Traveler’s Diarrhea in the Pediatric Population: Etiology and Impact

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Children who travel are at risk of developing the same, well-known illnesses that affect adult travelers. The etiology, treatment, and actual risk of these illnesses are not well defined in children. The limited amount of data available forces clinicians to extrapolate appropriate treatment for children. Recommendations for children have not been standardized. The role and judicious use of antimicrobials in the treatment of pediatric traveler’s diarrhea have evolved during recent decades and will be reviewed here. The past 2 decades have seen an unprecedented, sustained growth in travel. The epidemiology related to travel medicine has evolved to describe travelers and their illnesses more specifically. The development of the field of travel medicine has led to greater understanding and improved, targeted treatment of travel-related illnesses. Most of the data available today describe traveler’s diarrhea in adults. Children traveling to distant destinations from their home country have not been well studied, yet treatment parameters exist in practice and will be reviewed here.

DEFINING TRAVELER’S DIARRHEA IN CHILDREN

Traveler’s diarrhea in children has been defined in various ways. In adults, it has been classically defined as “greater than 3 watery stools per day, with or without blood and/or mucous” [1, page 1821]. There has not been strict application of this definition to child travelers to date. The pattern, consistency, and frequency of stools vary during the course of childhood. Infants may have many loose, unformed stools as their normal pattern, especially if they are breast-fed. One particular definition that applies well to all traveling children, regardless of age, is a recent change in a normal stool pattern, with an increase in frequency (at least 3 stools/24 h) and a decrease in consistency to an unformed state [2].

CHILDHOOD DIARRHEA IN DEVELOPING COUNTRIES VERSUS TRAVELER’S DIARRHEA IN CHILDREN

Diarrhea accounts for significant morbidity worldwide. The World Health Organization estimates that 1.5 billion episodes of diarrhea occur in children <5 years old annually, resulting in 3 million deaths [3]. Rotavirus is the leading cause of severe, dehydrating diarrhea in children worldwide. In hospitalized children, rotavirus is the predominant pathogen that causes severe, dehydrating diarrhea. Rotavirus accounts for 20%–70% of diarrhea-associated hospitalizations and 20% of all deaths due to diarrhea worldwide in children <5 years old. The World Health Organization reports that, in 2001, there were 2 million deaths due to diarrhea worldwide, with 600,000 deaths due to rotavirus infection in children <5 years old [4].

Community-based studies of childhood diarrhea, however, indicate that its etiology is similar to that of diarrhea in adult travelers. Enterotoxigenic Escherichia coli, Salmonella species, and Shigella species are the predominant pathogens. Enterotoxigenic E. coli is the most frequently isolated organism and is associated with 210...
Million episodes of diarrhea and 380,000 deaths among children yearly. The peak incidence of *E. coli*–associated diarrheal disease occurs during the first 2 years of life. This organism causes less dehydration than does rotavirus (5% vs. 36%), but the absolute number of cases that develop is greater [4]. Population-based studies implicate enterotoxigenic *E. coli* and *Salmonella* species as the most common pathogens, with rotavirus found less commonly [5–9]. In a study done in Tanzania, 35.7% of 451 stool specimens contained diarrheogenic *E. coli*. Enterotoxigenic, enteroaggregative, and enteropathogenic *E. coli* were the most prevalent pathogens. Enteropathogenic *E. coli*, *Shigella* species, and rotavirus were more prevalent during the dry season. Enterotoxigenic *E. coli* and *Giardia* species were more prevalent during the rainy season [10]. Hoge et al. [11] studied the etiology of diarrhea in 124 nonhospitalized children aged 6–60 months in Nepal who had acute diarrhea and mild-to-moderate dehydration. Table 1 summarizes their results. In traveling children, the etiologies of diarrhea are likely to be similar to those described for diarrhea in adults, although this possibility has not been systematically investigated.

