

Diarrhea in the Recent Traveler

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Key Words: travelers' diarrhea, dysentery, dehydration, antibiotics

TARGET AUDIENCE

Clinical entities who are involved in the evaluation of children with diarrhea during or after recent travel: emergency physicians, pediatric emergency physicians, pediatricians, family practitioners, and travel medicine health care providers.

LEARNING OBJECTIVES

After completion of this article, the reader will be able to:

1. Explain pretravel recommendations for the prevention of travelers' diarrhea (TD);
2. Identify the bacterial, viral, and parasitic enteropathogens causing travelers' diarrhea;
3. Relate and recommend treatment options for the symptoms of mild, moderate, and severe dehydration secondary to TD; and
4. Prepare antibiotic therapy in the pediatric traveler with diarrhea.

Before the terrorist attacks in the United States on September 11, 2001, international travel originating in the United States continued to grow annually at a steady pace. According to figures by the Bureau of Transportation in the year 2000, outbound travel to the United States was estimated at 171 million trips and inbound travel at 195 million. By the early 1990s, the growing national trend in destinations outside of North America were to Europe, Asia, South America, the Middle East, and Africa.¹ Most of these travel statistics consist of adult data, and these numbers far outweigh the number of children traveling to international destinations. However, the total number of children traveling

is also increasing each year as more adults are bringing children to vacation spots, family visits, summer camps, and to parental employment opportunities.

Travel in developing countries carries a significant number of medical and nonmedical risks. The most common travel-related illness to affect adult and pediatric travelers during and after travel is diarrhea. Worldwide, diarrheal disease accounts for more than 2 million deaths yearly in developing countries.² Mortality secondary to diarrheal disease is very rare in travelers. However, mild or moderate diarrhea may be problematic, especially if the traveler becomes incapacitated for any portion of a trip. The adult literature reports diarrheal illnesses affecting as many as 20% to 50% of travelers in developing countries, with higher attack rates in children younger than 3 years.³⁻⁵ This infection rate is in sharp contrast to a less than 5% rate of infection in travelers to developed countries in North America and Europe.⁶

Because of the large number of adult travelers, there is an abundance of literature on adult TD. However, the sources of travel-related infectious diarrhea, its treatment, and overall outcomes after illness have not been adequately studied in children. With these limitations, pediatric medical providers face an increased responsibility to advise, evaluate, prevent, and ultimately treat travel-related diarrheal illnesses based mostly on extrapolation and interpretation of adult data. With sound medical advice, there is the potential to avoid severe dehydration, parental anxiety, and disruption of travel plans because of diarrheal illness.

DEFINITION

Travelers' diarrhea is usually a self-limited syndrome resolving without specific therapy. The traditional definition of adult TD is defined as the passage of 3 or more unformed stools in a single day during or immediately after travel, or any number of loose stools if accompanied by fever, cramping, abdominal pain, or vomiting.⁷⁻⁹ Travelers' diarrhea may be very difficult to gauge in infants, toddlers in diapers, or in breastfeeding children, as the amount and consistency of stool may resemble diarrhea. In 1985, the National Institutes of Health presented a more explicit definition by defining TD as the 2-fold or greater increase in the occurrence of unformed stool lasting 2 to 3 days which is preceded by travel.¹⁰ By using these definitions, the medical evaluator can make a reasonable evaluation and give advice to families with respect to epidemiology, etiology, prevention, and management of illnesses.

EPIDEMIOLOGY

Several factors should be considered in determining the risk of acquiring TD. Determinants of high- and low-risk

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Dr. Juarez and Dr. Abramo have disclosed that they have no significant relationship with or financial interests in any commercial companies that pertain to this educational activity.

Lippincott CME Institutes, Inc. has identified and resolved all faculty conflicts of interest regarding this educational activity.

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ISSN: 0749-5161/06/2208-0602

travel factors are based upon travel season, host features, and destination. The most important risk factor associated with TD in the adult literature is geographic destination. High-risk destinations included developing countries located in Africa, Asia, Latin America, and the Middle East, with infection rates of 20% to 50%. Low-risk destinations included the United States, Canada, northern Europe, Australia, and Japan.⁹ This is mirrored in the pediatric population by a 1991 retrospective study of children and adolescents traveling from Switzerland to other continents. Travelers' diarrhea occurred in almost 75% of the children who traveled to North Africa, approximately 60% of those traveling to India, and 32% to 39% for those traveling to Southeast Asia, Latin America, and other African countries.¹¹

Infection rates for TD are highly correlated with local water and food supply, hotel and restaurant hygiene, and carriage rates of the local people. Contaminated food conferred a much higher risk for infectivity than contaminated water. Classic high-risk contaminated provisions include tap water, ice cubes, unpasteurized dairy products, ice cream, rare meat, raw or undercooked seafood, salads, creamy dressings, and food from street vendors.

