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# Diarrheal Diseases: Investigating Mechanisms, Causative Factors, and Innovations in Treatment Approaches

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## *Abstract*

Diarrheal diseases remain a critical global health concern, particularly affecting young children and under-resourced communities. This paper investigates the fundamental mechanisms and clinical impacts of diarrheal diseases, while also showcasing the latest advancements in their treatment. Focusing on the root causes, it offers an in-depth look at the innovative strategies developed to tackle these diseases. Diarrhea can arise from a range of factors, including viral, bacterial, and parasitic infections, as well as food allergies, intolerances, digestive tract disorders, and medication side effects. The main mechanisms underlying diarrhea include elevated osmotic load, increased secretions, and reduced absorption. These processes are frequently triggered by enteric infections from pathogens such as norovirus, rotavirus, Campylobacter, Escherichia coli, Giardia lamblia, Entamoeba histolytica, among others. Additionally, diarrheal diseases can cause severe dehydration, electrolyte imbalances, and malnutrition, particularly in at-risk populations. Persistent diarrhea, lasting beyond four weeks, may stem from ongoing infections, inflammatory bowel diseases, or other gastrointestinal disorders. These chronic conditions can profoundly affect quality of life, hinder cognitive development, and negatively impact overall health outcomes. On the other hand, recent advancements in treatment have introduced several promising approaches. Oral rehydration therapy has proven effective in reducing both the severity and recurrence of acute diarrhea. Moreover, improvements in molecular diagnostics have enhanced the detection of enteropathogens, allowing for more precise and targeted treatments. The use of probiotics and antimicrobial therapies is also being investigated to restore healthy gut flora and address infectious diarrhea more effectively.

## I. Introduction

Diarrhea is characterized by an increase in both the volume and weight of stools, often accompanied by more frequent bowel movements. This condition is defined by the passage of loose or watery stools, indicating both elevated stool volume and a higher frequency of evacuations [1]. On the other hand, according to the World Health Organization (WHO), diarrhea is defined as the passage of three or more loose or watery stools within a 24-hour period [2]. Diarrhea can be classified into two main categories:

acute and chronic. Acute diarrhea typically lasts up to 14 days, while chronic diarrhea persists for more than 30 days. The World Gastroenterology Organization defines acute diarrhea as a sudden increase in the frequency of semi-solid or liquid stools, usually lasting less than two weeks. Its causes are diverse, including infections by viruses, bacteria, or parasites; food intolerances; adverse reactions to medications; and gastrointestinal disorders. Symptoms vary in severity, ranging from loose, watery stools to more serious manifestations such as dehydration, fever, and abdominal pain [3,4]. In addition to their distinct durations, acute and chronic diarrhea exhibit distinct characteristics and underlying causes. Acute diarrhea usually appears to have a sudden onset and is commonly associated with infections caused by viruses, bacteria, or parasites. It commonly resolves spontaneously within a short time, with supportive care—particularly rehydration therapy—playing a vital role in its management [5]. In contrast, chronic diarrhea persists for more than 30 days and may arise from a broader range of underlying conditions, including malabsorption syndromes, inflammatory bowel disease (IBD), irritable bowel syndrome (IBS), and other non-infectious disorders. It is often accompanied by persistent loose stools, weight loss, and signs of malnutrition, requiring comprehensive diagnostic evaluations and tailored therapeutic interventions to manage the root causes effectively [5,6]. Diarrhea, on another hand, can be triggered by a variety of pathogens, including viral, bacterial, and parasitic agents. Among viruses, rotavirus, norovirus, adenovirus, and astrovirus are commonly responsible, particularly in children. Rotavirus, in particular, is the leading cause of severe acute gastroenteritis in young children [8,9]. Bacterial pathogens, including Escherichia coli, Salmonella spp, Shigella spp, and Campylobacter jejuni, are commonly associated with diarrhea, with Salmonella spp and Campylobacter jejuni being especially prevalent. Moreover, parasitic agents such as Cryptosporidium spp, Giardia spp, and Entamoeba histolytica are major contributors to diarrhea, particularly in regions with poor sanitation and hygiene [10,11]. Complications associated with diarrhea can be serious, with dehydration emerging as a main concern, particularly in vulnerable populations such as young children, the elderly, and immunocompromised individuals. If left untreated, dehydration can lead to severe consequences, including organ dysfunction, hypovolemic shock, and potentially coma. Therefore, prompt and appropriate treatment is essential to mitigate these potentially life-threatening outcomes [5, 12, 13]. Moreover, metabolic acidosis, a common complication of acute diarrhea, can arise from the significant loss of fluids and electrolytes [13]. Furthermore, electrolyte imbalances resulting from the loss of fluids and electrolytes can lead to serious complications, including hypovolemic shock and prerenal azotemia [14]. Additionally, although rare, Hemolytic Uremic Syndrome (HUS) is a complication frequently associated with infections caused by Escherichia coli O157. This condition can result in anemia, thrombocytopenia, and acute kidney failure [5]. Other complications of diarrhea include intussusception, toxic or hypovolemic shock with prerenal azotemia, and encephalitis. While these complications are

relatively rare, they are possible. Additionally, infections can spread to other parts of the body, such as the bones, joints, or meninges, particularly with pathogens like Salmonella. For example, Salmonella infections can lead to serious extraintestinal complications, including osteomyelitis, septic arthritis, and meningitis, all of which pose significant life-threatening risks [15,16]. Diarrhea remains a significant global health issue, ranking as one of the leading causes of morbidity and mortality worldwide. In 2016, it was the eighth leading cause of death globally, contributing to more than 1.6 million fatalities. Among children under the age of five, diarrhea was the fifth leading cause of death, responsible for 446,000 deaths [17]. This review seeks to discuss and clarify the various causes of diarrheal diseases, including both infectious agents and non-infectious factors. It will review the pathophysiology of diarrhea, with an emphasis on the disturbances in intestinal function and their wider systemic effects. The review will also assess clinical outcomes, discussing both common and severe complications. Additionally, it will focus on the latest advancements in treatment and prevention, underscoring the significance of continued research and global health initiatives in addressing the ongoing global burden of gastrointestinal diseases.

