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Guideline for managing acute diarrhea in the context of pharmaceutical care

Diretriz de manejo da diarreia aguda no contexto do cuidado farmacêutico

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ABSTRACT

Objective: To systematize, through evidence-based practice, the management of self-limited cases of acute diarrhea in the context of Pharmaceutical Care. **Methods:** To prepare the guideline, the ADAPTE method was adopted as a structured process of literature review and document construction. The AGREE II and GRADE tools were also used to analyze the practice guides selected during the process and to categorize the evidence, respectively. **Results:** After preparation, it was observed that the pharmaceutical anamnesis is an important step for confirming the self-limiting nature of acute diarrhea, preventing acute viral gastroenteritis, and referring in cases where warning signs such as severe dehydration or associated symptoms are suspected. Non-pharmacological measures generally showed strong degrees of recommendation. Oral rehydration therapy and continued breastfeeding in infants show high levels of evidence. Regarding pharmacological measures, as an adjunct to rehydration therapy, there is first-line treatment, which includes over-the-counter medications, and second-line treatment, which consists of antidiarrheals, antisecretory agents, antibiotics, and antiparasitic drugs. **Conclusion:** Pharmaceutical anamnesis proved to be fundamental. The pharmacist's role is relevant in improving clinical management, promoting rational drug use, and facilitating timely referral of patients with signs of greater severity.

Keywords: Management of Self-Limited Health Problems; Community pharmacy; Clinical Pharmacy.

RESUMO

Objetivo: Sistematizar, por meio da prática baseada em evidências, o manejo de casos autolimitados de diarreia aguda no contexto do Cuidado Farmacêutico. **Métodos:** Para elaboração da diretriz foi adotado o método ADAPTE como processo estruturado de revisão da literatura e construção do documento. Foram ainda utilizadas as ferramentas AGREE II e GRADE para análise dos guias de prática clínica selecionados durante o processo e para categorização das evidências, respectivamente. **Resultados:** Após elaboração, observou-se que a anamnese farmacêutica é passo importante para confirmação do caráter autolimitado da diarreia aguda, prevenção de gastroenterite viral aguda e encaminhamento na suspeita de sinais de alerta como desidratação grave ou sintomas associados. As medidas não farmacológicas apresentaram de uma maneira geral, fortes graus de recomendação. A terapia de reidratação oral e a amamentação contínua em lactentes, demonstram altos níveis de evidência. Em relação às medidas farmacológicas, como terapia adjunta à terapia de reidratação, há o tratamento de primeira linha, que abrange medicamentos isentos de prescrição, e segunda linha, que consiste em tratamento como antidiarreicos, agentes antissecretores, antibióticos e antiparasitários. **Conclusão:** A anamnese farmacêutica mostrou-se fundamental. A atuação do farmacêutico é relevante para qualificar o manejo clínico, promover o uso racional de medicamentos e favorecer o encaminhamento oportuno de pacientes com sinais de maior gravidade.

Palavras-chave: Manejo de Problemas de Saúde Autolimitados; Farmácia Comunitária; Farmácia Clínica.

Introduction

Diarrhea is characterized by a change in the frequency, consistency, or volume of stools. Although the frequency of peristaltic movements varies according to each individual, more than three bowel movements per day are considered abnormal. In addition, a decrease in stool consistency or an increase in stool weight (greater than 200 grams) are also interpreted as diarrhea. Diarrhea is considered a global public health problem with high morbidity and mortality, especially in developing countries. According to the World Health Organization (WHO), approximately 1.7 billion cases of diarrheal diseases are recorded worldwide each year, and it is considered the second leading cause of childhood mortality.[1,2,3]

The transmission of diarrheal diseases worldwide occurs predominantly through the ingestion of contaminated water and food. Thus, the main factors associated with cases of diarrhea are lack of access to adequate sanitation conditions, consumption of untreated water, and poor hygiene practices. Another related factor is the climate of different regions of the country, as climate change causes droughts or floods, generating a higher risk of population exposure to water from unknown sources.[1]

Diarrhea may present as acute, persistent, or chronic. Acute diarrhea is characterized by a duration of less than 14 days.[3,4] It may occur as acute watery diarrhea, when there is active secretion of water and electrolytes under the stimulation of certain substances, or as acute diarrhea with blood (dysentery), when an infectious agent invades the colonic mucosa. Persistent diarrhea is defined as diarrhea lasting 14 days or more. In this case, there is a continued infection by an agent causing damage to the villi and or inadequate regeneration of erythrocytes due to chronic malnutrition. It may manifest as watery diarrhea or dysentery. Chronic diarrhea, in turn, lasts longer than 30 days and occurs when there are different causes, such as chronic inflammatory conditions, food allergy, irritable bowel syndrome, and intestinal parasitoses.

