Bronchiolitis; Acute Infectious Diarrhea

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Table of Contents

Bronchiolitis .................................................. 2
  Diana R. Quintero, MD, and William M. Gershan, MD

Acute Infectious Diarrhea. ............................... 6
  Crenguta Stepan, MD, Iris Liou, MD, and Christina M. Surawicz, MD

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Bronchiolitis

Diana R. Quintero, MD, and William M. Gershan, MD

INTRODUCTION

Bronchiolitis is a common condition that affects 80% of the pediatric population in the United States younger than 12 months of age. Of affected children, 123,000 (2%–3%) will require hospitalization.1 The most common etiology for bronchiolitis is respiratory syncytial virus (RSV) infection.2 The virus has a worldwide distribution and infects almost all children by age 2 years. Children at high risk for developing complications and severe disease include premature infants; babies with history of chronic lung disease, immunodeficiencies, or congenital heart disease; infants with neurologic diseases; and healthy babies younger than 6 weeks.3,4 Exposure to postnatal maternal smoking has been associated with increased severity.5 The mortality resulting from RSV in the late 1990s was 2.0 per 100,000 live births in the United States,6 whereas in the United Kingdom it was 1.82 per 100,000 in the year 2000.7

CLINICAL PRESENTATION

Typical findings in children with bronchiolitis include coryza, nasal obstruction with or without rhinorrhea, fever, wheezing, and cough.8 However, there are no standardized criteria for making a diagnosis. In a review of 65 studies by Bordley et al,9 most identified wheezing and tachypnea as the prominent diagnostic features. Mulholland et al10 found that crackles and cyanosis correlate more with severity of disease than does respiratory rate, indicating that findings suggestive of bronchiolitis may not be as evident as thought. Auscultatory findings are variable and may include fine inspiratory crackles, expiratory wheeze, and prolonged expiration. Caution needs to be taken, as reliability of auscultation may be inconsistent among observers.11

Patients with RSV bronchiolitis tend to have the worst symptoms on day 3; symptoms may last for 7 to 10 days.12 Hypoxia maybe present for several weeks. In very young infants, prematures, and low-birth weight babies, bronchiolitis may present with apneic episodes.

DIAGNOSIS

In most cases, bronchiolitis is a clinical diagnosis and no further investigation is necessary.13,14 Most children with bronchiolitis present with mild symptoms and are managed as outpatients with no routine diagnostic testing. However, children who develop significant shortness of breath may require continuous observation in the hospital. There is no consensus on when to admit children, and the decision is usually made in the emergency department.

Chest radiographs are not needed to make the diagnosis and their use has not been shown to improve outcomes. They often yield nonspecific findings, including hyperinflation and areas of atelectasis. Atelectasis may be difficult to distinguish from a bacterial consolidation and may be seen in approximately 25% of patients with bronchiolitis.15 Despite this, chest radiographs are done in 61% of emergency department visits in the United States for suspected bronchiolitis. A survey done by Christakis et al16 revealed varied use of chest radiographs for diagnosis of bronchiolitis across 30 large hospitals. The test was associated with a longer length of stay as well as a more frequent use of antibiotics. In South Africa, Swingler et al17 reviewed outcomes in a randomized study of children aged 2 to 59 months presenting with the World Health Organization definition of pneumonia who were randomly assigned to have a chest radiograph done or not. Even though bronchiolitis was the most common diagnosis in both groups, those who had a chest radiograph done were more frequently diagnosed with pneumonia and treated with antibiotics than those who did not have a chest radiograph.

Rapid viral tests are available in the United States. Direct immunofluorescence and enzyme immunosassays are commonly used in most hospitals, with a sensitivity of 80% to 90%. The use of these tests has helped to decrease the use of antibiotics.16,18 RSV is found in 70% of patients with bronchiolitis, although other viral pathogens may be found.2 Coexistence of more than 1 virus causing symptoms has been described. Human metapneumovirus has been reported as a cause of infection.
as well as coinfection with RSV since its discovery in 2001. Other organisms, such as adenovirus, influenza, and parainfluenza virus, may also be responsible for bronchiolitis epidemics. Rhinovirus is the second most common causative pathogen of bronchiolitis and is associated with more severe disease.

**COMPLICATIONS**

Severe work of breathing leading to respiratory failure and mechanical ventilation may occur in 7% to 21% of children admitted with bronchiolitis, especially in those vulnerable to these complications (ie, prematurity, cardiac disease, chronic lung disease). Studies have shown that fever may be a protective factor against serious bacterial infection except for urinary tract infections. Caution must be taken with febrile infants younger than 2 months, as they may be at increased risk of systemic sepsis.