Certain host factors increased the risk of acquiring TD, including extremes of age, immunodeficient states, and states of gastric acid suppression. The geriatric and infant/toddler age are high-risk populations.⁹ Infants have a particularly high risk of infectivity because of active oral exploration and the potential for large bacterial/viral loads versus body weight.¹² These pediatric host factors have translated into more severe symptoms and complications.

States of gastric acid suppression (i.e., H₂ blockers, achlorhydria) also increase the risk of infection. The acidity in the stomach is a useful barrier to control the rampant multiplication of an enteropathogen. This holds true for most pathogenic strains of bacteria with the exception of *Shigella*, which may produce symptoms in small loads.¹³ Adolescents and young adults ages 20 to 29 years are considered the next highest risk group secondary to being adventuresome and willing to sample food and drink arbitrarily.^{11,14}

ETIOLOGY

A noninfectious cause of TD is usually a diagnosis of exclusion. In children, these causes may be related to a variety of issues such as fatigue, anxiety, dietary changes, and food allergies.

The adult literature consistently reports bacterial enteropathogens causing approximately 80% of TD, although 10% to 50% of cases have no identifiable pathogen. Bacterial etiologic causes in adults vary by season and geographic region. The most common causative pathogen in developing countries has been enterotoxigenic *Escherichia coli* (ETEC). The incidence of ETEC as the etiologic cause of TD is highest in Latin America (42%) and lowest in Asia (16%).^{15,16} *Campylobacter jejuni* predominates in parts of Thailand and Morocco with incidence up to 40% of cases.¹⁶ *Shigella* species account for up to 15% of TD in Africa and Central America. The major enteropathogens of TD are listed in Table 1. A Swiss study found 34 of 166 children

with diarrhea and documented travel to have an infectious cause. A strong association was demonstrated with bacterial causes: 2 of 3 of the cases of *Shigella* and ETEC were associated with travel, whereas only 4% of *Rotavirus* spp. was travel-related.

Viral and protozoal causes of TD are infrequent compared with bacterial sources. Protozoal diarrhea usually is more gradual in nature, with a prolonged period of diarrhea greater than 7 days. The most common protozoal agents worldwide are *Giardia* and *Cryptosporidium*. In some areas, a protozoal agent may be found in up to 15% of TD.¹⁷ Viruses account for a similar number of TD cases. Rotavirus and Norwalk virus were seen in 10% of TD from Mexico.¹⁸

Although most of the cases reveal single infections, there are numerous reports of multiple antigenic strains of bacteria or combinations of a virus and bacteria causing episodes of TD.

CLINICAL FEATURES

Typically, TD is an acute syndrome and usually subsides from 4 to 5 days, with a median of 2 to 3 days. Symptoms of TD may begin anytime during travel or shortly after returning from a foreign destination. A 1991 pediatric study reported an average diarrhea onset 8 days after departure, regardless of destination.¹¹ Children younger than 3 years had persistent symptoms with an average of 30 days (median, 18 days) versus 11.5 days average (median 3 days) in older children.^{11,19} The adult data support approximately

TABLE 1. Principal Enteropathogens of TD

Bacteria
<i>E. coli</i>
Enterotoxigenic
Enteraggregative
<i>C. jejuni</i>
<i>Shigella</i> spp.
<i>Salmonella</i> spp.
<i>Aeromonas</i> spp.
<i>Pleisomonas</i> spp.
<i>Vibrio</i> spp.
Non- <i>cholerae</i> spp.
<i>C. difficile</i>
<i>Yersinia</i> spp.
Viruses
<i>Rotavirus</i> spp.
<i>Norwalk</i> spp.
Hepatitis A
Hepatitis E
Protozoa
<i>G. lamblia</i>
<i>Cryptosporidium parvum</i>
<i>Cyclospora cayetanensis</i>
<i>Isoospora belli</i>
<i>E. histolytica/Entamoeba dispar</i>

10% of cases lasting longer than 1 week, 2% longer than 1 month, and less than 1% longer than 3 months.¹⁸

Travelers' diarrhea is associated with numerous symptoms, including abdominal cramps, fever, vomiting, dysentery (diarrhea mixed with visible blood), diarrheal mucous, fecal urgency, tenesmus, nausea, malaise, weakness, headache, and myalgia. The most common symptoms were abdominal pain (43%), vomiting (14%), and dysentery (16%).¹¹ Travelers' diarrhea-associated symptoms are equally prominent in adults and pediatric cases; however, infected children typically present in more severe states that may progress with severe outcomes, such as hepatobiliary involvement or failure to thrive.

