Treating Foodborne Illness

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KEYWORDS

• Antiemetics • Antidiarrheals • Diarrhea • Antibiotics

KEY POINTS

- Most foodborne illnesses are self-limited without treatment, but may have important long-term consequences in immune-compromised hosts and children.
- Oral rehydration therapy and other supportive measures have a significant impact on morbidity and mortality caused by enteric infections.
- Randomized, controlled trials have shown that antibiotic treatment improves outcomes in selected foodborne infections and specific hosts, although in general the benefits are relatively mild.

INTRODUCTION

Foodborne illnesses are among the most frequent diseases experienced worldwide. Most cases in developed countries are mild and self-limited, but severe and life-threatening complications do occur, even in previously healthy people. However, the greatest burden of disease is in developing areas, where gastrointestinal infections are a leading cause of mortality in early childhood and in patients with human immunodeficiency virus (HIV)/AIDS. Although many of these infections are capable of being spread through person-to-person contact, contaminated food and particularly water remain important transmission vehicles.

In addition to infectious agents, food and water can be the vehicle for transmission of illness caused by toxins, including those that originate from microbes (eg, *Staphylococcus aureus* enterotoxins, botulinum toxin) and environmental sources (eg, heavy metals, pesticides, mushrooms). This review focuses on those foodborne illnesses of microbial origin, but treating physicians need to remain aware of the possibility of environmental toxin ingestion, because the therapeutic and epidemiologic implications can be different.

PATIENT EVALUATION OVERVIEW

As a general rule, it is difficult if not impossible to definitively identify the specific cause of a foodborne illness from the clinical presentation alone. However, a thorough history (including symptoms, exposure, and timing) can almost always allow the treating

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clinician to identify the presenting syndrome, which guides the appropriate diagnostic and therapeutic algorithms. There are a few syndromes that are so characteristic that they can be diagnosed with high accuracy from the history alone (for example, ciguatera after consumption of barracuda, or norovirus infection during an institutional outbreak).

The major clinical syndromes of foodborne illness and some of the leading causes include:

- Acute bacterial toxin ingestion. The patient who ingests food that was improperly handled or stored, allowing for growth of toxigenic organisms, generally becomes ill 1 to 8 hours later with the abrupt onset of severe nausea and vomiting, sometimes followed by abdominal pain/cramps and watery diarrhea. Fever is usually absent and symptoms should resolve within 24 hours.[1] In some cases (such as with nonemetic *Bacillus cereus*), cramping and diarrhea are the predominant symptoms.[2] Many patients who present with this syndrome are already better by the time they are seen by a care provider. Often, there is a clear food exposure (such as a picnic or other informal gathering) and others attending the same event have a similar illness at the same time. The major causes are *Staphylococcus aureus*, *Bacillus cereus*, and *Clostridium perfringens*, and commonly implicated foods include prepared salads that are not kept cold enough during storage.
- Viral gastroenteritis. This category contains similar illnesses caused by a growing number of recognized viruses. Although most exposure is through direct contact, food can also be a source when it is handled by any person shedding virus.
  - Norovirus and related viruses. A patient exposed to norovirus generally presents after an incubation period of 12 to 48 hours with abrupt onset of nausea and vomiting followed by watery diarrhea.[3] Norovirus infections can easily be confused with acute bacterial toxin ingestion, but rather than resolving within a few hours, symptoms generally last for 1 to 3 days, and can be more prolonged in young children and the elderly. Many patients have an obvious exposure to a sick family member or coworker, but during annual winter outbreaks, there may be no clear source of the infection. Several more recently described enteric viruses can produce a similar syndrome.
  - Rotavirus syndrome. Rotavirus is most common and most dangerous in children, in whom it typically presents with diarrhea and fever, which can lead to fatal dehydration if not treated appropriately. Symptoms may be prolonged,[4] although the mean is about 6 days.[5] Immunity is not lifelong and rotavirus infection can present in healthy adults. An extended duration of symptoms and relative lack of vomiting can sometimes help to distinguish rotavirus from norovirus.[6]
- Microbial neurotoxin exposure. This term refers to ingestion of stable, preformed toxins produced by bacteria or protozoa that concentrate in foods and disseminate in the individual after ingestion. In a few of these cases, there is an acute gastrointestinal syndrome of nausea, vomiting, intestinal pain, or diarrhea immediately after ingestion, but generally the predominant symptoms occur after the toxin reaches its target cells. Some important examples include:
  - Botulism. *Clostridium botulinum* is a common environmental contaminant, and forms spores that are resistant to boiling. When canned products are not sterilized properly, the organism can germinate and produce the highly lethal botulinum toxins, which impair neurotransmitter function in motor neurons, leading to paralysis. The disease usually presents with descending paralysis,

beginning with the cranial nerves, and if not appropriately recognized and treated with antitoxin, can lead to diffuse paralysis, requiring respiratory support for a period of weeks.[7] The major item in the differential diagnosis is Guillain-Barré syndrome.

- Ciguatera. Ciguatoxins are a family of neurotoxins produced by ocean dinoflagellates that become concentrated as they move up the food chain, concentrating in tissues of large predator fish (particularly barracuda, red snapper, and other tropical and subtropical species). After an acute nonspecific gastrointestinal syndrome, ciguatera progresses to neurologic symptoms, which may include neuropathic pain, cold allodynia, headache, ataxia, and confusion.[8] Symptoms generally last for days to weeks (or occasionally years), and clinical relapses can occur after periods of well-being.
- Scombroid. Histidine in improperly stored fish can be converted to bioactive histamine, which is relatively heat stable. Patients who ingest large quantities of histamine can present with acute onset of headache, flushing, tachycardia, and occasionally diarrhea and nausea. These symptoms are self-limited to a few hours to days.

