

## EDUCATIONAL OBJECTIVES

At the end of this continuing education activity, pharmacists will be able to

- RECOGNIZE signs and symptoms associated with acute diarrhea, including those that require referral to a PCP or hospital
- IDENTIFY inappropriate oral rehydration techniques
- RECOGNIZE antidiarrheal misuse
- REVIEW the risks and benefits associated with the most commonly used strategies to manage diarrhea

At the end of this continuing education activity, pharmacy technicians will be able to

- LIST the basic pathology and symptoms of acute diarrhea
- RECALL treatments used in patients who have acute diarrhea
- IDENTIFY OTC products and dietary modifications that are useful in acute diarrhea
- IDENTIFY when to refer patients to the pharmacist for recommendations or referral



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## Let's Stop Moving: Management of Acute Diarrhea in the Ambulatory Setting

**ABSTRACT:** Although diarrhea is one of the most commonly managed medical conditions in the outpatient setting, it can also be one of the most serious if treated inappropriately. In addition, new therapies and concerns with older ones have led to several new practice recommendations. Patients infected with coronavirus disease (COVID)-19, especially younger ones, may experience significant gastrointestinal (GI) symptoms. Unlike adults, children may present only with GI complications, such as diarrhea, nausea, vomiting, and severe abdominal pain. In one early study of patients with COVID-19, one third reported GI symptoms prior to the onset of fever or respiratory symptoms. Another challenge is the escalating opioid crisis and loperamide's emergence as a drug of abuse. Patients addicted to opioids are now abusing over-the-counter (OTC) antidiarrheal medications, including loperamide, to help manage withdrawal symptoms. The purpose of this continuing education activity is to highlight several recent changes in diarrhea management and provide a general overview of the most commonly used OTC antidiarrheal agents.

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**FACULTY DISCLOSURE:** The author has no financial relationship with an ineligible company.

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### INTRODUCTION

*"When you're riding in a Chevy and you feel something heavy.  
When you're sliding into home and your pants are full of foam.  
When you're sitting in the bath and you feel something splash."<sup>1</sup>*

No one likes to talk about it, but everyone knows what it is. Some call it "Montezuma's revenge," "the runs," or worse. Although diarrhea is one of the most commonly managed medical conditions in the outpatient setting, it can also be one of the most serious if treated inappropriately. In addition, concerns with older approaches to acute diarrhea have led to several new practice recommenda-

tions. The novel coronavirus disease-2019 (COVID-19) pandemic is also associated with a significant gastrointestinal (GI) component. In one early United States (U.S.) study of patients with COVID-19, one third reported GI symptoms prior to the onset of fever or respiratory symptoms.<sup>2</sup>

Another challenge is the escalating opioid crisis. Patients addicted to opioids are now abusing over-the-counter (OTC) anti-diarrheal medications, such as loperamide, to help manage withdrawal symptoms. The purpose of this activity is to highlight several recent changes in diarrhea management and provide an overview of commonly used OTC anti-diarrheal agents and other treatment strategies.

The classic definition of diarrhea is passage of loose or watery stools. Some have defined it as the passage of three or more watery stools per day, but it is difficult to define absolute limits. Acute diarrhea typically lasts one to two days (starting with the first loose stool, not when treatment starts). Patients and caregivers should raise concerns whenever stool patterns deviating from the norm are accompanied by other signs of illness, not just based on the stool frequency or water content. **Table 1** summarizes the most common symptoms associated with acute diarrhea.

In the U.S., approximately 179 million cases of acute diarrhea occur annually.<sup>4</sup> The following sections describe its many causes. In immunocompetent individuals, the primary etiology of infectious diarrhea includes foodborne pathogens and norovirus outbreaks.<sup>5</sup>

Numerous factors predispose patients to developing acute diarrhea (see **Table 2**). Providers should not confuse acute diarrhea with chronic diarrhea (i.e., diarrhea lasting more than two weeks). In many instances, the etiology of acute diarrhea is unknown and it resolves without treatment. Acute diarrhea is most commonly infectious in nature or related to a medication adverse effect.

**Table 1. Symptoms Associated with Acute Diarrhea<sup>3</sup>**

- Abdominal pain
- Cramping
- Fecal incontinence
- Fecal urgency
- Nausea
- Three or more loose, watery stools daily

## INFECTIOUS CAUSES OF DIARRHEA

### Viral Gastroenteritis

Acute infectious diarrhea is often viral, resulting in more than 1.5 million outpatient visits in the U.S. annually.<sup>5</sup> Typically, patients with viral diarrhea experience low-grade fevers and watery, non-bloody diarrhea lasting one to two days. Rotavirus used to be the most common cause of diarrhea in the U.S., but as rotavirus vaccination rates have increased, norovirus has taken over this title. Infant rotavirus immunization starts as early as six weeks of age but no later than 15 weeks.<sup>6</sup> Healthcare providers should administer the final dose in the immunization series by eight months of age. Infants infected with rotavirus prior to receiving the full vaccine course should still initiate or complete the recommended schedule, as initial infection confers only partial immunity.

