavirus                      | 1-8%  | 0-6%          | 0-36%  |
| <b>Parasitary cause</b>        |       |               |        |
| <i>Entamoeba histolytica</i>   | 5-11% | < 1%          | 2-9%   |
| <i>Giardia lamblia</i>         | 1-12% | 1-2%          | 0-1%   |
| <i>Cryptosporidium</i>         | 1-5%  | < 1%          | 2%     |
| <i>Cyclospora cayetanensis</i> | 1-5%  | < 1%          | < 1%   |

produce thermo-labile and thermostable toxins. The first is structurally and functionally similar to the cholera toxin which produces the characteristic watery type diarrhoea.

*Campylobacter jejuni* may cause up to 30% of all the cases of traveller's diarrhoea, particularly in Asia<sup>3</sup>, as might *Aeromonas*<sup>10</sup> and *Plesimonas shigelloides*. *Salmonella* and *Shigella* are involved in 15% of the cases, respectively<sup>18,19</sup>.

Viruses are of little importance in this disease, although rotavirus may cause up to 10% of traveller's diarrhoea in Mexico<sup>20</sup>, which usually more frequently occur on cruises<sup>11</sup>.

Watery diarrhoea is usually considered to be caused by toxins producing bacteria (such as cholera or enterotoxigenic *E. coli*) and the dysenteric pictures produced by bacteria such as *Shigella*. However, the superposition of both syndromes in the initial phase leads to suspicion of invasive aetiologies on detection of greater systemic involvement such as fever or when the duration of the symptoms is longer than usual<sup>21</sup>.

## Chronic diarrhoea

Around 1% of diarrhoeas become chronic. In some studies protozoa such as Ameba or *Giardia lamblia* may be the cause of up to 27% of the cases while the causes of the remaining cases are usually not identified. Other protozoa (*Cryptosporidia*, *Cyclospora*, *Isospora microsporidia*) which may also produce chronic diarrhoea in both immunocompetent and immunosuppressed individuals are increasingly recognised<sup>22</sup>.

## Treatment

Specific, symptomatic treatment for traveller's diarrhoea is not usually necessary because it is a

self-limiting disease. Nonetheless, empiric therapy of most diarrhoea, regardless of its aetiology, may also be valid for traveller's diarrhoea with the aim of preventing dehydration, and reducing the symptoms and the duration of the disease<sup>23</sup>. Most travellers with diarrhoea can hydrate themselves by drinking sugar water and eating salted crackers without the need for taking any special preparation, although the frequency and amount of fluids taken should be augmented during the process. Different studies have suggested that diet restriction during antibiotic treatment is not associated with an improvement in the symptoms or a shorter duration of the diarrhoea<sup>24</sup>.

The effect of loperamide with or without hydration has been studied in patients with limited access to other oral fluids and in these cases hydration therapy did not show any additional benefit in the final clinical outcome<sup>25</sup>. Traveller's diarrhoea in adults rarely produces important dehydration with oral rehydration being recommended in children and the elderly as well as in patients with cholera type watery diarrhoea. In the specific case of infants, breast milk or lactose free formulas are recommended<sup>26</sup>.

Some medications which are useful for diarrhoeic symptomatology are not recommended since no clinically significant benefit has been demonstrated as occurs in the case of kaolin pectate, activated charcoal, anticholinergics, hydrophylic agents, and preparations with lactobacilli<sup>27</sup> except for attapulgit<sup>28</sup> which is a crystalloid preparation with magnesium, silicate and aluminium, a mineral which has shown to be safe and beneficial even during pregnancy.

#### *Antisecretory and intestinal motility inhibitor drugs*

These types of drugs reduce the number of depositions from 30-65% but do not cure the disease.

Bismuth salicylate has antisecretory, antibacterial and anti-inflammatory effects and may be used for prophylaxis, although its efficacy is very low for use as treatment<sup>29,30</sup>.