## II. THE MOST COMMON CAUSES OF DIARRHEA

Diarrhea can result from a range of factors, which are typically categorized into four main groups: infectious agents, dietary factors, medications, and underlying medical conditions. The following summarizes the key causes based on the available sources:

### 2.1. Infectious Causes

Infectious diarrhea refers to diarrhea caused by the invasion of pathogenic microorganisms, including bacteria, viruses, or parasites, into the gastrointestinal tract. These pathogens release toxins or provoke inflammation in the intestines, leading to enhanced bowel motility and fluid loss, which in turn causes diarrhea [18]. The primary pathogens responsible for infectious diarrhea include:

#### 2.1.1. Viruses

Viruses play a crucial role in causing diarrhea, especially in infants and young children. Some of the primary viral pathogens responsible for diarrhea include:

**a. Rotavirus**

Rotavirus, a member of the Reoviridae family, is recognized for its wheel-like appearance, with "Rota" deriving from the Latin word for wheel. The virus's inner capsid contains a genome composed of 11 segments of double-stranded RNA, which encode six structural proteins and six non-structural proteins. Its structural configuration features three concentric layers that enclose the double-stranded RNA genome, forming a triple-layered particle [23]. It’s crucial to mention that Rotavirus is a highly contagious virus that causes severe gastroenteritis, predominantly affecting infants and young children

under five years of age [19, 20]. Furthermore, it is the leading cause of acute diarrhea worldwide, accounting for approximately 200,000 deaths each year, with the highest impact observed in developing countries where healthcare resources are limited [20]. Rotavirus is also transmitted via the fecal-oral route, either through direct contact with infected individuals or through contaminated surfaces, food, or water [21]. Additionally, symptoms typically include severe, watery diarrhea, vomiting, fever, and abdominal pain, which can lead to dehydration if not addressed promptly. Despite the availability of effective vaccines, rotavirus continues to cause outbreaks, particularly among populations that remain unvaccinated [22] . The significance of maintaining proper hygiene, especially handwashing, in preventing rotavirus infections is well-documented in the literature. Research conducted in India demonstrated that handwashing with soap led to a 39% reduction in diarrheal episodes among children under the age of five [24]. Nonetheless, vaccination is recognized as the most effective measure for preventing rotavirus infections and mitigating related morbidity and mortality. The World Health Organization advises that all nations incorporate rotavirus vaccination into their national immunization programs [25].

**b. Norovirus**

Human norovirus, formerly referred to as Norwalk virus, was initially identified in stool samples collected during a gastroenteritis outbreak in Norwalk, Ohio. It was the first viral pathogen established to cause gastroenteritis. The illness associated with this virus was originally described in 1929 as "winter vomiting disease," reflecting its seasonal occurrence and the common presentation of vomiting as a predominant symptom [26]. Norovirus is an extremely contagious pathogen and stands as a leading cause of acute gastroenteritis worldwide, often surpassing rotavirus in developed nations where vaccination is prevalent [27]. This non-enveloped, positive-sense, single-stranded RNA virus belongs to the Caliciviridae family and can be transmitted via the fecal-oral route, with as few as 10 viral particles required to establish an infection (28). The typical clinical presentation includes nausea, vomiting, diarrhea, and abdominal pain, which can escalate to severe dehydration, especially among vulnerable groups such as young children and the elderly [26, 27]. Effective prevention primarily hinges on rigorous hygiene practices, including thorough handwashing with soap and water, as alcohol-based sanitizers prove less effective against this virus [27, 29]. While there is currently no FDA-approved vaccine for norovirus, several candidates are under development, underscoring the ongoing need for robust preventive measures to address the considerable health and economic impact of norovirus infections [28, 30]. Norovirus is responsible for approximately 16% of global cases of acute gastroenteritis, with prevalence varying by setting. It is more common in community (20%) and outpatient (18%) settings compared to inpatient environments (15%). Children under five and regions in South America (22%) are particularly affected. These findings highlight norovirus's significant impact

on acute gastroenteritis worldwide and the urgent need for targeted interventions, including vaccines, to mitigate its effects [31, 32].

**c. Enteric adenoviruses, astrovirus, and cytomegalovirus**

Enteric adenoviruses, astroviruses, and cytomegalovirus are well-established viral pathogens associated with diarrhea, particularly among pediatric populations. Human adenovirus types F40 and F41 are notable for their significant role in acute gastroenteritis, contributing to approximately 1% to 20% of diarrhea cases in children. Among these, serotypes 40 and 41 are particularly prominent due to their strong association with gastroenteritis [33, 34, 35]. Astroviruses are also recognized as important contributors to diarrhea in pediatric populations, especially in children under the age of five. These viruses are associated with causing mild to moderate gastroenteritis, playing a notable role in the spectrum of viral pathogens responsible for gastrointestinal ailments in young children [34, 36]. Cytomegalovirus, although predominantly affecting immunocompromised individuals, can cause gastrointestinal symptoms such as diarrhea, particularly in infants and those with HIV/AIDS [35, 37]. This underscores the varied viral origins of diarrhea and highlights the necessity for robust surveillance and preventive strategies to mitigate the public health impact of these viruses.

**2.1.2. Bacteria:**

Bacterial pathogens are a leading global cause of infectious diarrhea. Notable among these are Escherichia *coli*—which includes various pathogenic strains such as enteropathogenic (EPEC), enterohemorrhagic (EHEC), enteroaggregative (EAEC), enterotoxigenic (ETEC), and enteroinvasive (EIEC)—as well as *Shigella*, *Salmonella, Campylobacter*, *Clostridium difficile*, and *Vibrio cholerae* [38, 39, 40]. Each of these pathogens contributes uniquely to diarrheal disease, and detailed descriptions of their roles and impacts are as follows:

***a. Escherichia coli***

*Escherichia coli* (*E. coli*) is a gram-negative, facultative anaerobic, rod-shaped bacterium typically residing in the gastrointestinal tracts of humans and other warm-blooded animals. Although many *E. coli* strains are benign and beneficial, specific pathogenic variants are capable of inducing severe gastrointestinal infections, which often result in diarrhea [41, 42]. Moreover, *Escherichia coli* (*E. coli*) is a prominent cause of infectious diarrhea globally, with a significant impact in developing countries. This bacterium includes several pathogenic strains, each linked to specific gastrointestinal conditions: Enteropathogenic *E. coli* (EPEC) mainly causes diarrhea in infants; Enterohemorrhagic *E. coli* (EHEC/STEC) is known for severe complications like hemorrhagic colitis and hemolytic uremic syndrome; Enterotoxigenic *E. coli* (ETEC) is a key cause of traveler's diarrhea and infant diarrhea; Enteroaggregative *E. coli* (EAEC) is associated with persistent diarrhea; and Enteroinvasive *E. coli*

(EIEC) leads to dysentery-like symptoms [39, 43]. In addition, these bacterial strains attach to the epithelial cells of the intestines via specialized fimbriae and secrete toxins that interfere with normal intestinal function. This disruption results in diarrhea, which may manifest as non-inflammatory, characterized by watery stools, or inflammatory, leading to dysentery [43]. Transmission of the bacteria primarily occurs through the fecal-oral route, with heightened severity observed in infants and individuals living in conditions with inadequate sanitation. Preventative strategies emphasize the importance of maintaining proper hygiene practices, including regular hand-washing, appropriate food preparation, and ensuring the chlorination of water supplies [43].