Mortality is rare, but severe outcomes are more commonly seen in the geriatric and pediatric populations secondary to their inability to cope well with severe dehydration. Children have higher total body water per body mass versus adults which results in more severe complications caused by dehydration. These complications are caused by several factors including, but not limited, to increased insensible losses and infant dependence on milk with higher osmotic load and high renal protein solute load. Symptoms occurring during severe dehydration include weakness, decreased urine output, orthostasis, and altered mental status.¹² Intestinal perforation, sepsis, and death are rare.

A 1998 systematic review found certain risk factors contributing to dehydration: age less than 1 year, greater than 8 stools/day, greater than 2 emesis/day, failure to give oral rehydration solution, and discontinuation of breastfeeding. Specific pathogens were not associated with increased risk for dehydration with the exception of *Vibrio cholerae*.²⁰

The most severe complications of TD not associated with dehydration are extremely rare. Reiter syndrome is a known complication of infections with *C. jejuni*, *Salmonella* spp., *Shigella* spp., and *Yersinia enterocolitica*. *Campylobacter* has also been associated with Guillain-Barré. Hemolytic uremic syndrome has been associated with *Shigella* spp. and ETEC. *Salmonella* has been shown to invade other bodily systems causing septic arthritis and osteomyelitis. *Entamoeba histolytica* can be complicated by amebic hepatitis and abscesses.⁹

EVALUATION

A good history and physical examination is the first line of evaluation and usually supersedes the need for further evaluation in TD. It is important to identify potentially dangerous diarrhea with symptoms of large volumes, high fever, and bloody or mucoid stools.

The second line of evaluation should include a hemocult test and stool for fecal leukocytes. The absence of red or white blood cells in stools has a negative predictive value of 95% when ruling out invasive bacterial enteropathogens.²¹ The sensitivity and specificity of fecal leukocytes for inflammatory diarrhea is 0.73 and 0.84, respectively.²² However, a negative test does not rule out bacterial infection.

Immunoassays for the neutrophil marker lactoferrin may also provide speedy confirmation of an infectious etiology with a sensitivity and specificity of 0.92 and 0.79, respectively.²²

The etiology of TD may be distinguished by several laboratory methods currently in practice. Bacteria must be cultured on selective media for isolation purposes. Viruses can be observed under electron microscopy but most can be detected by specific antigen tests. Protozoa are detected by direct antigen testing and polymerase chain reactions.

The diagnostic yield of stool cultures is relatively low ranging from 1.5% to 5.6%.²³ However, stool culture for bacterial enteropathogens usually is warranted if symptoms are systemic, recurrent, marked with high fever, blood, or pus. In the United States, routine stool cultures are evaluated for *Salmonella* spp., *Shigella* spp., *C. jejuni*, and often Shiga-toxin-producing strains of *E. coli*. In chronic diarrhea, multiple stool samples should be obtained as the sensitivity improves with successive samples.

Protozoal diarrhea should be considered with an appropriate history. Detection of parasitic infections are improved using immunoassays such as the enzyme immunoassay and direct fluorescent antibody, giving specificities of approximately 95%.²⁴ Specific antigen tests are available for *Giardia*, *Cryptosporidium*, and *E. histolytica*, and should be obtained when traveling from regions where these organisms are endemic and with a history of persistent diarrhea.

Other organisms are suspected with the appropriate history and high index of suspicion. Recent ingestion of shellfish should prompt special cultures for *Vibrio* spp., cold enrichment cultures for *Yersinia* spp., and acid-fast staining of cultures for *Isospora* and *Cyclospora* spp.

The current evidence does not support the evaluation of electrolytes in routine diarrheal states, as electrolyte disturbances are rare. Reportedly, 1% of admissions for dehydration secondary to diarrhea have hypernatremia.²⁵ Standard World Health Organization (WHO) oral rehydrating solution, if distributed properly, is adequate to replace lost electrolytes if a child is tolerating oral rehydration. Monitoring of electrolytes and renal functions are recommended if there is a need for intravenous rehydration, when a physical examination is consistent with hypernatremia (i.e., doughy skin) or severe circulatory collapse.