Apnea may be present in 8% of infants with bronchiolitis and accounts for 20% of admissions to the intensive care unit. The underlying reason for this presentation is not clear, but it is known that it is not a consequence of central nervous system infection by RSV.

Viral infections may also affect the epithelial lining of the upper airway, including the middle ear, leading to acute otitis media, which may be present in 50% of cases of bronchiolitis.

Patients admitted to the hospital may have a prolonged length of stay, usually due to persistent hypoxemia. Readmission to the hospital may occur. Kemper et al reported a 3.7% readmission rate within a 30-day period. Median time between the 2 admissions was 2 days. Length of stay was usually longer in the second admission. The only risk factor for readmission was the lack of need for oxygen during the first hospitalization; the researchers hypothesized that these children might be at greater risk because they were seen early in the disease process and their disease eventually progressed to more severe illness.

Kim et al recently described an increase in alveolar macrophages from laryngeal aspirates during acute phase of bronchiolitis. This finding is suggestive of transient risk of aspiration likely due to increased work of breathing.

**MANAGEMENT**

When bronchiolitis is suspected, an assessment of the severity of disease should be made. Patients with mild disease will usually present with little or no respiratory distress, no hypoxemia, and no feeding difficulties. In this case, parents should be reassured and patients should be closely monitored.

Moderate disease is characterized by some retractions, hypoxemia corrected with oxygen, shortness of breath during feeding, and occasionally apneic spells. Caution should be taken with these patients, and close observation or admission to the hospital should be considered. Intravenous fluids may be indicated if the patient is not feeding or there is significant tachypnea that may increase the risk of aspiration.

Admission to the hospital due to bronchiolitis has increased significantly over the last 20 years, likely due to the routine use of pulse oximeters. Hypoxia is the main factor in deciding if a patient needs to stay. In a vignette-based survey in which the vignettes were identical except for given $\text{SpO}_2$ values (94% or 92%) and respiratory rate (50 or 65 breaths/min), emergency department physicians were twice as likely to admit a child with oxygen saturations of 92% versus 94%. A respiratory rate greater than 65 breaths/min was not a finding that would prompt an admission. The impact of pulse oximetry and oxygen therapy in infants with bronchiolitis needs further investigation in larger trials looking at outcomes of different levels and durations of oxygen desaturations.

In severe cases, individuals with bronchiolitis may present with severe respiratory distress, retractions, nasal flaring, and grunting. Increasing tiredness, persistent desaturation below 90% while receiving more than 40 to 50% of fractional inspired oxygen, and prolonged apnea warrants cardiorespiratory monitoring, ideally in an intensive care unit with the possibility of endotracheal intubation or positive pressure ventilation.

The degree of hypoxemia determines the need for oxygen. There are no validated studies that show giving oxygen will improve outcomes, but it is considered standard of care. There is no consensus on ideal oxygen saturation, although 2006 guidelines from the American Academy of Pediatrics recommend an oxygen saturation of 90% or greater. In published studies, oxygen is used to keep saturation in the range of 90% to 94%. Bajaj et al proposed that patients with hypoxia and uncomplicated bronchiolitis be sent home on oxygen after an 8-hour period on observation in the emergency department. The authors proved that it is safe, and the frequency of readmission was low. Larger trials need to be done to identify safety issues.

Pharmacologic interventions are widely used despite poor evidence of their usefulness. The use of bronchodilators has been controversial. Bronchodilators...
are prescribed to most infants with bronchiolitis in the United States and Europe. A Cochrane review revealed that several studies showed significant bronchodilator responsiveness in children affected with bronchiolitis. The results were questionable, as infants older than 12 months were included and the likelihood of asthma is increased in this group. Lenney and Milner concluded that there is no significant responsiveness to bronchodilators in infants younger than 18 months of age with bronchiolitis by using modified forced oscillation and plethysmography. Tepper et al found a subgroup of infants with bronchodilator response by applying end-tidal rapid thoracoabdominal compression technique. Modl et al looked at the same population but used the raised thoracoabdominal compression method and found that bronchodilator response is not age-dependent. Regardless of these findings, the overall consensus was that bronchodilators do not produce a clinically relevant response, with only a short-term recovery, and they do not improve oxygenation or hospital admission rates.

Several studies as well as a Cochrane review did not find that ipratropium bromide had any usefulness in patients presenting with bronchiolitis.

Nebulized epinephrine has been one of the medications of choice for acute bronchiolitis in emergency departments. Its use has been controversial, as it has been shown to cause short-term responses compared with placebo and may mislead to early discharges.

There is little proof that systemic steroids are helpful in bronchiolitis. Schuh et al demonstrated an acquisent response to high-dose dexamethasone in patients aged 2 to 24 months with mild to moderate bronchiolitis. However, this study contradicts a systematic review of 13 trials, which did not demonstrate any benefit in clinical outcomes in the use of steroids in bronchiolitis.