***b. Salmonella* and *Shigella***

*Salmonella* and *Shigella* are major bacterial pathogens responsible for gastrointestinal infections, which can lead to diarrhea and other serious complications. Salmonella, a Gram-negative, facultative anaerobic rod, is associated with a range of illnesses, from asymptomatic carriage to potentially fatal typhoidal fever. In developed countries, the predominant forms of Salmonella infection are food-borne acute gastroenteritis and enterocolitis, with approximately 1.2 million cases reported annually in the U.S [44, 45]. While on another hand. *Shigella*, a gram-negative bacterium that lacks motility and has a rod-like shape, is categorized into four distinct serological groups. This pathogen is notorious for inducing acute gastroenteritis characterized by bloody and mucous-laden diarrhea, fever, and abdominal cramping, typically manifesting within 1 to 4 days of exposure. Clinical manifestations of *Shigella* infection include elevated body temperature, general discomfort, watery stools, painful abdominal cramping, and muscle aches [44, 46]. Both pathogens are transmitted through the fecal-oral route, with spread occurring via contaminated food, water, or direct contact with an infected individual. Even though *Shigella* and non-Shiga toxin-producing *E. coli* share genetic similarities, distinguishing between them is essential for accurate epidemiological surveillance. These infections pose serious public health challenges, especially in developing countries, where they are linked to elevated rates of morbidity and mortality (46, 47, 48).

***c. Campylobacter***

*Campylobacter*, a genus of gram-negative, microaerophilic bacteria, is widely recognized as a leading cause of bacterial diarrhea worldwide. Among its various species, *Campylobacter jejuni* stands out as the main agent behind the majority of human infections, accounting for approximately 90% of cases. These infections typically result from consuming undercooked or raw poultry, drinking water contaminated with the bacteria, or coming into contact with infected animals, particularly birds and household pets [49]. Furthermore, *Campylobacter jejuni* is identified as a major cause of bacterial gastroenteritis globally, with a significant rise in cases observed over the past decade, especially in

developed areas like North America, Europe, and Australia. Data show that the incidence of campylobacteriosis increased from 67 cases per 100,000 people in 2014 to 93 cases per 100,000 in 2019, underscoring a troubling trend in public health [50]. While extensive epidemiological data from Africa, Asia, and the Middle East remains limited, current research indicates that *C. jejuni* infections are widespread in these areas, particularly affecting children [51].

***d. Clostridium difficile***

*Clostridioides difficile*, previously identified as *Clostridium difficile*, is a Gram-positive, spore-forming bacterium recognized as a principal etiological agent of antibiotic-associated diarrhea and colitis. This pathogen secretes a range of toxins that can manifest in symptoms varying from mild diarrhea to more severe gastrointestinal disorders, including pseudomembranous colitis and toxic megacolon, the latter of which poses a significant risk of mortality [52]. Moreover, the principal risk factor for infection with *Clostridioides difficile* is the administration of antibiotics, particularly broad-spectrum antibiotics, which disturb the equilibrium of intestinal microbiota and facilitate the overgrowth of *C. difficile*, leading to toxin production. Additional risk factors encompass advanced age, immunosuppressive states, preexisting health conditions, and recent hospitalizations. Transmission occurs via fecal contamination of surfaces and medical equipment. Hence, stringent infection control practices, including the application of EPA-registered disinfectants, are essential to mitigate the risk of spread [53, 54]. Furthermore, *C. difficile* infection (CDI) commonly occurs in individuals with preexisting health conditions. Recent data indicate that 56% of CDI cases were linked to antibiotic use within the previous 12 weeks, underscoring the importance of addressing these factors in the development of effective prevention and management strategies [55]. Additionally, in 2022, the incidence of CDI in Atlanta, Georgia, demonstrated an age-related increase. Moreover, the infection rates were notably higher among women compared to men and were more prevalent among White individuals relative to those of other racial backgrounds [55, 56]. The infection can present a spectrum of severity, from asymptomatic carriage to severe, potentially life-threatening colitis. In addition, transmission predominantly occurs via the fecal-oral route [57].

***e. Vibrio cholerae***

*Vibrio cholerae* is the pathogen responsible for cholera, a highly transmissible diarrheal disease marked by intense, acute watery diarrhea and significant dehydration [58]. Cholera is contracted through the consumption of food or water contaminated with the bacterium, particularly in regions with insufficient sanitation and limited access to clean drinking water [58]. Shockingly, cholera is considered one of the most pervasive and lethal diseases worldwide. Researchers estimate that each year, there are between 1.3 and 4.0 million cases of cholera, with global fatalities ranging from 21,000 to 143,000 [58]. This

Gram-negative, comma-shaped bacterium causes disease by producing cholera toxin, which stimulates intestinal fluid secretion and disrupts the mucosal barrier. This results in profuse watery diarrhea and vomiting [59]. Interestingly, cholera continues to pose a major public health challenge, having been responsible for seven significant pandemics, the most recent of which began in 1961 and has impacted millions globally. Treatment typically includes oral rehydration therapy, while severe cases may require intravenous fluids and antibiotics [59, 60]. The disease can be prohibited through vaccination, The Oral Cholera Vaccine (OCV) has been endorsed as a supplementary measure to enhance public health efforts in regions experiencing cholera outbreaks or at risk of such occurrences, alongside improvements in water, sanitation, and hygiene (WASH) [59]. The latest generation of OCV is both safe and effective, providing substantial protection for older children and adults, although its efficacy is somewhat limited in children under five years old. The synergy of direct vaccination benefits and the herd immunity it fosters renders OCV a cost-effective solution, making it particularly advantageous for implementation in developing nations [59, 61].

#### 2.1.3. Parasites

Diarrhea represents a significant global health challenge, especially in developing countries where intestinal parasites are a key contributing factor. Research indicates that parasitic infections, notably those caused by *Entamoeba histolytica* and *Giardia lamblia*, are widespread among children experiencing diarrhea, with infection rates reaching up to 22.67% in certain populations [62]. Additionally, these parasites can cause both acute and chronic diarrhea, with Giardia lamblia being particularly prevalent in regions characterized by inadequate sanitation and contaminated water sources [63]. It is essential to recognize that the relationship between parasites and diarrhea is further complicated by socio-economic factors. Variables such as maternal education and access to clean drinking water play a significant role in influencing the prevalence of these infections [62]. Furthermore, individuals who have traveled to regions with endemic parasitic diseases often experience persistent diarrhea upon their return. This highlights the critical need to comprehend the role of parasitic pathogens in the broader landscape of both local and international health [64]. The World Health Organization identifies *Cryptosporidium*, *Giardia*, and *Entamoeba* species as some of the most prevalent parasites linked to diarrhea [10].