Norovirus-induced diarrhea is less severe than rotavirus, especially in children. More commonly known as the “cruise ship virus,” norovirus is now one of the leading causes of foodborne disease and a common cause of traveler’s diarrhea.<sup>7</sup> Vomiting often accompanies diarrhea. In most cases, symptoms appear 12 to 48 hours after exposure and last one to three days, although the virus can continue to be shed in stools up to two weeks after resolution. Interestingly, not everyone is susceptible to norovirus infections. Individuals with type O blood are more prone to norovirus infections, while those with type B blood are least likely to contract them.<sup>8</sup>

**Table 2. Causes of Acute Diarrhea**

Cause	Description
Excessive intake of artificial sweeteners	Mannitol, sorbitol, xylitol (found in sugar-free products)
Food intolerance	Lactose intolerance
Infections	Bacterial (e.g., <i>E. coli</i> , <i>Salmonella</i> ) Parasitic (e.g., <i>Giardia</i> , <i>Cryptosporidium</i> , <i>E. histolytica</i> ) Viral (e.g., COVID-19, norovirus, rotavirus)
Medications	See <b>Table 3</b>
Travel (typically to developing countries)	Consuming food or drink contaminated by bacteria or parasites

COVID-19 = coronavirus disease-19

## Bacterial Gastroenteritis

It is sometimes difficult to distinguish between viral and bacterial gastroenteritis. Unlike viral gastroenteritis, bacterial infections associated with diarrhea have the potential to be more severe and are often associated with high fevers (exceeding 104°F), abdominal pain, and bloody stools.<sup>5</sup> Vomiting is less common. The most common causes of bacterial gastroenteritis in the U.S. are non-typhoidal *Salmonella* and *Campylobacter* species.<sup>5</sup> These usually occur after eating raw or undercooked poultry or something that came in contact with it. Reptiles, such as pet turtles, can also carry *Salmonella* in their stool and easily transmit the bacteria to their shells, tank water, and anywhere else they live and roam.<sup>9</sup>

Bacterial gastroenteritis is usually mild and self-limiting, but infants younger than three months of age may experience severe complications that can result in hospitalization.<sup>6</sup> In an otherwise healthy individual, bacterial gastroenteritis can resolve without any treatment. Antibiotics are reserved for treating diarrhea in immunocompromised patients, infants younger than three months of age, and patients who appear septic or toxic.<sup>5,6</sup>

## COVID-19-Related Diarrhea

Since the onset of the COVID-19 pandemic, respiratory symptoms have been the most common presentation of this viral illness. A growing number of patients, however, experience GI symptoms (e.g., anorexia, diarrhea, nausea, vomiting), sometimes without respiratory symptoms. COVID-19-induced diarrhea can last one day to as long as two weeks.<sup>2</sup> Although the mechanisms involved in the pathogenesis of COVID-19-related diarrhea are still unknown, the virus is likely altering intestinal permeability resulting in enterocyte malabsorption.<sup>10</sup>

## Foodborne Disease

Produce—especially leafy green vegetables—is the most common source of diarrhea due to foodborne pathogens.<sup>11</sup> Spinach and lettuce purchased from grocery stores often come from developing countries where water contamination is common and produce does not undergo agricultural inspection. Diarrhea-producing *E. coli* or *Salmonella* are common pathogens. Contaminated poultry is associated with the highest proportion of diarrhea fatalities (19%), mainly due to *Salmonella* or *Listeria* infection.<sup>11</sup>

To reduce this risk, consumers should soak leafy greens in water and rinse them thoroughly before eating. They must also use care when handling raw poultry. To prevent cross-contamination, cooks should prepare raw poultry separately from other foods. They should also clean food preparation surfaces and utensils (e.g., counters, cutting boards, forks, knives) and their hands with hot, soapy water after handling raw poultry. Finally, they must cook all raw poultry thoroughly. Updated weekly, the Centers for Disease Control and Prevention (CDC) provides extensive information on foodborne outbreak investigations on

their website:

<https://www.cdc.gov/foodsafety/outbreaks/index.html>.

Traveler's diarrhea—commonly caused by consuming contaminated food or drinking water in foreign countries—often appears within 10 days of travel to an area with poor public hygiene.<sup>12</sup> In most cases, traveler's diarrhea is not serious. However, in some instances, this type of diarrhea may last longer than usual due to infections with parasites and requires treatment with an antiprotozoal agent.<sup>13</sup> Although it can occur anywhere, the areas of greatest risk are in Africa, Asia (except Japan and South Korea), Central and South America, Mexico, and the Middle East.<sup>14</sup> The CDC publishes notices for travelers about potential health implications (e.g., disease outbreaks, gatherings, natural disasters) for destinations around the world, sorted by disease or country.<sup>15</sup>

## NON-INFECTIOUS CAUSES OF DIARRHEA

### Medication-Associated Diarrhea

Many medications can cause diarrhea as a side effect, usually because they affect gut motility or microbe balance.

#### *Antibiotic-associated diarrhea*

Antibiotic-associated diarrhea (AAD) results from an imbalance of intestinal bacteria where opportunistic bacteria like *C. difficile* are allowed to thrive.<sup>16</sup> AAD happens during a course of antibiotics or shortly afterward. The most commonly implicated antibiotics include clindamycin, macrolides, and other broad-spectrum antibiotics, but any antibiotic can disrupt the balance of non-pathogenic bacteria flora within the intestines.

Pharmacy staff may field questions about fecal transplants (also known as “poop pills” or “poop with a purpose”). The formal name for this is fecal microbiota transplant (FMT), which entails transferring stool from a healthy individual to a patient infected with *C. difficile*. The goal is to restore the balance of bacteria in the infected patient's gut. In patients with recurrent *C. difficile* infections, FMT may be more effective and significantly less expensive than a course of vancomycin.<sup>17</sup> It is not an approved therapy, but the FDA does allow clinicians to use it investigational to treat *C. diff* infections. It is not without risk, and patients have developed life-threatening infections from FMT contaminated with other pathogenic organisms.<sup>18</sup>

**Table 3** lists drugs that can cause acute diarrhea. Pharmacists should refer patients to their prescribers to discuss therapeutic alternatives without diarrheal adverse effects. For example, magnesium-containing OTC antacids may cause diarrhea, but calcium carbonate and aluminum hydroxide do not, making them suitable alternatives. Likewise, herbals, such as St. John's

**Pause and Ponder:** How can Halloween candy and fruit juices predispose children to diarrhea?

wort, aloe vera juice, and lobelia, have been linked with diarrhea.

