Management of Acute Infectious Diarrhea

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

JCOM CME

CME jointly sponsored by Wayne State University School of Medicine and JCOM

The following article, "Management of Acute Infectious Diarrhea" is a continuing medical education (CME) article. To earn credit, read the article and complete the CME evaluation on pages 390 and 391.

Program Audience

Primary care physicians.

Educational Needs Addressed

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 (0.72 episodes per person-year), with the elderly at greatest risk. 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.

Educational Objectives

After participating in this CME activity, primary care physicians should be able to

1. Describe the epidemiology of acute infectious diarrhea
2. Describe the approach to clinical assessment of the patient with acute infectious diarrhea
3. Know the steps that characterize early supportive treatment of acute infectious diarrhea
4. Discuss the appropriate use of antimicrobial therapy in acute infectious diarrhea
5. Understand the strategies used to prevent acute infectious diarrhea

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 [1] 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%) [2]. 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 [3]. 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 [4]. Thus, it is important for clinicians to understand the management of acute diarrhea with respect to evaluation, treatment, and prevention [5].

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 (**Table 1**). 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 [6–8].

Most acute infectious diarrhea is self-limited, lasting less than 3 days, with approximately 80% attributed to viruses. 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.

From the University of Washington School of Medicine, Seattle, WA.

extremely useful opportunity for housestaff to learn about the systems approach to quality improvement and at the same time attempt to build a more effective application. Although it represents an unusual approach to fulfilling the ACGME competencies, this path may be useful to other organizations. Increasingly, the face of education is changing, as didactic lectures, bedside teaching, and morbidity and mortality conferences compete with case-based learning modules, virtual patient encounters, and quality improvement grand rounds for time on an already busy educational calendar. As academic medical centers face the challenge of CIS implementation, medical educators can harness the energy and creativity of this large-scale organizational change to create new teachable moments.

Corresponding author: Amar A. Desai, MD, MPH, Div. of Nephrology, Box 0532, 513 Parnassus Ave., HSE 672, San Francisco, CA 94143.

References

1. Kohn LT, Corrigan JM, Donaldson MS, editors. To err is human: building a safer health system. Washington (DC): National Academy Press; 2000.
2. Institute of Medicine, Committee on Quality of Health Care in America. Crossing the quality chasm: a new health system for the 21st century. Washington (DC): National Academy Press; 2001.
3. Shojania KG, Grimshaw JM. Evidence-based quality improvement: the state of the science. Health Aff (Millwood) 2005;24:138–50.
4. Bates DW, Gawande AA. Improving safety with information technology. N Engl J Med 2003;348:2526–34.
5. Kawamoto K, Houlihan CA, Balas EA, Lobach DF. Improving clinical practice using clinical decision support systems: a systematic review of trials to identify features critical to success. BMJ 2005;330:765.
6. Chertow GM, Lee J, Kuperman GJ, et al. Guided medication dosing for inpatients with renal insufficiency. JAMA 2001;286:2839–44.
7. Hunt DL, Haynes RB, Hanna SE, Smith K. Effects of computer-based clinical decision support systems on physician performance and patient outcomes: a systematic review. JAMA 1998;280:1339–46.
8. Raschke RA, Gollihare B, Wunderlich TA, et al. A computer alert system to prevent injury from adverse drug events: development and evaluation in a community teaching hospital [published erratum appears in JAMA 1999;281:420]. JAMA 1998;280:1317–20.
9. Johnston ME, Langton KB, Haynes RB, Mathieu A. Effects of computer-based clinical decision support systems on clinician performance and patient outcome. A critical appraisal of research. Ann Intern Med 1994;120:135–42.
10. Koppel R, Metlay JP, Cohen A, et al. Role of computerized physician order entry systems in facilitating medication errors. JAMA 2005;293:1197–203.
11. Ash JS, Berg M, Coiera E. Some unintended consequences of information technology in health care: the nature of patient care information system-related errors. J Am Med Inform Assoc 2004;11:104–12.
12. Geyer S. Physicians: the key to IT success. Trustee 2004;57 (2):6–10.
13. Scott JT, Rundall TG, Vogt TM, Hsu J. Kaiser Permanente's experience of implementing an electronic medical record: a qualitative study. BMJ 2005;331:1313–6.
14. Accreditation Council for Graduate Medical Education. Outcome project: general competencies. Available at www.acgme.org/outcome/comp/compFull.asp. Accessed 20 Jun 2006.
15. Teich JM, Glaser JP, Beckley RF, et al. Toward cost-effective, quality care: The Brigham Integrated Computing System. Proceedings of the 2nd Annual Nicholas E. Davies CPR Recognition Symposium. Bethesda (MD): CPRI-HOST; 1996.
16. Achtmeyer CE, Payne TH, Anawalt BD. Computer order entry system decreased use of sliding scale insulin regimens. Methods Inf Med 2002;41:277–81.
17. Van Eaton EG, Horvath KD, Lober WB, et al. A randomized, controlled trial evaluating the impact of a computerized rounding and sign-out system on continuity of care and resident work hours. J Am Coll Surg 2005;200:538–45.