##### *a. Entamoeba histolytica*

*Entamoeba histolytica* is a ubiquitous parasitic protozoon linked to diarrhea, particularly in densely populated areas with inadequate sanitation and personal hygiene. This protozoan infects both humans and animals and is transmitted through the ingestion of food or drinking contaminated with its quad nucleated cysts. The subsequent disease, known as amoebiasis or amoebic dysentery, is characterized by

symptoms such as mucous or bloody diarrhea [65,66]. *E. histolytica* is recognized as one of the most prevalent parasites worldwide. Amoebiasis affects approximately 50 million individuals annually and leads to about 100,000 deaths each year [65, 66].

In addition, amoebic dysentery is characterized by bloody diarrhea, abdominal cramps, and fever. In more severe instances, *E. histolytica* can invade other organs, most commonly the liver, leading to the formation of abscesses. Approximately 10% to 20% of individuals infected with *E. histolytica* develop symptomatic disease, with the severity of symptoms often correlating with the parasite's density within the host [67].

***b. Giardia lamblia***

*Giardia lamblia*, also referred to as *Giardia intestinalis* or *Giardia duodenalis*, is a flagellated protozoan parasite responsible for giardiasis, an intestinal infection marked by symptoms such as diarrhea, abdominal cramps, and bloating [68]. This parasite is widespread globally, especially in regions with inadequate sanitation and unsafe water sources. *G. lamblia* exists in two life stages: the motile trophozoite, which attaches to the intestinal epithelium, and the cyst, a resilient form capable of surviving outside the host in the environment for extended periods [68, 69]. Remarkably, Giardiasis is mainly transmitted through the fecal-oral route, frequently involving ingestion of water or food tainted with the parasite. Symptoms generally manifest one to three weeks after exposure and may include foul-smelling, greasy stools and weight loss. Though the infection often resolves on its own, it can sometimes result in chronic malabsorption, particularly in children [68]. Treatment typically includes antimicrobial drugs like metronidazole or tinidazole, while prevention strategies emphasize enhancing water quality and maintaining rigorous hygiene practices [68, 70].

***c. Cryptosporidium***

*Cryptosporidium* is a genus of protozoan parasites responsible for cryptosporidiosis, a disease that predominantly impacts the intestines of humans and other vertebrates. The infection is frequently spread via the fecal-oral route, primarily through contaminated water sources, such as untreated drinking water and swimming pools [71]. Additionally, cryptosporidiosis is marked by symptoms including watery diarrhea, abdominal cramps, nausea, and vomiting. The severity of these symptoms can vary considerably depending on the host's immune status [71, 72]. Interestingly, *Cryptosporidium* exhibits a high resistance to chlorine disinfection, rendering waterborne outbreaks a major public health concern [73]. Effective preventive measures include maintaining rigorous hygiene practices, avoiding exposure to contaminated water, and ensuring proper sanitation in environments such as childcare settings and animal handling areas [73].

**2.2. Food Intolerances**

It is imperative to distinguish between adverse reactions to foods, excluding those caused by toxins, which result from individual intolerances to foods that are otherwise commonly tolerated [74]. Reactions triggered by an immune response are categorized as food allergies, while those that do not involve the immune system are referred to as food intolerances. Among these, IgE-mediated food allergies represent the most prevalent and severe form of adverse food reactions [74]. Furthermore, food intolerances are estimated to impact up to 20% of the population. However, the precise prevalence is challenging to determine due to the absence of standardized diagnostic tests [75]. In addition, the most prevalent food intolerances encompass lactose intolerance, gluten intolerance, and fructose malabsorption. Lactose intolerance arises from a deficiency in the lactase enzyme and affects approximately 65% of the global population. Gluten intolerance, which is distinct from celiac disease, can lead to gastrointestinal symptoms in individuals who are sensitive to gluten [75, 76]. Symptoms of food intolerances primarily affect the digestive system and may include diarrhea, bloating, gas, abdominal pain, and other gastrointestinal disturbances. Additionally, individuals may experience non-digestive symptoms such as headaches, fatigue, and skin rashes [75].

### 2.3. Medications

Over 700 different medications have been associated with the onset of diarrhea, with prolonged use of antibiotics, laxatives, magnesium-based antacids, and nonsteroidal anti-inflammatory drugs (NSAIDs) being particularly frequent offenders [81]. These substances can disturb the equilibrium of gut microbiota, often resulting in persistent diarrhea [81]. Obviously, medications can play a substantial role in causing diarrhea, especially those that affect gut motility, alter the gut microbiome, or induce gastrointestinal side effects. Broad-spectrum antibiotics, including ampicillin and clindamycin, are particularly notorious for disrupting the normal balance of intestinal flora, frequently resulting in diarrhea [77]. Moreover, a variety of medications can also induce diarrhea as an adverse effect. Among these, antibiotics such as amoxicillin and cephalosporins are notable for potentially leading to *Clostridioides difficile* infections. Stimulant laxatives, including bisacodyl and senna, are frequently associated with diarrhea, as are antacids containing magnesium, like magnesium hydroxide. Nonsteroidal anti-inflammatory drugs (NSAIDs), including ibuprofen and aspirin, may also contribute to gastrointestinal disturbances[78, 79]. As well, certain chemotherapy agents, such as irinotecan, are well-documented causes of diarrhea. Proton pump inhibitors (PPIs) like omeprazole can occasionally be linked to this condition, as can metformin, which is widely used in diabetes management. Furthermore, cardiac medications such as digoxin and quinidine are also implicated in causing [78, 79]. Lastly, chemotherapy agents and immunosuppressive drugs are recognized for inducing gastrointestinal symptoms, including diarrhea, owing to their cytotoxic effects on the intestinal lining [80].

### 2.4. Chronic Circumstances

Chronic diarrhea can be attributed to several underlying health circumstances, including irritable bowel syndrome (IBS), inflammatory bowel diseases (IBD) like Crohn's disease, ulcerative colitis, and malabsorption syndromes. IBS is particularly marked by persistent abdominal pain and alterations in bowel movements, frequently leading to chronic diarrhea [82]. Additionally, inflammatory bowel diseases (IBD), such as Crohn's disease and ulcerative colitis, result in chronic inflammation and damage to the intestinal lining. This ongoing inflammation often leads to symptoms including persistent diarrhea, abdominal pain, and weight loss [82, 83]. Malabsorption syndromes, which involve disorders that hinder the absorption of nutrients in the small intestine, can also result in chronic diarrhea. These conditions often present with additional symptoms related to nutritional deficiencies [82, 84].