### Laxative-Associated Diarrhea

Laxative-associated diarrhea is a specific form of medication-associated diarrhea.<sup>20</sup> Excessive intake of laxatives could be accidental (e.g., not understanding the directions) or intentional (e.g., child abuse, bulimia, anorexia nervosa). For example, there are cases reports of parents hiding laxatives in children’s food and/or medication as part of an ill-advised prank or an abusive gesture, resulting in serious harm.<sup>21,22</sup> A person buying multiple types and/or large quantities of laxatives or asking inappropriate questions about their use may be misusing them. Obtaining a thorough history and encouraging patients and caregivers to seek medical care is just as, if not more, important than recommending an antidiarrheal agent. When possible, pharmacy team members may want to discuss their observations regarding unusual laxative use with the patient’s PCP.

### Toddler Diarrhea

Toddler diarrhea—also known as functional diarrhea or non-specific diarrhea of childhood—often occurs when children drink considerable amounts of hyperosmolar fluids, such as fruit juices. According to the American Academy of Pediatrics, toddlers between one and three years of age should limit their juice intake to no more than four ounces per day.<sup>23</sup> Toddler diarrhea management involves reducing the volume of fruit juices or other osmotically-active carbohydrate beverages that contain sorbitol or fructose. Similarly, children may develop self-limiting “Halloween diarrhea” after ingesting sorbitol- and fructose-rich candies.<sup>24</sup>

### Lactase Deficiency or Food Intolerance

The brush border of the small intestine produces the enzyme lactase. It is necessary for breaking down lactose (“milk sugar”) to digest milk. Lactase deficiency can occur when an enteric (intestinal) infection causes mucosal (lining) injury. Approximately 68% of the world’s population has some form of lactose malabsorption.<sup>25</sup> Lactase deficiency is more prevalent in Asia and Africa, while it occurs less frequently in northern Europe where many people carry the gene that codes for lactase.<sup>26</sup> About 36% of Americans have some form of lactose malabsorption.

When lactose malabsorption occurs with a case of acute viral gastroenteritis, it tends to be mild and self-limiting. Regardless of the cause, when patients have inadequate lactase, ingested lactose is malabsorbed and gut bacteria use it as an energy source and to produce gas. Moreover, undigested lactose has an osmotic effect and pulls excessive water into the bowel, resulting in diarrhea.<sup>25</sup> Patients experience abdominal pain, flatulence, or diarrhea within several hours of ingesting a significant lactose load, and it resolves after several days of avoiding lactose-containing foods.

**Table 3. Drugs Associated with Acute Diarrhea<sup>19</sup>**

Medication Class	Examples
Antibiotics	<ul style="list-style-type: none"> <li>●Cephalosporins (e.g., cefdinir, cefpodoxime)</li> <li>●Clindamycin</li> <li>●Macrolides (e.g., erythromycin, clarithromycin, azithromycin, fidaxomicin)</li> <li>●Penicillins (e.g., amoxicillin, ampicillin)</li> </ul>
Cancer chemotherapeutics	<ul style="list-style-type: none"> <li>●Cyclophosphamide</li> <li>●Daunorubicin</li> <li>●Epirubicin</li> <li>●Fluorouracil</li> <li>●Gemcitabine</li> <li>●Ixabepilone</li> <li>●Methotrexate</li> <li>●Vincristine</li> </ul>
Copper chelators	<ul style="list-style-type: none"> <li>●Dimercaprol</li> <li>●Penicillamine</li> <li>●Trientine</li> </ul>
Corticosteroids	<ul style="list-style-type: none"> <li>●Dexamethasone</li> <li>●Prednisone</li> </ul>
Digitalis glycosides	<ul style="list-style-type: none"> <li>●Digoxin</li> </ul>
Magnesium salts	<ul style="list-style-type: none"> <li>●Magnesium hydroxide (Phillips’ Milk of Magnesia, Dulcolax Milk of Magnesia, Pedialax Chewable Tablets)</li> </ul>
Mood stabilizers	<ul style="list-style-type: none"> <li>●Lithium</li> </ul>
Nonsteroidal anti-inflammatory agents	<ul style="list-style-type: none"> <li>●Ibuprofen</li> <li>●Meclofenamate sodium</li> </ul>
Proton Pump Inhibitors	<ul style="list-style-type: none"> <li>●Lansoprazole</li> <li>●Omeprazole</li> <li>●Pantoprazole</li> </ul>

Other forms of food intolerance can also cause diarrhea. Drinking overly salted beverages and ingesting excessive fiber (e.g., sunflower seeds) can cause diarrhea.<sup>27</sup> Hot peppers (e.g., jalapeño peppers, cayenne peppers, and some chili peppers) contain the chemical irritant capsaicin (responsible for the “burn”) which can trigger diarrhea.<sup>28</sup> Similarly, onions and large amounts of spices, fruits, and vegetables can also predispose patients to dietary diarrhea.<sup>27</sup> Avoiding the causative food is the best approach to managing symptoms.

