WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.453
Volume 14, Issue 12, 108-125. Review Article ISSN 2277–7105

# A COMPREHENSIVE REVIEW ON ANTIDIARRHEAL ACTIVITY: CAUSES, EPIDEMIOLOGY, PATHOPHYSIOLOGY AND MEDICINAL PROSPECTS

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Article Received on
24 April 2025,

Revised on 14 May 2025,
Accepted on 04 June 2025

DOI: 10.20959/wjpr202512-37083

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## ABSTRACT

Diarrhea remains a significant global health concern, particularly in developing countries, contributing to high morbidity and mortality rates, especially among children. Antidiarrheal agents play a crucial role in managing both acute and chronic forms of diarrhea by targeting various physiological mechanisms such as motility reduction, fluid absorption enhancement, and secretion inhibition. This review provides a comprehensive overview of conventional and emerging antidiarrheal therapies, encompassing synthetic drugs, natural products, and probiotics. The mechanisms of action, pharmacological classifications, and experimental models commonly used to evaluate antidiarrheal activity are critically discussed. Special emphasis is placed on plant-derived compounds and traditional medicines, which have gained attention due to their potential efficacy and safety profiles. Despite significant progress, challenges such as drug resistance, limited access to healthcare, and the need for standardized evaluation models persist. This review highlights current advancements and identifies future directions for research and development in antidiarrheal therapeutics.

**KEYWORDS:** The mechanisms of action, pharmacological classifications, and experimental models commonly used to evaluate antidiarrheal activity are critically discussed.

## INTRODUCTION

Diarrhea is an increase in the frequency, fluidity, or volume of feces that is best characterized by duration (acute versus chronic), pathophysiologic mechanism, and anatomic location. Diarrhea is considered acute if it lasts for less than 14 days, and chronic when it persists for more than 14 days. Acute, self-limiting diarrhea is a relatively common problem in dogs and cats and usually requires minimal diagnostic testing and therapy. In contrast to most animals with acute diarrhea, chronic diarrhea can be particularly challenging to diagnose, because most animals will not respond to empirical therapies, necessitating a well-formulated and cost-effective diagnostic and therapeutic plan. Specific therapeutic modalities are based upon a definitive diagnosis or histologic characterization of intestinal biopsies.[1] The World Health Organization (WHO) and UNICEF estimate that there are over 2 billion cases of diarrheal illness globally each year, with 1.9 million children under the age of five dying from the illness each year, primarily in developing nations. This represents 18% of the fatalities of children under the age of five, meaning that over 5,000 children die each day from diarrheal illnesses. 78% of child deaths from diarrhea occur in South-east Asia and Africa. Every youngster under the age of five has an average of three episodes of acute diarrhea every year. Diarrhea is the second most common cause of death in this age group worldwide (after pneumonia), and children in this age range have the highest incidence and risk of dying from diarrheal diseases, especially during infancy. After that, rates gradually decrease. In nations with low resources, hunger, stunted growth, and decreased cognitive development are additional direct effects of diarrhea in children.[2] The word diarrhea is form the Ancient Greek διάρροια from διά *dia* "through" and ῥέω *rheo* "flow". *Diarrhea* is the spelling in American English, whereas *diarrhoea* is the spelling in British English.Slang terms for the condition include "the runs," "the squirts" (or "squits" in Britain), "Hershey squirts," "Montezuma's Revenge," and "the trots".[3,4] Extensive reviews of the global epidemiology of infectious diarrhea have been performed periodically since 1982. Although there remains significant uncertainty in both numerator and denominator data, it is estimated that each child under 4 years worldwide has an average of 3.2 episodes of diarrhea each year, and the associated mortality rate is 3.8 deaths per 1,000 children in this age group. Although the incidence of infectious diarrhea appears not to have changed, the mortality rate has fallen. This decrease is most pronounced in children younger than 1 year of age, and has been

attributed to the increasing use of ORT, as most other preventative interventions. such as breast-feeding, improved weaning practices, improved sanitation, and measles vaccination would be expected to reduce both mortality and morbidity.[5] However, the relative contributions of increasing use of ORS compared with other public health and sanitation measures are still debated.[6,7] Like most infectious diseases, the burden of disease falls mainly on populations in developing countries; up to a quarter of children are malnourished, over a billion people do not have access to safe water, and over 2 billion have inadequate sanitation[8] Adrenergic agonists such as norepinephrine stimulate Na and C1 absorption and inhibit HCO3 and C1 secretion in both large land small intestine[9] These effects of norepinephrine on ion transport are mediated through specific postsynaptic c~2-adrenergic receptors present on enterocytes Adrenergic receptor occupancy results in the decrease of stimulated intracellular cyclic AMP, likely through the inhibitory component of adenylate cyclase.[10]