**ENTEROHEMORRHAGIC *E. COLI* (O157:H7)**

Recent outbreaks of enterohemorrhagic *E. coli* (O157:H7) in the United States, Canada, and Japan have raised the general awareness of this pathogen. The complicating feature of infection with this organism is the development of hemolytic-uremic syndrome (HUS). The features of HUS include microangiopathic hemolytic anemia and renal failure, which often is irreversible. To date, enterohemorrhagic *E. coli* has been a pathogen found mainly in developed countries. A small study reported that recent or concurrent use of antimicrobials might worsen the clinical features of HUS [12]. This finding had made many clinicians hesitant to prescribe stand-by antimicrobial treatment for traveling children. Others have called this theory into question, and a meta-analysis of available data published in 2002 did not show a higher risk of HUS [13]. HUS has also been a reported complication of *Shigella* infection itself and is the result of production of Shiga toxin. Shiga toxin–producing *E. coli* has been reported in Latin America as a cause of bloody diarrhea [14]. Neither *E. coli* O157:H7 nor HUS has been reported in traveling children to date.

**WHAT DATA DO WE HAVE ON CHILD TRAVELERS AND DIARRHEA?**

The available data on traveler’s diarrhea in children are very limited. A single study done by Pitzinger et al. [15] in 1991 forms the main body of this literature. Expert travel medicine practitioners cite extrapolation of data from literature on traveler’s diarrhea in adults and shared experiences in formulating their formal and informal recommendations. Data from experience with and literature about children in developing countries adds to current practice, but little has been written to date.

In the study by Pitzinger et al. [15], 363 children from Switzerland were evaluated. Demographic characteristics of the study children are summarized in tables 2 and 3. Only 31% of the total number of subjects included in the study were <14 years old. The overall diarrhea attack rate during the first 2 weeks of travel was 39%, and the overall attack rate for travel of any duration was 30%. The attack rate for children <3 years old was 60%. Diarrhea attack rates by travel location were 73% for North Africa, 61% for India, and <40% for Southeast Asia, Latin America, and other African countries. Six of the 20 children <3 years old traveled to India, where the attack rate was quite high.

Hill [16] surveyed a large cohort of American travelers visiting developing countries. In this group, diarrhea was more severe in children <12 years old, compared with travelers ≥12 years old, in terms of frequency of vomiting (46% vs. 17%), use of medical care (39% vs. 9%), and alteration of activity (46% vs. 26% [not significant]).

**DIETARY TREATMENT OF DIARRHEA IN CHILDREN**

The first published mention of the “BRAT” diet dates to a 1926 report of the treatment of intestinal intoxication of infants [17]. The acronym stands for “bananas, rice, applesauce, and toast.” Diarrhea treatment historically included intravenous fluids, blood transfusions, and starvation. In the 1940s, the limited capacity for digestion of fat, lactose, and sucrose during acute infectious diarrhea was recognized. Adjustments were made to

<p>| Table 1. Etiology of diarrhea in 124 nonhospitalized children in Nepal. |</p>
<table>
<thead>
<tr>
<th>Organism</th>
<th>Incidence, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterotoxigenic <em>Escherichia coli</em></td>
<td>31</td>
</tr>
<tr>
<td><em>Giardia</em> species</td>
<td>13</td>
</tr>
<tr>
<td><em>Campylobacter</em> species</td>
<td>10</td>
</tr>
<tr>
<td><em>Shigella</em> species</td>
<td>2</td>
</tr>
<tr>
<td><em>Salmonella</em> species</td>
<td>1</td>
</tr>
</tbody>
</table>

*NOTE.* Data are from Hoge et al. [11].