- Small intestinal infection. Infectious agents that colonize the small intestine can produce symptoms through toxin production or local tissue invasion.
  - Nontoxigenic organisms (eg, *Giardia*, *Cryptosporidium, Cyclospora*) frequently lead to an inflammatory response that causes villous blunting, fluid hypersecretion, and impaired absorption. This response produces a syndrome of abdominal cramping, bloating, flatulence, and watery or loose stools, occasionally with a greasy appearance caused by fat malabsorption. Nausea may be present, but vomiting is generally less prominent. Symptoms may persist for days or weeks, depending on the organism. A history of consumption of untreated water (eg, from lakes or streams) or travel to a developing area is often present in these cases.
  - Toxin-producing bacteria (such as *Vibrio cholerae* and enterotoxigenic *Escherichia coli*) also produce mild mucosal inflammation, but most symptoms are caused by effects of the toxins on the epithelium, leading to fluid hypersecretion. Patients typically present with acute onset of nausea, occasionally vomiting, and high-volume, watery diarrhea. Fever, if present, is low-grade. If untreated, the illness is short-lived (typically <3 days), but can be fatal if appropriate rehydration is not provided.
- Inflammatory diarrhea. Invasive infections can present with a nonspecific diffuse gastroenteritis or a more characteristic dysentery syndrome. The symptoms are not specific enough to provide a diagnosis without microbiological investigation.
  - Inflammatory enterocolitis typically presents as diarrhea, significant abdominal pain, and fever. Nausea and vomiting may be present but are typically not the major symptoms. Patients may pass frequent, low-volume stools with blood or pus, or may have larger watery stools. The presence of a high fever and duration for more than 48 hours can usually help to distinguish this syndrome from viral gastroenteritis. Although foodborne bacteria such as *Salmonella* and *Campylobacter* are common causes, *Clostridium difficile* can present in an identical fashion and must be considered in any patient with recent hospitalization, antibiotic use, or gastrointestinal surgery.
  - Dysentery refers to colonic infection presenting with tenesmus and bloody or mucusy, small-volume stools, typically with fever and considerable discomfort. Although this infection is classically associated with *Shigella* or *Entamoeba histolytica* infection, it is neither sensitive nor specific for these

organisms, but clearly warrants evaluation and appropriate treatment. The differential diagnosis includes ulcerative colitis and sexually transmitted proctitis.

- Hemorrhagic colitis. This syndrome classically consists of acute onset of watery diarrhea and abdominal cramps and tenderness, progressing to frankly bloody diarrhea and severe abdominal pain, but with a conspicuous absence of fever in most cases.[9,10] Although intestinal symptoms are self-limited, the disease can progress to hemolytic-uremic syndrome (HUS) with potentially fatal consequences. There is no clear evidence for benefit, and some evidence for harm, with the use of antibiotics in this syndrome, which makes it important to recognize (discussed in detail later).
- Enteric fever. *Salmonella enterica* serovar Typhi and related strains can be transmitted through food and water after contamination by infected individuals. After ingestion, the bacteria invade the intestinal epithelium and take up residence in macrophages, which disseminate the organism. The typical presentation involves fever, abdominal discomfort, headache, and other nonspecific symptoms.[11] These symptoms often progress in a stepwise fashion, becoming more severe until either resolution or fatal complications result. Because the symptoms are so nonspecific, enteric fever should be considered in the differential diagnosis of fever in endemic areas or travelers to these areas, in whom it can be confused with malaria or dengue fever, particularly early in its course.
- Other pathogen-specific conditions. There are certain pathogens that are foodborne but do not fit easily into the other categories. Some examples are:
  - *Listeria monocytogenes.* This gram-positive bacillus grows well at refrigerator temperatures and is classically associated with ingestion of unpasteurized cheese or contaminated cold cuts. It frequently causes a nonspecific diarrheal illness, but this can be followed by bacteremia with meningitis or endocarditis, particularly in immune-compromised hosts, and fetal loss in pregnant women.
  - *Yersinia enterocolitica.* This organism can present as a nonspecific inflammatory enterocolitis, but has a propensity to cause mesenteric adenitis that can mimic acute appendicitis or ileal Crohn disease.
  - Helminthic infections. Various cestodes (tapeworms), trematodes (flukes), and nematodes (roundworms) are transmitted primarily through contaminated food or water. They are described in **Table 1**.
  - *Toxoplasma gondii.* This apicomplexan protozoon causes systemic infection after ingestion of infectious cysts. This infection can occur through 2 means. Food or water can be directly contaminated with oocysts excreted by cats, which are the definitive host for the organism. In addition, other animals that have ingested toxoplasma oocysts can develop infectious muscle cysts, allowing for transmission through contaminated meat. Although toxoplasmosis is benign in most people, immunocompromised hosts are at particular risk of serious consequences, and primary infection during pregnancy can lead to severe fetal anomalies.

NONPHARMACOLOGIC TREATMENT OPTIONS

Most foodborne illnesses are self-limited and require only symptomatic treatment, but there are certain diseases in which specific therapy is indicated by either randomized, controlled trial (RCT) data or expert opinion based on case series in the setting of severe illness. In the case of diarrheal foodborne infections, even in the absence of effective specific therapy, it is important to provide supportive treatment whenever possible to prevent potentially fatal complications, which include:

Table 1
Treatment of foodborne helminthic pathogens

Pathogen	Presentation of Infection	Complications if Untreated	Recommended Treatment
Nematodes			
Trichinella spp	Muscle cysts: intense pain, orbital edema	Rare cardiac or neurological involvement	Supportive care; albendazole ± corticosteroids
Ascaris lumbricoides	Usually asymptomatic	Obstruction with heavy worm burden, biliary sepsis	Single-dose pyrantel, levamisole, mebendazole, albendazole
Trichuris trichiura	Usually asymptomatic	Heavy infestation can lead to rectal prolapse	Mebendazole
Anisakis	Acute nausea, vomiting, abdominal pain	Self-limited	Worm may self-expel as a result of vomiting; can be extracted endoscopically
Cestodes			
Taenia solium	Adult phase: asymptomatic; cyst phase: seizures	Parenchymal brain calcifications leading to seizure foci	Adult worm: praziquantel Cysts: early phase: albendazole or praziquantel, often with steroids Late phase: treatment benefit unclear
Taenia saginata, Hymenolepis nana, Diphyllobothrium latum, and others	Generally asymptomatic	Rarely, vitamin deficiencies; growth impairment in children	Praziquantel or niclosamide
Echinococcus spp	Gradually expanding cyst	Compression of surrounding viscera; anaphylaxis caused by cyst rupture	Surgical removal, PAIR (percutaneous aspiration, injection, reaspiration). Treatment with albendazole or praziquantel alone occasionally successful
Trematodes			
Paragonimus westermani	Cough, dyspnea	Can mimic tuberculosis	Praziquantel
Fasciola hepatica	Typically asymptomatic	Biliary scarring, obstruction	Triclabendazole
Liver flukes	Acute phase nonspecific; chronic phase asymptomatic	Carcinoma of biliary tract	Praziquantel

- Volume depletion
- Electrolyte disturbances
- Nutritional deficiencies (particularly in children)
- Sepsis
- HUS

Oral Rehydration Therapy

The best studied of these nonpharmacologic treatments is oral rehydration therapy (ORT). ORT has been shown in numerous RCTs to improve outcomes in severe diarrheal illnesses, particularly cholera. Choleratoxin and related bacterial enterotoxins act by inducing hypersecretion of salts and water by intestinal crypt cells. The villi and their ability to absorb fluid are relatively preserved. Villous epithelial cells express several transport proteins that facilitate nutrient and salt absorption; one of the most highly expressed is SGLT-1, which cotransports 1 glucose molecule and 2 Na^+ ions, bringing more than 200 water molecules from the lumen into the enterocyte, leading to considerable water absorption.[12] Related cotransporters for other carbohydrates and amino acids are also active. As a result, administration of an ORT containing glucose and Na^+ in the appropriate concentrations (close to a 1:1 Molar ratio) leads to water absorption that can effectively balance out the hypersecretion, improving diarrhea and maintaining the patient's health until an appropriate immune response (or antibiotic treatment) clears the infecting organism. Standard ORT solutions also contain bicarbonate or citrate to correct acidosis and potassium to replace intestinal losses.

Progressive refinements in ORT have been made since its initial discovery. Current recommendations are found in **Table 2**. In particular, a reduction in the osmolarity has been recommended since 2004 based on several strong studies showing better control of diarrheal volume, albeit with occasional asymptomatic hyponatremia.[13,14] In addition, glucose polymers (eg, rice or wheat starch) have been shown in several large RCTs (and confirmed by a meta-analysis) to be superior to glucose in terms of duration of symptoms and need for rescue intravenous fluids.[15] However, some of these studies compared starch-based oral rehydration solution (ORS) with high-osmolarity glucose-based ORS. In addition, the differences between solutions are generally more pronounced in cholera than in other dehydrating diarrheal illnesses.

If the World Health Organization (WHO) ORS salts are not available, a simple home recipe is found in **Table 2**. The solution should taste similar to tears. Plain water or water with a bit of salt added are preferable to hyperosmolar home remedies like ginger ale or apple juice, which contain a high carbohydrate/sodium ratio, and can lead to greater intestinal fluid losses. Use of hypo-osmolar solutions can lead to asymptomatic hyponatremia, but this is preferable to potentially life-threatening dehydration.

Other Nonpharmacologic Treatments for Foodborne Illness

- Micronutrients.
  - Zinc deficiency is common in poor, developing areas with limited dietary diversity. Although young infants are relatively replete from maternal sources, older infants and children can suffer considerable gastrointestinal losses because of recurrent diarrheal episodes, leading to frank deficiency and resulting hypersusceptibility to infectious diarrhea. A recent meta-analysis of zinc supplementation trials[16] found that overall there was a small but statistically significant improvement in the duration of diarrhea with zinc administration compared with placebo. This effect was most pronounced in children older than 6 months

Table 2
Recommended oral rehydration solutions http://www.who.int/maternal_child_adolescent/documents/fch_cah_06_1/en/

Source	Carbohydrate	Sodium Chloride	Other Salts	Indication
Recommended				
World Health Organization reduced-osmolarity ORS	Glucose 13.5 g/L (75 mM)	2.6 g/L (75 mM Na^+, 65 mM Cl^-)	KCl 1.5 g/L (20 mM K^+); trisodium citrate 2.9 g/L (10 mM citrate)	Recommended for all diarrheal illness
Acceptable range	≥Na^+ concentration but <111 mM	60–90 mM Na^+; 50–80 mM Cl^-	15–25 mM K^+; 8–12 mM citrate	If World Health Organization solution not available
Starch-based ORS	50–80 g/L cooked rice powder	2.6 g/L (75 mM Na^+, 65 mM Cl^-)	KCl 1.5 g/L (20 mM K^+); trisodium citrate 2.9 g/L (10 mM citrate)	More effective than standard ORS in cholera
Home-made ORS	2 level tablespoonsful sugar (30 g)	Half a level teaspoonful salt (2.5 g)	Add 0.5 c. (125 mL) orange juice or mashed banana	Per liter of clean water
Not Recommended				
Sugared carbonated soft drink	700 mM	2 mM	Low in K^+	Osmolarity too high: can exacerbate dehydration
Apple juice	690 mM	3 mM	32 mM	Same
Gatorade	255 mM	20 mM	3 mM	Hyperosmolar
Tea	As desired	0	0	Inadequate electrolyte replacement

and in studies in Asia, where zinc-deficient diets are more common. No overall effect on mortality was identified, and zinc administration was associated with increased vomiting in children. There remains insufficient evidence to know whether zinc supplementation is beneficial in developed areas.[17]