## CAUSES

In the latter stages of human digestion, ingested materials are inundated with water and digestive fluids such as gastric acid, bile, and digestive enzymes in order to break them down into their nutrient components, which are then absorbed into the bloodstream via the intestinal tract in the small intestine. To provide enough hydration and general balance, the large intestine reabsorbs the water and other digestive solvents in the waste product before defecation.[11] A "loose" or watery bowel movement is the consequence of the large intestine's inability to adequately absorb the water or other digestive fluids from fecal matter for a variety of causes.[12]

## EPIDEMIOLOGY

### Acute Diarrhea

Acute diarrhea can occur in various epidemiological settings including community acquired, hospital acquired, and during travel (traveler’s diarrhea). Understanding of the epidemiological settings in which diarrhea occurs directs the approach to diagnosis and treatment.[13]

### Community Acquired Diarrhea

At least 30–40% of acute bouts of diarrhea in the USA and other affluent countries are caused by viruses, making them the most prevalent kind of community-acquired diarrhea.[14] The two most prevalent types of viruses are rotaviruses and noroviruses. A member of the calicivirus

family, norovirus (formerly known as Norwalk virus) affects individuals of all ages. Norovirus is the primary cause of gastroenteritis in the United States, accounting for 40–60% of nonbacterial gastroenteritis that affects 23 million individuals each year.[15] Rotavirus predominantly affects children below 5 years and is also the leading cause of diarrhea-associated death in children below 5 years worldwide.[16] It is responsible for childhood diarrhea in 35% of hospitalized and 10–30% of community-based cases. Although rotavirus predominantly affects children, adults can also be affected as immunity wanes off and outbreaks tend to occur in close settings where chances of person-toperson transmission are higher such as day care centers, long-term care facilities, and schools.[17]

**Hospital-acquired diarrhea**

Diarrhea that does not incubate at the time of hospital admission and that appears three days after hospitalization is known as hospital-acquired diarrhea. It may be challenging to distinguish between hospital-acquired and community-acquired diarrhea since it is not entirely possible that the infection was incubating at the time of hospital admission. Hospitalized patients' usage of tube feeds, nonantibiotic medicine use, or antibiotic use can all be linked to hospital-acquired diarrhea.[18] However, CDI is the most common recognizable infectious cause of antibiotic-associated diarrhea in the developed world.[19] The frequency of this infection has increased dramatically and is now recognized as the most common cause of hospital-acquired infectious diarrhea in developed countries.

**Traveler’s diarrhea**

The passing of more than three unformed stools in a 24-hour period, together with one additional sign or symptom of an enteric infection, such as fever, cramping or discomfort in the abdomen, excessive gas, nausea, blood or mucus in the feces, tenesmus, or vomiting, is known as traveler's diarrhea.[20] According to the US Department of Commerce, 30 million Americans traveled to developing nations, with Mexico accounting for the majority of these trips . Of these, 40–60% of US visitors visiting Mexico are thought to get diarrheal sickness within a brief trip, with bacterial infections accounting for up to 85% of cases.[21] The frequency of traveler’s diarrhea varies between 4 and 40% with the highest rates (40%) seen in Latin America, Africa (except South Africa), most of the Middle East, and the Indian subcontinent.[22]

**Persistent Diarrhea**

Diarrhea that lasts two to four weeks is referred to as persistent. Like acute diarrheas, chronic diarrheas are mostly caused by infectious etiologies. The etiology differs based on the underlying host's immune system, recent travel history, and the area (developed or developing). Because persistent diarrhea frequently coexists with nutritional malabsorption, it can be linked to substantial morbidity.[23] Salmonella and Campylobacter are uncommon bacterial infections that cause chronic diarrhea in poor nations, but EPEC and EAEC are the most frequent culprits. Viruses like rotavirus and norovirus can cause chronic diarrhea in affluent nations, especially in youngsters.[24]

