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Gastroenterology

An approach to acute and chronic diarrhoea

Learning objectives

You will learn:

- The causes of and risk factors for acute and chronic diarrhoea
- How to screen and diagnose acute and chronic diarrhoea
- The general principles of treating diarrhoea, with a focus on anti-diarrhoeal agents used adjunctively to oral rehydration and, if necessary, antimicrobials.

Introduction

In the healthy adult, diarrhoea is often viewed as a 'nuisance' disease. However, serious complications including severe dehydration and renal failure can occur and may necessitate admission to hospital. Elderly people and those in long-term care have an increased risk of death as a consequence of diarrhoea. Diarrhoea is reported to cause more deaths, an estimated 2.5 million annually, than any other condition in children under five years of age living in resource-poor countries. In South Africa, diarrhoea accounts for 19% of deaths of children under five years of age; dehydration is the key factor in these deaths.[1-3]

Oral rehydration therapy is central to the management of acute diarrhoea, being sufficient in most patients to prevent complications due to dehydration, but it has no effect on the duration of the disease or frequency of bowel motions

Diarrhoea is classified as acute (short-term, less than 7 days), prolonged (a form of acute diarrhoea lasting more than 7 days), or chronic (long-term, more than 2 weeks in children or 4 weeks in adults). It is also classified as mild, moderate, or severe, with dehydration reflecting severity of symptoms. Oral rehydration therapy (ORT) is central to the management of acute diarrhoea, being sufficient in most patients to prevent complications due to dehydration, but it has no effect on the duration of the disease or frequency of bowel motions.[4,5]

This review considers an approach to the management of acute and chronic diarrhoea in adults and children, with a special focus on anti-diarrhoeal agents that safely decrease the duration of diarrhoea adjunctive to ORT.

Cipla

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Causes of diarrhoea

Diarrhoea almost always occurs by one or more of four mechanisms: disruption of osmotic forces in the intestine; disruption of normal secretory processes; disruption of epithelial cells or the epithelial tight junctions; or motility disorders (Table 1).[5]

Table 1. Mechanisms by which diarrhoea can occur[5]

Osmotic	Large quantities of poorly absorbed, low molecular-weight solutes in the lumen drive the transport of excessive water into the lumen via osmotic forces
Secretory	Overstimulation of the secretory capacity of the intestinal tract, usually as a result of bacterial and viral enterotoxins
Exudative	Bacterial and viral pathogens destroy epithelial cells or disrupt the tight junctions of the intestinal epithelium; this allows water and electrolytes, mucus, and proteins to exude into the lumen due to the hydrostatic pressure differential, where they may accumulate and cause diarrhoea
Motility disorders	Accelerated intestinal transit time can decrease absorption, causing diarrhoea even when the absorptive process itself is proceeding normally

Parasitic pathogens are less common, although there is a higher likelihood of this being the cause of diarrhoea in HIV-positive individuals

There are numerous potential causes of diarrhoea (Table 2). Viral pathogens are most likely to be responsible for infectious diarrhoea in infants, with rotavirus being the most severe enteric pathogen in children. Norovirus is the most common viral cause of diarrhoea in adults. Many bacterial species produce toxins that can cause diarrhoea through different mechanisms. Parasitic pathogens are less common, although there is a higher likelihood of this being the cause of diarrhoea in HIV-positive individuals.

Infectious causes often lead to acute symptoms, but in some cases can result in chronic diarrhoea in immunodeficient patients or in persistent diarrhoea due to a malabsorptive enteropathy. It remains unclear whether gut microbiota alterations are the cause or the consequence of chronic disorders with multifactorial pathogenesis, such as inflammatory bowel disorder (IBD). Non-infectious aetiologies of diarrhoea include medications, food allergy or intolerance, digestive disorders, and anatomical disorders.[4,6]

Table 2. Causes of diarrhoea[4,6]

Viral infection	Norovirus Rotavirus Cytomegalovirus	Adenovirus Astrovirus Sapovirus
Bacterial infection	*Escherichia coli* *Shigella dysenteriae* *Clostridium perfringens* *Clostridium difficile* *Staphylococcus aureus*	*Bacillus cereus* *Aeromonas hydrophila* *Campylobacter jejuni* *Salmonella enterica*
Parasitic infection	*Cryptosporidium parvum* *Entamoeba histolytica* *Giardia lamblia*	*Cyclospora cayetanensis* *Listeria monocytogenes*
Medication	Antibiotics Long-term use of proton pump inhibitors Magnesium-containing products	

Food allergy or intolerance	Cow's milk Egg Seafood	Soy Fructose/lactose intolerance
Digestive disorder	Coeliac disease Crohn's disease Irritable bowel syndrome (IBS)	Inflammatory bowel disease (IBD) Ulcerative colitis
Anatomical disorder	Gastroschisis Necrotising enterocolitis (NEC)	Acute volvulus can cause short-bowel syndrome (SBS) Surgical resection

Risk factors for diarrhoea

The cause of infectious diarrhoea depends on geographical location, standards of food hygiene, sanitation, water supply, and season

The cause of infectious diarrhoea depends on geographical location, standards of food hygiene, sanitation, water supply, and season. Exposure to infectious agents is the major risk factor for acute diarrhoea, with bacteria and viruses often transmitted by the faecal-oral route. Hand washing and hygiene are important to prevent infection.