### 2.5. Travelers' Diarrhea

Traveler's diarrhea is a prevalent condition affecting 40 to 60% of individuals journeying to destinations with limited resources. It is primarily caused by bacterial infections, with *Escherichia coli* being the most common pathogen, though other bacteria, viruses, and parasites can also be involved [85]. The condition presents with symptoms such as diarrhea, abdominal cramps, nausea, vomiting, and fever, which can lead to dehydration and severe complications if not addressed promptly. To prevent traveler's diarrhea, it is advised to consume safe food and water, maintain good hygiene practices, and consider prophylactic medications. Effective management includes staying hydrated, using antidiarrheal agents, and, when necessary, administering antibiotics or antiparasitic treatments [85, 86, 87]. Figure 1 below illustrates the key underlying causes of diarrhea as identified in this study.

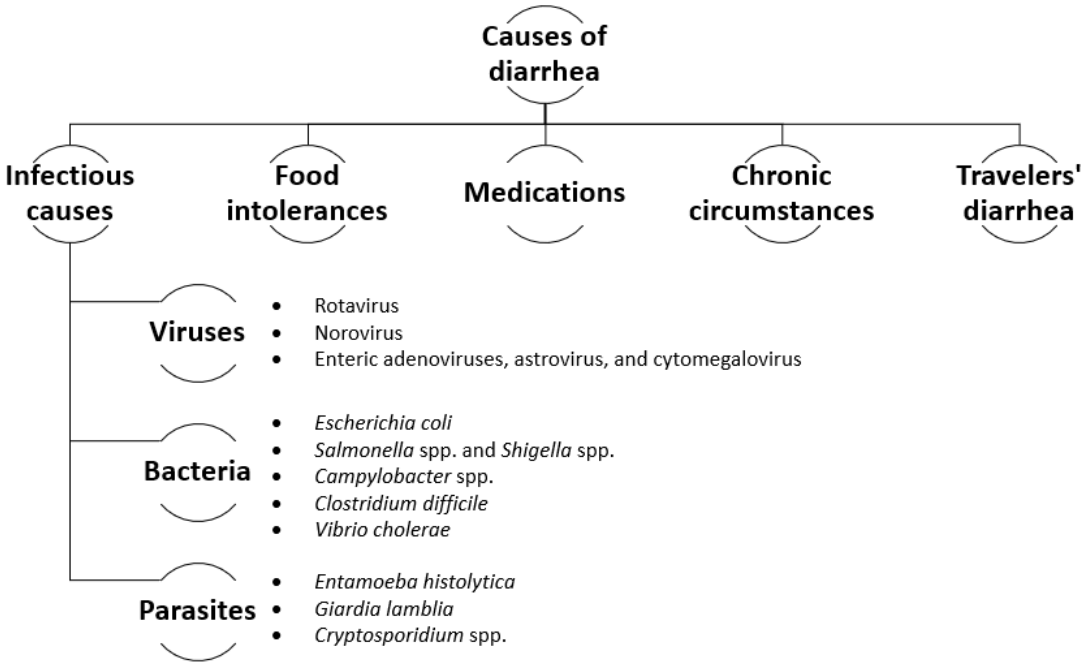

**Figure 1.** The most common causes of diarrhea based on the reviewed literature

## III. MECHANISMS OF DIARRHEA

### 3.1. Secretory Diarrhea

Secretory diarrhea results from an increase in active intestinal fluid secretion or a reduction in absorption, typically occurring without substantial structural damage to the intestinal epithelium [88]. Furthermore, common causes of secretory diarrhea include toxins, bile acid malabsorption, short-chain fatty acids, microscopic colitis, and specific medications such as laxatives, antiarrhythmics, and chemotherapeutic agents [88, 89]. As previously discussed, this type of diarrhea arises from the abnormal secretion of fluids and electrolytes into the intestinal lumen. It is frequently triggered by bacterial enterotoxins, such as those produced by *Vibrio cholerae* and specific strains of *Escherichia coli*. These toxins activate adenylate cyclase or other signaling pathways, resulting in increased secretion of chloride ions and water into the intestinal lumen [90, 91]. Additionally, the secretion of chloride ions establishes an osmotic gradient that draws water into the intestinal lumen, leading to the production of watery stools. This process is often mediated by transporters such as the cystic fibrosis transmembrane conductance regulator (CFTR) and other chloride channels [91]. It is important to note that sodium accompanies chloride to maintain electrical balance, which further exacerbates fluid loss. Current treatments focus on replenishing fluids and electrolytes through oral rehydration solutions. Meanwhile, emerging therapies aim to target intestinal ion channels and transporters to inhibit excessive secretion and enhance nutrient absorption [88, 91].

### 3.2. Osmotic Diarrhea

Osmotic diarrhea occurs when unabsorbed solutes in the intestine attract excess water into the bowel, resulting in increased stool volume and a watery consistency. This type of diarrhea is commonly linked to malabsorption syndromes, where the body struggles to absorb specific nutrients effectively, as seen in conditions such as lactose intolerance or celiac disease [92, 93]. Common causes of osmotic diarrhea include the ingestion of poorly absorbed sugars, such as lactose and fructose, sugar alcohols like sorbitol, and certain medications, including magnesium-based laxatives and some antibiotics [92, 93]. Unlike secretory diarrhea, osmotic diarrhea typically resolves with fasting or by removing the offending substances from the diet. This reduction in osmotic load facilitates the normal absorption of water and electrolytes, leading to symptom relief [92, 93, 94].

### 3.3. Inflammatory Diarrhea

Inflammatory diarrhea is distinguished by inflammation of the intestinal mucosa, leading to symptoms such as abdominal pain, fever, and the presence of blood in the stool [95]. This condition is often

associated with inflammatory bowel diseases (IBD), including Crohn's disease and ulcerative colitis, both of which are characterized by persistent inflammation and injury to the digestive tract [95]. Not only does inflammatory diarrhea result from the disruption of the intestinal barrier, which allows pathogens to invade and trigger an immune response that intensifies tissue damage and fluid loss, but it is also commonly caused by infectious agents. These include bacteria such as Salmonella, Shigella, and Campylobacter, as well as parasites like *Entamoeba histolytica* [96, 97]. The diarrhea associated with this condition is typically marked by smaller stool volumes, urgency, and tenesmus. Treatment primarily aims to address the underlying cause, which may include anti-inflammatory medications, antibiotics for infections, and supportive care to maintain hydration and electrolyte balance. Proper management of inflammatory diarrhea is essential, as it can substantially affect quality of life and potentially lead to complications if not effectively treated [89, 98].