Corneli et al recently published the largest multicenter randomized controlled trial using a single dose of dexamethasone versus placebo. They did not find any difference in the rate of hospital admissions, clinical status after 4 hours of observation, length of hospital stay, later office visits, or adverse events.

Ribavirin has been used extensively as antiviral therapy in the treatment of bronchiolitis. Trials of ribavirin for RSV have been unreliable in estimating its effects. A Cochrane review of 12 studies showed that in 3 small trials ribavirin may reduce the duration of mechanical ventilation, length of stay, and the long-term incidence of recurrent wheezing following RSV disease. There are several practical issues limiting the use of ribavirin, including difficult administration, high cost, and occupational hazard exposure.

Montelukast, a novel therapy, was examined by Bisgaard in a randomized, double-blind, placebo-controlled, parallel-group study of 130 infants aged 3 to 36 months. A daily dose of a 5-mg chewable tablet was administered within 7 days of the onset of illness for 28 days. Children taking montelukast were symptom-free on 22% of the days and nights compared with 4% of the days and nights for infants on placebo. This medication needs to be investigated in a larger cohort to confirm its effects.

Nebulized 3% hypertonic saline (HS) versus normal saline were used in a randomized multicenter study during the acute phase of disease in admitted pediatric patients with acute bronchiolitis. The HS group had a shorter length of stay compared with the normal saline group. Further studies are needed to identify dosing, frequency, and other side effects that may have not been encountered during this study.

**PREVENTION**

The most important preventive measure to stop the spread of infection is frequent and adequate hand-washing. Studies have not shown that the use of gowns, masks, gloves, and goggles help stop the spread of RSV; however, a lower incidence of transmission was identified.

In 1994, RSV-IGIV was introduced as an effective monthly infusion to help decrease the symptoms and recurrence of RSV bronchiolitis. This led to the production of palivizumab, which has been the major advance in the control of RSV infection. Palivizumab is a human recombinant monoclonal antibody against a surface glycoprotein of RSV administered by monthly injection during the prevalent months (October–April). The costs versus benefits of this vaccine has been a subject of controversy, with some studies showing the cost of palivizumab prophylaxis high relative to benefits realized. The average cost per child per season is $5000 to $6000. In a cost-effectiveness study, palivizumab was most cost-effective for babies born at 32 weeks or less, who had a long-term oxygen requirement, and who were discharged home between September and November. The estimated cost per admission forestalled was calculated at $12,000. Infants born with congenital heart disease were also found to have a 45% reduction in admission rate. The American Academy of Pediatrics has issued recommendations on appropriate candidates for RSV prophylaxis (Table).
babies who did not have chronic lung disease and were not candidates for RSV prophylaxis according to the current recommendations.

**REFERENCES**


**Table. American Academy of Pediatrics Recommended Candidates for RSV Prophylaxis**

Consider for:

- Infants and children younger than 2 years with chronic lung disease who have required medical therapy (ie, supplemental oxygen, bronchodilator, diuretic, or corticosteroid therapy) within 6 months before the start of RSV season.
- Infants born at 32 weeks’ gestation or earlier without chronic lung disease.
- Infants born between 32 and 35 weeks of gestation if 2 or more risk factors present (ie, child care attendance, school-aged siblings, exposure to environmental air pollutants, congenital abnormalities of the airways, or severe neuromuscular disease).

Children who are 24 months or younger with hemodynamically significant cyanotic and acyanotic congenital heart disease will benefit from 5 monthly intramuscular injections of palivizumab (15 mg/kg).

**Adapted with permission from American Academy of Pediatrics Committee on Infectious Diseases and Committee on Fetus and Newborn. Revised indications for the use of palivizumab and respiratory syncytial virus immune globulin intravenous for the prevention of respiratory syncytial virus infections. Pediatrics 2003;112:1442–6.**
Acute Infectious Diarrhea

Crenguta Stepan, MD, Iris Liou, MD, and Christina M. Surawicz, MD

INTRODUCTION

Worldwide, acute infectious diarrhea remains a major cause of morbidity and mortality among children younger than 5 years. Recent estimates suggest that diarrhea accounts for 1.4 to 2.5 million deaths per year in children worldwide and about 500 every year in the United States. In U.S. adults, the incidence of diarrhea is still high, with 0.72 episodes per person-year, but the mortality is low, with the elderly at greatest risk. A study from 1991 showed that most diarrheal deaths were among those older than 74 years (51%), followed by adults 55 to 74 years (27%) and young children (11%). Age is also an important risk factor for death following hospitalization for gastroenteritis, with a case-fatality ratio higher in the elderly than in children. Traveler’s diarrhea is another challenge in treatment and prevention, with a risk of about 7% in travelers to developed countries and 20% to 50% in travelers to the developing world. Thus, it is important for clinicians to understand the management of acute diarrhea with respect to evaluation, treatment, and prevention.