- Vitamin A is another micronutrient frequently low in developing areas, and deficiency is associated with xerophthalmia and blindness as well as childhood mortality. Several RCTs have examined the benefits of vitamin A supplementation to improve childhood mortality, and a meta-analysis found a significant improvement in overall mortality and specifically mortality caused by diarrhea.[18] However, use of vitamin A in the treatment of acute diarrheal episodes is not beneficial.[19]

- Feeding. Adults and older children with enteric infection often suffer from anorexia during their illness, and may experience transient weight loss, but generally recover quickly. The same is not true for young children, in whom repeated episodes of diarrheal illness, particularly persistent episodes (those lasting >14 days), can lead to permanent deficits in growth and even cognitive development.[20,21] Specific feeding approaches to prevent this situation have not yet been identified. Infants are at even greater risk, because they cannot control their own food and fluid intake. Cultural practices such as withholding

breastfeeding during diarrheal illness can lead to fatal consequences, and parents should be encouraged to continue feeding infants normally as tolerated.[22]

- Infection control and public health considerations. Many foodborne infections are highly transmissible, and efforts should be made to limit spread, particularly in health care settings. The Society for Healthcare Epidemiology of America recommends that all hospitalized patients who develop diarrhea be placed on contact isolation (gown and gloves) and in a private room where possible, to reduce the spread of *Clostridium difficile*.[23] Often, more intensive measures such as closure of wards and banning of visitation are required during norovirus outbreaks.[3] In addition, many enteric infections must be reported to public health authorities. This strategy is instrumental for outbreak identification and also to advise people at risk of transmission (such as food service workers) when it is safe for them to resume work.
- Probiotics. There has been considerable interest in the use of nonpathogenic bacteria and yeast supplementation to prevent or treat infectious diarrhea. It is hypothesized that these organisms would colonize the intestine heavily to reduce the environmental niche for the offending pathogen, and many clinical studies have been performed. There is no solid evidence for a clear benefit of any specific probiotic preparation in the treatment of foodborne illness, although some have been proved to improve diarrheal symptoms in specific situations (such as irritable bowel syndrome[24] and antibiotic-associated diarrhea in children[25]). There is some trial evidence that addition of *Lactobacillus* GG to ORS can improve pediatric infectious diarrhea,[26] but not enough to warrant a universal recommendation.[22]

PHARMACOLOGIC TREATMENT OPTIONS

Pharmacologic treatments for foodborne infections include drugs used for symptomatic benefit, such as antiemetics, antispasmodics, and antimotility agents, and drugs used specifically to treat infection. Most of the latter are antimicrobials, although there are some agents that are not antibiotics per se, but either facilitate the activity of antibiotics (such as proton pump inhibitors in the treatment of *Helicobacter pylori* infection) or target microbial toxins (such as cholestyramine used in the treatment of *Clostridium difficile* infection). Antimicrobials are discussed later for each specific infectious syndrome.

Drugs used specifically to treat the symptoms of foodborne illness include:

- Antimotility agents. One of the most troubling symptoms of foodborne illness is diarrhea, particularly when prolonged. There are several available agents that act to reduce stool frequency, volume, and urgency, which can allow patients to carry out their daily activities more comfortably. These drugs are effective, particularly in relatively mild illness. For example, in combination with antibiotics, they significantly shorten the duration of illness in travelers' diarrhea.[27] However, they are not effective in high-volume secretory diarrhea (eg, cholera) or in inflammatory colitis. They are relatively contraindicated during inflammatory diarrheal illness because of a risk of potentially fatal complications such as toxic megacolon.[28] For example, rare fatal cases of *Campylobacter* infection were reported in association with antimotility drug use.[29] Moreover, use of antimotility drugs has been associated with worse outcomes (including HUS) in hemorrhagic colitis.[30] However, a retrospective review of patients with *Clostridium difficile* infection found no harmful effect of antimotility agents when coadministered with metronidazole or vancomycin.[31] The most recent Infectious Diseases Society of

America guidelines (2001) recommend avoiding these agents during bloody diarrhea or proven infection with enterohemorrhagic *E coli*.

Specific antimotility agents include:

- Loperamide. This opioid agonist acts largely on μ-opioid receptors in the intestinal myenteric plexus, reducing intestinal motility and increasing transit time. This situation can reduce cramping and allows greater contact time with the colonic mucosa, reducing diarrheal volume.[32] It is available over the counter as a generic medication in many countries (including the United States and Canada) for treatment of adults and children older than 2 years. Side effects include constipation and bloating; in addition, coadministration with *P*-glycoprotein inhibitors (such as quinidine) can lead to accumulation in the central nervous system, with central opioid activity as a result, leading to sedation and analgesia.
- Diphenoxylate/atropine. This combination drug, marketed for years as Lomotil, combines an opioid agonist (diphenoxylate) with the anticholinergic agent atropine. It is generally reserved for more chronic intestinal disorders rather than foodborne illness, because of its increased side effects, which include dry mouth, blurry vision, and sedation from the anticholinergic action.
- Opiates. All opiate agonist drugs have the potential to decrease motility and reduce diarrhea as a result of their effects on intestinal neurons. Generally, their sedating qualities and potential for dependence preclude their routine use for foodborne illness in modern times, although preparations such as paregoric and tincture of opium were used through much of the twentieth century and are still available in some countries.