<p>| Table 2. Age of Swiss pediatric travelers. |</p>
<table>
<thead>
<tr>
<th>Age, years</th>
<th>No. of children</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;1</td>
<td>3</td>
</tr>
<tr>
<td>1–2</td>
<td>17</td>
</tr>
<tr>
<td>3–6</td>
<td>47</td>
</tr>
<tr>
<td>7–14</td>
<td>46</td>
</tr>
<tr>
<td>15–20</td>
<td>250</td>
</tr>
</tbody>
</table>

*NOTE.* Data are from Pitzinger et al. [15].
the recommendations [18]. There are few data and no evidence to support the widespread use of the BRAT diet. The awareness of the diet, however, is nearly ubiquitous in pediatrics and parenting, despite evidence and guidelines advising against its use. Although the foods are easily tolerated, they are low in energy density, protein, and fat, all of which are necessary for the healing process.

Through the 1970s, pediatric textbooks continued to recommended a period of bowel rest and starvation, followed by gradual refeeding. Studies from the 1980s shifted the focus from starvation to early refeeding after the initial rehydration period [18]. The nutritional benefits of returning to solid foods after a diarrheal episode have been well described since then and form the basis for current recommendations. Lactose-free formula preparations have not proven to be definitively better in treating diarrheal diseases and are not included in first-line management recommendations. Both the World Health Organization and the American Academy of Pediatrics published formal guidelines on the treatment of diarrhea in children in 1996 [19]. Health care providers have not overwhelmingly adhered to providing the dietary advice recommended [20].

ANTIMOTILITY AGENTS

Antimotility agents have traditionally enjoyed an unfavorable reputation with pediatricians. Reports of associated adverse events, along with the possibility that the medication may prolong the infections, have led to a low level of usage by pediatricians. Many of these agents are available over the counter, however, and parents have access to them. Doses are written for children as young as 2 years old. Published case reports and studies of the use of loperamide describe high rates of adverse effects, including lethargy, ileus, and coma, when used in infants [21].

In a placebo-controlled study of 258 children in Mexico, aged 2–11 years, loperamide significantly shortened the time to the last unformed stool and reduced the severity of acute nonspecific diarrhea. No significant adverse effects were reported, but the group given loperamide had a higher rate of adverse effects, compared with the group given placebo (15% vs. 7%) [22]. An earlier study of a 2-center, placebo-controlled clinical trial conducted in Liverpool, England, and Libya reported no statistically significant differences in the course of gastroenteritis [23]. The American Academy of Pediatrics does not recommend the use of antimotility agents for the treatment of acute diarrhea [19].

BISMUTH SUBSALICYLATE

Bismuth subsalicylate has been shown, in frequent doses, to decrease the number of unformed stools produced by adult travelers. Controlled trials of bismuth subsalicylate in children have shown that, when administered every 4 h, it decreases the duration and frequency of diarrhea, with no measurable associated toxicity [24]. General practice guidelines regarding gastroenteritis do not recommend the routine use of bismuth subsalicylate, but, rather, focus on the use of oral rehydration as primary therapy. The use of bismuth subsalicylate has not been studied in child travelers but can be considered as adjunctive treatment with the use of oral rehydration solution packets and antimicrobials.

ANTIMICROBIAL TREATMENT RECOMMENDATIONS

Traditional advice to traveling families has focused on dietary avoidance of “unsafe foods” and the importance of oral rehydration solution packets when vomiting and diarrhea occur. The availability and use of oral rehydration solution packets is widespread in developing countries. Appropriate use of the packets is an important component of pretravel advice to parents, because parents are often unfamiliar with oral rehydration solution formulations worldwide.

Historically, clinicians have been hesitant to recommend antimicrobial treatment of childhood traveler’s diarrhea. Frequently heard reasons include “They don’t get it that badly” or “Medication may be harmful/unnecessary or may mask other problems.” There has been a general void in both consensus and practice for presumptive prescribing to child trav-

<table>
<thead>
<tr>
<th>Year</th>
<th>Children</th>
<th>Adults</th>
</tr>
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<tbody>
<tr>
<td>1992</td>
<td>Not mentioned</td>
<td>TMP-SMZ, ciprofloxacin</td>
</tr>
<tr>
<td>1996</td>
<td>TMP-SMZ&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>1998</td>
<td>TMP-SMZ&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>1999</td>
<td>TMP-SMZ&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>2002</td>
<td>Azithromycin, TMP-SMZ&lt;sup&gt;b&lt;/sup&gt;</td>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>2004</td>
<td>Azithromycin</td>
<td>Ciprofloxacin</td>
</tr>
</tbody>
</table>

<sup>a</sup> Resistance has become common in many areas.