### 3.4. Motility-Related Diarrhea

Diarrhea related to motility arises when abnormal intestinal motility accelerates the passage of content through the gastrointestinal tract, leading to loose or watery stools. The condition is often linked to various gastrointestinal disorders, such as irritable bowel syndrome (IBS) [90].. In particular, IBS with diarrhea (IBS-D) is characterized by increased colonic motility and heightened propulsive contractions, which contribute to the onset of diarrhea [90]. Motility-related diarrhea can result from a variety of factors, including structural abnormalities, nerve damage, and specific gastrointestinal conditions. Small intestinal bacterial overgrowth (SIBO) and inflammatory bowel diseases (IBD) such as Crohn's disease and ulcerative colitis can significantly contribute to this condition by disrupting normal intestinal motility patterns [100. In SIBO, the excessive bacterial growth in the small intestine can enhance motility and induce diarrhea. In IBD, the inflammation and damage to the intestinal wall interfere with regular motility, leading to diarrhea. Moreover, these conditions can further aggravate bowel motility, thereby perpetuating the symptoms of diarrhea [100, 101]. Excessively rapid entry of chyme into the small or large intestine results in propulsive motor patterns that accelerate transit time. Inflammation is typically linked with a reduction in normal mixing motor patterns while increasing propulsive motility, including high amplitude propagated contractions (HAPCs) [102]. The evidence regarding abnormal small intestinal motility in diarrhea associated with irritable bowel syndrome (IBS) is mixed, with any observed differences being relatively minor. Conversely, increased colonic HAPCs and enhanced propulsion are commonly observed in irritable bowel syndrome with diarrhea (IBS-D) [102].

### 3.5. Cellular and Molecular Mechanisms

In addition, diarrhea involves intricate alterations in several physiological mechanisms, including ion transport, tight junction integrity, and neuroimmune interactions. Ion transport plays a pivotal role,

particularly in secretory diarrhea, where increased chloride secretion drives water into the intestinal lumen. This process is often mediated by transporters and channels such as the cystic fibrosis transmembrane conductance regulator (CFTR) [103]. Furthermore, tight junctions between epithelial cells are crucial for maintaining the integrity of the intestinal barrier. Not only do these junctions ensure proper barrier function, but their disruption can also lead to increased permeability, resulting in enhanced fluid loss and compromised barrier integrity [104, 105]. Additionally, neuroimmune interactions are pivotal, as both the enteric nervous system and the immune system play key roles in regulating intestinal function. Not only do alterations in these systems, such as those induced by infections or inflammatory responses, contribute to the onset of diarrhea, but they also exacerbate its severity [106]. Figure 2 below demonstrates the main mechanisms of diarrhea, clinical implications, risk factors, and innovations in treatment.

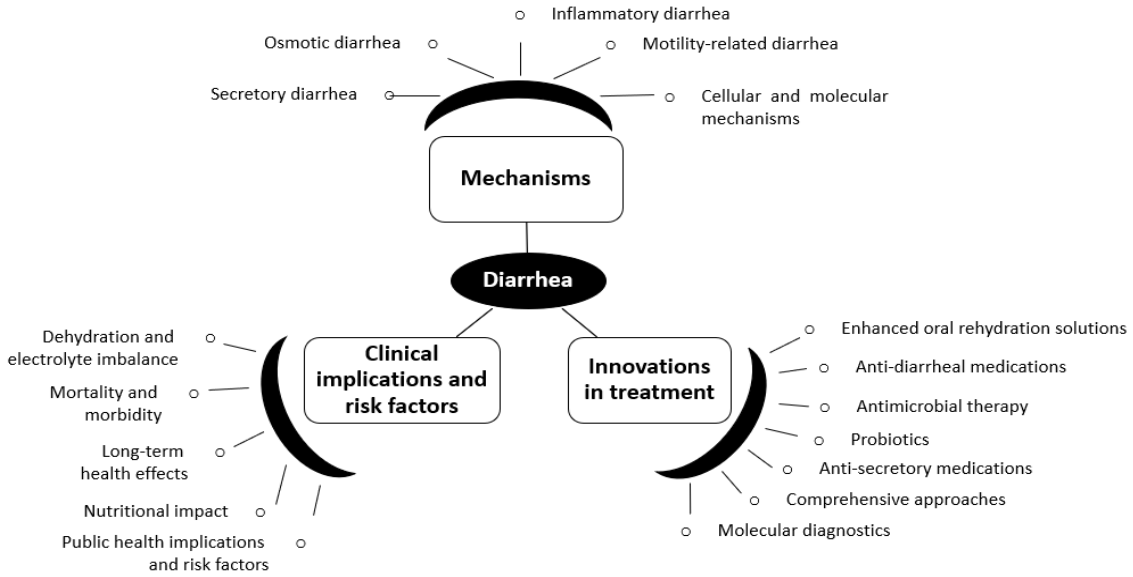


**Figure 2.** Main mechanisms of diarrhea, clinical implications, risk factors, and innovations in treatment

## IV. CLINICAL IMPLICATIONS AND RISK FACTORS

Diarrhea represents a major global public health issue, particularly impacting vulnerable groups like children and the elderly. Its clinical repercussions can be severe, resulting in a range of health complications and placing a greater strain on healthcare systems, the most common implications are:

### 4.1. Dehydration and Electrolyte Imbalance:

Diarrhea can lead to dangerous levels of dehydration and imbalances in electrolytes, making swift intervention essential. Effective management often hinges on rehydration strategies, such as oral rehydration solutions or, in more critical situations, intravenous fluids [107, 108]. Besides, Diarrhea not only leads to dehydration and electrolyte imbalances but also exacerbates these issues through the significant loss of fluids and essential minerals via frequent, watery stools. Common disturbances include low sodium levels (hyponatremia), decreased potassium (hypokalemia), and metabolic acidosis due to the loss of bicarbonate [09, 110]. Otherwise, in children, these imbalances can develop rapidly, with research indicating that up to 80% of pediatric patients with diarrhea show electrolyte disturbances, greatly raising the risk of mortality if not swiftly managed [111]. These imbalances stem from disrupted water and electrolyte transport in the intestines, further aggravated by factors like vomiting, fever, and insufficient fluid intake [111]. Furthermore, electrolyte imbalances may manifest through symptoms like headaches, nausea, fatigue, and muscle spasms. In more severe cases, they can escalate to serious conditions such as seizures, coma, or cardiac arrest [119]. It's essential to note that effective management demands rapid rehydration with suitable electrolyte solutions to restore balance and avert severe complications, such as cardiovascular collapse and neurological issues [112].