Diarrhoea is common in infants and is usually acute. If chronic, it is commonly caused by allergies and by infectious agents. Incidence of diarrhoeal disease varies greatly with the seasons and child's age but is mostly due to either bacterial or viral pathogens, with a high number of cases due to bacterial enteropathogens in the summer months and rotavirus in the winter months. Prolonged diarrhoea, due to a longer and more serious infection, is associated with reduced growth.[4,6]

People living with HIV are at increased risk of diarrhoea because of drug interactions with antiretroviral therapy. This may be further aggravated by malnutrition and other infectious diseases, which are frequent, and the complications of immunocompromise, gastrointestinal manifestations of primary HIV disease, and other challenges.[1,2]

Screening and diagnosis

Acute diarrhoea

Acute diarrhoea of infectious aetiology is generally associated with other clinical features suggesting enteric involvement including nausea, vomiting, abdominal pain and cramps, bloating, flatulence, fever, passage of bloody stools, tenesmus, and faecal urgency. Specific investigation is not normally required in the majority of cases of acute watery diarrhoea because it is usually self-limiting and resolves without specific treatment. Conventional diagnostic approaches to diarrhoeal disease (Table 3) are seldom used or required in patients with acute watery diarrhoea. Routine clinical laboratory detection of bacterial pathogens requires the use of differential culture media, which select for the growth of certain bacteria but may fail to detect other bacteria, especially in the setting of antibiotic use. Features that may warrant microbiological stool testing are outlined in Table 4.[5,7]

Table 3. Conventional diagnostic approaches to diarrhoeal disease[7]

- Bacterial culture
- Microscopy with and without stains or immunofluorescence
- Stool antigen tests for detection of protozoa and for detecting viral agents
- Electron microscopy
- Antigen-based tests.

Table 4. Indications for considering microbiological stool testing

- Severe illness with:
  - Profuse watery diarrhoea with signs of hypovolaemia
  - >6 unformed stools per 24 hours
  - Severe abdominal pain
  - Need for hospitalisation
- Other signs and symptoms of inflammatory diarrhoea:
  - Bloody diarrhoea
  - Many small volume stools containing blood and mucus
  - Fever ≥38.5°C
- High-risk host features:
  - Age ≥70 years
  - Comorbidities such as cardiac disease which may be exacerbated by hypovolaemia or rapid infusion of fluid
  - Immunocompromising condition, including AIDS
  - IBD
  - Pregnancy
- Public health concerns.

Specific investigation is not normally required in the majority of cases of acute watery diarrhoea because it is usually self-limiting and resolves without specific treatment

In the evaluation of the patient with persistent symptoms that have not responded to empiric treatment, it is important to test for parasitic organisms and to evaluate other non-infectious processes that may be the cause of the diarrhoea. Every child with persistent diarrhoea should be examined for non-intestinal infections such as pneumonia, sepsis, urinary tract infection, and otitis media, and treated for these with antimicrobials following standard guidelines.[7]

A thorough and directed history is essential to direct further investigations as to the cause of persistent diarrhoea. Relevant questions would include:

- Travel history
- Nature of the initial symptoms
- Onset (sudden or gradual)
- Duration, frequency, and characteristics of bowel movements (particularly the presence of blood or mucus)
- Stool volume
- Tenesmus
- Association with particular foods
- Use of antibiotics
- Presence or absence of other associated symptoms such as nausea, vomiting, incontinence, fever, and weight loss.

The answers to these questions may direct further investigations.

Chronic diarrhoea

Chronic diarrhoea requires a different diagnostic and therapeutic work-up than acute diarrhoea. Differential diagnosis is vast. However, a careful history and thorough physical examination with judicious use of selected tests often leads to a specific diagnosis and an appropriate treatment plan. The main distinction in patients with chronic diarrhoea is between functional and organic aetiologies and it is important to consider comorbid symptoms and epidemiologic clues when constructing a differential diagnosis.