Persistent and chronic diarrheal diseases are generally secondary to other conditions or chronic medical treatments and require referral to specialized medical care.[3,4] Given this context, the objective of this guideline was to systematize, through evidence-based practice, the management of self-limited cases of acute diarrhea in the context of Pharmaceutical Care. The focus of this guideline is acute diarrheal diseases, as they represent a self-limited health problem.

Métodos

For the development of this guideline, the ADAPTE method was used as a reference, divided into three consecutive phases: (i) set-up, (ii) adaptation, and (iii) finalization. The method consists of a structured process for the development of practice guidelines based on pre-existing documents in the scientific literature. In the case of this work, the following reference documents were selected: (i) guidance documents from evidence synthesis databases; (ii) clinical guidelines on the topic; (iii) systematic reviews on treatments; and (iv) guidelines or specific articles related to pharmaceutical care.[5,6]

Searches were conducted in January 2021 using MeSH terms and Boolean operators “Diarreia” OR “Diarrhea in children” OR “Diarrhea in adults” OR “Diarrhea management” OR “Acute diarrhea” OR “Diarrhea” OR “Doença diarreica” AND “Guideline” OR “Management” OR “Treatment” OR “Pharmaceutical” OR “Tratamento da diarreia”. Searches were performed in evidence synthesis databases Best Medicine Journal (BMJ), Dynamed, and UpToDate; on guideline developers’ websites, including The National Institute for Health and Care Excellence (NICE), World Gastroenterology Guidelines, Protocolos de Indicación Farmacéutica y Criterios de Derivación al Médico en Síntomas Menores, American College of Gastroenterology (ACG), Canadian Association of Gastroenterology (CAG), Japanese Society of Gastroenterology (JSG), American Society of Gastrointestinal Endoscopy (ASGE), and National Health Service United Kingdom (NHS UK); in the Cochrane Database of Reviews; in the PubMed and Biblioteca Virtual de Saúde databases; and finally in Google Scholar,

Agência Nacional de Vigilância Sanitária (ANVISA), MedlinePlus, and Micromedex.

The inclusion criteria were publications from January 2005 to January 2021, written in English, Spanish, or Portuguese, with free access to the full text, and related to acute diarrhea. Exclusion criteria were publications whose scope included the management of chronic diarrhea, diarrhea related to specific microorganisms, diarrhea secondary to other diseases, and diarrhea in specific situations not applicable to the topic of interest.

For the preliminary appraisal of the identified guidelines and as a model for defining the sections and writing of this guideline, the AGREE II tool (Appraisal of Guidelines for Research and Evaluation) was used.[7-9]

An analysis of the quality of available evidence for potential pharmacological and non-pharmacological interventions was also conducted using the GRADE tool (Grading of Recommendations Assessment, Development and Evaluation), which is widely used internationally for categorizing recommendations and supporting decision-making. According to the method, interventions were classified by level of evidence as (i) high, (ii) moderate, (iii) low, and (iv) very low, and by strength of recommendation as (i) strong or (ii) weak.[10,11]

Results

After searching the databases, 7,549 references were identified, of which 167 studies were selected after duplicate removal for title screening and, subsequently, 79 for abstract screening. A total of 77 studies were selected after applying the eligibility criteria for full-text reading. However, during the set-up and signaling phases, additional references were included for the development of this guideline, which is structured into the following sections:

- Objectives of Pharmaceutical Care;
- Causes, Signs, Symptoms, and Pharmaceutical Anamnesis;
- Non-pharmacological Interventions;
- Pharmacological Interventions;
- Warning Signs and Referrals;
- Outcome Monitoring.

Objectives of Pharmaceutical Care

1. To support the patient in relieving discomfort and reducing symptoms associated with acute diarrhea, with a primary focus on preventing dehydration;[3,4,12]

2. To provide guidance on infection prevention measures and non-pharmacological care for the management of diarrhea;[3,4,12]

3. To advise patients on hygienic measures prior to traveling to high-risk locations;[3]

4. To reduce the duration and severity of diarrhea through pharmacological support when necessary;[3,4,12]

5. To identify typical warning signs, such as dehydration, and refer patients to other healthcare professionals when appropriate.[3]

Causes, Signs, Symptoms, and Pharmaceutical Anamnesis:

Acute diarrhea presents the following characteristics, sudden onset, presumed infectious etiology, potentially self-limiting course, duration of less than 14 days, and increased stool volume and or frequency, resulting in increased losses of water and electrolytes.[3,4,12] It may be classified according to the underlying pathophysiological mechanisms that alter normal intestinal function:[13,14,15]