ETIOLOGY AND CLINICAL PRESENTATION

Acute diarrhea is defined as 3 or more stools per day (or at least 200 g of stool/day) lasting 14 days or less. In most cases, the etiology is infectious. Estimates show that pathogens are identified in less than 20% of cases because many patients do not seek medical attention and stool tests are not sensitive in identifying pathogens.

Most acute infectious diarrhea is self-limited, lasting less than 3 days, with approximately 80% attributed to viruses (Table). Viruses causing acute diarrheal illnesses...
are noroviruses (formerly Norwalk agent), rotaviruses, caliciviruses, astroviruses, and enteric adenoviruses. Viral illnesses are typically associated with watery stools, nausea, vomiting, myalgia, fatigue, and low-grade fever. In these cases, supportive fluid therapy to maintain hydration is generally sufficient.

The most common causes of bacterial diarrhea are Salmonella, Campylobacter, and Shigella species. Other pathogens are Yersinia, Aeromonas, and Plesiomonas species. Bacteria can cause watery diarrhea that can turn into bloody diarrhea, sometimes with tenesmus and fever.

Among the protozoa, Giardia, Cryptosporidium, Entamoeba histolytica, and Cyclospora are the most common, and can have a prolonged course in immunosuppressed patients.

### EVALUATION

Most cases of infectious diarrhea in developed countries are self-limited, so diagnostic evaluation is generally not indicated. Further evaluation for invasive pathogens is indicated in patients younger than 2 years or older than 70 years or when there is blood or mucus in the stool, signs of dehydration, immunocompromised status, or high fever.

Evaluation begins with a careful patient history (onset, duration, the character of the stool, frequency, amount, associated symptoms). Epidemiologic factors (travel, ill family members, day care, history of contact with pets, consumption of “unusual” food items) and incubation period may provide clues to etiology of the diarrheal illness. Medication history is also important, especially recent antimicrobial therapy. Certain underlying medical conditions (eg, AIDS), immunosuppressive medications, or prior gastrectomy can predispose to infectious diarrhea.11 The predictive value of any clinical feature, however, is relatively low for any particular pathogen. Based on the history and physical examination, the clinician should be able to determine the severity of the diarrhea and choose an appropriate treatment approach.

The next step in the management of acute diarrhea, if needed, includes diagnostic testing: stool culture, fecal leukocyte test, and/or stool lactoferrin. These tests are usually positive in patients infected with Shigella, Salmonella, Campylobacter, Aeromonas, Plesiomonas, noncholera vibrios, and Clostridium difficile.12

Because stool cultures are often inappropriately ordered, they are one of the most inefficient and costly tests (about $900 per positive result). Stool culture typically takes at least 2 days to yield results, and positive results occur in only 1.5% to 5.8% of specimens.5 In cases of bloody diarrhea, however, pathogens can be identified in up to 20% of cases. Given these considerations, stool culture for invasive pathogens is appropriate when there is a history of bloody diarrhea, fever, and recent travel to high-risk areas. Other indications for stool culture are a positive fecal leukocyte test or stool lactoferrin, which indicate an inflammatory process. When the presence of inflammation is demonstrated, the yield of stool culture for invasive pathogens will be increased.13 However, inflammation can be seen in inflammatory bowel disease and other colitis as well.

Microscopic examination for fecal leukocytes has long been used to screen for inflammatory diarrhea. The test is limited by the need for fresh specimens and experienced microscopists, difficulties present especially in developing countries. An alternative to fecal leukocyte test is latex agglutination test for detection of fecal lactoferrin. This is more sensitive than fecal leukocyte examination but is more expensive and may have false-positive results in breast-fed infants.14 In addition, patients infected with Escherichia coli O157:H7 often have bloody diarrhea and negative or low levels of lactoferrin and thus need a specialized approach to diagnosis.15 Some suggest a positive fecal lactoferrin test be used as an indication for immediate empiric therapy in the

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**Table. Common Causes and Associated Risk Factors for Infectious Diarrhea**