Among the protozoa, *Giardia, Cryptosporidium, Entamoeba histolytica*, and *Cyclospora* are the most common, and can have a prolonged course in immunosuppresed 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 (**Figure**).

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 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 (**Table 2**).

Table 1. Common Causes and Associated Risk Factors for Infectious Diarrhea

Etiology	Annual Cases by Stool Culture per 100,000 Population (U.S.)	Risk Factors
Norovirus	8500 [9]	Winter outbreaks in adults, raw oyster consumption, cruise ships
Rotavirus	1100 [9]	Winter outbreaks in children under 2 years
Giardia	750 [9]	Contaminated water; recreational exposure in lakes, rivers, or swimming pools; day care centers
Salmonella	14.7 [10]	Raw eggs, undercooked poultry and turkey, unrefrigerated dressing, pet reptiles, family members with *Salmonella*
Campylobacter	12.9 [10]	Undercooked poultry, contaminated milk, tuna salad
Shigella	5.1 [10]	Contaminated water and vegetables
E. coli O157:H7	0.9 [10]	Undercooked beef, unpasteurized milk, apple cider, visits to animal farms or petting zoos
C. difficile	NA	Antiblotic use

NA = not available.

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

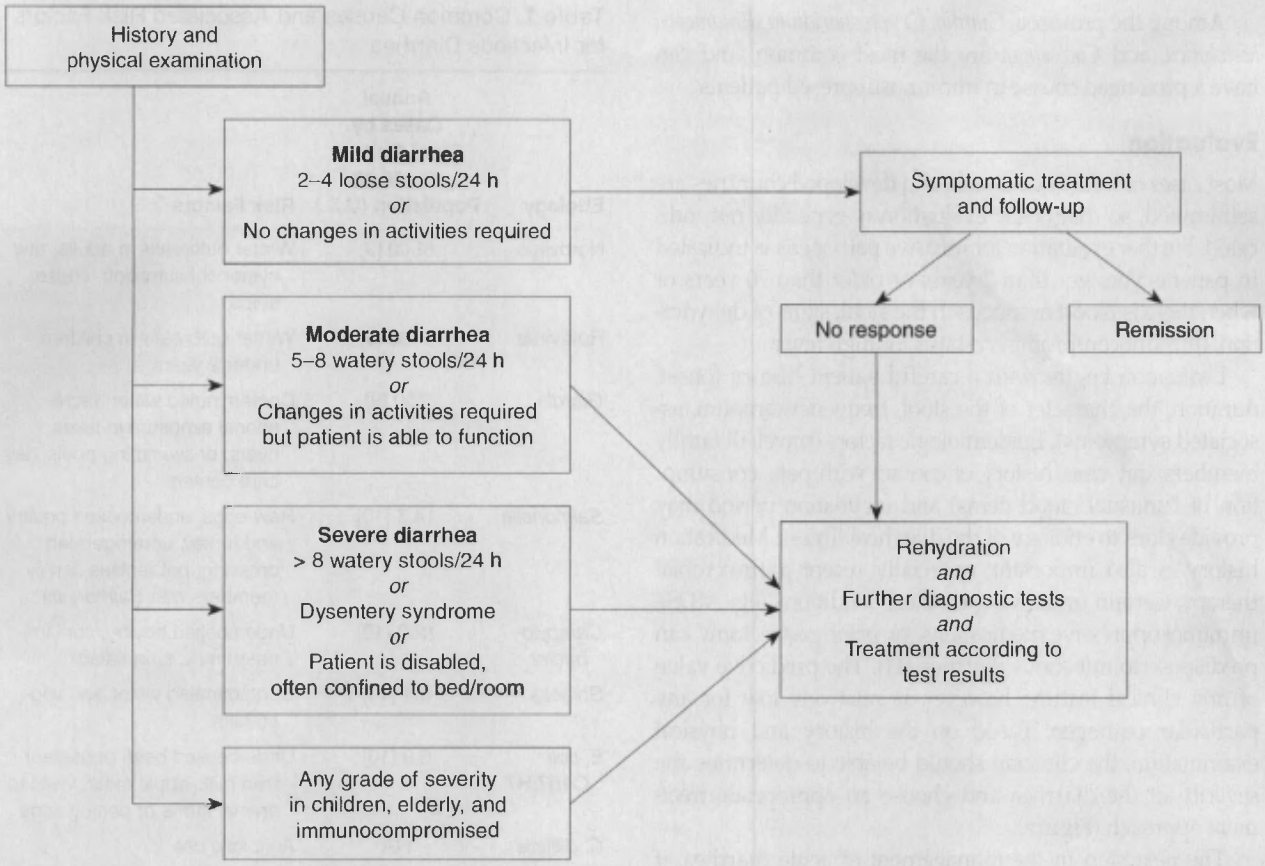

Figure. Evaluation and treatment of infectious diarrhea according to severity.

starch-containing electrolyte solution. Studies have shown that glucose-containing solutions help the absorption of sodium and water through a mechanism of cotransport 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 [16]. 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 [17].

The introduction of hypo-osmotic solution, resistant starch and glutamine [18] 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, racecadodril, 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 [19]. 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 [20]. 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 [21]. 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 [22].

