Diarrhea as a Clinical Challenge: General Practitioner Approach

Aleksandra Sokic-Milutinovic^{a, b} Aleksandra Pavlovic-Markovic^{a, b}
Ratko S. Tomasevic^{b, c} Snezana Lukic^{a, b}

^aClinic for Gastroenterology and Hepatology, University Clinical Center of Serbia, Belgrade, Serbia;

^bFaculty of Medicine, University of Belgrade, Belgrade, Serbia; ^cClinic of Internal medicine, University Clinical-Hospital Centre Zemun-Belgrade, Belgrade, Serbia

Keywords

Acute diarrhea · Chronic diarrhea · Etiology · Diagnosis · Therapy

Abstract

Background: Diarrhea is defined as the passage of loose stools and increase in stool frequency, weight, or volume. Diarrhea is an important health issue since it accounts for 2.5 million deaths in the world each year. **Summary:** Diarrhea can be acute, persistent, or chronic. Acute diarrhea (AD) is usually infectious, caused by viruses, less frequently by bacteria and parasites. The majority of cases of AD are self-limiting and do not require diagnostic workup. The use of diagnostic tests in AD should be limited to patients with signs of severe dehydration, bloody stools, persistent fever and those suffering from immunodeficiencies using immunosuppressive therapy or to cases of suspected nosocomial infection. These patients should be referred to gastroenterologists or infectious disease specialists. Therapy in AD consists of early oral refeeding, antidiarrheal medications, antibiotics, and probiotics. Chronic diarrhea (CD) has diverse etiology. The majority of patients have self-limiting symptoms or functional gastrointestinal disorders. Patients with blood in stool, weight loss, clinical and laboratory signs of anemia,

and palpable mass in the abdomen (red flag symptoms) need urgent gastroenterology referral. Therapy in CD is possible when the underlying cause of symptoms is identified.

Key Messages: The general practitioner should identify high-risk patients with AD and/or red flag symptoms for urgent gastroenterology referral.

© 2021 S. Karger AG, Basel

Definition

Diarrhea is usually defined by patients as passage of loose stools. According to the British Society of Gastroenterology (BSG) guidelines, apart from altered stool consistency, diarrhea can be defined in terms of stool consistency, frequency, stool weight, and/or stool volume [1]. The ability of the intestine to “hold water” determines, among other factors, stool consistency. Based on the underlying pathophysiological mechanism, diarrhea is classified as follows:

- **Secretory:** There is increased active secretion or inhibition of fluid absorption with little or no structural damage. A well-known etiology is cholera toxin-stimulating anion secretion. Diarrhea is not related to oral intake; it is present even during fasting [2].

- **Osmotic:** There is an increased influx of water into the bowel. It can result from excessive sugar and salt accumulation in the lumen and also from maldigestion and malabsorption in pancreatic or celiac disease when nutrients in the lumen of the bowel, as a result of osmosis, drive water into the lumen of the bowel. In healthy people, excess magnesium or vitamin C intake can lead to osmotic diarrhea. Other possible causes in healthy individuals include the use of sorbitol and laxatives and lactose intolerance. This type of diarrhea is related to the ingestion of food or the offending agent.
 - **Exudative:** This occurs with the presence of pus or blood in stool in severe forms of *E. coli*- or other pathogen-induced food poisoning and also in inflammatory bowel disease (IBD) patients.
 - **Inflammatory:** Damage of the mucosal lining leads to the loss of protein-rich fluids and a decreased ability to absorb these lost fluids. It is usually caused by bacterial, viral, or parasitic infections but can also occur in patients with IBD, tuberculosis, or colon cancer [3].
- Diverse etiology and aforementioned underlying mechanisms of diarrhea make it both a diagnostic and a therapeutic challenge. On the other hand, diarrhea accounts for 2.5 million deaths every year [4]. According to the American College of Gastroenterology (ACG) guidelines, based on the symptoms and duration, diarrhea should be classified as acute diarrhea (AD) (symptoms of loose stools lasting up to 14 days), persistent diarrhea (symptoms last 14–30 days), and chronic diarrhea (CD) (symptoms persisting over 30 days) [5]. This review will focus on the role of the general practitioner (GP) in diagnosis and treatment of patients with AD and CD.