<table>
<thead>
<tr>
<th>Etiology</th>
<th>Annual Cases*</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Norovirus</td>
<td>8500 [9]</td>
<td>Winter outbreaks in adults, raw oyster consumption, cruise ships</td>
</tr>
<tr>
<td>Rotavirus</td>
<td>1100 [9]</td>
<td>Winter outbreaks in children under 2 years</td>
</tr>
<tr>
<td>Giardia</td>
<td>750 [9]</td>
<td>Contaminated water; recreational exposure in lakes, rivers, or swimming pools; day care centers</td>
</tr>
<tr>
<td>Salmonella</td>
<td>14.7 [10]</td>
<td>Raw eggs, undercooked poultry and turkey, unrefrigerated dressing, pet reptiles, family members with Salmonella</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>12.9 [10]</td>
<td>Undercooked poultry, contaminated milk, tuna salad</td>
</tr>
<tr>
<td>Shigella</td>
<td>5.1 [10]</td>
<td>Contaminated water and vegetables</td>
</tr>
<tr>
<td>E. coli O157:H7</td>
<td>0.9 [10]</td>
<td>Undercooked beef, unpasteurized milk, apple cider; visits to animal farms or petting zoos</td>
</tr>
<tr>
<td>C. difficile</td>
<td>NA</td>
<td>Antibiotic use</td>
</tr>
</tbody>
</table>

*By stool culture per 100,000 U.S. population.

NA = not available.
elderly and travelers, whereas a negative test makes an invasive infection unlikely. Other tests may be used when pathogens not identified by usual stool culture are suspected.

If the patient is moderately to severely ill, a general evaluation is needed in order to assess severity of disease, dehydration, or possible complications; evaluation may also include serum chemistry analysis, complete blood count, blood cultures, and abdominal radiography.

### TREATMENT

#### REHYDRATION

If the patient is able to drink, oral hydration is the first choice. This can be accomplished with an oral glucose or starch-containing electrolyte solution. Studies have shown that glucose-containing solutions help the absorption of sodium and water through a mechanism of co-transport of electrolytes. This simple measure is superior to administration of intravenous fluids for persons who are able to take oral fluids. More severe diarrhea (with dizziness, orthostatic hypotension, or reduced urinary output) requires the use of intravenous fluids.

Dietary changes are also part of the management, because a better nutritional status helps to decrease intestinal permeability and hasten recovery. Food should be reintroduced as soon as possible, and breastfeeding should be continued in infants. It is recommended that fruits (especially bananas, rich in potassium), salty food (rich in sodium), and bread and rice (sources of carbohydrates) be increased. Milk products can be eliminated from the diet during the first days of a diarrheal bout, even though transient lactose intolerance is usually not significant. Recently, consumption of yogurt has been associated with a clinically relevant decrease in stool frequency and duration of diarrhea in children who have reducing sugars in stools.

The introduction of hypo-osmotic solution, resistant starch and glutamine incorporating nutrition therapy are promising new approaches to diarrheal management.

#### ANTIDIARRHEAL MEDICATIONS

When rehydration and dietary changes do not improve symptoms, antidiarrheal medication is the next step. There are 3 types of antidiarrheal agents: antisecretory (bismuth subsalicylate, racecadotril, provir), adsorbents (kaolin pectin, attapulgite), and antimotility (loperamide, opioids).

Among antimotility agents, loperamide is the drug of choice for self-treatment of mild diarrhea. Loperamide decreases the intestinal transit and has some antisecretory properties, reducing the passage of loose stools by about 50%. Loperamide combined with antibiotics reduces the duration of traveler’s diarrhea or bacillary dysentery by 1 day. Other antimotility drugs are opioid-based (eg, diphenoxylate, codeine, and paregoric); their use is limited by the neurologic side effects. Antimotility agents should be avoided in children and infants and in patients with severe bloody diarrhea and suspected C. difficile disease.

Among the antisecretory agents, bismuth subsalicylate is most commonly used in adults and children. It works by multiple mechanisms: inhibition of intestinal secretion, anti-inflammatory action and anti-bacterial effects. In children, bismuth subsalicylate shortens illness and leads to significant weight gain and has been shown to improve viral gastroenteritis with less vomiting and shorter median duration. In adults, it can be used for the treatment of watery diarrhea and traveler’s diarrhea with a significant reduction in the passage in loose stool. Pregnancy and immunosupression are contraindications to its use.

The adsorbents, such as kaolin pectin or attapulgite, are also antisecretory agents, but their use in the management of infectious diarrhea needs further investigation related to efficiency and safety.

#### NEW AGENTS

Racecadotril is a promising new antisecretory agent, which potentiates the action of enkephalins in the gastrointestinal tract. It can reduce stool frequency and volume and is safe even in children. However, in 1 study itching was described in 28% of those treated. Compared with loperamide, the clinical success is just slightly better, but the benefit is related to the lower incidence of treatment-related constipation for racecadotril.

SP 303 (Provir) is a chloride channel blocker that has been used for more than 10 years and has been proved to be safe and effective in management of AIDS-related diarrhea, reducing stool volume and frequency. It was shown effective in treatment of traveler’s diarrhea in Jamaica and Mexico, shortening duration by 21% and with no risk of invasive diarrhea or posttreatment constipation. It is not commercially available.