### 4.2. Mortality and Morbidity

Diarrhea stands as a major contributor to both mortality and morbidity, particularly affecting children under five. This condition accounts for about 1.236 million deaths each year in this age group, positioning it as the second leading cause of death[113].. The intensity of diarrhea incidents among these young children varies significantly: 64.8% are mild, 34.7% moderate, and 0.5% severe [113]. Pursuant to the World Health Organization, diarrhea is the third leading cause of death among children aged 1 to 59 months, despite its preventability and treatability. Annually, it results in the deaths of approximately 443,832 children under five and another 50,851 aged 5 to 9 years [10]. Enhancing access to safe drinking water, improving sanitation, and promoting better hygiene practices could prevent most of these fatalities [10]. Globally, childhood diarrhea affects an estimated 1.7 billion cases each year and plays a major role in contributing to malnutrition in children under five [10].

### 4.3. Long-term Health Effects:

Diarrhea, resulting from infections by various bacteria, parasites, or viruses, is prevalent in low-income countries with inadequate water and sanitation facilities. This condition is often linked to short-term weight loss, though its long-term effects on weight and growth are less clear and subject to debate. While some studies suggest a persistent impact on ponderal growth, others do not, and the relationship between diarrhea and linear growth shows mixed results [114, 115]. Factors such as socioeconomic status, dietary quality, access to healthcare, breastfeeding practices, and the specific causes of diarrhea,

as well as variations in study methodologies, contribute to these inconsistencies [114, 115]. Moreover, the reasons behind the poor growth associated with early childhood diarrhea are multifaceted. Diarrhea increases the body's demand for energy and essential nutrients such as proteins, fats, and micronutrients, while simultaneously reducing the child's appetite and food intake. Additionally, frequent infections can damage the small intestine's lining, impairing the finger-like villi that are crucial for nutrient absorption [116, 117]. This damage diminishes the child's ability to absorb nutrients effectively, thereby adversely impacting their future growth [116, 117]. Interestingly, diarrhea is linked with stunted growth and cognitive delays that can affect educational success and productivity later in life. For instance, research from The Gambia found that newborns suffering from diarrhea had a notable weight deficit of 1.2 kilograms, with half of this weight loss directly resulting from the diarrhea-related illness. This highlights the long-term effects diarrhea can have on a child's nutritional health and overall development [118]. Moreover, the impact of diarrhea stretches well beyond childhood, with emerging evidence linking early-life diarrhea to a heightened risk of non-communicable diseases in adulthood, including obesity, diabetes, and cardiovascular conditions [115].

### 4.4. Nutritional Impact:

As previously noted, diarrhea has a substantial impact on nutrition and electrolyte balance, leading to a range of complications. It frequently results in dehydration and significant electrolyte imbalances, which can be severe and are linked to higher mortality rates, particularly in children [109, 110]. These imbalances can exacerbate malnutrition and hinder growth, further compounding the health challenges faced by affected individuals [109, 110]. Additionally, the loss of fluids and essential minerals through watery stools hampers nutrient absorption, accelerates the breakdown of nutrient reserves, and disrupts the gut mucosal barrier. This creates a vicious cycle where malnutrition and diarrhea perpetuate each other, compounding the overall health challenges [109, 110]. Effective management demands a comprehensive approach that includes the use of oral rehydration solutions (ORS) and ongoing feeding. This strategy helps to prevent nutrient depletion and supports catch-up growth, ensuring a more complete recovery and better overall health outcomes [109].

## V. PUBLIC HEALTH IMPLICATIONS AND RISK FACTORS:

As outlined earlier, diarrheal diseases have substantial public health implications, especially for children under five. These diseases result in over 760,000 child fatalities annually, predominantly due to dehydration and malnutrition, thus imposing a significant burden on public health systems [120]. Moreover, the burden of diarrhea is considerable and frequently underestimated. Utilizing disability-adjusted life years (DALYs) provides a comprehensive measure of its impact, encompassing both mortality and morbidity. This approach facilitates more effective public health planning and resource

allocation by capturing the full extent of the disease's effects [121]. In addition, the repercussions extend beyond immediate health issues, leading to long-term effects such as stunted physical growth, cognitive impairments, and a reduced quality of life [115]. Unequivocally, factors such as poor socio-economic status, limited access to safe water, and inadequate hygiene and sanitation practices significantly heighten the risk of diarrheal diseases, fostering a vicious cycle of malnutrition and recurrent diarrhea. Additional issues, including insufficient exclusive breastfeeding, inadequate handwashing, and unsanitary living conditions, further exacerbate this vulnerability [122]. Additionally, the economic and educational repercussions are considerable, as missed school and workdays impact cognitive development and strain family resources [115]. Understanding these complex relationships is vital for developing informed interventions to reduce the burden of diarrhea. This underscores the necessity for comprehensive health education programs, improved water storage practices, and enhanced hygiene facilities to effectively address and mitigate the impact of the disease [120].

## VI. INNOVATIONS IN TREATMENT

Recent advancements in diarrhea treatment are focusing on several crucial areas to enhance outcomes, particularly in resource-limited settings. Significant areas of innovation include:

### 6.1. Enhanced Oral Rehydration Solutions (ORS):

Oral rehydration solution (ORS) has been a key treatment for dehydration from infectious diarrhea for about 40 years, as it leverages glucose to enhance sodium and fluid absorption in the small intestine. This has significantly reduced child mortality from diarrhea in developing countries [123]. However, ORS use remains inconsistent. Recent advancements have focused on reformulating ORS to include high-amylose maize starch (HAMS), which delivers unabsorbed carbohydrates to the colon, producing short-chain fatty acids (SCFA) that promote fluid absorption [123]. Trials in India have shown that HAMS-ORS reduces diarrhea duration, and efforts are underway to make it the standard treatment for dehydration in acute diarrhea cases [123]. Besides, Oral rehydration therapy (ORT) remains essential in managing diarrhea, particularly in children. ORS, composed of sodium chloride, potassium chloride, trisodium citrate, glucose, and water, replenishes fluids and electrolytes. When combined with zinc, ORS further reduces the severity and recurrence of acute diarrhea, boosts immune responses, and supports the healing of intestinal cells [124].

### 6.2. Anti-Diarrheal Medications:

Anti-diarrheal medications like loperamide offer relief by absorbing water, thickening stools, and reducing stool frequency. However, they are typically recommended for short-term management of secretory diarrhea [124]. Additionally, Bismuth subsalicylate (found in products like Pepto-Bismol and Kaopectate) plays a key role in managing diarrhea by preventing intestinal secretion, promoting fluid

and electrolyte reabsorption, reducing inflammation, and inhibiting bacterial growth that may contribute to diarrhea [125]. As well as, Alosetron (Lotronex) is used for severe cases of irritable bowel syndrome with diarrhea (IBS-D) in women. It can help manage symptoms but may cause side effects such as constipation and reduced blood flow to the colon [126]. Rifaximin (Xifaxan) is an antibiotic that targets specific gut bacteria and is typically used for short-term treatment, including for traveler's diarrhea [127].