Acute Diarrhea

Etiology of AD

The most common etiology of AD is infectious, while noninfectious etiology is less frequent. Infectious causes of AD include viruses as the most common causes, less frequently bacteria, while parasite-induced AD is rare in developed countries, but not uncommon in developing countries. Noninfectious causes of AD include medication side effects and gastroenterological and endocrinologic diseases. Sometimes, AD can be caused by an acute abdominal process [5–7].

Infectious diarrhea, from clinicians’ point of view, comprises 2 pathophysiological syndromes mentioned as follows:

Table 1. List of mandatory questions for patients presenting with AD

Symptom
Onset of diarrhea
Duration of diarrhea
Stool consistency
Watery
Bloody (large amount of blood!)
Mucus-filled
Purulent
Bilious
Frequency of diarrhea
Vomiting
Fever
Tenesmus
Relevant questions for possible cause
Food history
“Sugar-free” food
Fat substitutes
Milk products
Shellfish
Heavy intake of fruits, fruit juices, or caffeine
Travel history
Recent sick contacts
Medication used
Antibiotics
Laxatives
New drug initiated
Dose of current drugs increased
Sexual practices (oral-anal contact or receptive anal contact)
Symptoms of dehydration
Thirst
Dizziness
Decreased urine output
Headache
Fatigue
AD, acute diarrhea.

- **Noninflammatory diarrhea (NID)** is characterized by a milder disease course. Etiology is usually viral, but it can also be bacterial or parasitic. NID results from intestinal secretion, while intestinal mucosa remains intact in the majority of cases. Patients present with nausea, vomiting, watery and voluminous stools, and abdominal cramping. Pathogens that lead to NID include *Rotavirus*, *Norovirus*, enterotoxigenic *Escherichia coli*, *Clostridium perfringens*, *Bacillus cereus*, *Staphylococcus aureus*, *Giardia*, *Cryptosporidium* and *Vibrio cholerae* [7].

Table 2. Characteristics of outpatients and hospitalized patients with AD with indication for diagnostic tests

Outpatient	Hospitalized patients
Grossly bloody stools	Diarrhea begins >3 days after admission
Severe dehydration	Nosocomial outbreak
Signs of inflammatory disease	HIV
Symptoms lasting >3–7 days	Neutropenia
Immunosuppression	Older than 65 years with significant comorbidity (end-stage renal, liver, or pulmonary disease; leukemia; and hemiparesis caused by cardiovascular accident and IBD)

AD, acute diarrhea; IBD, inflammatory bowel disease.

- Inflammatory diarrhea (ID) has more severe disease course since it is usually caused by invasive or toxin-producing bacterial strains that lead to mucosal barrier disruption and tissue destruction. Patients present with fever, abdominal pain, tenesmus, and bloody stools of smaller volume than in NID. Common pathogens that induce ID include *Shigella*, *Salmonella* species (*non-Typhi* species), *Campylobacter* sp., *E. coli* (enteroinvasive and *Shiga* toxin-producing strains), *Clostridium difficile*, *Entamoeba histolytica*, and *Yersinia* sp. [7].

GP Approach to Patients with Acute Diarrhea

In the GP office, a detailed history from the patient with AD should be taken and physical examination performed. The list of questions that should be included in the checklist is given in Table 1. A detailed history can be very helpful, since vomiting suggests ingestion of bacterial toxins or viral disease, while fever and tenesmus together with blood in stool suggest ID. The GP should identify patients in high risk of infectious diarrhea (children in day care, nursing home residents, food handlers, recently hospitalized patients, and pregnant women).