• ***Diet-induced (osmotic)***:diarrhea occurs when osmotically active substances are present in the intestinal lumen, resulting in water retention. This may occur due to impaired absorption of a dietary solute, such as lactose, or the administration of a non-absorbable solute.[14,16]

• ***Electrolyte transport-related (secretory):*** diarrhea occurs when alterations in ion transport mechanisms within epithelial cells lead to increased secretion or reduced absorption of fluids and electrolytes. This category includes different types of diarrheal diseases, such as those caused by enterotoxigenic bacteria and viruses. Non-infectious causes of secretory diarrhea include those mediated by gastrointestinal peptides, those caused by physiological substances, such as bile acids, certain medications, and congenital defects, such as congenital chloride diarrhea.[14] This type of diarrhea may

be considered adaptive, as it facilitates pathogen elimination.[13,14,16]

• ***Motility-related diarrhea***: alterations in gastrointestinal motility, which can significantly influence fluid absorption, particularly in the colon. Hypomotility results in stasis with subsequent bacterial overgrowth and secondary bile acid deconjugation, bile acid malabsorption, and activation of colonic secretion. Conversely, hypermotility may lead to secondary diarrhea.[14,16]

Inflammation-related diarrhea: may occur through multiple mechanisms, such as viral, bacterial, or parasitic infection. It may also have a diet-induced component, as inflammatory processes cause destruction or impairment of epithelial cells, resulting in loss of surface area and transport capacity and, consequently, reduced nutrient absorption and increased osmotic load in the intestinal lumen. It may also be related to transport mechanisms through active induction of chloride (Cl-) secretion and reduced sodium (Na+) absorption. In addition, inflammation may disrupt intestinal barrier function, leading to exudation of mucus, protein, and blood into the intestinal lumen.[13,14,16]

The pathophysiological mechanisms involved in most cases of acute diarrhea are osmotic and secretory, whereas motor and exudative mechanisms are generally associated with chronic diarrheal diseases.[3]

There is also so-called traveler's diarrhea, which refers to episodes of diarrhea occurring during or after travel, usually in low- or middle-income countries where resources are limited.[17] The risk of diarrhea varies according to travel destination and is higher in regions with inadequate sanitation and hygiene practices.[18,19,20]

Infections caused by viruses, bacteria, and parasites are the most common causes of acute diarrhea worldwide. Transmission occurs mainly through ingestion of contaminated water or food,[21,22] but may also occur through contact with contaminated objects or individuals, as well as contact with animals.[1] Most infections are potentially self-limiting or easily treatable.[23]

However, acute diarrhea may have other causes, such as the use of certain medications, food intolerance, or association with other acute or chronic conditions, including sepsis, hemolytic uremic syndrome, pseudomembranous colitis, appendicitis, toxic megacolon, among others.[3,24]

Food intolerance may cause diarrhea and may result from food allergy or the ingestion of excessively fatty or highly seasoned foods, or foods containing large amounts of seeds. Dietary carbohydrates commonly include the disaccharides lactose and sucrose, which are normally hydrolyzed into monosaccharides by the enzyme lactase. When these disaccharides are not hydrolyzed, they accumulate in the intestinal lumen, where they ferment and produce osmotic imbalance with altered pH. The resulting hyperosmolarity draws fluid into the intestinal lumen, causing diarrhea.[3]

Many medications may cause diarrhea. In addition to laxatives, which have an intended effect, diarrhea may occur as a common adverse effect in individuals using antacids, proton pump inhibitors, antineoplastic agents, certain medications acting on the nervous system, and many antibiotics.[25,26]

The clinical presentation of acute diarrheal disease is generally characterized by changes in bowel movement frequency, three or more episodes within 24 hours, and stool consistency, which may be loose or watery. In some cases, blood or mucus may be present in the stool, along with other symptoms such as fever, abdominal pain, flatulence, nausea, and vomiting.[27-30] Traveler's diarrhea is commonly accompanied by at least one of these symptoms, which may vary depending on the causative pathogen.[17,31]

During episodes of diarrhea, fluid loss may occur and, when excessive, may lead patients to experience symptoms such as thirst, dark-colored urine, and, less frequently, dry eyes or mouth, restlessness or irritability, delayed capillary refill time, reduced skin turgor, or drowsiness, characterizing dehydration.[24,32,33] In infants and children, signs of dehydration include accelerated heart rate, dry mouth, tongue, and lips, lack of energy, reduced skin turgor, absence of tears when crying, and dry diapers for three hours or more. Sunken eyes, sunken fontanelle on the top of the head, drowsiness, and irritability in infants and children suggest more severe dehydration.[29,34,35]

Acute diarrhea usually presents a characteristic clinical course, but it is important to investigate potential aggravation due to other health conditions. In infants, intussusception is one of the main conditions to be considered in the differential diagnosis of acute diarrhea.[36]