**Chronic Diarrhea**

Diarrhea that lasts more than four weeks is referred to as chronic. Depending on the population questioned and the definition of chronic diarrhea's inconsistencies, the prevalence of chronic diarrhea varies. However, the prevalence of chronic diarrhea in the United States varies between 14 and 18 percent if the criteria of excessive stool frequency (>3 times/day) or loose stools (more than 25% of the time) is used.[25,26] A majority of these patients may have irritable bowel syndrome with co-existing abdominal pain. When patients with abdominal pain are excluded, the reported prevalence is 3%.[27]

**PATHOPHYSIOLOGY OF DIARRHEA**

**Evolution**

According to two researchers, Nesse and Williams, diarrhea may function as an evolved expulsion defense mechanism. As a result, if it is stopped, there might be a delay in recovery.[28] They cite in support of this argument research published in 1973 that found that treating *Shigella* with the anti-diarrhea drug (Co-phenotrope, Lomotil) caused people to stay feverish twice as long as those not so treated. The researchers indeed themselves observed that: "Lomotil may be contraindicated in shigellosis. Diarrhea may represent a defense mechanism".[29]

**Diagnostic approach**

The following types of diarrhea may indicate further investigation is needed.

1. In babies.
2. Young toddlers who have moderate to severe diarrhea
3. Blood-related symptoms persist for more than two days.
4. Weight loss, fever, and non-cramping stomach discomfort are all related.

5. In passengers
6. In food handlers because to the risk of spreading the disease to others, at establishments like medical facilities, daycare centers, or homes for the elderly and convalescent.
7. Children's diagnoses are aided by a severity score.[30]

When diarrhea lasts for more than four weeks a number of further tests may be recommended including.[31]

1. Complete blood count and a ferritin if anemia is present
2. Thyroid stimulating hormone
3. Tissue transglutaminase for celiac disease
4. Fecal calprotectin to exclude inflammatory bowel disease
5. Stool tests for ova and parasites as well as for *Clostridioides difficile*
6. A colonoscopy or fecal immunochemical testing for cancer, including biopsies to detect microscopic colitis
7. Testing for bile acid diarrhea with SeHCAT, 7α-hydroxy-4-cholesten-3-one or fecal bile acids depending on availability
8. Hydrogen breath test looking for lactose intolerance
9. Further tests if immunodeficiency, pelvic radiation disease or small intestinal bacterial overgrowth suspected.

## PREVENTION OF DIARRHEA

### Sanitation

Improvements in drinking water and sanitation (WASH) have been linked to lower rates of diarrhea, according to several research. Water filters, high-quality piped water, and sewage hookups are a few examples of such improvements.[32] Interventions that encourage hand washing with soap result in notable decreases in the prevalence of diarrhea in homes, communities, and institutions.[33] The same goes for giving everyone in the community access to better sanitation and reducing open defecation.[34,35] This covers using restrooms as well as carrying out the full sanitary chain that is linked to them (collecting, moving, disposing of, or reusing human waste). There is limited evidence that safe disposal of child or adult feces can prevent diarrheal disease.

### Hand washing

Diarrheal illness transmission can be significantly impacted by basic sanitation practices. For instance, it has been scientifically demonstrated that hand washing with soap and water

reduces the incidence of illness by around 30 to 48%.[36,37,38] However, the CDC admits that poverty compromises hand washing in underdeveloped nations: "Access to soap and water is limited in a number of less developed countries, despite the fact that handwashing is essential to disease prevention worldwide. One of the several obstacles to good hygiene in less developed nations is this lack of availability. Implementing educational initiatives that promote hygienic practices is necessary to overcome this obstacle.[39]

**Water**

Given that water contamination is a major means of transmitting diarrheal disease, efforts to provide clean water supply and improved sanitation have the potential to dramatically cut the rate of disease incidence. In fact, it has been proposed that we might expect an 88% reduction in child mortality resulting from diarrheal disease as a result of improved water sanitation and hygiene.[40,41] Similarly, a meta-analysis of numerous studies on improving water supply and sanitation shows a 22–27% reduction in disease incidence, and a 21–30% reduction in mortality rate associated with diarrheal disease.[42] Chlorine treatment of water, for example, has been shown to reduce both the risk of diarrheal disease, and of contamination of stored water with diarrheal pathogens.[43]