During physical examination, the GP should look for signs of dehydration, such as dry mouth, swollen tongue, change in mental status, and palpitations. Furthermore, the assessment of the degree of dehydration should be performed. The GP should actively look for the presence of dry mucous membranes, increase in the heart rate, delayed capillary refill time, and overall ill appearance of the patient. Abdominal examination should be done in order to confirm or exclude acute abdominal processes. Rectal examination is mandatory to assess the presence of blood in stool and stool consistency [7].

Diagnostic Testing in Acute Diarrhea

Since the majority of acute watery diarrhea is self-limited, diagnostic tests are usually not indicated. The use of diagnostic tests should be limited to patients with AD presenting with signs of severe dehydration, bloody stools, persistent fever, patients suffering from immunodeficiencies, patients using immunosuppressive therapy, or cases with suspected nosocomial infection [5, 7]. A summary of patient categories in whom diagnostic tests are indicated is given in Table 2, and possible diagnostic tests are given in Table 3.

The fecal occult blood test is a rapid and inexpensive test and if used together with fecal calprotectin can distinguish inflammatory from other types of AD. The ACG recommends strongly, with a low level of evidence, the use of stool tests to clarify the etiology of the patient's illness and to enable specific therapy in cases of suspected dysentery (bloody stools with tenesmus) and in cases of moderate to severe disease and/or symptoms lasting for >7 days [5].

Traditional methods of diagnosis include bacterial stool culture, antigen testing, direct microscopy, and immunofluorescence. The diagnostic yield of these methods is low. Lee et al. [8] established diagnostic yield of stool cultures using series of 13,327 patients with diarrhea. In 196 patients (1.47%) with positive stool culture, the most common pathogens were *Salmonella* spp. (75.0%) and *Vibrio* (19.4%). According to their results, positive stool culture is to be expected in patients with fever (>37.8°C), vomiting, high C-reactive protein, and >5 bowel movements a day [8].

Culture-independent diagnostic tests (CIDT) are recommended by different guidelines, if available [5, 9]. CIDT are based on stool multiplex polymerase chain reaction that identifies bacterial pathogens in patients with AD. A study by Ahn et al. [10] involving 400 patients with infectious AD revealed higher diagnostic yield of CIDT,

Table 3. Available diagnostic tests for patients with AD

Diagnostic test	Characteristics
FOBT	Rapid and inexpensive
Calprotectin in stool	Suggests inflammation in GI tract
Stool cultures	Limited use due to low diagnostic accuracy, expensive and time consuming but should be used if CIDT are not available
<i>C. difficile</i> testing	Within 3 months of antibiotic use (increased risk of contracting <i>C. difficile</i>) 7–10 time risk increase during and 1 month after antibiotic therapy 3 times higher risk during 2nd and 3rd months
Ova and parasites	Considered not cost-effective in developed countries. Testing is recommended in developing countries. Test should be done also in developed countries in cases of persistent diarrhea lasting >7 days infants in day care or travel to endemic regions diarrhea in persons with AIDS men who have sex with men community waterborne outbreaks bloody diarrhea with few fecal leukocytes
Molecular testing (CIDT)	Increase likelihood of identifying etiology of AD, results within hours, if available should be used, instead of stool cultures
Endoscopy	Consider if the diagnosis is unclear after routine blood and stool tests empiric therapy is ineffective symptoms persist

FOBT, fecal occult blood test; CIDT, culture-independent diagnostic tests; AD, acute diarrhea; *C. difficile*, *Clostridium difficile*.

namely, CIDT detected bacterial pathogens in 49.2% of specimens, as opposed to 5.2% detected by traditional stool culture. The authors used this test for simultaneous detection of 7 enteropathogenic bacteria (*Salmonella*, *Campylobacter*, *Shigella*, *Escherichia coli* O157:H7, *Aeromonas*, *Vibrio*, and *Clostridium difficile*), and their results revealed *Campylobacter* in 54% of all positive findings [10]. According to the available guidelines, antibiotic sensitivity testing is not recommended in patients with acute infectious diarrhea [5, 6]. Based on the aforementioned facts, the ACG recommends new technologies including CIDT of a broad range of potential pathogens and suggests that CIDT provide more comprehensive assessment of disease etiology [5]. As an additional advantage, CIDT can be obtained within hours, leading to the conclusion that stool cultures are inefficient and time-consuming compared to CIDT [5]. Main limitations of CIDT are the cost and the fact that CIDT are not available in all countries. Study by Ahn et al. [10] also revealed that a positive result of CIDT is correlated with calprotectin expression; thus, the authors conclude that these tests if used simultaneously can predict severity of infectious di-

arrhea. For travelers' diarrhea, both culture-based and empiric treatment are acceptable; thus, stool tests are not mandatory [5, 6].