Loperamide has antisecretory and motility inhibitor properties and is the drug of choice since it reduces the number of depositions up to 65% thanks to its rapid absorption. Different studies have demonstrated that the combination of an antibiotic and loperamide is better than their administration alone<sup>31,32</sup>. In cases of invasive diarrhoea with fever or blood, it should be administered with precaution since the clinical course of the diarrhoea may worsen with post-diarrhoea

constipation. Loperamide should not be prescribed for children (especially those under 2 years of age) because of the pronounced narcotic effect<sup>33</sup>.

Enteric bacterial pathogens are the main cause of traveller's diarrhoea and, thus, the administration of antibiotics with or without loperamide is an effective treatment which minimises the severity and the duration of the diarrhoea while also improving the symptoms and the time of incapacity<sup>23</sup>. These findings have been confirmed in a recent Cochrane metaanalysis<sup>34</sup> in which the number of patients free of diarrhoea 72 hours after the initiation of an antibiotic was significantly favourable for those who received the drug in comparison with those who received a placebo in the 6 studies reviewed, with an odds ratio of 5.9 (CI 95%; 4.1-8.6) shown in Figure 1.

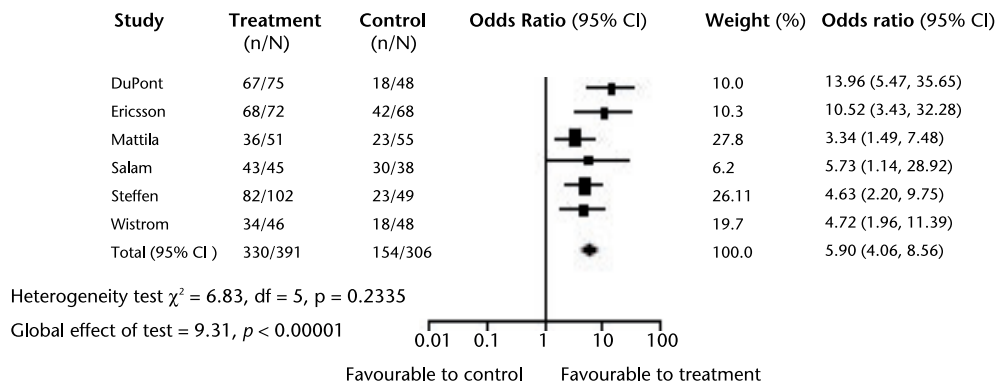
#### *Antibiotic treatment*

The administration of an antibiotic is recommended in most patients with traveller's diarrhoea (Table 2).

Cotrimoxazol (trimethoprim-sulphamethoxazole) was the drug of choice for many years but the progressive appearance of resistances has limited its use<sup>32,35</sup> and it is, therefore, currently recommended only for cases resistant to fluoroquinolones or anti-protozoaric agents (metronidazole) in areas where *Cyclosporiasis* is common (Nepal in the spring, Mexico during the summer)<sup>3</sup>.

Fluoroquinolones have demonstrated elevated activity in traveller's diarrhoea and are considered the first choice in moderate or severe adult cases. These drugs present oral absorption, maintaining high faecal concentrations. In addition, their mean half life allows a comfortable therapeutic schedule. Several studies have shown that fluoroquinolones reduce the duration of diarrhoea from 3 or 4 days to 1.5 or less and also produce a clinical improvement in regard to the symptoms<sup>36-38</sup>. A single dose of a fluoroquinolone is as effective as 3 days of treatment with another antibiotic except when the symptoms persist or suggest an invasive type of diarrhoea (fever and blood in the depositions)<sup>39</sup>. In these cases, and with the objective of specifically treating infection by *Shigella* or *Campylobacter*, a 3-day treatment is recommended. Secondary, albeit mild, effects include: cutaneous rash, photosensitivity or gastrointestinal discomfort.