During pharmaceutical anamnesis, several important data should be collected, including onset, duration, and severity of symptoms, changes in bowel movement frequency, stool quantity and consistency, presence of mucus or blood in the stool, whether family members or acquaintances have similar symptoms, presence of chronic diseases, recent travel, signs of dehydration, such as thirst, dizziness, altered mental status, reduced urine output, dietary history, fluid and food intake before and after symptom onset, associated symptoms, such as abdominal pain, nausea, vomiting, abdominal distension, flatulence, fever, and tenesmus, medication history, medical or surgical history, social history, including sexual practices, drug and alcohol use, and occupational history.[4,16,31,37,38]

Chart 1. Pharmaceutical anamnesis in patients with acute diarrhea (INDICO strategy)

Domain	Questions/Assessment*
Patient Identification	What is the patient's age? If female, is she pregnant?
Nature of Signs and Symptoms	Does the patient appear pale or show signs of dehydration? Has there been any recent change in diet? Is the patient experiencing pain? In which region? Is there fever? Vomiting? Weight loss? Other associated symptoms? Which ones? What is the appearance and consistency of the stools, and what is the frequency of bowel movements? Is there mucus or blood present? If so, are there anal fissures or hemorrhoids? Has the patient ingested foods that may cause confusion, such as beetroot or red fruits? Has the patient recently traveled to any endemic or epidemic area for diarrheal diseases?
Duration	What is the duration of the current symptoms, onset and length? Are the symptoms intermittent or continuous? Have there been previous episodes? Are they frequent? What is the periodicity?
Initiation of Treatment	Has any medication been used? For how long has it been used? Has it been effective? Has the patient used any antibiotics recently? Does the patient notice worsening or improvement of symptoms with the intake of any food or medication?
Comorbidities	Does the patient have other health conditions? Does the patient use any medication regularly? Does the patient have dysmenorrhea, diabetes, dyspepsia, intolerance to certain foods, or significant hormonal changes? Does the patient consume alcohol frequently? Is there a current or previous history of cancer or chemotherapy treatment?
Other Special Situations	Is there a recurrent history of diarrhea in specific situations, such as travel or ingestion of certain foods? Is there suspicion of any specific trigger already identified? Does any family member or acquaintance have the same symptoms?

* Suggestive questions. They are not intended for diagnostic purposes, but rather to support better case understanding and the identification of potential warning signs for referral.
Source: Prepared by the authors

Non-pharmacological Interventions:

Primary prevention actions for diarrhea are based on the adoption of basic personal and food hygiene measures. The main measures include health education on modes of transmission; handwashing after using the toilet, before and after preparing food, and before eating; ensuring the availability of safe drinking water; appropriate disposal of human waste; safe food handling and processing; use of adequate sanitation; and avoiding contact with infected individuals.[2,31,33,39-41]

Non-pharmacological treatment for diarrhea consists of rehydration, preferably oral, and dietary management. Intravenous rehydration is recommended only in cases in which oral administration is not possible. Immediate rehydration is essential to prevent or correct dehydration.[2,42]

Rehydration therapy consists of the administration of appropriate oral solutions to prevent or correct dehydration, which may occur in diarrheal conditions.[43] Oral rehydration salts are the treatment of choice in cases of mild to moderate diarrhea, as they contain specific amounts of salts that are lost during bowel movements.[3,30,43] It is important to emphasize that patients with diabetes may use oral rehydration salts, but they should be advised to carefully monitor blood glucose levels.[44]

According to the patient's degree of dehydration, three treatment plans may be followed: Plan A, for patients without signs of dehydration, in which treatment is home-based; Plan B, for patients with signs of dehydration who are able to ingest fluids, in which treatment is carried out with oral rehydration solution in a health care unit; and Plan C, for patients with severe dehydration, who are treated in a health care unit with parenteral rehydration therapy. The pharmacist may follow Plan A for the management of patients with acute diarrhea without signs of dehydration; however, if the patient already presents any degree of dehydration, they should be immediately referred to a health care unit.[36,45]

Most oral rehydration salts commonly found in pharmacies are available in liquid form. For powdered formulations, it is essential that the pharmacist appropriately advises patients on how the powder should be reconstituted. Only water should be used to prepare the solution, never fruit juice or soft drinks, preferably boiled and cooled water, especially when administered to children under one year of age. Boiling water should not be used directly, as it causes the release of carbon dioxide. The solution may be stored for up to 24 hours if kept refrigerated. Carbonated and sugary beverages should never be used to prepare rehydration fluids, as they produce a hyperosmolar solution that may worsen the condition. The sodium and glucose content of these beverages may be high.[30,34]