Endoscopy is not routinely recommended in patients with AD. In patients with persistent symptoms, in whom infectious etiology of diarrhea has been excluded, further diagnostic workup should include endoscopic evaluation in search of the possible cause of diarrhea after the work-up, as described in the section for chronic diarrhea [5]. Colonoscopy with biopsies and cultures are indicated in cases of suspected tuberculosis and diffuse colitis and for detection of noninfectious causes of AD (IBD, NSAID enteropathy, ischemic colitis, and cancer).

Therapy of AD

Therapeutic options in patients with AD include oral rehydration, early refeeding, antidiarrheal medications, antibiotics, probiotics, and zinc supplementation. Oral rehydration is the first step in treating AD. An optimal oral rehydration solution contains a mixture of salt and glucose in combination with water. The World Health Organization endorsed an oral rehydration solution with

reduced osmolality, aiming to decrease episodes of nausea and emesis and the number of stool outputs [5–7, 11].

Early refeeding is important since it decreases intestinal permeability caused by infections and decreases the illness duration, leading to improved nutritional outcomes. It is of greatest importance in developing countries where patients tend to be malnourished before disease onset. A common recommendation of bananas, rice, applesauce, and toast diet and avoidance of dairy are traditional therapeutic strategies with limited data to confirm their efficacy. Also, patients should not be advised to refrain from solid food for 24 h, since data suggesting the efficacy of this measure is lacking. It is postulated by various guidelines that resumption of an age-appropriate usual diet should begin during or immediately after rehydration [5–7, 11].

Antidiarrheal medications include loperamide, bismuth subsalicylate, and racecadotril, while there are no strong data to support the use of absorbents such as kaolin, pectin, or activated charcoal. Loperamide (Imodium) may reduce the duration of diarrhea and increase the likelihood of clinical cure at 24 and 48 h when given with antibiotics for travelers' diarrhea [5, 7]. Also, combination of loperamide and simethicone provides fast and effective improvement in patients with noninfective AD and gas-related symptoms [5, 7]. Nevertheless, a prolonged use of loperamide may cause serious prolongation of disease and poor outcome in patients with bloody diarrhea or ID [7]. The current recommendation for loperamide is that its use should be limited to patients with nonbloody stools [5, 7]. Bismuth subsalicylate (Pepto-Bismol) is a safe alternative in patients with fever and ID [5, 7]. Recent meta-analysis that included 14 studies revealed that bismuth subsalicylate is effective for both prevention and treatment of travelers' diarrhea. Their results show that subjects treated with bismuth subsalicylate for up to 21 days have 3.5 times greater odds of preventing travelers' diarrhea than placebo, while subjects with infectious diarrhea treated with bismuth subsalicylate had 3.7 times greater odds of diarrhea relief [12]. Racecadotril, a peripheral enkephalinase inhibitor, prevents degradation of enkephalines, thus reducing water and electrolyte secretion in the bowel lumen [13]. A randomized study by Wang et al. [14] revealed similar success rate of loperamide and racecadotril in patients with AD, namely, the median duration of diarrhea was 13 h in loperamide and 19.5 h in the racecadotril group with similar clinical success rates. Loperamide was effective in 92% and racecadotril in 95.7% of patients. Nevertheless, loperamide leads to reactive con-

stipation in 29% as opposed to only 12.9% of patients in the racecadotril group [14].