PREVENTIVE COUNSELING

Travel medicine has greatly improved its knowledge, prevention, and treatment of the bacterial causes of TD. Yet, the incidence of TD worldwide has not declined. For the recent traveler, the most desirable result is the avoidance of the symptoms of TD altogether. Preventative measures have been advocated by the medical community as the best method to minimize the effects of diarrheal infection. Avoidance of fecal-contaminated food and water is the mainstay of prevention. It is surprising to note that children younger than 3 years have the best dietary compliance but had the highest rate of TD, likely caused by host factors. It is also common for parents of traveling older children to ignore dietary guidelines in up to 60% of the time.¹²

Sage advice promoting the prevention of TD worldwide is embodied in the rule: “boil it, cook it, peel it—or forget it.” Foods purchased from street vendors, raw or undercooked meat and seafood, unpeeled fruits and vegetables, and unpasteurized dairy products should be avoided. However, a handful of recent adult studies which specifically addressed the correlation of food/personal hygiene with diarrheal rates demonstrated no association.¹⁷

An older study, cited often as the basis for the dietary precautions promoted worldwide, did show a link in the first 5 days of travel with increasing occurrences of diarrhea and the number of dietary mistakes made by the traveler.²⁶ Unsuspecting travelers may not fully realize the hardness of infective pathogens as some have survived temperatures of water hot to touch (50°C) and freezing temperatures as found in ice cubes.

Pretravel advice should also include precautions about high-risk activities such as swimming in contaminated waters and avoidance of high-risk sexual activity. Without fecal contamination, TD is rarely spread in a person-to-person fashion. Some viruses may be spread by aerosol and are thought to be major pathogens especially on cruise ships. High-risk sexual activity should also be avoided as fecal-oral transmission may cause symptomatic states. Swimming pool water infected by enteropathogens such as *Giardia* and *Cryptosporidium* cysts are able to survive chlorinated water.

In infants, preparation of formula with bottled or boiled water is advised. Breastfeeding should always be encouraged as it decreases the need for possibly contaminated water-based formulas. If access to bottled water is poor, water should be boiled for at least 1 minute (3 minutes in altitudes >6000 ft).²⁷ Heated water with electric coils is also an acceptable alternative. Carbonated drinks may be safe for older children.^{28,29} If milk cannot be avoided, it should be boiled or replaced with reconstituted powdered milk with bottled or boiled water.

Filters are also available which are effective in eliminating most organisms, but may be unreliable in preventing protozoan contamination. Halogen preparations and chlorine treatments are another option in the sterilization of water. This is important as contaminated food and water may act as a vehicle for non-TD enteropathogens, such as hepatitis A and E, viruses, and typhoid. Raw fruits and vegetables should be peeled or properly rinsed with soapy water and/or in a halide solution. Even when washed, strawberries, raspberries, and grapes should not be considered safe.²⁹ Daily hygienic precautions should be observed when preparing food by always washing hands with soap and water or with a sanitizing napkin.

PREVENTIVE MEDICATIONS

Few antidiarrheal medications have been proven effective in the prevention of TD by randomized, controlled trials. Only in the cases of loperamide and bismuth subsalicylate has sufficient evidence of efficacy and safety been collected for adults.²⁴ Because of a deficiency of

evidence, none of the antidiarrheal agents are recommended in children.

The nonantibiotic drug bismuth subsalicylate has both antimicrobial and antisecretory protection. This is the active compound in Pepto-Bismol which is commercially available in North America in liquid and tablet form. Bismuth subsalicylate confers about 60% protection when taken by adults as prophylaxis.¹³ In adults, the recommended dose is 2 tablets (524 mg) 4 times a day. In adults, bismuth subsalicylates had odds ratios of 0.19 to 0.48 for the prevention of TD.³⁰ A 1993 study in infants older than 3 months revealed that bismuth subsalicylate decreased total stool output and duration of diarrhea.³¹

Side effects may deter use by the traveler such as blackening of the tongue or stool and ringing of the ears. Travelers with aspirin allergies, pregnant, or using certain anticoagulant drugs should avoid its use. There are the potentials for salicylate accumulation and theoretical risk of Reye syndrome in children. However, it is used with little side effects in the eradication of *Helicobacter pylori* and in chronic conditions such as cystic fibrosis.¹²

Probiotics are another avenue of recent pursuit in the research of TD. Probiotics are thought to give protection through multiple mechanisms: alterations in adhesion properties, production of antimicrobial substances such as hydrogen peroxide, stimulation of the immune system, and competitive inhibition for local nutrients.³² The different strains of *Lactobacillus* have been studied in trials, and the most success was found with *Lactobacillus GG*, giving up to 63% reduction of TD.³³ In a study of nontravel-related rotavirus diarrhea, *Lactobacillus GG* showed a significant reduction in duration of diarrhea and hospital stay.³⁴ There are no known side effects for lactobacillus, and it may be used as a preventative medication in all traveling populations, including pediatrics. It is available over the counter and dosed in the following: children younger than 2 years should take 1 capsule/day and children older than 2 years should take 2 capsules/day. Another probiotic, *Saccharomyces boulardi*, has been shown effective in limited areas of North Africa and Turkey, but not in other destinations.³⁵