<sup>b</sup> Can be used, but resistance has become common in many areas.
Treatment recommendations for pediatric traveler’s diarrhea have come from expert opinion, anecdotes, limited case reports, the Centers for Disease Control and Prevention “Yellow Book,” the World Health Organization, The Medical Letter [26–31], and extrapolation from treatment recommendations for traveler’s diarrhea in adults.

Reluctance to offer antimicrobials for presumptive treatment of traveler’s diarrhea in children likely stems from scarce definitive recommendations. Authoritative sources either have not mentioned children in their algorithms or have made limited recommendations. Table 4 summarizes the changes made in the recommendations of The Medical Letter “Advice for Travelers” publication over the years.

Since the emergence of trimethoprim-sulfamethoxazole-resistant E. coli in the late 1980s, recommendations for the treatment adults have changed. The treatment of traveler’s diarrhea in adults with fluoroquinolones first emerged in 1990. Until recently, fluoroquinolones had not been approved by the US Food and Drug Administration for any use in children. In August 2000, ciprofloxacin was approved for use in children for inhalational exposure to anthrax. In June 2004, fluoroquinolones were given limited approval by the Food and Drug Administration for resistant urinary tract infections and pyelonephritis in children aged 1–17 years [32]. Fluoroquinolone ophthalmic preparations are approved for use in children >1 year old.

The adverse events that limited the approval of fluoroquinolones for pediatric use were noted in cartilage of immature beagle puppies during initial testing of the drugs. The potential effects of fluoroquinolones, as well, on the growth of developing cartilage in children have limited their widespread use or approval. Fluoroquinolones have been widely used to treat children with cystic fibrosis. Rare adverse events, including acute renal failure and arthralgias, have been noted in this group of children. No direct arthropathy has been reported. Experiences in a multicenter trial in France indicated that musculoskeletal adverse events were more frequent in the exposed children than in control subjects (frequency of adverse events, 3.8% vs. 0.4%) [33]. Another study showed little difference in joint complaints between the groups using a fluoroquinolone and azithromycin [34]. As a result of these concerns, widespread use and indications for fluoroquinolones remain unapproved.

Should children with traveler’s diarrhea be treated with a fluoroquinolone? Would a single dose or, perhaps, a 3-day course of a fluoroquinolone cause the theoretical cartilage abnormality not seen to date in association with longer and successive courses of this drug? Data on this group, if available, would be revealing. The risk of the disease, whether it is di-

<table>
<thead>
<tr>
<th>Table 5. Drugs used to treat traveler’s diarrhea in children.</th>
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<tbody>
<tr>
<td><strong>Drug</strong></td>
</tr>
<tr>
<td>Azithromycin</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
</tr>
<tr>
<td>Furazolidone</td>
</tr>
<tr>
<td>Nalidixic acid</td>
</tr>
</tbody>
</table>

**NOTE.** E. coli, Escherichia coli; FDA, Food and Drug Administration; V. cholera, Vibrio cholera.
Diarrhea and dehydration or dysentery, versus the risk of using this class of medications is a factor in making this decision.