Antibiotics should be given in cases of AD with proven bacterial etiology. The Infectious Diseases Society of America recommends empirical use of either a fluoroquinolone such as ciprofloxacin or azithromycin [6]. This recommendation is based on the low failure rates of empirical antimicrobial therapies that have been repeatedly reported [15–17]. Empiric antibiotic therapy is recommended for travelers' diarrhea since the likelihood of bacterial etiology is very high and surpasses the possible side effects of antibiotics [5, 6]. Antibiotics should be given for travelers' diarrhea usually as a single dose or 3-day course. A single dose and 3-day course of 500 mg levofloxacin, ofloxacin, ciprofloxacin, and azithromycin are possible antibiotic options, and a 3-day course of rifaximin is also a valid option in previously reported doses [6]. Nevertheless, in the majority of cases, AD is caused by viruses; thus, antibiotics are useless [6]. The use of antibiotics without proven bacterial etiology is advisable in patients who are older than 65 years, immunocompromised, septic, or severely ill. Caution and consideration of prophylactic antibiotic use is also advisable in patients with mechanical heart valves and recent vascular grafts and patients with congenital hemolytic anemia. According to the available guidelines, antibiotics of choice are ciprofloxacin 500 mg bid 3–5 days or metronidazole 250 mg qid for 7 days [7]. Appropriate microbial identification may be helpful in assessing the need for antibiotic therapy [5].

Probiotics stimulate the host immune system and compete for binding sites on intestinal epithelial cells with a variety of pathogens. The use of probiotics in prevention and treatment of diarrhea increased in the recent years [18]. In 2017, the Infectious Diseases Society of America recommended that probiotics can be offered to immunocompetent adults and children with both infectious and antibiotic-associated diarrhea to reduce symptoms, severity, and duration [6]. Probiotic efficacy has been demonstrated in children with AD where they reduce severity and the duration of illness (one less day of illness) [11, 18, 19]. On the other hand, effects of strain-specific probiotics need to be verified in adult studies before a specific evidence-based recommendation can be made. According to ACG guidelines, the use of probiotics or prebiotics for treatment of AD in adults is limited to cases of antibiotic-associated illness [5].

In 2015, Guarino et al. [18] found 12 available guidelines on acute gastroenteritis: 5 that recommended probiotics and 7 that did not. The authors revealed that guidelines recommended probiotics based on evidence

from both clinical trials and meta-analyses. *Lactobacillus rhamnosus* GG and *Saccharomyces boulardii* proved to be most effective and lead to reduction in the disease duration by 24 h [18]. As for antibiotic-associated diarrhea, they describe variable efficacy of probiotics in preventing diarrhea. The most effective strains for antibiotic-associated diarrhea prevention were *Lactobacillus rhamnosus* GG and *S. boulardii*. A Cochrane review included 63 studies that met the inclusion criteria, but only 7 trials were in the adult population, while remaining 56 were in pediatric patients. The authors came to the conclusion that probiotics reduced the duration of diarrhea [20]. Wilkins and Sequoia [19] consider probiotics effective for bacterial AD, while data on effects in viral diarrhea are inconsistent. Wilkins and Sequoia [19] suggest that therapy with probiotics should start when the symptoms occur and continue for 1–2 weeks after symptoms have resolved. Probiotics are, according to the available meta-analysis of 12 RCTs, beneficial in the prevention of travelers' diarrhea [21] and should be started 2 days before travel and continued during the travel. In immunocompromised patients, probiotics should be introduced with caution since case reports of bacteremia and fungemia in critically ill and immunocompromised patients have been described [22–24].

The rationale for the use of zinc supplementation in treatment of AD is that zinc deficiency is a common dietary deficiency, especially in developing countries [7]. Zinc deficiency is associated with an increased risk of gastrointestinal (GI) infections. The recommended daily dose of zinc is 20 mg, and it affects the duration of diarrhea and nausea [7]. A meta-analysis by Lazzerini [25] concluded that there is enough evidence to support the use of oral zinc in treating diarrhea in children aged 6 months–5 years, especially if at risk of zinc deficiency, while these findings have to be confirmed in children at low risk of zinc deficiency. As opposed to data in pediatric populations, a systematic review by Gottlieb and Heather [11] that presented information on effectiveness and safety of different therapeutic options in AD in adults found no evidence for the use of zinc supplementation. Therefore, the use of zinc in treatment of AD in adults is not recommended by the available guidelines [5].