**Vaccination**

A good way to avoid diarrheal illness is to immunize against the microorganisms that cause it, however this requires vaccination against specific infections. The use of a Rotavirus vaccine in 1985 produced a slight (2–3%) decrease in the overall incidence of diarrheal disease while reducing overall mortality by 6–10%. Rotavirus was responsible for about 6% of diarrheal episodes and 20% of diarrheal disease deaths in children in developing countries. Similar to this, a vaccine against cholera shown a significant decrease in morbidity and death; but, as cholera is not a major cause of diarrheal illness, the total effect of immunization was negligible.[44] Since then, more powerful vaccinations have been created that might save thousands of lives in underdeveloped countries while lowering medical costs and societal expenses.[45.46]

**Nutrition**

Promoting healthier eating habits can help address dietary deficits in developing nations. When compared to a control group, zinc supplementation shown a substantial reduction in the incidence of diarrheal illness.[47,48] The vast majority of research indicates that taking vitamin A supplements can help lower the risk of illness.[49] The fact that zinc plus vitamin A

supplementation was found to be much more cost-effective than vitamin A supplementation in lowering the incidence of diarrhea should be taken into account when developing a supplementing plan.[50]

**Breastfeeding**

It has been demonstrated that breastfeeding habits significantly reduce the prevalence of diarrheal illness in underprivileged communities. Research from several underdeveloped countries has demonstrated that infants who are exclusively breastfed for the first six months of their lives are more resistant to contracting diarrheal illnesses.[51] According to a Brazilian research, babies who were not breastfed had a 14-fold higher risk of dying from diarrhea than those who were.[52] The WHO presently recommends exclusive breastfeeding for the first six months of an infant's life[53], with sustained nursing until the child is at least two years old.[54]

**Others**

Probiotics decrease the risk of diarrhea in those taking antibiotics.[55] Insecticide spraying may reduce fly numbers and the risk of diarrhea in children in a setting where there is seasonal variations in fly numbers throughout the year.[56]

**MANAGEMENT**

Replacing lost liquids and salts is often the sole therapy required for diarrhea. Oral rehydration treatment is often administered orally; in more severe situations, intravenously. Restrictive diets like the BRAT diet are no longer advised.[57] Limiting milk consumption in children is not supported by research because it has no influence on the length of diarrhea. In contrast, the World Health Organization advises children who have diarrhea to keep eating since this promotes the return of normal intestinal functioning and ensures that enough nutrients are typically still absorbed to enable continued development and weight increase. The CDC advises cholera patients, including adults and children, to keep eating.[59] Early refeeding in children has not been linked to an increased risk of chronic diarrhea, vomiting episodes, or inappropriate intravenous fluid usage.[60] Bismuth subsalicylate and loperamide (Imodium) are two examples of medications that may be helpful but may not be appropriate in other circumstances.[61]

**Fluids**

Dehydration can be avoided by using oral rehydration solution (ORS), which is a slightly salted and sweetened water. Salty vegetable and chicken soups, salted rice water, and salted

yogurt drinks are examples of common home remedies. A half-teaspoon to a full teaspoon of salt (one and a half to three grams) can be added per liter to home remedies including water in which cereal has been boiled, unsalted soup, green coconut water, weak tea (unsweetened), and unsweetened fresh fruit juices. Several fluids can be provided, including clean simple water.[62] There are commercial solutions such as Pedialyte, and relief agencies such as UNICEF widely distribute packets of salts and sugar. A WHO publication for physicians recommends a homemade ORS consisting of one liter water with one teaspoon salt (3 grams) and two tablespoons sugar (18 grams) added (approximately the "taste of tears".[63] Rehydration Project recommends adding the same amount of sugar but only one-half a teaspoon of salt, stating that this more dilute approach is less risky with very little loss of effectiveness. Both agree that drinks with too much sugar or salt can make dehydration worse.[64] If available, add the recommended quantities of extra potassium and zinc. However, rehydration shouldn't be delayed by the availability of them. The most crucial thing is to start avoiding dehydration as soon as possible, as the WHO notes. The CDC advises continuing to provide Oral Rehydration Solution for the treatment of cholera while traveling to medical treatment, which is another instance of how timely ORS should help avoid dehydration. Vomiting frequently happens in the first hour or two of ORS therapy, particularly if a kid consumes the solution too rapidly. However, since the majority of the fluid is still absorbed, vomiting seldom stops effective rehydration. If a kid throws up, the WHO advises waiting five to ten minutes before reintroducing the solution more gradually. Soft drinks and fruit juices, which are particularly high in simple sugars, are not advised for children under five since they might worsen dehydration. Similar to drinking seawater, a too rich solution in the stomach pulls water from the rest of the body. If more targeted and efficient ORT preparations are not available or are not appetizing, plain water may be utilized.[65] In order to provide a medium level of sodium overall, the same person can also be given a combination of simple water and beverages that may be overly high in sugar and salt. If necessary, fluids can be given to young children via a nasogastric tube.[66]