**PAUSE AND PONDER:** How does an antidiarrheal alter the symptoms associated with diarrhea?



## DIARRHEA TREATMENT AND PREVENTION

Some recommendations for diarrhea are the same across the board, while others are on a case-by-case basis. In cases of infectious diarrhea, all pharmacy staff should emphasize the need for good hand hygiene, especially after using the bathroom or performing diaper changes to protect others from becoming infected. People should wash their hands with soap and water for at 15 to 30 seconds paying special attention to the fingernails, between fingers, and wrists. Alcohol-based hand sanitizers are ineffective at preventing all types of diarrhea (i.e., norovirus, *Clostridiodes*).<sup>29</sup> People must also use soap and water to wash visibly soiled hands. In cases of COVID-19 infection, experts recommend using an alcohol-based rub that contains at least 60% alcohol in addition to soap and water.<sup>30</sup> Pharmacy teams should be prepared to help patients and caregivers select appropriate diarrhea treatments.

### Oral Rehydration Solutions

Provided they are able to drink, most patients with mild-to-moderate dehydration should use oral rehydration solutions (ORSs) to manage diarrhea symptoms. Although ORSs do not treat diarrhea, they help prevent dehydration and electrolyte losses. ORSs are safer, inexpensive alternatives to intravenous fluids. They contain dextrose and electrolytes to replace fluid and electrolytes. The dextrose in ORSs enables the intestine to absorb fluid and salts more effectively.<sup>31</sup> **Table 4** describes commonly-used ORS products. Breastfed infants should continue to drink breastmilk during the bout of diarrhea.

Pharmacy staff should advise patients to avoid tea, rice water, fruit juice, or gelatin as ORS substitutes, as they contain insufficient electrolytes and may be too hypertonic which could worsen diarrhea. Given the widespread availability of premixed products, people should not try to prepare their own ORS. Pharmacy staff should caution patients to avoid using sports drinks as ORS, as these products contain significant amounts of sugar and can exacerbate diarrhea. Furthermore, if the patient is experiencing significant vomiting or diarrhea, sports drinks contain inadequate amounts of electrolytes, such as sodium, and cannot effectively replace losses.

In the event a commercial ORS product is unavailable, some have recommended adding table salt to G2 Gatorade (not regular Gatorade) to increase its sodium content to match traditional ORSs.<sup>32</sup> This option, however, is prone to error and adding too much salt is just as detrimental as not adding enough. Some errors in making homemade ORS have been fatal.<sup>33</sup>

### Dietary Measures

The practice of holding solid foods and dairy products for the first 24 hours after acute diarrhea onset has come under scrutiny.<sup>34</sup> In patients who are adequately hydrated, food is allowed. Caregivers can provide bland, easily-digestible foods and beverages for the first 24 hours after diarrhea onset in patients with nausea or vomiting. Pharmacy teams should advise patients and caregivers to withhold food if antiemetics are unable to control vomiting.

Individuals may read they should eliminate specific foods while they have diarrhea. Patients should avoid foods rich in fructose (e.g., fruit juices), as they are often difficult to digest.<sup>35</sup> Similarly, sugar-sweetened drinks can worsen diarrhea, cramping, and flatulence. Most juices also contain little fiber and, in comparison to whole fruits, offer no nutritional advantage. Because they may stimulate bowel function, patients should avoid foods containing roughage (e.g., beans, Brussels sprouts, cabbage), as these may exacerbate diarrhea. Instead, during a bout of diarrhea, patients should follow a low-fiber diet limiting dietary fiber intake to 10 grams/day.<sup>36</sup> **Table 5** (next page) describes foods that are appropriate during episodes of diarrhea and foods to avoid.

Some people use astringent herbs and teas rich in tannins (e.g., blackberry, raspberry teas) as a treatment for diarrhea. When treating diarrhea, only dried berries or juice are recommended, as fresh berries may actually exacerbate symptoms.<sup>37</sup> Moreover, patients should be aware that in large doses, blackberry tea might cause more GI upset and trigger nausea and vomiting. Pregnant women should use raspberry and raspberry leaf preparations with caution as they may stimulate contraction of uterine tissue.<sup>38</sup>

**Table 4. Comparison of Oral Rehydration Solutions<sup>31,32</sup>**

	WHO Reduced-Osmolarity ORS	Pedialyte	Cerelyte 70	Gatorade	G2 + ½ teaspoon table salt
Glucose	28 g/L	25 g/L	40 g/L*	58 g/L	28 g/L
Sodium	75 mEq/L	45 mEq/L	70 mEq/L	23 mEq/L	63 mEq/L
Potassium	20 mEq/L	20 mEq/L	20 mEq/L	< 1 mEq/L	3 mEq/L
Citrate	10 mEq/L	30 mEq/L	30 mEq/L	None	None
Chloride	65 mEq/L	35 mEq/L	60 mEq/L	17 mEq/L	32 mEq/L
Osmolarity	311 mOsm/L	250 mOsm/L	220 mOsm/L	280-360 mOsm/L	254 mOsm/L

G2 = G2 Gatorade; ORS = oral rehydration solution; WHO = World Health Organization

\*as rice base

**Table 5. Foods that Should Be Avoided or Allowed During Bouts of Diarrhea<sup>35, 36</sup>**

Foods to Avoid	Foods That Are Permitted
<ul style="list-style-type: none"> <li>●Alcohol</li> <li>●Dairy products (if lactose intolerant)</li> <li>●Foods containing artificial sweeteners (sorbitol, mannitol, and xylitol)</li> <li>●Foods high in roughage (e.g., beans, broccoli, Brussels sprouts, cabbage, cauliflower)</li> <li>●Fructose-containing products</li> <li>●Fruits (e.g., apples, peaches, pears) and fruit juices</li> <li>●High-fat, greasy foods</li> <li>●Spicy foods</li> </ul>	<ul style="list-style-type: none"> <li>●Applesauce</li> <li>●Baked chicken with skin removed</li> <li>●Bananas</li> <li>●Boiled or baked potatoes with skin peeled</li> <li>●Bread or toast</li> <li>●Chicken soup</li> <li>●Hot cereals (e.g., cream of wheat, oatmeal)</li> <li>●Plain white rice</li> <li>●Unseasoned crackers</li> </ul>