The possibility of pharmacologic interactions, especially with warfarin, phenytoin, cyclosporine and theophylline should be taken into account. Fluoroquinolones maintain excellent *in vitro* activi-



**Figure 1.** Metaanalysis of the effect of antibiotic treatment 72 hours after its initiation on the duration of traveller's diarrhoea. The odds ratio is shown in a logarithmic scale.

ty against most bacterial pathogens associated with traveller's diarrhoea, although there has been an increase in the prevalence of resistances for *C. jejuni*<sup>35</sup>. Their use during pregnancy or in children is not recommended<sup>26,40</sup>.

Azithromycin has good *in vitro* activity against many enteric pathogens being more active than erythromycin and its activity has been shown to be similar to that of ciprofloxacin in the treatment of traveller's diarrhoea. Azithromycin has shown to be more effective in reducing exacerbations by *Campylobacter* among military personnel in the USA in Thailand<sup>41</sup>. It is a safe, well tolerated drug which may be used in children<sup>42</sup> but is not authorised during pregnancy. It does not provoke interactions with other drugs since it does not inactivate cytochrome p450 and, therefore, does not modify the pharmacokinetics of other compounds<sup>43</sup>. This drug is considered an alternative to fluoroquinolones in areas with a high incidence of *Campylobacter*.

Rifaximin is a semisynthetic antibiotic derived from rifampicin but with a ring of pyridoimidazole which impedes its absorption<sup>44</sup>. Four large studies

have demonstrated its efficacy in the treatment of traveller's diarrhoea<sup>45</sup> describing its beneficial effect on diminishing the duration of the diarrhoea maintaining an effectiveness similar to that of ciprofloxacin and significantly greater than placebo. These studies included only patients without dysentery since rifaximin is not recommended in these cases<sup>46</sup>.

Self-medication in traveller's diarrhoea must be accepted, although the causal pathogenesis is unknown because it allows rapid alleviation of the symptoms. It is especially useful when medical treatment is not accessible whether because of a lack of knowledge of the healthcare system of the country, the distance from a healthcare centre or due to language barriers. Sometimes the case may be diarrhoea without strictly knowing the definition of diarrhoea, confusing changes in stool consistency which may be produced by states of stress, menstruation, changes in the diet or excess alcohol intake with real diarrhoeic processes<sup>17</sup>.

Figure 2 shows the measures recommended for self-management of diarrhoea according to its severity, with emphasis on the importance of hy-

**Table 2.** The main drugs which may be used in traveller's diarrhoea<sup>2</sup>

| Drug               | Dose  | Comment   |
|--------------------|---|---|
| Loperamide         | 4 mg followed by 2 mg after each deposition. Maximum 16 mg/day.         | Do not administer in children < 2 years. Improves the efficacy of fluoroquinolones. Post-diarrhoeic constipation. |
| Bismuth salicylate | 524 mg every 30 minutes 5 times. Can be repeated the second day.        | Brush teeth and tongue after each dose. Only available in the USA. Contraindicated during pregnancy.              |
| Ciprofloxacin      | Single dose 750 mg or 500 mg/12 h for 3 days.                           | Indicated in children. Effective versus <i>Campylobacter</i> . Indicated in children. Indicated in pregnancy.     |
| Norfloxacin        | Single dose 800 mg or 400 mg/12 h for 3 days.                           |   |
| Levofloxacin       | Single dose 500 mg or 500 mg/24 h for 3 days.                           |   |
| Azithromycin       | Single dose 1,000 mg or 500 mg/24 h for 3 days.                         |   |
| Rifaximin          | 10 mg /Kg for 3 days in children. 200 mg/8 h or 400 mg/12 h for 3 days. |   |

dration as the first step. In general, if rapid improvement is not achieved, the traveller usually seeks urgent medical advice which is recommendable on the appearance of the following clinical characteristics: signs of dehydration, persistence of blood in the stools or dark stools suggestive of upper digestive haemorrhage, frequent vomiting and difficulty in oral hydric restoration, important abdominal pain, high fever, absence of improvement after 24 hours or when the diarrhoea persists for more than 3 or 4 days<sup>47</sup>.