- Antispasmodics. These drugs are muscarinic cholinergic antagonists that act to reduce the intensity of smooth muscle contractions in the intestinal wall. These drugs can provide relief from pain caused by abdominal cramping, but are also associated with anticholinergic side effects, and the potential to induce toxic megacolon, although there are no reports of this occurring in infectious diarrhea. Currently used drugs in this class include butylscopolamine (Buscopan), hyoscyamine, dicycloverine, and the older drugs scopolamine and atropine.
- Bismuth salts. Bismuth subsalicylate is marketed worldwide as an agent to treat diarrhea, nausea, and dyspepsia. Its precise mechanism of action is unknown, but it does have antisecretory, antiinflammatory, and antibacterial properties. It is more effective than placebo in the prevention of travelers' diarrhea,[33,34] although antimicrobials are preferred for treatment based on clinical trial evidence.[35] It is a weak antacid but can reduce gastric discomfort, possibly because of the antiinflammatory activity of the salicylate moiety. Because it contains a salicylate, it should not be used in children with fever, because of risk of Reye syndrome. It also causes black discoloration of stool.
- Other antidiarrheals. Clay minerals have been used for years to treat diarrhea, and a combination of kaolin and pectin (Kaopectate) was marketed in the United States. This antidiarrheal was later (around 1990) changed to a different mineral, attapulgite. However, a review by the US Food and Drug Administration in 2003 found insufficient evidence of efficacy of attapulgite in earlier studies and withdrew approval for the drug as an antidiarrheal. The manufacturer changed the formulation in the United States to contain bismuth subsalicylate instead of attapulgite, although the latter is still available in Canada. Racecadotril is an enkephalinase inhibitor marketed in Europe but not North America; there is evidence of benefit in childhood diarrhea.[36,37]

- Antiemetics. Nausea and vomiting can be the most unpleasant symptoms of foodborne illness. They can also impair the ability to use oral rehydration, leading to hospital admissions for intravenous therapy, particularly in children. There are many different classes of antiemetics for various indications, although surprisingly few have been studied in acute gastroenteritis.
  - 5-HT_3 receptor antagonists. These drugs inhibit serotonin signaling in the brain chemoreceptor trigger zone, impairing the central nausea/vomiting response. They also inhibit serotonin signaling in the enteric nervous system. They were initially marketed for the prevention and treatment of chemotherapy-induced emesis, but because of their safety and efficacy, their use has expanded to other indications. The only member of this class studied in foodborne illness is ondansetron, which has been shown in several RCTs to effectively improve nausea and vomiting in children with gastroenteritis.[38] Recent meta-analyses have confirmed that this drug is safe and effective in reducing vomiting, need for intravenous hydration, and immediate hospitalization in children with acute gastroenteritis.[39,40] It can be administered orally or intravenously. Some studies have shown an increase in diarrhea, but this has been inconsistent.
  - Dopamine antagonists. Before the introduction of 5-HT_3 antagonists, these antagonists were the mainstay of antiemetic therapy, although they have fallen out of favor because of increased side effects, which include sedation and rare extrapyramidal neurologic symptoms (akathisia, muscle stiffness). Drugs in this class specifically used as antiemetics include prochlorperazine, domperidone, and metoclopramide. Metoclopramide also has prokinetic activity. Metoclopramide was shown to be equivalent to ondansetron in 1 RCT in children,[41] although the study was underpowered to show a significant difference. One RCT in adults found prochlorperazine to be slightly better than ondansetron in nausea scores but equivalent in terms of reducing vomiting.[42]
  - Antihistamines. Histaminergic neurons are found in the emesis pathway from the chemoreceptor trigger zone to the vomiting center in the brainstem, and numerous over-the-counter and prescription agents that block histamine 1 receptors are marketed as antiemetics. Their primary benefit is in motion sickness rather than acute gastroenteritis. Dimenhydrinate (Gravol, Dramamine) is specifically marketed for nausea, although the only RCT in acute gastroenteritis[43] found a reduction in vomiting but not need for intravenous fluids or hospitalization. These drugs are generally very sedating.
  - Ginger. Ginger root preparations have been used as a folk remedy for nausea and vomiting for years, and recent clinical trials have begun to study the activity of ginger in a rigorous fashion, but not in acute gastroenteritis. A recent meta-analysis found insufficient evidence of activity in chemotherapy-induced nausea and vomiting.[44]
  - Acupuncture/acupressure. Acupuncture by a trained practitioner or self-stimulation of the ventral surface of the wrist have been studied as treatments for anesthesia-induced and chemotherapy-induced nausea and vomiting. One small, noncontrolled study found good success in the treatment of vomiting in acute gastroenteritis in children.[45]
- Treatments for noninfectious/toxin-mediated food poisoning. The major benefit in this category is the treatment of botulism with antitoxin antibodies, which, when administered promptly, can stop symptoms from progressing but cannot reverse the effect on neurons that have already bound the toxin.[46] Equine trivalent, pentavalent, and heptavalent preparations have been used but can cause

serum sickness reactions; a human immunoglobulin Ig-based product is available for infants. Scombroid poisoning responds to antihistamine drugs, although it is self-limited regardless. There are no antitoxin agents for ciguatera and related illnesses, and supportive/symptomatic treatment is recommended. Intravenous mannitol was suggested in case reports[47] to be beneficial, but a more recent clinical trial found no efficacy, and as a result this is no longer recommended.[48]

ANTIMICROBIAL THERAPIES FOR FOODBORNE ILLNESS

Antimicrobials are of no use in toxin-mediated foodborne illness, including those caused by ingestion of bacterial, preformed toxins. In addition, there are no agents to treat viral gastroenteritis. Bacterial and protozoal agents, on the other hand, are almost always susceptible to 1 or more commercially available antibiotics. Before instituting treatment of one of these infections, is it important to consider the following:

- Does this infection need to be treated? Most causes of foodborne illness are self-limited and specific antibiotic treatment in general provides only modest benefit. Nevertheless, certain infections (*Shigella*, typhoid fever) have clear RCT evidence of a benefit of treatment. However, many other infections lack evidence of a benefit of antibiotic treatment, even when the isolate and drug susceptibilities are known (eg, *Yersinia enterocolitica).* In addition, there are some infections (nontyphoidal *Salmonella*) in which treatment can benefit some patients but lead to unwanted outcomes in others. There is competing evidence of both harm and benefit of antibiotics in the treatment of hemorrhagic colitis caused by enterohemorrhagic and related strains of *E coli*, and as a result, treatment is not generally recommended.
- Should the syndrome be treated before the cause is known? In some cases, the clinical features are enough to warrant specific antibiotic treatment even without a clear cause. The best example of this is travelers' diarrhea, in which empiric antibiotic treatment has been shown in many RCTs to shorten the severity and duration of illness (reviewed in Ref.[49]). There is also evidence that empiric treatment of severe diarrhea that persists beyond 72 hours is beneficial, although the choice of agent depends on the index of suspicion and the local susceptibility patterns (see later discussion).[50] However, treatment should generally be avoided in the syndrome of hemorrhagic colitis (frankly bloody diarrhea without fever), for reasons discussed later.
- Which antibiotic should be used? The broad variety of infectious agents that can, in many cases, produce indistinguishable clinical syndromes makes treatment challenging. Moreover, many of the drugs studied in well-designed RCTs can no longer be recommended because of increasing resistance, which can vary according to geographic area. Whenever possible, treatment should be tailored based on culture and susceptibility reports; when this is not feasible, an updated knowledge of local susceptibility patterns should guide therapy as much as possible.

A list of major bacterial and protozoal pathogens and the recommended antibiotic treatment is shown in **Tables 3** and **4**. Specific cases meriting mention are the following:

- *Salmonella. Salmonella* gastroenteritis is a self-limited illness, and treatment with antibiotics can prolong the duration of shedding and lead to some clinical

Table 3
Treatment of foodborne protozoal pathogens

Pathogen	Presentation of Infection	Complications if Untreated	Recommended Treatment
Giardia lamblia	Small bowel syndrome	Self-limited but often prolonged	Tinidazole, albendazole, metronidazole
Cryptosporidium	Small bowel syndrome; fulminant chronic diarrhea in AIDS	In AIDS, fatal wasting syndrome and dehydration; cholangiopathy	Nitazoxanide in immune competent; antiretroviral therapy in AIDS
Cyclospora cayetanensis	Small bowel syndrome; fatigue	Self-limited but often prolonged	TMP-SMX; ciprofloxacin if allergic
Microsporidia (*Enterocytozoon bieneusi, Encephalitozoon intestinalis)*	Chronic diarrhea in AIDS; rarely in transplant recipients	Wasting syndrome; cholangiopathy	Antiretrovirals or reduce immune suppression; albendazole for *Encephalitozoon intestinalis*
Entamoeba histolytica	Asymptomatic colonization to severe dysenteric colitis	Ameboma, liver abscess, other parenchymal abscess	Invasive disease: tinidazole or metronidazole, followed by paromomycin or iodoquinol Asymptomatic cyst passer: paromomycin or iodoquinol
Blastocystis hominis	Generally asymptomatic; some patients experience diarrhea, bloating, flatulence, and so forth	None	Treatment controversial; metronidazole, TMP-SMX, iodoquinol may be effective
Toxoplasma gondii	Acute: localized or disseminated lymphadenopathy, sometimes with fever; rarely chorioretinitis, encephalitis	Reactivation in immune compromise to encephalitis or chorioretinitis; fetal anomalies if acquired during pregnancy	Acute: treatment not clearly indicated[86] Reactivation: TMP-SMX or pyrimethamine/sulfadiazine or pyrimethamine/clindamycin
Trypanosoma cruzi	Rarely acquired through ingestion of crushed trematode bugs in food (eg, sugar cane juice)	Chronic sequelae of Chagas disease: organomegaly; chagoma in immune compromise	Acute or early chronic disease: benznidazole Late chronic disease with organomegaly: treatment benefit remains uncertain Chagoma: benznidazole

Abbreviation: TMP-SMX, trimethoprim-sulfamethoxazole.

relapses.[51] A recent meta-analysis[52] found no overall benefit of antibiotic treatment of *Salmonella* gastroenteritis in healthy adults, and confirmed increased likelihood of shedding the organism at 30 days. Most of the studies were considered to have low-quality evidence. Nevertheless, it is recommended not to use antibiotics in uncomplicated cases. Some experts do recommend treatment of severe cases (requiring hospitalization, high fever, multiple daily stools) based on efficacy in 1 RCT. In addition, treatment of children younger than 2 years and elderly patients is recommended by many experts.

One important consideration is that *Salmonella* can cause prolonged, metastatic, or lethal infection in immune-compromised hosts. These hosts include patients with AIDS, solid organ transplants, asplenia, or corticosteroid treatment. Although there are no RCT data in these cases, it is recommended that they be treated, given the relatively high risk of prolonged or recurrent bacteremia (reviewed in Ref.[53]).