Chronic Diarrhea

Etiology of CD

CD can have different underlying pathophysiological mechanisms. Most common causes of secretory CD are

Table 4. List of mandatory questions for patients presenting with CD

Symptom
Onset of diarrhea
Duration of diarrhea
Stool character
Watery
Bloody (large amount of blood especially)
Mucus-filled
Purulent
Bilious
Frequency of diarrhea
Diarrhea pattern
Nocturnal diarrhea that interferes with sleep
Presence of fecal incontinence
Relevant questions for possible cause
Family history of celiac disease
Family history of IBD
Travel history
Risk contacts
Medication used
Antibiotics
Laxatives
New drug initiated
Dose of current drugs increased
Food history
“Sugar-free” food
Fat substitutes
Milk products
Heavy intake of fruits, fruit juices, or caffeine
Other related symptoms
Abdominal pain
Aggravating factors
Relieving factors
Fever
Weight loss
Extraintestinal manifestations
CD, chronic diarrhea; IBD, inflammatory bowel disease.

laxative abuse; chronic abuse of alcohol; previous bowel surgery; bowel disease; or presence of fistula, diabetic enteropathy, Addison's disease; and hormone-producing tumors, such as colon villous adenoma, medullary thyroid cancer, or neuroendocrine tumors (i.e., VIPoma and carcinoid tumor). Osmotic CD occurs in cases of abuse of osmotic laxative, lactose intolerance, or other disaccharidase deficiencies and also in cases of maldigestion (pancreatic insufficiency) and malabsorption (celiac disease and Whipple disease). Inflammatory CD is seen in pa-

tients with IBD, infections, irradiation injury, malignancies of GI tract, or food allergies and in cases of both primary and secondary immune deficiencies. Dysmotility-related CD is typical in irritable bowel syndrome, use of prokinetics, and hyperthyroidism.

Diagnostic Algorithm for CD Patients in GP Office

In this section of the review, we will try to identify patients who need laboratory and stool testing and those who need gastroenterology referrals. Overall, only a minority of patients will be referred to the gastroenterologist. Around 10% of all GP consults are gastroenterological [26]. The majority of patients have self-limiting symptoms or functional GI disorders, while only a minority have CD or persistent diarrhea. A primary care physician with an average list size of 1,700 patients may have 50–85 such patients each year [1]. The GP approach to the patient with CD should include medical history (Table 4) and physical examination.

Physical examination should be detailed, and the GP is to assess the hemodynamic status of the patient and furthermore look for the presence of thyroid mass, wheezing, heart murmurs, edema, abdominal mass, lymphadenopathy, mucocutaneous abnormalities, and presence of perianal fistula. The presence of “red flag symptoms” such as blood in stool, weight loss, and clinical signs of anemia confirmed with laboratory findings and palpable mass in the abdomen are indications for urgent gastroenterological referral. If there are no red flag symptoms, the algorithm for CD evaluation should include full blood count, C-reactive protein, liver function test, serum iron, TIBC, ferritin, and, in cases where there is no visible blood, fecal occult blood test. These findings together with fecal calprotectin, if available, can discriminate functional from organic disease. If calprotectin is used in a GP setting, limitations of calprotectin should be considered, namely, calprotectin can distinguish organic from functional disease with high specificity and sensitivity [1], but any inflammation will increase calprotectin including infectious causes of CD [1]. In CD patients, stool testing should be done in order to exclude enteropathogenic *E. coli*, *Giardia lamblia*, *Entamoeba*, *Cryptosporidium*, and *Yersinia*.