## Prevention

### *Modify risk behaviour*

On journeys to high risk areas it is important to receive medical advice before travelling, with special importance as to what to eat and drink as well as taking chemoprophylaxis in special circumstances. Generally information related to safe foods, the importance of hydric reposition in case of diarrhoea and when the traveller should seek medical help is provided<sup>48</sup>. Hand washing prior to food preparation is emphasised<sup>49</sup> or the use of sterilisation products when water and soap are not adequate. All these indications are included in the recommendations of the WHO for the prevention of traveller's diarrhoea<sup>50</sup>.

Care in the choice of food and drink reduces the infective dose but this is small evidence which does not produce any difference in the incidence of traveller's diarrhoea. It is recommended to eat only recently prepared foods, peeled fruit and raw vegetables should be well washed and later boiled. The interior of the food should be 70°C to kill microorganisms and parasites<sup>51</sup> and once cooked it should be kept at temperatures of less than 10°C. Dry foods such as bread are relatively safe. Travellers may eat syrups, gelatine and citric fruit. Raw or little cooked seafood should not be eaten due its high content of viruses, bacteria and pathogenic parasites<sup>52</sup>. Typical advice for individuals travelling to developing countries is to avoid drinking tap water, although previous boiling will make it safe to drink. Most enteropathogenic bacteria die in less than one minute at more than 65°C and *Giardia* cysts are inactivated after 5 minutes in water at 55°C. Thus, it is usually sufficient to bring water to a boil to kill most pathogens. In addition, tetraglycin hydroperiiodine pills are commercially available, being an easy, practical way to purify water<sup>3</sup>. Unbottled water and ice should be considered as contaminated and the latter may contain microorganisms such as *Shigella* which have a very

small infective dose. It should be remembered that carbonated water reduces the pH and creates a bactericide environment, although precautions should also be taken with other uses of water such as inadequately chlorated swimming pools, avoiding immersion and swallowing of water<sup>53</sup>. In addition, rivers or seas may be contaminated by residual waters since the oocytes of *Cryptosporidium* are resistant to the chlorination process used in swimming pools and water supplies. Using education as a method of prevention is difficult because it does not necessarily modify the behaviour of tourists<sup>53</sup>. "Boil it, cook it, peel it and forget it" should be the norm to follow but may be difficult to follow<sup>16</sup>. Part of the problem is that travellers are oblivious and are enthusiasts with respect to knowing new cultures and gastronomy represents an important part of this knowledge<sup>54</sup>.