The Centers for Disease Control and Prevention website does not recommend antimicrobial drugs for prevention but, nonetheless, antibiotics are sometimes prescribed for prevention by medical personnel. Tetracycline, trimethoprim-sulfamethoxazole (TMP-SMX), and fluoroquinolones have been the traditional drugs with proven efficacy in prevention, but this property may be outweighed by concerns of bacterial resistance, increasing cost, and side effect profiles. The side effect profiles are a genuine risk in children using prolonged antibiotics. The use of TMP-SMX is worrisome secondary to concerns of Stevens-Johnson syndrome and a high resistance pattern. Tetracyclines are not recommended in children younger than 8 years secondary to dental discoloration, retardation of bone growth, photosensitivity, and also a high resistance pattern. Fluoroquinolones are not recommended below the age of 18 years secondary to a theoretical risk of cartilage damage and arthropathies. Chemoprophylaxis may be considered in the high-risk group

TABLE 2. Dehydration Levels in Infants¹⁹

Symptom	Mild	Moderate	Severe
General condition	Thirsty, restless, agitated	Thirsty, restless, irritable	Withdrawn, somnolent or comatose, rapid deep breathing
Pulse	Normal	Rapid, weak	Rapid, weak
Anterior fontanelle	Normal	Sunken	Very sunken
Eyes	Normal	Sunken	Very sunken
Tears	Present	Absent	Absent
Mucous membranes	Slightly dry	Dry	Dry
Skin turgor	Normal	Decreased	Decreased, with tenting
Urine	Normal	Reduced, concentrated	None for several hours
Weight loss	4%–5%	6%–9%	>10%

of children who are immunodeficient such as those with HIV and IgA deficiencies.

REHYDRATION MANAGEMENT

It is imperative in the initial evaluation of TD to focus on severity of illness, the need for rehydration, and then the identification of infectious causes for further treatment. Because of the usually benign nature of TD, treatment may be implemented by the parents and/or patient without the need for a medical facilitator. There have been consensus statements or recommendations produced both in the United States by the American Academy of Pediatrics and in the United Kingdom by various consensus panels as to the guidelines for treating acute diarrhea. These guidelines were developed in reference to rehydration and electrolyte replacement in all ranges of severity.^{20,25,36}

Fluid and electrolyte replacement is the mainstay for treating TD. Table 2 reflects the physical characteristics of infants and toddlers in the presence of mild, moderate, and severe dehydration. Oral rehydration has not been shown to decrease duration or stool volume, but may decrease the need for intravenous rehydration and decrease the morbidity and mortality associated with moderate to severe dehydration. Medical personnel should base therapy upon the clinical findings of the individual child. Mild to moderate dehydration should prompt a trial of oral rehydration versus the necessity of intravenous fluids and likely admission of a child in moderate-severe category. Unnecessary intravenous fluid hydration may have severe consequences. If done improperly, secondary symptoms caused by incorrect fluid hydration may include decreased consciousness, seizures, and coma caused by hypovolemic hyponatremia.

TABLE 3. Composition of WHO Oral Rehydration Solution

Ingredient	Amount Added to 1 L Water (g/L)
Sodium chloride	2.6
Potassium chloride	1.5
Glucose	13.5
Trisodium citrate	2.9

If oral rehydration solution is not available, 7 tsp sugar + 1 tsp salt to 1 L of bottled water may be substituted.

Table 3 shows the composition of the WHO recommended oral rehydration solution recently restructured from the 20-year-old formula. The restructured formula composition reflects a decreased osmolarity from 311 mOsm/L to 245 mOsm/L, leading to a 33% decrease in the need of intravenous fluids for noncholera pediatric diarrheal patients. Solutions containing glucose are preferred for rehydration; usually with a concentration of 2.5%. This is given to prevent potential diarrhea caused by osmotic water loss. The WHO oral rehydration solution may be substituted by other commercial products if the child does not tolerate the taste—remembering that replacement of glucose, fluids, and electrolytes is the key.