Patients should also be advised to drink plenty of fluids, especially older adults. Frequent intake in small sips may be the best way to avoid stomach discomfort.[40]

An age-appropriate diet should be introduced as soon as the patient has been rehydrated. It is recommended to continue normal feeding in cases without signs of dehydration, avoiding interruptions in food intake longer than four hours.[43]

Patients, or their caregivers, should be advised to avoid fatty foods, foods rich in simple sugars that may cause osmotic diarrhea, and spicy foods that may cause gastrointestinal disturbances. Beverages containing caffeine should also be avoided because they may increase cyclic adenosine monophosphate levels, promoting fluid secretion and potentially worsening diarrhea.[3] In addition, coffee, cold beverages, alcoholic beverages, soft drinks, and sparkling water should be avoided.[42,46]

Boiled starches and cereals, such as potatoes, pasta, rice, wheat, and oats, with salt, are recommended for patients with watery diarrhea; crackers, bananas, soup, and cooked vegetables may also be consumed.[23,30] Dairy products, except for yogurt, may be difficult to digest in the presence of diarrheal diseases because the enzyme responsible for milk digestion, lactase, is inactivated in the intestine, potentially producing temporary lactose intolerance and worsening diarrhea.[30] Therefore, it is recommended to temporarily avoid foods containing lactose.[21,42,47]

Isolated episodes of diarrhea after treatment are normal. However, persistent diarrhea associated with cramps, fever, or blood requires immediate medical consultation.[17]

Chart 2. Summary of evidence on non-pharmacological interventions for acute diarrhea.

MANAGEMENT	TECHNICAL RATIONALE	GRADE	
		Level of Evidence	**Strength of Recommendation**
ORAL REHYDRATION THERAPY	Fluid loss can be treated with the administration of oral rehydration therapy, a simple and cost-effective treatment that can relieve dehydration in affected individuals. A Cochrane systematic review compared oral rehydration therapy with intravenous therapy and showed that there were no clinically important differences between them for secondary rehydration in children with gastroenteritis. For every 25 children treated with oral rehydration therapy, one would fail treatment and require intravenous rehydration therapy.	High ****	Strong
APPROPRIATE DIET	Continuation of the usual age-appropriate diet during or after the rehydration process is recommended. A meta-analysis showed that early feeding, after the initiation of rehydration, was as safe and effective as delayed feeding in children under 6 years of age with acute diarrhea in low-, middle-, and high--income countries.	Low **	Strong
CONTINUED BREASTFEEDING	Feeding with human milk should be continued in infants and children throughout the entire episode of diarrhea. Breastfeeding not only has a well-known protective effect against the development of enteritis, but also promotes faster recovery and provides better nutrition. It may be necessary to feed the infant more frequently or prolong breastfeeding sessions.	High ****	Strong
HOMEMADE ORAL REHYDRATION SOLUTIONS AND FLUIDS	For patients with diarrhea without signs of dehydration, in addition to oral rehydration salts, the use of homemade fluids, such as homemade oral rehydration solution, may be indicated. For young children, older adults, or patients with mild signs of dehydration, homemade solutions tend to be less effective due to imprecision in their preparation, even when guidance is provided by health professionals. Home preparation should be performed with caution, especially in settings of greater vulnerability and limited access to good-quality water.	Low **	Weak
FOOD RESTRICTION	Fatty foods may cause osmotic diarrhea because they are difficult to digest and absorb, remaining in the intestine and causing excessive water retention in the stool. Spicy and highly seasoned foods may cause gastrointestinal disturbances because they can increase irritation of the intestinal mucosa, leading to epithelial cell damage, loss of absorptive surface and transport, and consequently reduced nutrient absorption and increased osmotic load in the intestinal lumen. Caffeine may increase cyclic adenosine monophosphate levels, promoting fluid secretion and potentially worsening diarrhea. Dairy products may be difficult to digest in the presence of diarrheal diseases because, during diarrhea, the intestinal enzyme responsible for milk digestion, lactase, is inactivated, which may lead to temporary lactose intolerance and worsen diarrhea. A meta-analysis involving children under 6 years of age with acute diarrhea found that a lactose-free diet reduced the duration of diarrhea and halved treatment failure. Although dairy-restricted diets are commonly recommended, supporting evidence for this intervention is limited.	Low **	Strong

Source: Prepared by the authors

Pharmacological Interventions

Prevention of acute viral gastroenteritis is primarily achieved through vaccination. The rotavirus vaccine has been available in the Unified Health System (SUS) through the Plano Nacional de Imunização (PNI) since 2006. In this context, vaccination should be encouraged by pharmacists as a means of preventing hospitalization and complications related to gastroenteritis. Outbreaks should be reported to local sanitary and epidemiological surveillance authorities so that isolation measures for infected individuals, investigation, and elimination of viral reservoirs can be reinforced.[15,53,54]

For the management of diarrhea in more severe cases, rehydration therapy alone may not be sufficient to treat the patient. However, before recommending any treatment, serious underlying causes of diarrhea must be considered and excluded.[3,44] Pharmacists may prescribe Over-the-Counter Medicines when, based on anamnesis, the patient's condition is determined to be self-limited. As first-line treatment, in addition to oral rehydration therapy, some medications may be prescribed as adjunctive therapy.