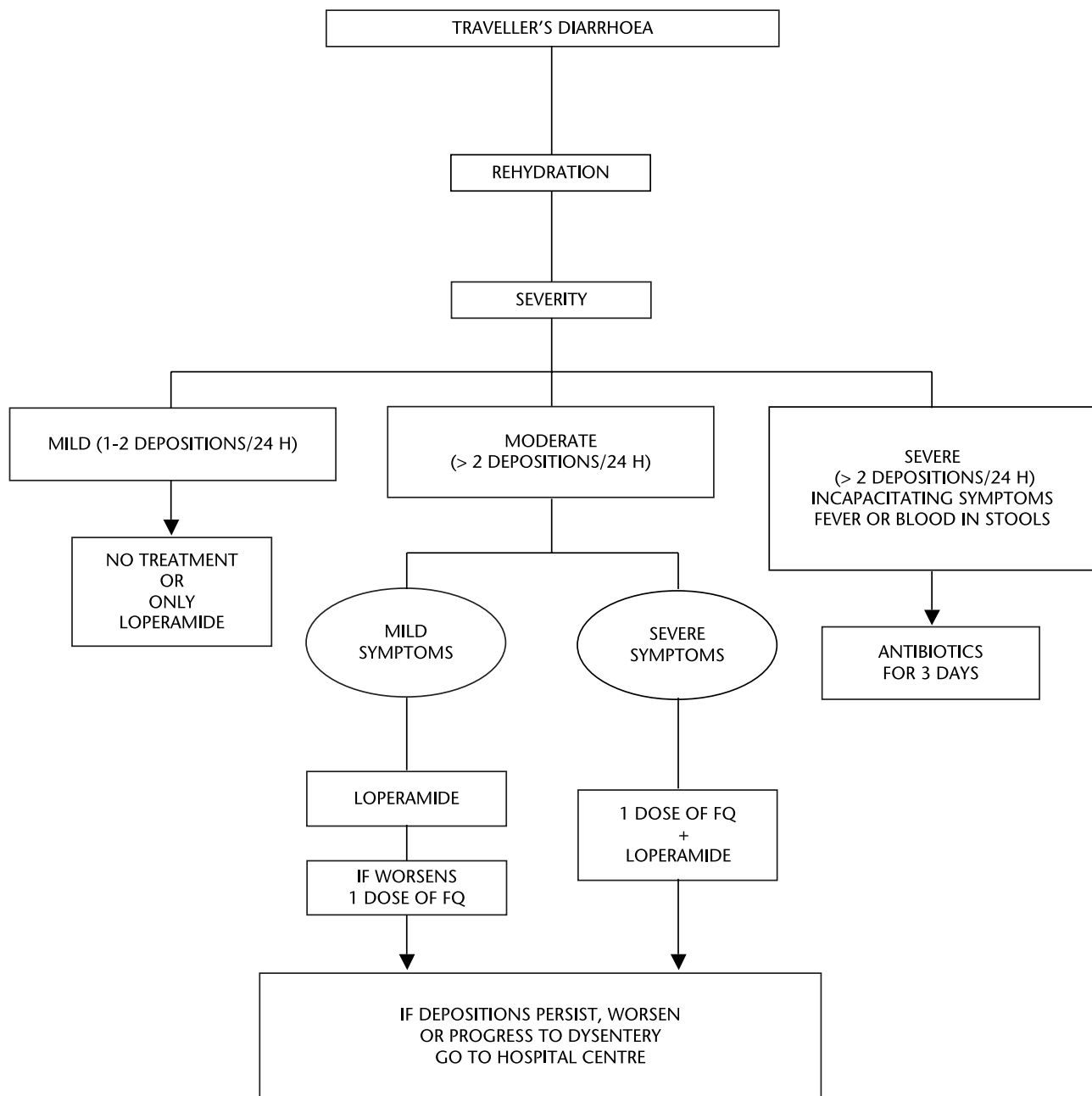
### *Use of vaccinations*

The great diversity of the causal pathogens of traveller's diarrhoea limits the possibilities of developing an effective vaccine for prophylaxis. The development of a combined vaccine for enterotoxigenic *E. coli*, *Campylobacter* and *Shigella* may be possible in the future. At present, the only combination available is Dukoral<sup>®</sup> which is an oral recombinant vaccine against cholera and enteroaggregative *E. coli* which is administered in two doses in a one week interval for children and adults and provides satisfactory protection one week after completion of immunisation. Although protection against cholera is clearly demonstrated, Dukoral<sup>®</sup> is only administered in determined countries for traveller's diarrhoea such as Sweden and Canada<sup>55</sup>. One study including 615 tourists who travelled to Morocco from Finland demonstrated 52% of protection for traveller's diarrhoea caused by some strains of enteroaggregative *E. coli* and 71% of protection with the combination of *E. coli* and another pathogen<sup>56</sup>.

### *Chemoprophylaxis*

Effective, well tolerated prophylaxis for traveller's diarrhoea has been sought since the 1970s<sup>57</sup>. The 1985 consensus document of the conference of the National Health Institute of the United States<sup>58</sup> is available, although this consensus rejects the general recommendation of administering chemoprophylaxis in all settings due to the potential adverse effects.

In addition, prophylaxis promotes a false sense of safety leading the traveller to ignore the precautions with food and thereby causing an increase in non bacterial diarrhoea. Some aspects



**Figure 2.** Algorithm for the management of traveller's diarrhoea<sup>64</sup>.

should be considered for the administration of chemoprophylaxis such as the cost, pharmacological interactions, secondary effects, bacterial resistances and alteration in intestinal flora.