Recent studies have also shown that rice-based formulations have improved hydration and decreased diarrheal output versus the glucose composition. Oral rehydration solutions should be taken in entirety or discarded after 24 hours of refrigeration or after 12 hours at room temperature.¹⁹ In mild to moderate dehydration, infants should take the oral solution over 2 to 4 hours with a goal of 50 mL/kg and 100 mL/kg in mild and moderate dehydration, respectively. More generalized rates of oral rehydration may be used as seen in Table 4. If TD occurs in an infant who is breast feeding or on formula, it is generally recommended to continue these solutions if there is no persistent emesis. Emesis may be seen in up to 15% of children with TD.¹¹ It is recommended that infants and young children seek medical attention as soon as possible if there are signs of moderate to severe dehydration, bloody diarrhea, temperature more than 38°C (>102°F), or persistent emesis.

Continuation of a regular diet is recommended if vomiting is minimal, and there are no signs of dehydration. If rehydration is required, the child should be fed an age-appropriate diet after rehydration as tolerated as soon as

TABLE 4. Treatment of Diarrhea with Standard Oral Rehydration Solution³⁹

Age	Oral Rehydration Solution to be Given
<2 y	1/4–1/2 cup (50–100 mL) after each stool
2–10 y	1/2–1 cup (100–200 mL) after each stool
>10 y-adult	Unlimited

4 hours after initial rehydration. This may help decrease duration of diarrhea up to 12 hours.^{36–38} Complex carbohydrates such as yogurt, vegetables, and fruits are suggested early in the course of the disease. Suitable fluid replacements if the standard oral rehydration solution is not available include tea, bottled drinks, salty soups, and fruit juices.

ANTIMOTILITY MEDICATION

Antimotility agents (loperamide, diphenoxylate/atropine, difenoxin/atropine, and tincture of opium) have been used in the treatment of acute diarrhea because these medications act by decreasing gut transit time, allowing for reabsorption of intestinal fluids. Specifically, loperamide is chemically related to meperidine and affects the μ -opiate receptor. Clinical adult and pediatric trials have shown a decrease in the total number of days with diarrhea. Loperamide is contraindicated in pregnancy and the pediatric population younger than 2 years. It should not be taken for more than 48 hours secondary to the possibility of necrotizing colitis, lethargy, ileus, toxic megacolon, respiratory depression, and coma.⁴⁰ Antimotility agents should not be taken if there is high fever or bloody diarrhea because they have been shown to prolong or worsen diarrhea caused by invasive enteropathogens. Diphenoxylate + atropine (Lomotil) should not be used as an antimotility agent secondary to central nervous system effects, respiratory depression, and ileus.

For adults, trials have shown that the combination of an antimotility drug with an antibiotic gives the best relief of the symptoms of TD.⁴¹

ANTIBIOTIC MANAGEMENT

Bacterial enteropathogens have been implicated as the causative agents of TD in over 80% of the cases.^{4,5,35,42,43} Antimicrobial drugs have become the recommended treatment for adult cases of TD, as treatment has been shown to reduce both the duration and severity of TD (Table 5). There is a growing body of evidence that recommends antibiotic treatment of TD in children; however, antimicrobial use in children still remains controversial as little data has been prospectively collected.

In a medical evaluation of TD-associated diarrhea, the clinician must weigh the side effect profile versus the benefits of using an antibiotic in a limited duration diarrheal state. In a nontraveling child, the WHO recommends oral rehydration therapy alone. Antibiotics are not recommended because most of the causes are due to viruses in developed countries.¹² Use of antibiotics is recommended to shorten the length of symptoms, decrease complications, and improve severity in diarrhea associated with travel. The use of antibiotics may improve the anxiety of both child and parent and improve the convenience of travel if used in the appropriate situation. As mentioned previously, using antibiotics increases the risk of certain complications. Additionally, there are always the risks of allergic reactions, secondary *Clostridium difficile* enteritis, and antibiotic-associated diarrhea. However, these risks are rare and are

TABLE 5. Antibiotic Dosages for Treatment of TD

Drug	Dosage	Duration
Rifaximin	Adults: 200 mg TID Children: age \geq 12 y, same	3 days
TMP-SMX	Adults: 1 DS tablet BID Children: 8 mg/kg per day BID Maximum dose 320 mg/d	3 days
Furazolidone	Children: 5 mg/kg per day QID Maximum dose 100 mg/d	7–10 days
Ciprofloxacin	Adults: 500 mg BID Children: 20–30 mg/kg per day BID Maximum dose 1 g/d	3 days
Azithromycin	Adults: 500 mg QD Children: 10 mg/kg per day QD Maximum dose 500 mg/d	3 days
Nalidixic Acid	Children: 55 mg/kg per day QID Maximum dose 1 g/d	5 days

usually outnumbered by the benefits of treating a bacterial cause of TD.