For the GP setting, Calpro Quest is an advisable guideline for the rational use of calprotectin. It was designed as the 8-item questionnaire aiming to increase the pretest probability for a positive calprotectin. It postulates major and minor criteria, namely, 2 major or 1 major and 2 minor criteria should be fulfilled in order to request fecal calprotectin in a GP office. Major criteria include abdominal pain at least 3 times a week for at least 4 weeks, diar-

rhea (>3 bowel movements daily) for 7 consecutive days, diarrhea at nighttime, awakening from sleep because of abdominal pain or diarrhea, and bloody stool. Minor criteria include mucus in stool for >4 weeks, unwanted weight loss (5% of normal body weight over 6 months), fever over the last 4 weeks (temperature >38°C), and fatigue over the last 4 weeks. The sensitivity and specificity of Calpro Quest for fecal calprotectin levels >50 µg/g was 36 and 57%. In this study, out of 150 endoscopic results in 101 (67.3%), organic disease was diagnosed, namely, 80 patients had IBD and 21 other pathology such as diverticulitis, diverticulosis, polyps, and microscopic colitis [27].

If the aforementioned diagnostic algorithm reveals red flag symptoms or leads to clinical suspicion of IBD, colonic cancer, or other organic disease arising from the GI tract, the patient should be referred for gastroenterologist consult.

In conclusion, GP-oriented guidelines for patients with diarrhea are lacking. Based on the available guidelines and data, the GP should diagnose and treat mild-to-moderate cases of AD. Severe cases of AD with dehydration should be referred for hospital admission. In cases of CD, a subset of patients with suspected organic disease will need referral to the gastroenterologist. Timely referral for patients with CD and red flag symptoms is mandatory. Patients with functional diarrhea should be treated in the GP setting, and only cases refractory to treatment should be referred to the gastroenterologist.

Statement of Ethics

This kind of study is exempt from ethical approval.

Conflict of Interest Statement

The authors have no conflicts of interest to disclose.

Funding Sources

None of the authors received any funding relevant to this review.

Author Contributions

A.S.-M. drafted, wrote, and critically revised the manuscript. A.P.-M., R.S.T., and S.L. wrote the manuscript.