Zinc supplementation may reduce the duration of diarrhea, particularly in children in developing countries, where zinc deficiency is common. A meta-analysis demonstrated a reduction in episodes of severe diarrhea, dysentery, and persistent diarrhea, as well as respiratory infections such as pneumonia.[36,43,45]

Probiotics are used both in the treatment and prevention of diarrhea in certain situations. They are microorganisms administered to restore the intestinal microbiota, reestablishing normal intestinal function and suppressing the growth of pathogenic microorganisms. The probiotics Saccharomyces boulardii, Lactobacillus rhamnosus GG, and Lactobacillus acidophilus reduce the duration of infectious diarrhea and antibiotic-associated diarrhea in adults and children and may also be used to prevent antibiotic-associated diarrhea. Their use is recommended as adjuncts in the treatment of acute diarrhea, together with rehydration therapy and maintenance of feeding.[2,55,56] The action of probiotics occurs mainly through antagonism, immunomodulation, or pathogen exclusion. Effects related to reduction of diarrheal episodes, clinical improvement, and reduction of complications have been reported in many studies, although in more robust analyses with lower risk of bias these effects are less pronounced or inconsistent.[55,57,58]

There are some medications that are also used in the treatment of diarrhea but require medical prescription. In this context, second-line treatment consists of antidiarrheal agents, antisecretory agents, antibiotics, and antiparasitic drugs.

Diarrhea should be understood as a natural mechanism to expel infectious agents and toxins present and accumulated in the intestine. From this perspective, the use of antidiarrheal agents such as loperamide, which are intestinal antimotility agents or adsorbents, is considered unnecessary and sometimes undesirable. On the other hand, it is recognized that patients often wish to reduce diarrhea for reasons of convenience, and there is no evidence that antidiarrheals, when used appropriately, are unsafe or prolong the disease.[30,43,59]

Loperamide is an effective antidiarrheal medication for use in adolescents, young adults, and adults. It is a synthetic opioid agonist that produces antidiarrheal effects by stimulating μ-opioid receptors located in the circular intestinal muscles. This action slows intestinal motility, allowing absorption of electrolytes and water by the intestine. Stimulation of gastrointestinal μ-opioid receptors also reduces gastrointestinal secretion, which may contribute to the antidiarrheal effects of the drug. Other related mechanisms may include interruption of cholinergic and non-cholinergic mechanisms involved in the regulation of peristalsis, inhibition of calmodulin function, and inhibition of voltage-dependent calcium channels. Inhibitory effects on calmodulin and calcium channels may contribute to the antisecretory effects of loperamide.[3,30] Its therapeutic effects include reduction in daily fecal volume, increased stool viscosity and bulk, and reduced loss of fluids and electrolytes.[3] It is mainly recommended for traveler's diarrhea of mild to moderate intensity,

in the absence of clinical signs of invasive microorganisms. It should be avoided in dysentery, in suspected inflammatory diarrhea with fever, or in the presence of intense abdominal pain, which may also suggest inflammatory diarrhea. The use of loperamide is not recommended for children, as it may increase disease severity and complications.[30,43,59]

An antisecretory agent that may be used is racecadotril, an enkephalinase inhibitor, the enzyme responsible for the degradation of enkephalins. By prolonging the action of enkephalins, intestinal secretion of water and electrolytes is reduced, thereby controlling acute diarrhea. Racecadotril does not interfere with intestinal motility, ensuring greater safety as an adjunct in treatment, and thus plays an important role in reducing diarrheal losses and the duration of acute diarrhea. Treatment should be discontinued as soon as clinical improvement occurs. It is also not indicated for enteroinvasive diarrhea characterized by fever and blood, or for diarrhea caused by treatment with broad-spectrum antibiotics.[43,55]

Antibiotic treatment is generally not used in cases of acute diarrhea. It should be reserved for cases of dysentery, diarrhea with blood, with systemic involvement, in immunosuppressed patients, in patients with sickle cell anemia, in individuals with prostheses, in children with signs of extraintestinal bacterial dissemination, and in cases of severe cholera.[27,36] The main cause in these cases is infection by Shigella spp.; however, other agents that cause severe disease and require antibiotic therapy include enteroinvasive Escherichia coli, Yersinia enterocolitica, Vibrio cholerae, Clostridium difficile, and non-typhoidal Salmonella.[36,43] In other situations, antibiotics are not effective and should not be prescribed.