New surveillance data in the 1990s revealed an evolution in the resistance patterns of the agents causing TD, and ultimately created a need for newer and better antibiotics. Trimethoprim, once a staple of prophylaxis and treatment of TD, is all but useless because of widespread resistance. Patterns of resistance to the tetracyclines, ampicillin, and nalidixic acid have been documented as well. Spontaneous mutation has been the culprit in the development of resistance, but in developed countries around the world, occurrences of resistance has also been related to the use of fluoroquinolones in chicken feed giving rise to resistance in strains of *Salmonella* spp., *Shigella* spp., and *E. coli* spp.⁴⁴ Isolated resistance remains and varies among the different pathogens. For example, ETEC and the *Shigella* spp. show very little resistance worldwide to fluoroquinolones with the exception of *S. dysenteriae* in India with a resistance pattern of 60%.¹⁷

Fluoroquinolones are standard therapy in adult prophylaxis and acute treatment of TD. Courses are recommended from 1 to 3 days in duration. With this regimen, TD has decreased from 3 to 4 days to 1 to 2 days in duration. Ciprofloxacin is the preferred antibiotic of choice in adults, but the United States has not approved its use in children younger than 18 years. The reluctance for approval is secondary to animal models in which prolonged use has been damaging to cartilaginous growth. However, its use is common in other arenas of pediatric medicine such as in cystic fibrosis.⁴⁵ Future studies of fluoroquinolones will most likely support the current sentiment that ciprofloxacin has little increased complications when used in infants and children. Careful thought should be given when deciding on this class of antibiotics as there is increasing resistance to *Campylobacter* spp. and *E. coli* spp. Of note, ciprofloxacin suspension can only be stored for 2 weeks and is expensive.

Azithromycin has a good spectrum of coverage for the enteropathogens causing TD. It is an azalide drug with high intracellular concentrations and long half-life. This drug has been effective especially in Southeast Asia, where fluoroquinolone (specifically ciprofloxacin)-resistant *Campylobacter* spp. are prevalent.⁴⁶ This drug is an excellent choice secondary to its safety in both children and pregnant woman and is highly effective against ETEC, the most common cause of TD worldwide.⁴⁷ Some benefits over ciprofloxacin include a once daily dosing and improved taste profile. In children, the powdered form (no need for refrigeration) may be dispensed with recommendation of reconstitution and a shelf life of no longer than 2 weeks.

Other antibiotics used in the treatment of childhood TD include TMP-SMZ, cefixime, nalidixic acid, and furazolidone. Furazolidone is a precursor to the fluoroquinolones and is more obtainable in Europe and Asia than in the United States. It is usually used as treatment against *Giardia* spp., but its efficacy against the more common bacterial causes of TD is about half that of the fluoroquinolones.¹³

The next generation of antibiotics used in the treatment of TD may be found in those that are nonabsorbent by the gut. These agents have high concentration levels in the mucosa, with little to no systemic side effects. Bicozamycin and aztreonam are not currently being investigated in an available oral form.

Rifaximin (Xifaxan; Salix Pharmaceuticals, Morrisville, NC), a structural analog of rifampin, is a semisynthetic, nonsystemic antibiotic which is excreted primarily in the feces with approximately 97% unchanged and minimal amounts in the liver and kidneys. This drug has not been studied in the geriatric or pediatric populations. Rifaximin has been shown to be active against *E. coli* (ETEC and enteroaggregative *E. coli* strains). Current labeled uses are for the treatment of patients (≥ 12 years of age) with TD caused by noninvasive strains of *E. coli*. Contraindications include anyone with hypersensitivity reactions to the rifamycin antimicrobials or diarrhea complicated with fever and/or blood in the stool. The label warns that effectiveness has not been tested for *Shigella* spp., *Salmonella* spp., or *C. jejuni*. This relatively new drug has been marketed in Europe for over 15 years in non-TD diarrhea and licensed for use in Latin America, Asia, and Africa.⁴⁸ Recently, in May 2004, the United States Food and Drug Administration approved its use for adults older than 12 years.⁴⁸

Vaccines against TD pathogens have been investigated since the late 1800s but have become an emerging topic of interest since the 1960s. A major problem in developing workable vaccines is the large number of serotypes per bacterial species. An injectable cholera vaccine was first used in the 1880s. Live attenuated *Shigella* vaccine was developed in the 1960s and later discontinued. An oral rotavirus vaccine, licensed in the United States in 1998 was removed from the market in 1999, but it is currently being investigated again in stage III clinical trials. Oral cholera and typhoid vaccines give limited protection and are in use in many countries but not the United States. There is current data on the development of ETEC and *Campylobacter* vaccines.