Significant abdominal pain, fever, or gastrointestinal bleeding suggests an inflammatory cause for the diarrhoea. Gas and bloating suggest carbohydrate malabsorption. Substantial weight loss suggests malabsorption, maldigestion, or a malignancy (particularly in an older person). Fatigue and night sweats suggest lymphoma, whereas anaemia or change in stool calibre suggests colorectal malignancy.[8]

Important causes of chronic diarrhoea that can be suspected on the basis of history alone include diet, medications, and surgery or radiation therapy. Specific dietary components may cause or aggravate chronic diarrhoea, although true food allergies are rarely the cause. The identification of a dietary cause of diarrhoea may be facilitated by a food diary. Careful review of current medications is essential as more than 700 drugs have been implicated as causing diarrhoea, accounting for approximately 7% of drug adverse effects.[8]

Further investigation is indicated when alarm features are present, when there is no evident cause, or the differential diagnosis needs further delineation, and may include testing of blood and stool, endoscopy, imaging studies, histology, and physiological testing. For disorders without definitive diagnostic tests, therapeutic trials may be reasonable. Routine blood tests may provide clues to aetiology and fluid and electrolyte status. Other blood tests should be obtained only when demanded by the clinical presentation.[8]

Lower gastrointestinal endoscopy with mucosal biopsy is valuable in inflammatory and secretory diarrhoeas. Colonoscopy has a greater yield than sigmoidoscopy, but multiple biopsies must be obtained. Biopsy of normal-appearing terminal ileum is not recommended. Upper endoscopy or enteroscopy with biopsies of the duodenum or jejunum should be done in patients with unexplained steatorrhoea.[8]

Treatment of diarrhoea

Careful review of current medications is essential as more than 700 drugs have been implicated as causing diarrhoea, accounting for approximately 7% of drug adverse effects

The main goal of therapy is to prevent complications secondary to dehydration and its associated electrolyte disturbances and metabolic acidosis. The World Health Organization recommends ORT treatment for acute diarrhoea, with antibiotics and antiparasitic drugs prescribed only in specific cases. The major value of ORT is treatment of dehydrating forms of diarrhoea, but it may not reduce number of stools or shorten illness. Alternative or adjunctive anti-diarrhoeal agents that decrease the duration of diarrhoea and are safe are therefore a valuable addition to ORT in the management of diarrhoea. The three main classes of anti-diarrhoeal drug that are used to reduce stool frequency and/or volume and duration of symptoms are anti-motility agents, anti-secretories, and adsorbents.[4,5,7]

The use of probiotics or prebiotics for treatment of acute diarrhoea in adults is not recommended, except in cases of post-antibiotic-associated illness. Empiric antimicrobial therapy for routine acute diarrhoeal infection is not recommended, except in cases of traveller's diarrhoea where the likelihood of bacterial pathogens is high enough to justify the potential side effects of antibiotics. Numerous studies have demonstrated that antibiotics shorten the overall duration of moderate-to-severe traveller's diarrhoea to a little over 24 hours. Use of antibiotics for community-acquired diarrhoea should be discouraged as epidemiological studies suggest that most community-acquired diarrhoea is viral in origin (norovirus, rotavirus, and adenovirus) and is not shortened by the use of antibiotics.[5,7]

Treatment of the diverse causes of chronic diarrhoea is beyond the scope of this review; however, if diarrhoea symptoms persist despite normal first-line investigations and treatment, then referral for specialist investigation is recommended.

Symptomatic therapy using anti-diarrhoeal agents

Although anti-motility drugs may reduce the frequency of stool passage in adults, they are not recommended for use in children as they do not decrease the volume of stool and they may prolong infection by delaying elimination of the causative organisms. For this same reason, anti-motility agents should be avoided in patients with clinical features suggestive of dysentery. Adsorbents are safe for use as an adjunct to ORT.

Diosmectite

Diosmectite is a natural aluminomagnesium silicate clay with a lamellar, non-fibrous crystalline structure that confers strong adsorbent properties. Its mechanisms of action are not yet fully understood but are probably multiple. Diosmectite reduces inflammation; possible anti-inflammatory mechanisms include adsorption of luminal antigens produced during the inflammation process and modulation of cytokine production by mucosal cells. Diosmectite modifies mucus rheologic properties, inhibits mucolysis and significantly increases colonic expression of mucin 2, the main secretory gel-forming mucin in the colon. Diosmectite also adsorbs bacteria, bacterial enterotoxins, viruses and

other potentially diarrhoeagenic substances. Diosmectite can provide anti-diarrhoeal activity several days after administration (by which time it would have been eliminated from the intestinal lumen), suggesting that there is also likely to be a reinforcing effect of the natural defence mechanisms contributing to the overall anti-inflammatory effect.[5,9]