Antiparasitic drugs should be administered to patients diagnosed with amebiasis in whom treatment of dysentery caused by Shigella spp. has been ineffective and in whom trophozoites of Entamoeba histolytica containing erythrocytes are identified in stool samples. In addition, these medications may also be used in patients diagnosed with giardiasis when cysts or trophozoites are identified in stool or intestinal aspirates.[27]

Antiemetics are unnecessary in the management of acute diarrhea, as they have sedative effects and may hinder rehydration therapy. In general, they provide no practical benefit for children with acute or persistent diarrhea.[43] Adsorbents such as kaolin-pectin, activated charcoal, and attapulgite have no proven efficacy and therefore should not be recommended.[43,60]

Warning Signs and Referral:

Some patients have a higher risk of complications during an episode of diarrhea. These include children, especially those under one year of age, older adults, individuals living in environments with poor sanitation and who are in constant contact with contaminated food and water, immunocompromised patients (people living with HIV, neoplasms, or those requiring organ transplantation), pregnant women, patients with pre-existing medical conditions (for example, inflammatory bowel disease, diabetes mellitus, chronic kidney disease, immunodeficiency), and patients with gastric hypochlorhydria or using antacids, especially proton pump inhibitors. [27,39,70,71]

Children, particularly younger ones, are at greater risk due to their natural curiosity and tendency to indiscriminately touch various objects and place them in their mouths. In addition, they are less selective regarding the type and source of food they consume and are less likely to adhere to recommended hygiene measures. [70] In cases of repeated episodes of acute diarrhea in this group of patients, linear growth impairment may occur, predisposing them to new episodes of infectious diseases. [72] This condition may also be associated with other long-term outcomes, such as reduced cognitive function and an increased likelihood of developing chronic diseases. [73]

In these situations, the pharmacist should alert the patient about potential complications and refer the patient for further investigation to: (i) a Primary Health Care unit of the Unified Health System (SUS); (ii) consultation with a private general practitioner or gastroenterologist, either privately or through a health insurance plan.

Chart 3. Summary of pharmacological interventions for acute diarrhea

MEDICATION	STANDARD USE	PATIENT COUNSELING	GRADE	
			Level of Evidence	**Strength of Recommendation**
Zinc sulfate OTC/SUS (Tablet 20 mg and Oral solution 17.60 mg/mL)	**ADULTS**: 1 to 2 tablets of 20 mg/day OR 7.5 mL/day. **CHILDREN** (up to 6 months of age): 2.5 mL/day for 10 to 14 days; over 6 months of age, 5 mL/day for 10 to 14 days.	"Zinc absorption is impaired in the presence of food; therefore, it should be administered between meals." "Nesh Zinco® may be chewed, swallowed directly with water, or dissolved in 100 mL of water."	Moderate ***	Strong
Bacillus cereus OTC (Suspension 5×10^6 endospores)	**ADULTS**: 1 vial every 4 hours/ day. **CHILDREN:** 1 vial every 4 hours/ day.	"Use with caution in patients with diabetes." "The suspension should be shaken before use."	Moderate ***	Strong
L. acidophilus + *L. rhamnosus* + *L. paracasei* + *B. lactis* OTC (Sachet 1 g)	**ADULTS**: 1 to 2 sachets per day. **CHILDREN:** 1 to 2 sachets per day.	"The sachet should be consumed immediately after opening." "Preferably use at night, when no further food intake is expected."	Moderate ***	Strong
Saccharomyces boulardii MIP (Cápsulas 100 mg, 200 mg e 250 mg e Pó 200 mg e 250 mg)	**ADULTS**: 1 tablet of 200 mg or 2 tablets of 100 mg every 12 hours. **CHILDREN:** 1 sachet of 200 mg diluted in water or semi-solid foods once daily OR 1 tablet of 100 mg every 12 hours..	"Do not mix with carbonated beverages or foods, or those containing alcohol." "Use on an empty stomach or at least 30 minutes before meals." "It is a non-toxic, non-transmissible yeast with a bioregulatory effect on the intestinal flora."	Moderate ***	Strong
Loperamide (Tablet 2 mg)	**ADULTS**: 2 tablets (4 mg) orally, followed by 1 tablet (2 mg) after each loose stool. Maximum dose: 8 tablets/day. **CHILDREN:** This medication is contraindicated in children.	"Treatment should be discontinued after the production of solid stools or after 24 hours without bowel movements." "Avoid activities requiring mental alertness or coordination until the onset of drug effects." "Small amounts may be excreted in breast milk."	Moderate ***	Strong
Racecadotril (Hard gelatin capsule 100 mg and granules 10 mg and 30 mg)	**ADULTS**: 1 capsule of 100 mg three times a day. Maximum dose: 4 capsules/day. **CHILDREN**: 10 mg for children over 3 months, 20 mg for children over 10 months, or 30 mg for children over 3 years, three times a day. Maximum dose: 6 mg/kg/day.	"Treatment should not exceed 7 days." "Granules should be taken with water after agitation, mixed with a small amount of food on a spoon, or placed directly in the mouth." "Use with caution in patients with diabetes."	Moderate ***	Weak