CONCLUSIONS

Travelers' diarrhea should be considered a major health problem associated with international travel in terms of frequency, economic impact, morbidity, and tourism deterrence. Travelers' diarrhea affects all age ranges of the population, with more severe complications in the very young pediatric age group. Although there are large amounts of data supporting the use of antidiarrheal and antimicrobial drugs in the prevention and treatment of adult TD, the staple of pediatric care is the prevention of severe dehydration through adequate oral rehydration. As the pediatric surveillance data grow with the ever-increasing travel population, the recommendations may eventually reflect the same recommendations found in the adult population.

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CME EXAM

Instructions for the *Pediatric Emergency Care* CME Program Examination

To earn CME credit, you must read the designated article and complete the examination below, answering at least 80% of the questions correctly. Mail a photocopy of the completed answer sheet to the Lippincott CME Institute, Inc., 770 Township Line Road, Suite 300, Yardley, PA 19067. Only the first answer form will be considered for credit and must be received by Lippincott CME Institute, Inc. by October 15, 2006. Answer sheets will be graded and certificates will be mailed to each participant within six to eight weeks after LCMEI, Inc. receipt. The answers for this examination will appear in the November 2006 issue of *Pediatric Emergency Care*.

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CME EXAMINATION

August 2006

Please mark your answers on the ANSWER SHEET.

Diarrhea in the Recent Traveler, *Juarez and Abramo*

1. Worldwide, which of the following enteropathogens is considered the most common etiologic agent in travelers' diarrhea?
 - a.) *Campylobacter jejuni*
 - b.) Rotavirus
 - c.) *Giardia lamblia*
 - d.) Enterotoxigenic *Escherichia coli*
2. Pretravel advice to avoid the symptoms of travelers' diarrhea include all of the following, except
 - a.) Avoid raw or undercooked meats and seafood, unpeeled fruits and vegetables, unpasteurized dairy products, and street vendor foods
 - b.) Infective pathogens may survive in water temperatures of 50°C or freezing temperatures
 - c.) Strict dietary compliance in children under the age of 3 years produce the lowest rates of travelers' diarrhea
 - d.) The major pathogens on cruise ships is thought to spread by aerosolized viruses
3. The treatment of choice in pediatric travelers' diarrhea is
 - a.) Fluoroquinolones
 - b.) Fluoroquinolones + loperamide
 - c.) Probiotics
 - d.) Treatment of diarrhea-induced dehydration with oral rehydration therapy
4. Current labeled uses for the antibiotic rifaximin include treatment for which of the following bacteria
 - a.) *Shigella* spp.
 - b.) *Campylobacter jejuni*
 - c.) Noninvasive strains of *Escherichia coli*
 - d.) *Salmonella* spp.
5. Travelers' diarrhea has all the following characteristics, except
 - a.) Usually self-limited without the need for specific therapy
 - b.) The passage of 3 or more unformed stools in a day during or after travel
 - c.) 20% rate of bacterial etiology
 - d.) Higher risk of infectivity associated with gastric acid suppression states and immunosuppression

**ANSWER SHEET FOR THE PEDIATRIC EMERGENCY CARE
CME PROGRAM EXAM**

August 2006

Please answer the questions on page 610 by filling in the appropriate circles on the answer sheet below. Please mark the one best answer and fill in the circle until the letter is no longer visible. To process your exam, you must also provide the following information:

Name (please print): _____

Street Address _____

City/State/Zip _____

Daytime Phone _____

Specialty _____

- 1. (A) (B) (C) (D) (E)
- 2. (A) (B) (C) (D) (E)
- 3. (A) (B) (C) (D) (E)
- 4. (A) (B) (C) (D) (E)
- 5. (A) (B) (C) (D) (E)

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Yes No

2. On a scale of 1 to 5, with 5 being the highest, how do you rank the overall quality of this educational activity as it pertains to your practice?

5 4 3 2 1

3. As a result of meeting the learning objectives of this educational activity, will you be changing your practice behavior in a manner that improves your patient care? If yes, please explain.

5 4 3 2 1

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CME EXAM ANSWERS

Answers for the Pediatric Emergency Care CME Program Exam

Below you will find the answers to the examination covering the review article in the May 2006 issue. All participants whose examinations were postmarked by July 15, 2006 and who achieved a score of 80% or greater will receive a certificate from Lippincott CME Institute, Inc.

EXAM ANSWERS

May 2006

1. D
2. B
3. C
4. B
5. C