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 [23]. 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 [24]. 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), enteroaggregative *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].

Table 2. Diagnostic Tests for Specific Pathogens

Pathogen	Diagnostic Test
E. coli O157:H7	EIA kit for Shiga toxin, confirmed by culture on sorbitol-MacConkey agar
Vibrio cholerae	Dark field microscopy, confirmed by culture on thiosulphate-citrate-bile salts medium
Salmonella, Campylobacter, V. parahemolyticus	RT-PCR
C. difficile	Stool assay for toxin
Giardia	Stool antigen test
Giardia, Cryptosporidium	Immunofluorescent antibody test
Giardia, Cryptosporidium, Entamoeba hystolytica	Stool ova and parasites
Rotavirus	Rapid antigen detection in the stool followed by EIA for further characterization
Norwalk, Norwalk-like virus	EIA, RT-PCR
Yersinia	Cold enrichment medium

EIA = enzyme immunoassay; RT-PCR = reverse transcription-polymerase chain reaction.

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* [29] or *Shigella dysenteriae* [30]. 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 showed 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* [31]. 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 *C. 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 *nontyphi 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 [28]. 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 [33]. 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 [34].

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 [35]. 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, pivmecillin, and ceftriaxone should further be evaluated for treatment of shigellosis [30]. 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 [36].