#### ANTIMICROBIAL THERAPY

Routine use of antimicrobial agents for acute infectious diarrhea is not recommended because of the self-limited nature of most cases (about 80%), the cost, and
the potential antibiotic resistance of enteric pathogens. There are 2 types of antimicrobial therapy: empiric and targeted.

Empiric antimicrobial therapy is recommended in the following situations: in moderate to severe forms of traveler’s diarrhea, in moderate to severe invasive diarrhea (with temperature > 38°C, positive stool test for leukocytes and/or lactoferrin, and/or blood), in patients with high risk of diarrhea-related complications, and in severe nosocomial diarrhea in highly suspicious cases of *C. difficile* infection. The Centers for Disease Control and Prevention has reported on recent emergence of nonantibiotic-associated severe *C. difficile* diarrhea in peripartum women.

Approximately 80% of traveler’s diarrhea cases with an identified pathogen are caused by bacteria, including enterotoxigenic *E. coli* (ETEC), enteraggregative *E. coli* (EAEC), *Salmonella* spp., *Shigella* spp., *Campylobacter* spp., *Plesiomonas shigelloides*, *Aeromonas* spp., and noncholera vibrios. Usually at the time of therapeutic decision, no microbial isolation is done, so the chosen antibiotic needs to cover most of the possible spectrum. Antibiotics decrease severity and duration of diarrheal episodes (the number of patients free of traveler’s diarrhea 72 hours after starting treatment was 84.4% compared with 50.3% taking placebo).25

Fluoroquinolones are the drugs of choice for traveler’s diarrhea in most regions of the world. Their advantages are good absorption with a high fecal concentration, excellent spectrum of activity, and effectiveness in shortening of duration of diarrhea from 3 to 4 days to 1.5 days. Treatment with fluoroquinolones can be a single dose or a 3-day course; both have the same efficacy.26 For invasive diseases, with bloody diarrhea or fever, and for persistent diarrhea with symptomatic treatment, a 3-day course of fluoroquinolone is recommended. The drug of choice in children is trimethoprim-sulfamethoxazole (TMP/SMX), long used for empiric therapy in the general population, but lately restricted because of increasing prevalence of resistance. Both options (fluoroquinolone and TMP/SMX) are highly effective for *E. coli*, *Shigella* and *Vibrio cholerae* infections, but their efficacy against *Salmonella* and *Campylobacter* is modest. Thus, in case of antimicrobial empiric treatment, the clinicians should be aware of the importance of taking stool samples for stool culture before starting antibiotics.

Worldwide, antibiotic resistance has increased for several classes of antimicrobials. Recently, more studies report an increase of partially fluoroquinolone-resistant strains of ETEC especially in India, Cambodia, Nepal, and Egypt (from 3.4% in 1996 to 15.8% in 1999).27 No high-level fluoroquinolone-resistant strain of ETEC has been reported, but careful monitoring of the antimicrobial susceptibility pattern worldwide is needed.

Resistance to fluoroquinolones has been also reported for *Campylobacter* (in Thailand and Spain), *Shigella* (India, Japan, and Bangladesh), and *Salmonella* (Taiwan, Spain, Southeast Asia, and Japan).28 Azithromycin is an alternative to fluoroquinolones, with a good activity against most enteric pathogens and comparable efficacy to fluoroquinolones for traveler’s diarrhea, shortening EAEC infection in adults and children, and efficacy in quinolone-resistant *Campylobacter* or *Shigella dysenteriae*.29 Also, its advantage compared with fluoroquinolones is a lower potential for interaction with other medication.

In May 2004, the U.S. Food and Drug Administration (FDA) approved the use of rifaximin for treatment of traveler’s diarrhea in patients older than 12 years infected with noninvasive *E. coli* strains. Rifaximin is a nonabsorbable antibiotic that is very well tolerated with no significant adverse effects. It has been shown to be as effective as ciprofloxacin for traveler’s diarrhea treatment and for diarrhea caused by EAEC infection. Its efficacy has not been shown for invasive pathogens such as *Campylobacter*, *Salmonella*, or *Shigella*.30 Rifaximin should not be used in pregnant women, lactating women, or children younger than 12 years.

For moderate to severe invasive diarrhea, empiric antibiotic treatment should be indicated only when there is no suspicion of *E. coli* O157:H7 (eg, bloody diarrhea in an afebrile patient). The drugs of choice are fluoroquinolones in adults and TMP/SMX in children; when there is a strong suspicion for fluoroquinolone resistance, azithromycin is recommended. Stool tests results may determine if a specific antimicrobial therapy is needed.

Watery diarrhea that lasts for more than 7 days should raise the concern of a protozoal infection such as *Giardia* or *Cryptosporidium*. Metronidazole efficacy against *Giardia* is about 90%,32 but cases of resistance have been reported worldwide. It is contraindicated in pregnant women when the treatment should be postponed until the stool test results.