- *Shigella.* Shigellosis can produce a particularly severe colitis, and is an independent risk factor for mortality in children hospitalized with diarrhea.[54] Although the illness is self-limited in most patients, antibiotics have been shown in several studies to shorten the duration of both illness and bacterial shedding, and because *Shigella* spreads readily from person to person, it is generally recommended that all cases be treated.[55] Antibiotic resistance has been increasing in different parts of the world.[56] In North America, most isolates remain susceptible to ciprofloxacin and third-generation cephalosporins.
- *Campylobacter.* Fatalities caused by *Campylobacter jejuni* gastroenteritis are rare, although bacteremias do occur, largely in immunocompromised hosts, with a mortality in those cases of 15% in 1 series.[57] A recent meta-analysis found that antibiotic treatment in uncomplicated cases does shorten the duration of illness, particularly when administered early, but the effect is modest.[58] Many patients are already better, or beyond the window of antibiotic usefulness, by the time the culture result is received. However, many experts do recommend treating severe cases and cases in immune-compromised hosts. As with most other bacterial diarrheal pathogens, *Campylobacter* is becoming increasingly resistant to first-line agents in some parts of the world, although macrolides (eg, azithromycin) remain active against most US isolates.[59]
- Enterohemorrhagic *E coli* (EHEC). The gastrointestinal symptoms of EHEC infection are self-limited, but the major complication, HUS, can be fatal or lead to permanent neurologic or renal sequelae. The predominant pathogen in this class, *E coli* O157:H7, remains antibiotic sensitive.[60] However, there is strong evidence from in vitro and animal models that antibiotics can induce increased toxin release from EHEC, leading to worse outcomes. For *E coli* O157:H7, the best evidence against the use of antibiotics was a prospective study of infected children in the United States,[61] in which antibiotic use was an independent risk factor for HUS in multivariate analysis, controlling for disease severity. However, the data were derived from only 10 HUS cases, and the antibiotics used were trimethoprim-sulfamethoxazole and β-lactam drugs. In contrast, retrospective data from the large Japanese outbreak in the late 1990s suggested that fosfomycin (the most commonly used antibiotic in that outbreak) was protective against HUS when used in the first 2 days of illness.[62] However, given the absence of RCT data and, more importantly, no good evidence of benefit, most authorities recommend against antibiotic treatment of *E coli* O157:H7 infection. In patients who do develop HUS, the C5 complement inhibitor eculizumab has been reported to be beneficial in a

Table 4
Treatment of bacterial foodborne and waterborne pathogens

Pathogen	Syndrome	Benefits of Treatment	Risks of Treatment	Recommendation	Recommended Drugs
Nontyphoidal *Salmonella*	Inflammatory diarrhea	Shortens duration of illness; prevents bacteremic seeding	Prolonged shedding; risk of clinical relapse	Treat only specific hosts (extremes of age, immune compromised, asplenic, and so forth)	TMP-SMX, FQ, Ceph3, amoxicillin
Typhoid fever	Enteric fever	Improves survival, eliminates shedding in most	Some patients may remain colonized and infectious	Treat	Ceph3; FQ, TMP-SMX if from area of low resistance
Shigella spp	Inflammatory diarrhea or dysentery	Reduced duration of illness, reduced shedding	Minimal	Treat	FQ, Ceph3, azithromycin; TMP-SMX if susceptible
Campylobacter spp	Inflammatory diarrhea	Reduced duration of illness if started early	Minimal	Consider treatment in severe or persistent cases	Azithromycin, FQ if from susceptible area
Enterohemorrhagic *E coli*	Hemorrhagic colitis	Reduces shedding; may or may not reduce risk of HUS	Increased toxin release and potential predisposition to HUS	Do not treat (from current evidence)	
Enteropathogenic *E coli*	Infantile diarrhea	ORS life saving; no evidence antibiotics are helpful	Unknown	Antibiotics not indicated for infantile diarrhea	
Enterotoxigenic *E coli*	Travelers' diarrhea	Significantly shortens duration of illness	Minimal	Empirical treatment indicated for travelers' diarrhea	Azithromycin, FQ, TMP-SMX, rifaximin

Enteroaggregative *E coli*	Endemic diarrhea, travelers' diarrhea, prolonged diarrhea in AIDS	Improves symptoms in AIDS; treatment of travelers' diarrhea beneficial as for ETEC	Unknown	Empirical treatment indicated for travelers' diarrhea; treat if found in persistent diarrhea	FQ, TMP-SMX, Ceph3, azithromycin
Yersinia spp	Inflammatory diarrhea or pseudoappendicitis	Reduces shedding but does not improve clinical outcomes	Unknown	No clear recommendation	Usually resistant to ampilillin and Ceph1
Listeria monocytogenes	Nonspecific gastroenteritis; bacteremia; meningitis; endocarditis	Treatment of invasive disease improves mortality	Minimal	Treat invasive disease or disease in pregnant women	Ampicillin or penicillin; TMP-SMX if allergic
Vibrio cholerae	Fulminant watery diarrhea	Self-limited without antibiotics but antibiotics shorten illness	Minimal	ORS as mainstay; antibiotics if feasible	Doxycycline, FQ, TMP-SMX
Noncholera *Vibrio*	Inflammatory or nonspecific diarrhea	No evidence for benefit	Minimal	Consider treating severe cases	Doxycycline, FQ
Aeromonas hydrophila	Inflammatory or nonspecific diarrhea	Most cases self-limited; case series of benefit in prolonged illness[87]	Minimal	Treat severe or prolonged cases (>7–10 d)	TMP-SMX, doxycycline, FQ

Abbreviations: Ceph1/3, first-generation/third-generation cephalosporin; FQ, fluoroquinolone; TMP-SMX, cotrimoxazole.

small case series,[63] although prospective, randomized data are lacking. Plasma exchange is frequently used, although it also lacks supporting randomized data.