**Eating**

A kid with diarrhea should continue to be fed, according to WHO guidelines. Normal intestinal function is restored more quickly with continued meals. Children whose diet is restricted, on the other hand, experience diarrhea that lasts longer and recovers intestinal function more slowly. "Food should never be withheld, and the child's regular foods should not be diluted," the WHO advises. Continue breastfeeding at all times. The CDC recommends

the same course of action in the particular case of cholera.[67] Infants with diarrhea who are breastfed frequently decide to continue breastfeeding, and this is something that should be supported. A lactose-free diet may help young children in the industrialized world who are not breastfed recover more quickly.[68] Insoluble fiber may exacerbate the condition, whereas soluble fiber-containing foods may aid.[69]

**Medications**

The four categories of antidiarrheal agents are antimotility, antisecretory, adsorbent, and anti-infectious.[70] Antibiotics are typically not used unless absolutely necessary, however they can be helpful in some cases of severe diarrhea.[71,72] Antibiotics may raise the risk of hemolytic uremic syndrome in individuals with Escherichia coli O157:H7 infections.[73] Antibiotic therapy may be helpful in nations with limited resources. But some germs, including Shigella, are becoming resistant to antibiotics.[74] Diarrhea may also be brought on by antibiotics, and the most frequent side effect of using generic antibiotics is antibiotic-associated diarrhea. Bismuth compounds (Pepto-Bismol) reduced the frequency of bowel movements in travelers' diarrhea patients, but they did not shorten the duration of their sickness.[75] Although they don't prolong the illness, anti-motility drugs like loperamide are also good in decreasing the quantity of stools.[76] Only in the absence of bloody diarrhea can these medications be administered.[77] Children's acute diarrhea symptoms can be effectively relieved by diosmectite, a natural aluminomagnesium silicate clay.[78] It also has some impact on chronic functional diarrhea, radiation-induced diarrhea, and chemotherapy-induced diarrhea.[79] Kaopectate is another absorbent medication used to treat moderate diarrhea.

Diarrhea in adults and children can be treated with the antisecretory drug racecadotril.[80] Because it produces less flatulence and constipation than loperamide, it is more tolerable.[81] It doesn't help much with children's acute diarrhea, either.[82]

Chronic diarrhea caused by bile acid malabsorption may benefit from bile acid sequestrants like cholestyramine. If bile acid malabsorption cannot be identified by a particular test, such SeHCAT retention, therapeutic trials of these medications are recommended for persistent diarrhea.[83]

**Alternative therapies**

In regions where malnutrition or zinc deficiency are prevalent, children older than six months who have diarrhea may benefit from taking zinc supplements.[84] Although not in the very

young, this confirms the World Health Organization's zinc recommendations. According to a 2020 Cochrane Review, there is no evidence that probiotics shorten the length of diarrhea and they have little to no effect on those who have it for two days or longer.[85] In adults, but maybe not in children, the probiotic lactobacillus can help avoid antibiotic-associated diarrhea.[86]

## CONCLUSSION

Diarrhea remains a widespread and significant public health issue, particularly in developing countries where access to clean water, sanitation, and healthcare may be limited. It can be caused by a variety of factors including infections (viral, bacterial, or parasitic), food intolerances, and underlying medical conditions. While often considered a minor illness, diarrhea can lead to severe dehydration, malnutrition, and even death if not properly treated, especially among children under five and the elderly. Effective prevention strategies, such as promoting good personal hygiene, ensuring the availability of safe drinking water, proper food handling, and increasing awareness about sanitation practices, play a crucial role in reducing its incidence. In addition, prompt treatment through oral rehydration therapy (ORS), zinc supplementation, and medical care when necessary can greatly improve outcomes. In conclusion, addressing diarrhea requires a combination of individual responsibility, community awareness, and strong healthcare infrastructure. Through education, improved public health systems, and global cooperation, we can significantly reduce the impact of this preventable yet potentially deadly condition.

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