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### BRAT Diet

This diet is intended to manage diarrhea by providing a bland diet that may improve diarrhea symptoms. However, its low nutritional content has resulted in its abandonment.<sup>39</sup> Similarly, only providing clear liquids for several days can potentially prolong the duration of diarrhea, a condition often referred to as “starvation stools.”<sup>40</sup> This form of diarrhea is green and watery. The green bile is excreted into the stool when there is no food to digest. It is not harmful and management simply entails increasing food intake.<sup>41</sup> Pharmacy teams should not recommend the BRAT diet to patients with diarrhea, as it is outdated.

### Probiotics and Prebiotics

To prevent or treat antibiotic-associated diarrhea, healthcare providers often recommend probiotics (see **Table 6** for examples). Probiotics—microorganisms that replace colonic bacteria—suppress pathogenic microorganisms’ growth thus restoring normal intestinal function. The most commonly used probiotics to decrease the duration and severity of diarrheal episodes include *Saccharomyces boulardii*, *Lactobacillus GG*, and *Lactobacillus acidophilus*. Some foods contain naturally-occurring probiotics, but probiotic supplements are also available.

One meta-analysis showed probiotic use may prevent antibiotic-induced diarrhea in adults but was not effective in those old-

**Table 6. Examples of Probiotics<sup>44</sup>**

Type	Examples	
<b>Probiotic-containing foods</b>	aged soft cheeses beet kvass cottage cheese dark chocolate green olives kefir kimchi kombucha	miso natto pickles sauerkraut sourdough bread tempeh yogurt
<b>Align Resistance Formula Capsule</b>	10 Billion CFU of <i>Saccharomyces boulardii</i> CNCM1-1079	
<b>Culturelle Capsule</b>	Lactobacillus GG 10 billion CFU Inulin (chicory root extract) 200 mg Vitamin C 3 mg	
<b>FlorastorPre capsule</b>	Prebiotic and probiotic blend: <i>Saccharomyces boulardii</i> lyo CNCM I-745 250 mg Prebiotic fiber (chicory root –inulin) 300 mg	
<b>Physician’s Choice Probiotics 60 billion CFU (per serving)</b>	10 Probiotic strains (220 mg): <i>Lactobacillus casei</i> <i>Lactobacillus acidophilus</i> <i>Lactobacillus paracasei</i> <i>Lactobacillus salivarius</i> <i>Lactobacillus plantarum</i> <i>Lactobacillus bulgaricus</i> <i>Bifidobacterium lactis</i> <i>Bifidobacterium bifidum</i> <i>Bifidobacterium longum</i> <i>Bifidobacterium breve</i>	Prebiotic fiber blend: Jerusalem artichoke root 50 mg Gum Arabic (Fibergum Bio) 50 mg Chicory Root powder 50 mg

er than 65 years of age.<sup>42</sup> To be most effective, patients should start probiotics early when signs of diarrhea first appear. Patients who are also receiving antibiotics should separate probiotic administration by at least two hours from the antibiotic dose. Evidence supporting probiotic use in managing viral diarrhea is mixed.<sup>43</sup>

Typically used in combination with probiotics, prebiotics are oligosaccharides that stimulate growth of commensal intestinal bacteria (i.e., naturally-occurring flora that induce protective responses to prevent pathogen invasion and colonization). Data supporting the use of prebiotics to reduce severity or duration of diarrhea is weak, and they are not universally recommended.<sup>45</sup> Currently, prebiotics are only available in combination products containing a probiotic.

### Bismuth Subsalicylate

Patients use bismuth subsalicylate (Pepto-Bismol) to treat mild, nonspecific diarrhea. It has anti-secretory, anti-inflammatory, and antimicrobial properties.<sup>46</sup> Developed more than 100 years ago by a physician to treat cholera, it was originally called Mixture Cholera Infantum.<sup>47</sup> Despite its cheery pink color, pharmacy staff should remind patients and caregivers that bismuth subsalicylate can darken the stools and tongue with repeated use. Typical dosing for patients older than 12 years of age for acute diarrhea is 524 mg every 30 to 60 minutes or 1,050 mg every 60 minutes as needed for up to 2 days (maximum: 4,200 mg/24 hours).<sup>46,47</sup> Most patients will experience relief within 30 to 60 minutes of a dose. Children and adolescents who have or are recovering from influenza or chicken pox should not use bismuth subsalicylate due to the association of Reye syndrome.<sup>46,47</sup>

Patients with histories of salicylate allergy, coagulopathy, or ulcers should not use bismuth subsalicylate. Patients receiving anticoagulants or medications for gout or arthritis (e.g., allopurinol, colchicine, ibuprofen, indomethacin, naproxen) should also avoid it. It can bind with tetracyclines and may also interfere with GI contrast studies. Use of bismuth subsalicylate during a contrast study can potentially cause misinterpretation of images and decrease the test's sensitivity.<sup>48</sup> Because it is hyperdense liquid, it can mimic the appearance of an acute GI bleed, which may lead to potential diagnostic errors. Patients taking bismuth subsalicylate must also stop using this product if they develop ringing or buzzing in the ears (i.e., tinnitus) because it indicates salicylate toxicity.