*C. difficile* causes about 20% of cases of antibiotic-associated diarrhea, following the use of clindamycin, the second- and third-generation cephalosporins, and quinolones. Diarrhea is usually mild, and stopping the antibiotic resolves the illness in 2 to 3 days. For severe forms, metronidazole is the drug of choice. In case of failure, the option is vancomycin. In case of severe nosocomial diarrhea with high suspicion of *C. difficile* infection, the empiric antibiotic treatment can be started pending the results for toxin assay test. For relapse, a second course of metronidazole is recommended or tapering courses
of vancomycin or probiotics. Antimotility agents such as loperamide are contraindicated for the treatment of *Clostridium difficile* colitis because of the risk of toxic megacolon.

**TARGETED ANTIMICROBIAL TREATMENT**

The use of specific antimicrobial agents may be necessary in some cases due to an increase in antimicrobial resistance among some enteropathogens. Once the stool culture and sensitivity are available, treatment can be continued, changed, or discontinued accordingly.

*Salmonella* gastroenteritis does not require antibiotic treatment because of the risk of a carrier state. There are a few exceptions, such as in severe forms, very old or young patients, and immunocompromised or other patients with high risk of complications. Fluoroquinolones usually cover the non-typhi *Salmonella* infection, but the appearance of multidrug resistance may warrant the use of ceftriaxone in some parts of the world. Most cases of *Campylobacter* enteritis do not require antimicrobial treatment. However, in severe and prolonged cases of enteritis, septicemia, and other extraintestinal infections, antibiotics are needed. Antibiotics do not alter the course of the illness when started after 4 days after the onset of symptoms. Starting earlier than 3 days, erythromycin might reduce the severity of illness and the carriage of pathogens. Fluoroquinolones are also an option in case of susceptible *Campylobacter*; unfortunately, the use of fluoroquinolones in poultry feeds has increased resistance. Azithromycin remains the best alternative in case of resistance to fluoroquinolones, although in Thailand, azithromycin resistance was reported in 7% to 15% of *Campylobacter* isolates. A new treatment option that rises is tigecycline; its high in vitro activity against ciprofloxacin-resistant strains suggests a potential therapeutic role in the treatment of infections that involve *Campylobacter* spp. *Shigella* is a highly infectious agent, and antibiotic treatment is required for all patients with confirmed shigellosis. Antibiotics are necessary to reduce fecal excretion preventing further transmission, to manage infection (shortening the duration of fever, diarrhea, and toxemia), and to reduce the risk of complications. *S. sonnei* is at present the predominant species in the United States and other developed countries, but in developing countries and low socioeconomic conditions, *S. flexneri* is still the predominant serotype. The drug of choice for shigellosis is fluoroquinolones but lately, resistance to fluoroquinolones has been reported, especially among *S. flexneri* and *S. dysenteriae*. Alternative drugs like azithromycin, pimaviren, and ceftriaxone should further be evaluated for treatment of shigellosis. Because of increased resistance to TMP/SMX (80%–94%) in children with shigellosis, the options are azithromycin or parenteral ceftriaxone, especially in those who are hospitalized.

The most common protozoal infections are caused by *Giardia* and *Cryptosporidium*. For *Giardia*, the drug of choice is metronidazole. In refractory cases, a combination of quinacrine and metronidazole can be used with good results. *Cryptosporidium* infection requires treatment only in immunocompromised patients and in children. The FDA-approved nitazoxanide for treatment of *Cryptosporidium* diarrhea and *Giardia* infection in children also for the treatment of *Giardia* in adults. Nitazoxanide demonstrates a 67% and 71% rate of eradication of *Cryptosporidium* and *Giardia*, respectively, 7 to 10 days after initiation of a 3-day course of treatment. Amebiasis is treated with metronidazole or iodoquinol with the addition of paromomycin or tinidazole for the luminal phase.

**PREVENTION**

With 2 billion cases of acute diarrhea per year worldwide, prevention is important. Prevention should be focused on infection control and medical prevention.

Infection control by public health measures and improved sanitation are very important to decreased infectious diarrhea. A study conducted in Pakistan showed a decreased incidence of diarrhea among children living in households that received hand washing promotion with soap (53% lower incidence than in control group and 39% fewer days of diarrhea). In adults, sanitation is important in prevention of traveler’s diarrhea and includes hand washing, careful choice of food, and drinking bottled or boiled water. “Boil it, cook it, peel it, or forget it” is the best advice for any traveler, but data on the effectiveness of dietary precautions in preventing traveler’s diarrhea are inconclusive.