- Enteroaggregative Shiga toxin–producing *E coli* O104:H4. This strain caused a large European foodborne outbreak of hemorrhagic colitis in 2011, in which the HUS rates in adults were a frightening 22%.[64] This isolate carried an extended-spectrum β-lactamase, rendering it resistant to cephalosporins, but it remained susceptible to fluoroquinolones, rifaximin, and azithromycin. There are conflicting reports as to whether antibiotics induce toxin production and release from this strain.[65,66] No randomized data are available on antibiotic use and the risk of HUS with this infection, but many patients in the outbreak received treatment with antibiotics, and no association with worse outcome was found. Treatment with ciprofloxacin was associated with reduced HUS risk in 1 case series.[67] Another case series[68] found reduced duration of shedding in patients who received azithromycin, with no apparent effect on HUS onset or outcomes, which could have implications for reducing secondary spread. There is insufficient evidence that antibiotics are either harmful or beneficial in O104:H4 infection, but the outbreak data are still being analyzed. In 1 prospective case series,[9] eculizumab was not found to be beneficial in 7 patients with severe HUS with neurologic symptoms. Plasma exchange was also not found to be beneficial in 1 case-control study.[69]
- *Giardia.* Metronidazole for 7 days has long been the recommended treatment of giardiasis, and although generally effective, it is poorly tolerated by many patients. Newer drugs active against *Giardia* have advantages of shorter treatment duration or better side-effect profile, although the studies comparing them have not been of high quality. A recent meta-analysis[70] found that tinidazole, nitazoxanide, and albendazole are likely to be as effective as metronidazole, and with generally fewer side effects. Relapses are not uncommon after metronidazole treatment, and resistance can develop. The optimal treatment in these cases remains uncertain.
- *Cryptosporidium.* This protozoan is a common cause of self-limited infections in immune-competent children and adults, although symptoms can be prolonged in some cases. In contrast, patients with advanced HIV/AIDS or other severe immune defects can develop devastating, fatal diarrheal illness. The only drug approved for this infection, nitazoxanide, provides modest symptomatic benefit in immune-competent hosts, with significantly better symptom resolution and decreased shedding at 4 days.[71] However, results in patients with HIV infection have been less encouraging, particularly in those with CD4 counts less than 50/μL[72] and in children in developing areas,[73] as confirmed in 1 meta-analysis.[74] The mainstay of treatment of cryptosporidiosis in HIV/AIDS is antiretroviral therapy, which leads to lasting remission, although relapse of infection can occur if therapy is stopped.[75]
- *Entamoeba histolytica.* Metronidazole has been the mainstay of therapy for invasive amebiasis for years, although a recent meta-analysis of 8 RCTs[76] found that tinidazole is equally effective but with a shorter treatment duration and better side-effect profile. Nevertheless, metronidazole remains a first-line agent for invasive disease. It is recommended to use a luminal agent such as paromomycin to clear cysts after treatment of invasive disease, because nitroimidazoles do not reliably eradicate the cyst form. *Entamoeba histolytica* can be mistaken under microscopy for the nonpathogenic *Entamoeba dispar*, which does not require treatment.

TREATMENT RESISTANCE/COMPLICATIONS

Antibiotic resistance among enteric pathogens is continuously evolving, but large geographic differences remain. For example, fluoroquinolone resistance rates among *Campylobacter* isolates are more than 95% in Thailand,[77] but less than 20% in North America.[78] The driving forces behind evolving resistance include widespread human prescription as well as animal feed supplementation. It is important for treating practitioners to review the most recent available data on local resistance patterns when selecting empirical antibiotics to treat an enteric infection, and to follow the antibiotic sensitivity report on an isolate when available.

In general, treatment courses for foodborne infections are short and well tolerated. As with any antibiotic, allergic reactions and secondary *Clostridium difficile* infection are ever-present concerns. Among nonantibiotic agents, the greatest concern is with inappropriate use of antimotility agents during inflammatory or hemorrhagic colitis, because of a potential to increase the risk of toxic megacolon or HUS, respectively.

EVALUATION OF OUTCOME AND LONG-TERM RECOMMENDATIONS

In general, patients recover quickly from foodborne infections and permanent sequelae are relatively rare. Stool analysis for test of cure is not generally recommended for individual patients, although screening of certain individuals (such as food preparation workers) may be indicated for public health reasons.[79] Although most patients can expect to recover fully from a foodborne illness, population-based studies from large-scale outbreaks such as the *E coli* O157:H7 and *Campylobacter* outbreak in Walkerton, ON in 2000, have shown an increased risk of postinfectious irritable bowel syndrome[80,81]; moreover, the rates of chronic kidney disease and hypertension are increased in those who recover from HUS.[82] *Campylobacter* is a well-recognized trigger for Guillain-Barré syndrome.[83] Moreover, population studies suggest that an acute episode of infectious gastroenteritis is associated with about a 2-fold increased risk of developing inflammatory bowel disease.[84] Any enteric infection can precipitate reactive arthritis, which can be self-limited to a few weeks or months, or evolve into a chronic spondyloarthropathy. It is not known whether antibiotic treatment of these infections affects these long-term risks; it does not seem to improve outcomes in established reactive arthritis.[85]

SUMMARY/DISCUSSION

Foodborne illnesses come from a wide variety of infectious and noninfectious sources, and can produce several relatively distinct clinical syndromes. Recognition of these syndromes, along with a careful exposure history, can usually provide enough information to guide rational use of diagnostic testing, empiric supportive therapy, and occasionally specific antimicrobial therapy. With appropriate treatment of dehydration (ideally with ORS), the risk of mortality or long-term morbidity is generally low. Key recent advances in the management of foodborne illness include the introduction of reduced-osmolarity ORS, the benefit of zinc supplements in children in developing areas, and the usefulness of ondansetron in pediatric gastroenteritis. Antimicrobial therapy still plays a small role in enteric foodborne infections. The most worrisome foodborne illness in otherwise healthy people in developed countries is hemorrhagic colitis, with its attendant risks of HUS. Moreover, patients with immune compromise are at risk for potentially devastating consequences of enteric infection. Most of the world's children, who live in impoverished areas without appropriate sanitation, remain vulnerable to repeated bouts of foodborne illness, which are frequently fatal

and in survivors produce long-term consequences that are only now beginning to be appreciated.

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