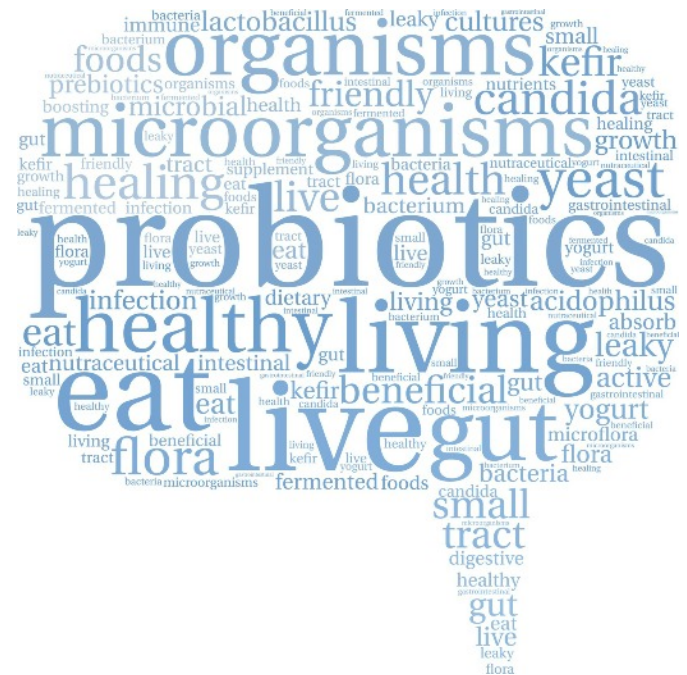
### Loperamide

Loperamide (Imodium A-D) is an opioid-receptor agonist that inhibits peristalsis (muscle contractions in the GI tract) by acting directly on the musculature of both the small and large intestine.<sup>49</sup> It has been available OTC since 1988. Typical OTC dosing is 4 mg, followed by 2 mg after each loose stool.<sup>49</sup> At the Food and Drug Administration (FDA)-recommended OTC maximum dose of 8 mg per day, it does not predispose patients to

the usual side effects associated with opioid use (e.g., euphoria, lethargy, nausea, vomiting). Patients should limit use to fewer than two days unless they are receiving medical supervision. Most patients will see improvement in symptoms within one hour after a dose.<sup>49</sup> Caregivers should not give loperamide to children younger than three years old, as there are case reports associating it with toxic megacolon (severe swelling of the colon) and ileus (intestinal obstruction).<sup>49</sup>

When taken at recommended doses, loperamide does not cross the blood-brain barrier or yield the "high" seen with other opioids. However, at extremely excessive doses (i.e., more than 100 to 200 mg/day), loperamide enters the central nervous system and produces effects similar to those associated with centrally-acting opioids like heroin, hydrocodone, or morphine.<sup>49</sup> Some individuals withdrawing from opioids use loperamide to ameliorate their symptoms, or simply to induce euphoria.

Loperamide overdoses have been associated with serious cardiac complications, including arrhythmias, loss of consciousness or fainting, and myocardial infarction. Moreover, even standard doses of loperamide may interact with medications that can cause QT prolongation such as azole antifungal drugs and macrolide antibiotics. In response to these concerns, in September 2019, the FDA approved changes to OTC loperamide products. These changes limit each container to no more than 48 mg of loperamide and require the tablets and capsules to be individually packaged (i.e., unit-dosed).<sup>50</sup>



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## Supplements

Many patients prefer to use OTC supplements to prevent or treat diarrhea. For this indication, a variety of natural products and enzyme supplements are used.

### Lactase Enzymes

For individuals prone to diarrhea due to lactose intolerance, lactase enzymes are beneficial for prevention.<sup>51</sup> Most lactose intolerant individuals do not have to give up all dairy products, as they can manage their symptoms by using lactase supplements or lactase-fortified products. There are several ways to provide lactase, and **Table 7** lists commonly available products. The typical dose of lactase supplementation to prevent diarrhea in intolerant individuals is 6000 to 9000 international units at the start of a lactose-containing meal.<sup>51</sup> Some patients prefer to add lactase supplementation to milk. In this case, patients mix 2000 international units of a lactase solution into 500 mL of milk immediately before drinking.

### Zinc

Zinc supplements reduce the duration of a diarrhea episode by 25% and are associated with a 30% reduction in stool volume.<sup>52</sup> Zinc is available in a variety of salt forms, including zinc-gluconate, -acetate, -ascorbate, -chloride, and -sulfate. Providers may use zinc to manage acute diarrhea in children older than six months of age, but evidence supporting its efficacy is mixed. According to the World Health Organization, patients should start zinc supplementation in conjunction with ORS at the first sign of diarrhea, as it may shorten the duration and severity of episodes and prevent subsequent episodes.<sup>53</sup> In infants younger than six months of age and children, providers sometimes use doses of 20 mg elemental zinc once daily for 10 to 14 days. The most common adverse reactions associated with oral zinc include dysgeusia (altered taste), mouth irritation, nausea, and vomiting.

### Goldenseal/Berberine

Capsules of dried goldenseal appear to kill many bacteria that cause diarrhea, including *E. coli*. The key component in the herb is berberine. In addition to its antimicrobial effects, berberine may reduce diarrhea by enhancing sodium and water absorption by the intestinal lumen.<sup>54</sup> In animal models, berberine appears to slow GI motility by activating opioid pathways.<sup>55</sup>

Doses of goldenseal used in studies vary considerably, from 250 mg to 1 g administered three times daily.<sup>56</sup> Studies of berberine taken alone used doses of 300 to 500 mg three times daily.<sup>57</sup> Typically, patients take goldenseal capsules daily until diarrhea improves. Patients should be aware that, although rare, very high doses of goldenseal may cause anxiety, depression, nausea, paralysis, or seizures.<sup>58</sup> Goldenseal may also affect the cytochrome P450 system and may alter patient response to medications metabolized by those enzymes.