Azithromycin was introduced to the pediatric market during the 1990s. It is an azalide, a subclass of the macrolide antimicrobials. Data on enteric pathogen coverage were first published in an in vitro study in 1994 [35]. Azithromycin is available in a flavored powered form that can be reconstituted and stored without refrigeration. It is administered only once daily, further increasing its easy use in children. The current practice of daily dosing for 3 days is widespread for treatment of otitis media and pneumonia. This dosing practice has evolved to the current use of azithromycin for the treatment of pediatric traveler’s diarrhea, replacing trimethoprim-sulfamethoxazole. Azithromycin also covers quinolone-resistant Campylobacter jejuni and, therefore, is advantageous for children traveling to Thailand.

**ANTIMICROBIAL TREATMENT: WHY, WHEN, AND WITH WHICH DRUG?**

Aside from the medical risks of a potentially serious gastrointestinal infection and the inherent dehydration, there are additional factors associated with diarrhea in a child traveler. The effect of an ill child on the rest of the travelers in the family should be considered as well. These are exceptionally difficult parameters to quantify, and, hence, formulation of evidence-based recommendations remains challenging. Treating traveler’s diarrhea empirically with antimicrobials, as adults are advised to do, resolves this uncomfortable condition quickly and more effectively than not treating it. Although the focus on oral rehydration should not be underestimated, it is only part of the equation regarding the treatment of travelers. Many questions remain (figure 1).

Diarrheal stools frequently cause diaper dermatitis. This irritating and painful skin rash may simply be caused by the chemical composition of the stool breaking down the skin or may be a result of superinfection with Candida species. Skin may rapidly erode and easily bleed, causing more pain and discomfort. It is often underappreciated as a consequence of diarrhea, except by parents and the affected child. No formal studies have quantified the severity of or quality-of-life issues associated with diarrhea-induced diaper dermatitis.

Treatment of diaper dermatitis involves discontinuing use of the commercially prepared diaper wipes and using a liquid hypoallergenic soap and gentle cloth for hygiene. A barrier ointment, such as zinc oxide or petrolatum, along with hydrocortisone (1% strength) for treating the breakdown of the skin, can be applied. An antifungal cream can be used during alternate diaper changes. Decreasing diaper dermatitis by decreasing the stool volume is rarely a focus of the discussion of traveler’s diarrhea; nevertheless, effective treatment of the underlying cause resolves this consequence most rapidly.

Diarrhea and gastrointestinal illness are common among children even in their home environments. When traveling, the challenge for parents is deciding whether to treat with medication or to ‘wait it out,’ as they likely do at home. Educating parents about the signs of diarrhea is unnecessary, because the symptoms are obvious. When fever and bloody diarrhea occur, antimicrobial treatment is clearly indicated. Less-severe diarrhea that occurs when traveling is readily treated in adults. Anecdotally, travel medicine providers and pediatricians have been reluctant to recommend antimicrobial treatment for children with diarrhea that has not been accompanied by systemic symptoms. Consensus opinion of travel medicine physicians is to advise antimicrobial treatment when diarrhea symptoms occur while traveling in developing countries typically known for high rates of traveler’s diarrhea. Antimicrobial choices are shown in detail in table 5.

**WHAT DO WE KNOW?**

In summary, data support the fact that children in developing countries develop diarrhea. Limited data indicate that children who travel develop diarrhea at nearly the same rate as adults. The predominant pathogen in adults is enterotoxigenic E. coli. E. coli O157 has not been reported in developing countries; therefore, concerns about precipitating HUS by treatment with antimicrobials are not supported to date. Oral rehydration solution use is recommended, whereas the BRAT diet is not. We still have few statistics on child travelers and the diarrheal pathogens that affect them. The best treatment choice for the pediatric traveler must address a combination of efficacy, palatability, adherence, and cost. Although firm evidence-based guidelines are lacking, antimicrobial treatment choice, at this point, favors azithromycin use versus off-label quinolone use. Ongoing surveillance and evolving treatments will contribute to the evidence supporting treatment choices and recommendations.

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Potential conflicts of interest. S.M.: no conflict.

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6. Nguyen PK, Khanh NG, Tuong CV, Quy PP, Anh DN, Thuy HT. Persistent...