References

- 1 Arasradnam RP, Brown S, Forbes A, Fox MR, Hungin P, Kelman L, et al. Guidelines for the investigation of chronic diarrhoea in adults: British society of gastroenterology, 3rd edition. *Gut*. 2018 Aug;67(8):1380–99.
- 2 Moon C, Zhang W, Sundaram N, Yarlagadda S, Reddy VS, Arora K, et al. Drug-induced secretory diarrhea: a role for CFTR. *Pharmacol Res*. 2015 Dec;102:107–12.
- 3 Camilleri M. Intestinal secretory mechanisms in irritable bowel syndrome-diarrhea. *Clin Gastroenterol Hepatol*. 2015 Jun;13(6):1051–2.
- 4 Kosek M, Bern C, Guerrant RL. The global burden of diarrhoeal disease, as estimated from studies published between 1992 and 2000. *Bull World Health Organ*. 2003;81(3):197–204.
- 5 Riddle MS, DuPont HL, Connor BA. ACG clinical guideline: diagnosis, treatment, and prevention of acute diarrheal infections in adults. *Am J Gastroenterol*. 2016 May;111(5):602–22.
- 6 Shane AL, Mody RK, Crump JA, Tarr PI, Steiner TS, Kotloff K, et al. 2017 infectious diseases society of America clinical practice guidelines for the diagnosis and management of infectious diarrhea. *Clin Infect Dis*. 2017 Nov;65(12):e45–80.
- 7 Barr W, Smith A. Acute diarrhea. *Am Fam Physician*. 2014;89(3):180–9.
- 8 Lee JY, Cho SY, Hwang HSH, Ryu JY, Lee J, Song ID, et al. Diagnostic yield of stool culture and predictive factors for positive culture in patients with diarrheal illness. *Medicine*. 2017 Jul;96(30):e7641.
- 9 Janda JM, Abbott SA. Culture-independent diagnostic testing: have we opened pandora's box for good? *Diagn Microbiol Infect Dis*. 2014 Nov;80(3):171–6.
- 10 Ahn JS, Seo SI, Kim J, Kim T, Kang JG, Kim HS, et al. Efficacy of stool multiplex polymerase chain reaction assay in adult patients with acute infectious diarrhea. *World J Clin Cases*. 2020 Sep 6;8(17):3708–17.
- 11 Gottlieb T, Heather CS. Diarrhoea in adults (acute). *BMJ Clin Evid*. 2011 Feb 15;2011:0901.
- 12 Brum JM, Gibb RD, Ramsey DL, Balan G, Yacyshyn BR. Systematic review and meta-analysis assessment of the clinical efficacy of bismuth subsalicylate for prevention and treatment of infectious diarrhea. *Dig Dis Sci*. 2020 Aug 8.
- 13 Matheson AJ, Noble S. Racecadotril. *Drugs*. 2000;59:829–7.
- 14 Wang HH, Shieh MJ, Liao KF. A blind, randomized comparison of racecadotril and loperamide for stopping acute diarrhea in adults. *World J Gastroenterol*. 2005 Mar;11(10):1540–3.
- 15 Wikswo ME, Kambhampati A, Shioda K, Walsh KA, Bowen A, Hall AJ. Centers for disease control and prevention (CDC). Outbreaks of acute gastroenteritis transmitted by person-to-person contact, environmental contamination, and unknown modes of transmission: United States, 2009–2013. *MMWR Surveill Summ*. 2015 Dec 11;64(12):1–16.
- 16 Date KA, Newton AE, Medalla F, Blackstock A, Richardson L, McCullough A, et al. Changing patterns in enteric fever incidence and increasing antibiotic resistance of enteric fever isolates in the United States, 2008–2012. *Clin Infect Dis*. 2016 Aug 1;63(3):322–9.
- 17 Saphra I, Winter JW. Clinical manifestations of salmonellosis in man; an evaluation of 7779 human infections identified at the New York Salmonella Center. *N Engl J Med*. 1957;256:1128–34.
- 18 Guarino A, Guandalini S, Lo Vecchio A. Probiotics for prevention and treatment of diarrhea. *J Clin Gastroenterol*. 2015 Nov–Dec;49(Suppl 1):S37–45.
- 19 Wilkins T, Sequoia J. Probiotics for gastrointestinal conditions: a summary of the evidence. *Am Fam Physician*. 2017 Aug 1;96(3):170–8.
- 20 Allen SJ, Martinez EG, Gregorio GV, Dans LF. Probiotics for treating acute infectious diarrhoea. *Cochrane Database Syst Rev*. 2010 Nov 10;2010(11):CD003048.
- 21 McFarland LV. Meta-analysis of probiotics for the prevention of traveler's diarrhea. *Travel Med Infect Dis*. 2007;5(2):97–105.
- 22 Bassetti S, Frei R, Zimmerli W. Fungemia with *Saccharomyces cerevisiae* after treatment with *Saccharomyces boulardii*. *Am J Med*. 1998;105:71–2.
- 23 Lherm T, Monet C, Nougère B, Soulier M, Larbi D, Le Gall C, et al. Seven cases of fungemia with *Saccharomyces boulardii* in critically ill patients. *Intensive Care Med*. 2002;28:797–801.
- 24 Tommasi C, Equitani F, Masala M, Ballardini M, Favaro M, Meledandri M, et al. Diagnostic difficulties of *Lactobacillus casei* bacteraemia in immunocompetent patients: a case report. *J Med Case Rep*. 2008;2:315.
- 25 Lazzerini M. Oral zinc provision in acute diarrhea. *Curr Opin Clin Nutr Metab Care*. 2016 May;19(3):239–43.
- 26 Jones R. Primary care research and clinical practice: gastroenterology. *Postgrad Med J*. 2008;84:454–8.
- 27 Chmiel C, Senn O, Hasler S, Rosemann T, Rogler G, Zahnd N, et al. Can the CalproQuest predict a positive calprotectin test? A prospective diagnostic study. *PLoS One*. 2019 Nov 21;14(11):e0224961.