### 6.3. Antimicrobial Therapy

For infectious diarrhea, antibiotics such as levofloxacin and ciprofloxacin can help reduce the duration of illness. The selection of the appropriate antibiotic should be based on local patterns of antibiotic sensitivity [124, 128]. Metronidazole is highly effective for treating infections, especially those causing diarrhea, including anaerobic bacteria, protozoa, and microaerophilic microorganisms. It is particularly useful against *Trichomonas vaginalis*, *Giardia lamblia*, *Entamoeba histolytica*, *Clostridium difficile*, and *Helicobacter pylori*. However, its use should be weighed against potential side effects [129].

### 6.4. Probiotics:

Probiotics are live microorganisms that confer health benefits, notably in gastrointestinal health, by reestablishing the equilibrium of gut microbiota disrupted by antibiotics and infections [130, 131]. These beneficial microbes have demonstrated efficacy in alleviating diarrhea symptoms, particularly those associated with pathogens like *Clostridium difficile* and *Giardia lamblia*. Clinical research suggests that particular strains, such as *Lactobacillus rhamnosus* and *Saccharomyces boulardii*, can markedly decrease both the duration and severity of diarrhea in individuals across different age groups [130, 131]. Moreover, probiotics exert their benefits through multiple mechanisms, including the competitive inhibition of harmful microorganisms, modulation of the immune system, and reinforcement of gut barrier integrity [132]. Additionally, probiotics can help prevent antibiotic-associated diarrhea by supporting a balanced gut microbiome during and after antibiotic therapy [133]. Integrating probiotics into dietary routines can therefore be a beneficial approach for managing diarrhea and enhancing overall digestive health. Anti-secretory medications are drugs that reduce the secretion of gastric acid and other fluids in the gastrointestinal tract, primarily used to treat conditions such as gastroesophageal reflux disease (GERD), peptic ulcers, and Zollinger-Ellison syndrome. The main classes of anti-secretory medications include proton pump inhibitors (PPIs) and histamine-2 receptor antagonists (H2RAs) [134]. PPIs, such as omeprazole and lansoprazole, work by irreversibly inhibiting the proton pump in the gastric parietal cells, leading to a significant reduction in gastric acid production [134]. Interestingly, anti-secretory medications are crucial in managing diarrhea, especially in cases of secretory diarrhea, which involves excessive fluid secretion into the intestinal lumen. These drugs function by suppressing

intestinal secretions, thereby decreasing fecal loss and alleviating symptoms. A prominent example in this category is racecadotril, an enkephalinase inhibitor. Racecadotril has demonstrated effectiveness in reducing both stool output and the duration of diarrhea while leaving intestinal motility unaffected [135]. Furthermore, Racecadotril functions by boosting the activity of endogenous enkephalins, which help reduce secretory activity in the gut. Clinical research has shown that racecadotril can significantly decrease the volume of diarrhea in children, positioning it as a valuable complement to oral rehydration therapy (ORT) for managing acute watery diarrhea [136,137].

### 6.6. Comprehensive Approaches:

Effective treatment of diarrhea requires a multifaceted approach that integrates rehydration, nutritional support, pharmacotherapy, and preventive strategies, all tailored to the specific cause and severity of the condition [108]. Central to this approach is fluid replacement, predominantly achieved through oral rehydration solutions (ORS), which are crucial for replenishing lost fluids and electrolytes in patients experiencing mild to moderate dehydration [108]. In cases of severe dehydration, intravenous fluid administration may be necessary to promptly reestablish fluid and electrolyte balance [138]. On the other hand, nutritional support is essential; patients should be advised to follow a bland diet, such as the BRAT diet (bananas, rice, applesauce, toast). This diet is generally well tolerated and may assist in firming stools [108]. It is important to note that pharmacotherapy for diarrhea often involves anti-diarrheal agents such as loperamide and racecadotril, which help reduce stool frequency and volume. However, these medications should be avoided in cases of bloody diarrhea or high fever [108]. It is important to note that pharmacotherapy for diarrhea often involves anti-diarrheal agents such as loperamide and racecadotril, which help reduce stool frequency and volume. However, these medications should be avoided in cases of bloody diarrhea or high fever [3]. Additionally, probiotics can be advantageous in shortening the duration of diarrhea and aiding in the restoration of gut flora [108]. Overall, employing a multifaceted approach that integrates these elements is essential for effective management and prevention of diarrhea.

### 6.7. Molecular Diagnostics:

Recent innovations in diagnostics feature molecular-based technologies, such as multiplexed systems, which enable the simultaneous detection of multiple enteropathogens with high sensitivity and specificity. These advancements are pivotal for early detection and targeted treatment, especially in low-resource settings [128]. Furthermore, quantitative molecular techniques have been employed to more precisely characterize the causes of diarrhea, providing insights at both the population and individual levels, for example, a bespoke TaqMan Array Card effectively identified 32 enteropathogens in the GEMS case-control study, thereby providing critical insights into the prevalence and impact of specific

pathogens [139]. In contrast, culture-independent diagnostic tests (CIDTs) utilizing multiplex PCR have shown markedly superior diagnostic yields compared to conventional stool cultures, identifying bacterial pathogens in as many as 49.2% of specimens [140]. Although molecular diagnostics provide numerous benefits, their heightened sensitivity can lead to concerns about overdiagnosis and overtreatment, especially in cases of infections such as C. difficile. Therefore, it is essential to use these tests judiciously and to integrate clinical presentation and additional supporting evidence for the most effective management of diarrheal illnesses [140, 141]. The current study revealed that diarrheal diseases remain a significant global health challenge, particularly in low-resource settings. Effective management necessitates a comprehensive strategy that includes oral rehydration therapy, advanced diagnostics, and targeted treatments. Tackling underlying issues such as inadequate sanitation and limited access to safe water is crucial. A concerted effort among healthcare providers, policymakers, and communities is vital to reducing the impact of diarrheal diseases and improving health outcomes. By integrating these approaches, we can substantially decrease both morbidity and mortality, promoting healthier communities around the world.

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**Authors' contributions**

**Z.D**. served as the principal author of the manuscript, overseeing data collection, Writing, drafting the article, and performing comprehensive revisions to align with journal requirements. **L.E**. contributed by assisting in the writing process and meticulously reviewing the manuscript. **M.A**. provided critical feedback through an in-depth review of the article. **S.B.** undertook the final review, supervised the overall research process, and provided essential advice and information to enhance the study.

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