**Table 7. Common Lactase Supplements**

Tablet, Oral	Tablet Chewable, Oral	Drops (added to liquid dairy Products)	Powder
Lactaid: 3000 units	Lactaid Fast Act: 9000 units	Elepure lactase drops: 750 units per 5 drops	Nutricost Lactase Powder: 10,000 units per 10 grams
Lactaid Fast Act: 9000 units	Milkaid: 3000 units	Seeking Health Lactase Drops: 750 units per 7 drops	
Lactase Enzyme: 3000 units			
Lactase Fast Acting: 9000 units			
Surelac: 3000 units			

### Psyllium

Ground psyllium seeds are found in the flowering plant of the plantago genus absorb excess fluid in the intestines. Patients often use psyllium to treat constipation, so patients may be unaware that it can help with diarrhea, too. Typical doses are one to three tablespoons mixed in water each day, but the product is also available as capsules and wafers.<sup>59</sup> When taken concurrently, psyllium may bind with some medications (e.g., carbamazepine, lithium) and may decrease blood glucose levels, so caution is advised in patients taking antidiabetic agents. Adverse effects associated with psyllium use include bloating, flatulence, indigestion, nausea, and vomiting.

## UNSAFE OR INEFFECTIVE TREATMENTS

Complementary and alternative medicine refer to those medical products that are not standard of care. Many patients will use “home remedies” to manage their symptoms, employing special diets or supplements to manage bouts of diarrhea. In many instances, insufficient evidence exists to support their safety or efficacy. Pharmacy teams should be aware of the more commonly used remedies in their geographic locations (as they vary by population) and understand their limitations.<sup>60</sup>

**PAUSE AND PONDER:** Why are sports drinks not used for fluid and electrolyte replacement in patients experiencing diarrhea?



## Wood-Tar Creosote

Some alternative medicine circles use wood-tar creosote (found in a product called Seirogan) as an antidiarrheal treatment. Wood creosotes come from the resin of the leaves of the creosote bush and beechwood.<sup>61</sup> In its classic form, it is a dark brown round pill, but a sugar-coated tablet is also available that masks its bitter taste and distinct medicinal odor. It is not a benign therapy, as ingesting high levels of creosote may cause burning in the mouth and throat or gastritis. Moreover, creosote may be carcinogenic with long-term use. Pharmacy teams should communicate these risks to patients seeking to use wood-tar creosote and encourage them to use a safer alternative.

## Attapulgite

Attapulgite is a naturally-occurring, orally-administered clay named for the U.S. town of Attapulgus, Georgia, where it is abundant.<sup>62</sup> It is a non-absorbable medication that adsorbs large numbers of bacteria and toxins and thereby reduces fluid loss.<sup>63</sup> Its binding action reduces the frequency of bowel movements and improves the consistency of stools. Attapulgite can absorb eight times its weight in water. It used to be present in Kaopectate, but in 2003, the manufacturer reformulated the product and replaced attapulgite with bismuth subsalicylate as the active ingredient. The FDA did not include attapulgite as a monograph ingredient, citing that efficacy data was inadequate.<sup>64</sup> Attapulgite is still used as a veterinary drug in the U.S. and is available in many countries as an OTC antidiarrheal.

## “RED FLAGS” TO REFER PATIENTS FOR MEDICAL ATTENTION

Fluids and OTC antidiarrheal products cannot manage all cases of acute diarrhea. Cases accompanied by fever or excessive mucus in the stool suggest evaluation by a primary care provider (PCP) is necessary. Dehydration is another concern, especially in cases where patients report weight loss or decreased urine output (i.e., more than six hours since last urination, decreased number of wet diapers). If patients fail to improve despite oral rehydration, they should seek medical attention.

Patients with a history of recent travel to an undeveloped country, backcountry camping, or consumption of processed meat may develop infectious or parasitic diarrhea. Children in daycare or using community swimming pools may also be at risk for contracting bacterial diarrhea, such as giardiasis. These patients should see their PCPs for further evaluation, as antimicrobial therapy might be necessary.

Toxic exposures to contaminated food, plants, and other substances can cause diarrhea. Obtaining a good history and knowing when to refer patients to their PCPs or hospital is an important step in managing care. For example, profuse diarrhea that occurs with excessive salivation or tearing may be suggestive of organophosphate ingestion.<sup>65</sup>

Although most acute diarrhea cases are self-limiting, children younger than three years of age and adults older than 60 with multiple co-morbidities should seek immediate medical care.<sup>66</sup> **Table 8** highlights other “Red Flags” that warrant immediate medical attention.

## CONCLUSION

There is no “one size fits all” approach to diarrhea treatment, and pharmacy teams should be prepared to assist patients in selecting the most appropriate approach to manage symptoms. Acute cases of diarrhea usually resolve on their own without treatment, but preventing dehydration is crucial. Before recommending an antidiarrheal agent, pharmacists should obtain a good medication history to avoid potential drug interactions and identify red flags. It is important to remind patients that anti-diarrheal treatments do not necessarily cure the diarrhea, but they help to lessen its severity and duration. Just as important as assisting patients in selecting the best therapy, pharmacy staff can identify when prompt medical attention is necessary. Abuse of antidiarrheal agents is possible, and pharmacists and technicians should be vigilant if they encounter unusual purchasing patterns involving these products. Figure 1 (next page) presents key takeaway points.