Cost-effectiveness analyses have compared the cost of chemoprophylaxis and the cost of treatment and have demonstrated that short-term prevention of traveller's diarrhoea is effective but the most important contribution is the cost represent-

ed by one day of incapacitation due to the disease<sup>59</sup>. Combined treatment even with a single dose of antibiotic together with a motility inhibitor produces a very important reduction in the duration of the disease to only hours. For prolonged stays (3 weeks or more), antibiotic treatment together with a motility inhibitor has greater cost-effectiveness than the administration of prophylaxis alone<sup>60</sup>.

Routine administration of a prophylactic antibiotic is not recommended for healthy travellers<sup>58,61</sup>. Nonetheless, if it is administered, it should be initiated the first day of the trip or at the beginning or the period of risk and be continued during following 2 days to diminish the risk. Prophylaxis should be considered particularly in high risk groups such as: individuals who can not tolerate a brief disease (athletes, business executives and politicians) or those with a high susceptibility (individuals with achlorhydria or gastrectomy), immunosuppressed subjects (HIV infection), chronic patients (ischaemic cardiopathy...) or individuals with a repeated history of diarrhoea.

Bismuth salicylate has antisecretory, antibacterial and antiinflammatory effects and may therefore be used as prophylaxis of traveller's diarrhoea. Secondary effects include: darkening of teeth and gums, and the volume of the preparations required for administration is an inconvenience (it will soon be available in pill form). This preparation is not available in European countries<sup>29</sup>. Combination with doxycycline should be avoided because of modification in its absorption.

Probiotics such as preparations containing *Lactobacillus* spp. are very attractive because they do not produce adverse effects or pharmacologic interactions, although they have not been found to provide relevant protection in traveller's diarrhoea.

Doxycycline is one of the first antibiotics to demonstrate effectiveness in this disease due to its wide spectrum and coverage for pathogens causing traveller's diarrhoea throughout the world<sup>63</sup>. Unfortunately, strains resistant to doxycycline in many tourist areas have limited its use for therapy and prophylaxis. Travellers who take this drug for the prophylaxis of malaria are not protected against traveller's diarrhoea.

Cotrimoxazole has been used as chemoprophylaxis but is not a valid option due to the resistance which a wide group of enteropathogens present<sup>64</sup>.

Azithromycin is active against several enteric pathogens, especially *Campylobacter* and also has a long half life. Nonetheless, studies defining the appropriate dose for prophylaxis are lacking and this drug can therefore not be included in the recommendations of prevention.

Fluoroquinolones have been very attractive in the last decade as a consequence of their high safety and wide spectrum against enteropathogens. The growing resistance of many pathogens, particularly the resistance of *Campylobacter jejuni* to fluoroquinolones in Thailand and Southern Asia is wor-

risome since they are the drugs of choice when chemoprophylaxis is indicated<sup>65</sup>.

Rifimixin is under study as prophylaxis for traveller's diarrhoea, although some studies have already indicated greater benefits in comparison with the administration of placebo in travellers to Mexico where enterotoxigenic *E. coli* is predominant as a cause of traveller's diarrhoea<sup>66</sup>.

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## La diarrea del viajero

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Esta revisión aborda los aspectos más relevantes acerca de la diarrea del viajero, en relación a la epidemiología, las características clínicas, la microbiología, el tratamiento recomendado y sus mecanismos de prevención. La diarrea del viajero se debe, en la mayoría de los casos, a una etiología bacteriana, constituyendo un problema frecuente cuya incidencia puede reducirse tomando sencillas precauciones. Las fluoroquinolonas se consideran actualmente el tratamiento de elección, si bien tanto azitromicina como rifamixina pueden ser buenas alternativas. En la actualidad, sólo disponemos de vacunas para la prevención del cólera y para una pequeña proporción de viajeros con diarrea producida por cepas de *E.coli* enterotoxigénica. [Emergencias 2008;20:260-268]

**Palabras clave:** Diarrea del viajero. Hidratación. Loperamida. Macrólidos. Quivolona. Rifamixina.