Medical prevention includes prophylactic drugs (absorbable/nonabsorbable antibiotics, bismuth subsalicylate), probiotics, and vaccines.

Antibiotic therapy is generally reserved for curative treatment of diarrhea caused by invasive pathogens. During recent years, the increasing number of traveler’s diarrhea cases (46% of the Americans traveling to developing countries) has required more effective prophylactic measures, and antibiotic therapy has been the most accessible method. Although the Centers for Disease Control and Prevention does not recommend antibiotic prophylaxis, it can be used in some instances, such as inflammatory bowel disease, renal diseases, and severe immunocompromised with high-risk illnesses.
Quinolones are the first choice with an efficacy of 80% to 100%. The drawbacks are antibiotic-induced diarrhea and the possibility of developing resistant pathogens (an increased resistance to quinolone for *Campylobacter* has been recognized in many areas of Asia).

Rifaximin has been approved for prophylaxis of traveler’s diarrhea. A randomized study in Mexico showed that rifaximin offers protection in 72% to 77% of cases in dosages of 200 mg/day, 400 mg/day, and 600 mg/day. The results are limited by the fact that most of the cases of traveler’s diarrhea are caused by *E. coli* in Mexico. Therefore, further studies are needed to assess its efficacy with other invasive pathogens.

The increasing incidence of antibiotic-resistant pathogens is a good incentive for investigating other prevention options. Bismuth subsalicylate is a nonantimicrobial agent that can provide a rate of protection of 65% for high-dose (2 tablets 4 times daily) and 40% for low-dose (1 tablet 4 times daily) against traveler’s diarrhea for periods up to 3 weeks. It is less effective than rifaximin for the prevention of traveler’s diarrhea and the required doses are less convenient. In terms of safety, the product is well tolerated, with side effects such as blackening of tongue and stool and very low incidence of tinnitus. Because bismuth subsalicylate interferes with the absorption of doxycycline, it should not be taken by travelers using doxycycline for malaria prophylaxis. Bismuth subsalicylate is not considered a recommendable option for prophylaxis in Europe because it is frequently administered and provides only moderate protection.

Probiotics are another alternative to conventional prophylaxis. Different members of the *Lactobacillus* genus have been used in controlled trials to assess their effectiveness in prevention of traveler’s diarrhea and antibiotic-associated diarrhea. In 1 study, the probiotic *Lactobacillus* GG was found to provide 49% protection against traveler’s diarrhea, but results with this agent and other probiotics as well have been variable and inconsistent. Lactobacilli and *S. boulardii* are both effective in preventing antibiotic-associated diarrhea, but *S. boulardii* seems to be the first choice. Treatment with probiotics is relatively safe but not risk-free. Several reports describe patients with fungemia in whom the probiotic origin was proven by DNA fingerprinting, and bacteremia with *Lactobacillus* GG. Recombinant probiotics capable of binding the toxin have shown a considerable potential and may be the next step for the prophylaxis of ETEC-induced traveler’s diarrhea.

**VACCINATION**

The most effective way to prevent infectious diseases is vaccination. For some pathogens there are already available vaccines, for others it is a work in progress.

**Rotavirus**

Given the rotavirus burden, developing a vaccine against rotavirus is a high priority. RotaShield was the first rotavirus vaccine approved in the United States but because of a presumable association with intussusception, it was taken off the market after a year. In 2006, RotaTeq, a new live reassortant virus vaccine, was approved by the FDA to prevent rotavirus gastroenteritis in infants. The vaccine was found to prevent 74% of all rotavirus gastrointestinal cases and 98% of the severe cases. RotaTeq also prevents approximately 96% of hospitalizations due to rotavirus gastroenteritis. It seems to be well tolerated and is not associated with increased risk of intussusception.

**Norovirus**

There are undergoing studies on oral vaccine against norovirus, but the results show modest antibody titers; further studies are needed to evaluate its protective value.

**Salmonella typhi**

Typhoid fever, causing more than half a million deaths annually, is of great risk to travelers in South Asia and South America. There are 2 vaccines commercially available, but the recommendation is just for international travelers. The attenuated Ty21a is administered orally and the liquid protection is of 77% over 7 years. The purified Vi PS is a parenteral vaccine, demonstrating a 69% protective efficacy. Live vaccines are also undergoing clinical studies.

**Cholera**

Currently, there are 2 types of vaccines available. The inactivated vaccines confer 50% to 53% protection over 3 years. The live attenuated vaccine, CVD 103-HgR, shows efficacy of 80% against all diarrhea and 90% against severe diarrhea 3 months after vaccination. The recommendation is for travelers and prevention of cholera outbreaks in developing countries.

Although many studies are in process at this point, there are no available vaccines against *E. coli*, *Shigella* species, or *Campylobacter* species.

**REFERENCES**