Source: Prepared by the authors

Chart 4. Warning signs for referral of patients with acute diarrhea.

KEYWORD	WARNING SIGNS
DYSENTERY	Presence of blood or mucus in the stools and/or bowel movements over a 72-hour period without any improvement and/or profuse watery diarrhea.
PERSISTENT DIARRHEA	Persistent diarrhea for a period ≥ 14 days OR diarrhea lasting more than one day in children under one year of age OR lack of improvement with oral rehydration therapy.
DEHYDRATION	Signs of severe dehydration (thirst, decreased urinary frequency, restlessness, and dry eyes or mouth, tachycardia, orthostatic hypotension, lethargy).
DRUG-INDUCED	Suspected reaction induced by prescription medications.
RISK GROUPS	Diarrhea accompanied by severe abdominal pain in patients over 50 years of age OR pregnant women OR infants OR immunocompromised patients.
POTENTIAL INFECTIOUS OUTBREAK	Potential for an infectious outbreak, such as when the patient handles large quantities of food or lives or works in a nursing home or daycare center, where other individuals with common food exposure also present symptoms of diarrhea.
ASSOCIATED SYMPTOMS	Signs and/or symptoms suggestive of severe disease, fever ≥ 38.5°C with no improvement for ≥ 48 hours, severe dehydration, weight loss, and/or intense vomiting.

Source: Prepared by the authors

Outcome Monitoring:

Most patients with acute diarrhea, even when untreated, recover spontaneously within 48 hours, and the average duration of diarrhea is often four to five days.[70] Approximately 5% and 1% of affected individuals experience diarrhea that persists for more than 14 days and 1 month, respectively. The clinical course tends to be more severe and prolonged in children, especially those under two years of age.[77]

Pharmaceutical prescribing aims to reduce the symptoms of acute diarrhea and prevent dehydration. The pharmacist should evaluate the outcomes based on the recommendations provided to the patient. The purpose of follow-up is to monitor and assess patient progress in order to verify:[2,20]

- Whether there was improvement in diarrhea and related symptoms;
- Whether signs of dehydration appeared;
- The presence of adverse effects (for example, abdominal pain, constipation);
- Patient adherence to the treatment plan;
- Periodic reassessment until resolution of the condition.

Patients should be monitored for dehydration by measuring body weight, vital signs, and level of mental alertness. The literature does not specify the exact time interval the professional should wait after the agreed interventions to perform outcome monitoring. It is suggested, however, that outcome assessment occur within 24h-48h, and may occur over a shorter period in patients in special situations (such as children and older adults). With effective symptomatic relief, patients may expect a reduction in stool frequency and a return to normal stool consistency, as well as relief of generalized symptoms such as lethargy and abdominal pain.[20,70,77]

The effectiveness of pharmacological treatment is assessed by improvement in diarrhea and related symptoms, taking into account patient adherence to the treatment plan. [2] The safety of pharmacological treatment is evaluated through patient monitoring and verification of the occurrence of adverse drug reactions or signs of worsening dehydration or other symptoms. [3]

Conclusion

This study, organized in the form of a guideline, systematized the management of self-limiting acute diarrhea in the context of pharmaceutical care, based on evidence-based practice. The pharmaceutical history proved fundamental in confirming the self-limiting nature of the condition, identifying warning signs, and supporting clinical decision-making. In general, non-pharmacological measures form the basis of management, with emphasis on oral rehydration therapy and maintaining feeding and breastfeeding in infants, while pharmacological interventions should be used in an adjunctive and judicious

manner. In this context, the pharmacist's role is relevant to improve clinical management, promote the rational use of medications, and facilitate the timely referral of patients with more severe symptoms.

Authors' Contributions
LFB, FMC, LAMM, NAL, RFL, RBA, JMAV, RSS, and TMR were responsible for project conception, data analysis, and manuscript drafting. RFL, RSS, and TMR were responsible for manuscript review and approval.

Conflicts of Interest
There are no conflicts of interest to declare in relation to this work.

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