**Table 8. “Red Flag” Symptoms Indicating Patients Should Seek Immediate Medical Attention<sup>3</sup>**

People of All Ages	Infants/Young Children
<ul style="list-style-type: none"> <li>● 6 or more loose stools per day</li> <li>● Bloody, black, tarry, or pus-containing stools</li> <li>● Dizziness or lightheadedness</li> <li>● Fever &gt; 102°F and chills</li> <li>● Severe pain in abdomen or rectum</li> <li>● Vomiting</li> <li>● Severe dehydration, evidenced by:               <ul style="list-style-type: none"> <li>▪ Dark urine</li> <li>▪ Decreased skin turgor</li> <li>▪ Fainting/lightheadedness</li> <li>▪ Oliguria (decreased urination)</li> <li>▪ Thirst/dry mouth</li> <li>▪ Severe fatigue</li> <li>▪ Sunken eyes/cheeks</li> </ul> </li> </ul>	<ul style="list-style-type: none"> <li>● Diarrhea persists &gt; 24 hours               <ul style="list-style-type: none"> <li>▪ &lt; 3 months old: seek medical attention at first signs of diarrhea</li> </ul> </li> <li>● &lt; 3 months old: any fever</li> <li>● Severe dehydration, evidenced by signs in left column, plus:               <ul style="list-style-type: none"> <li>▪ No tears when crying</li> <li>▪ No wet diapers for more than 3 hours</li> <li>▪ Sunken soft spot in an infant’s skull</li> </ul> </li> </ul>

## Figure 1. Helping Patients Experiencing Diarrhea

### Best

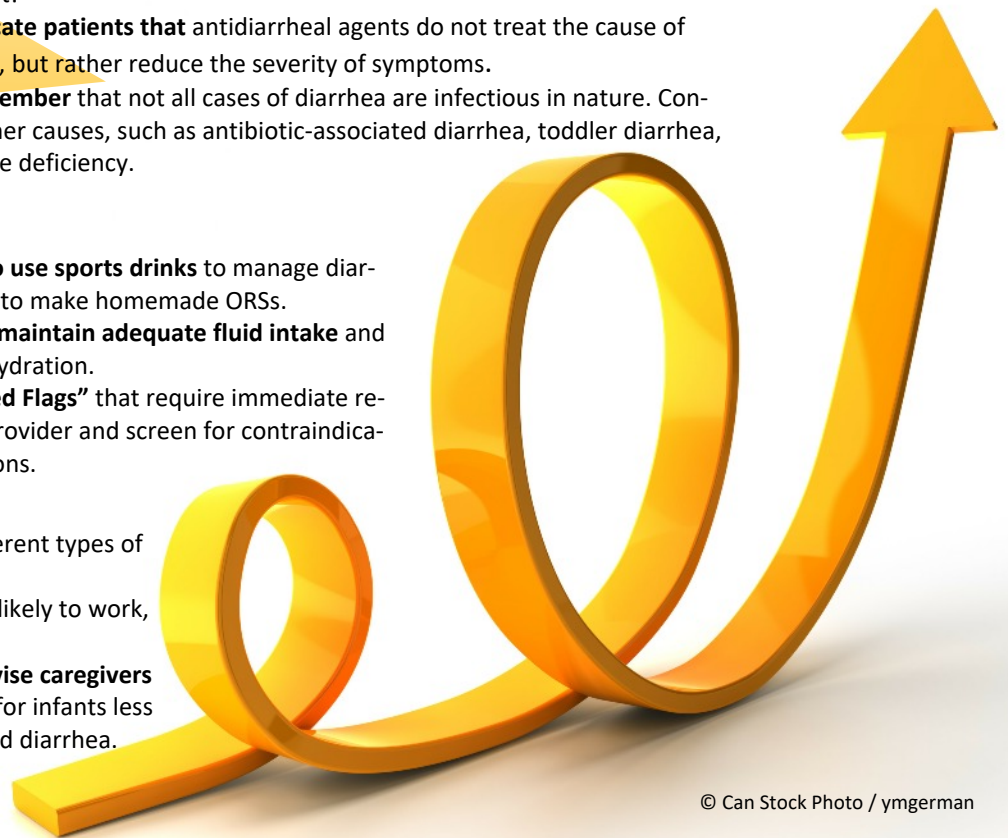
- 1 **BE COMMUNITY CHAMPIONS.** When you see what appears to be outbreaks of contagious diarrhea or food poisoning, contact your health department!
- 2 **Educate patients that** antidiarrheal agents do not treat the cause of diarrhea, but rather reduce the severity of symptoms.
- 3 **Remember** that not all cases of diarrhea are infectious in nature. Consider other causes, such as antibiotic-associated diarrhea, toddler diarrhea, or lactase deficiency.

### Better

- 1 **Remind patients not to use sports drinks** to manage diarrhea and to never attempt to make homemade ORSs.
- 2 **Encourage patients to maintain adequate fluid intake** and to monitor for signs of dehydration.
- 3 **Assess patients for “Red Flags”** that require immediate referral to their healthcare provider and screen for contraindications or potential interactions.

### Good

- 1 **Know the difference** between different types of diarrhea.
- 2 **Know which OTC medications** are likely to work, and which should be avoided.
- 3 **Regardless of suspected cause, advise caregivers to seek immediate medical attention** for infants less than 3 months of age with vomiting and diarrhea.



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