Diarrhea as a Clinical Challenge: General Practitioner Approach

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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.

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 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 endocrinological 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:

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

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

AD, acute diarrhea.
• 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,
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 diarrhea. 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

| **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 |
| C. difficile testing          | Within 3 months of antibiotic use (increased risk of contracting C. difficile) |
|                              | 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.
reduced osmolarity, 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 raccelodotril, 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]. Raccadotril, 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 raccelodotril in patients with AD, namely, the median duration of diarrhea was 13 h in loperamide and 19.5 h in the raccelodotril group with similar clinical success rates. Loperamide was effective in 92% and raccelodotril in 95.7% of patients. Nevertheless, loperamide leads to reactive constipation in 29% as opposed to only 12.9% of patients in the raccelodotril 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 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 malabsorption (pancreatic insufficiency) and malabsorption (celiac disease and Whipple disease). Inflammatory CD is seen in pa-
tients with IBD, infections, irradiation injury, malignan-
cies of GI tract, or food allergies and in cases of both pri-
mary 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 pa-
tients who need laboratory and stool testing and those
who need gastroenterology referrals. Overall, only a mi-
nority of patients will be referred to the gastroenterolo-
gist. Around 10% of all GP consults are gastroenterologi-
cal [26]. The majority of patients have self-limiting symp-
toms 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 pa-
tient 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 fur-
thermore look for the presence of thyroid mass, wheezing,
heart murmurs, edema, abdominal mass, lymphadenopa-
thy, mucocutaneous abnormalities, and presence of peri-
anal 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 gastroenterologi-
cal referral. If there are no red flag symptoms, the algo-
rithm 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 cal-
protectin, if available, can discriminate functional from
organic disease. If calprotectin is used in a GP setting, lim-
itations of calprotectin should be considered, namely, cal-
protectin can distinguish organic from functional disease
with high specificity and sensitivity [1], but any inflamma-
tion 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 lam-
blia*, *Entamoeba*, *Cryptosporidium*, and *Yersinia*.

For the GP setting, Calpro Quest is an advisable guide-
line 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 mi-
nor criteria should be fulfilled in order to request fecal
calprotectin in a GP office. Major criteria include abdom-
inal pain at least 3 times a week for at least 4 weeks, diar-
hea (>3 bowel movements daily) for 7 consecutive days,
diarrhea at nighttime, awakening from sleep because of
abdominal pain or diarrhea, and bloody stool. Minor cri-
tera 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 fa-
tigue 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 diver-
ticulitis, diverticulosis, polyps, and microscopic colitis
[27].

If the aforementioned diagnostic algorithm reveals red
flag symptoms or leads to clinical suspicion of IBD, co-
lonic 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 guide-
lines and data, the GP should diagnose and treat mild-to-
moderate cases of AD. Severe cases of AD with dehydra-
tion 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 refer-
ral for patients with CD and red flag symptoms is manda-
tory. 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**

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