The efficacy of diosmectite in the treatment of acute diarrhoea in children has been investigated in several controlled clinical studies. Despite varying inclusion criteria and outcome parameters, results have consistently demonstrated the efficacy of diosmectite, with Cochrane review showing that it may reduce the duration of diarrhoea by approximately a day, may increase clinical resolution at day 3, and may reduce stool output. Numerous studies have shown that diosmectite reduces the duration of diarrhoea and decreases the frequency of bowel motions after two days of treatment in children with mild-to-moderate acute diarrhoea. Diosmectite was found to be particularly effective in rotavirus-positive children.[5,9]

Because of its lack of systemic absorption, diosmectite is well tolerated even by very young children and can be used as an adjunct to ORT, as well as to antibacterial therapy if needed. Due to the adsorbent properties of diosmectite, it should be administered at a different time to other medications; a delay of 60–90 minutes is recommended between administration of diosmectite and other orally administered agents that rely on absorption. ORT is not adversely affected when administered concomitantly with diosmectite.[5,9]

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Gelatine tannate

Gelatine tannate is emerging as a promising intestinal barrier modulator. It is a combination of tannic acid and gelatine that may act by creating a protective film, forming bonds with the mucin, thereby protecting the gut from the aggressive penetration of pathogens. Gelatine tannate is commonly used as an intestinal faecal output regulator. It passes unaltered through the stomach and once in the intestine it may exert its action by restoring the physiological barrier function and by reducing the pro-inflammatory effects of lipopolysaccharide in human intestinal epithelial cells.[4]

Gelatine tannate has a good safety profile and is significantly more effective than placebo; adults treated with gelatine tannate had significantly less watery stools and less abdominal pain compared to patients treated with placebo. In children between 3 months and 12 years of age with acute diarrhoea, a significant decrease in the number of stools and an improvement in the consistency of stools has been observed when using gelatine tannate as compared to placebo.[4]

Loperamide

Loperamide is a phenylpiperidine opioid that slows intestinal transit time by stimulating μ-opioid receptors in the myenteric plexus. It possesses antisecretory properties and also blocks intestinal calcium channels. Loperamide works through two mechanisms, the most important being the production of segmental contraction of the gut, which slows the intraluminal movement of fluids and allows greater absorption. A secondary effect is the inhibition of calmodulin leading to reduced mucosal secretion. Loperamide is predominantly metabolised by intestinal and hepatic CYP3A4 and CYP2C8 to inactive metabolites, with the potential for many drug interactions.[7,10]

Loperamide is indicated for the treatment of various forms of diarrhoea, including traveller's diarrhoea, IBS-associated chronic diarrhoea, acute nonspecific diarrhoea in patients two years of age and older, and for reducing ileostomy output. The off-label uses include the management of chemotherapy-related diarrhoea. Loperamide is contraindicated in patients less than two years old and patients with acute ulcerative colitis, bloody diarrhoea, and diarrhoea associated with bacterial infections.[7]

Systematic review and meta-analysis of loperamide therapy for acute diarrhoea has shown that in children who are younger than 3 years, malnourished, moderately or severely dehydrated, systemically ill, or have bloody diarrhoea, adverse events associated with loperamide outweigh benefits, even at doses 0.25mg/kg per day. In children who are older than 3 years with no/minimal dehydration, loperamide may be a useful adjunct to ORT

and early refeeding. In numerous studies in children, all of those who had serious adverse effects due to loperamide were younger than 3 years of age.[3]

A common complaint of loperamide therapy in acute diarrhoea is post-treatment constipation. The drug has a wide margin of safety, largely owing to its extremely low bioavailability (0.3%). Common and severe adverse effects of loperamide are listed in Table 4.

Although loperamide is relatively safe at therapeutic doses, increasing reports describe its misuse and abuse at very high doses either for euphoric effects or to attenuate symptoms of opioid withdrawal; loperamide-induced cardiac toxicity may be seen in the young patient presenting in cardiac arrest or with unheralded, recurrent syncope in conjunction with ECG abnormalities, including marked QT-interval prolongation, QRS-interval widening, and ventricular dysrhythmias. [7,10,11]

Table 4. Adverse effects of loperamide

Common adverse effects	• Dry mouth • Flatulence • Abdominal cramps • Nausea • Ileus • Constipation • Urinary retention • Dizziness • Drowsiness
Serious adverse effects	• Toxic megacolon • Necrotising enterocolitis • Stevens-Johnson syndrome • Toxic epidermal necrolysis • Syncope • QT/QTc interval prolongation • Torsades de pointes • Ventricular tachycardia • Other ventricular arrhythmias • Cardiac arrest

Gelatine tannate has a good safety profile and is significantly more effective than placebo

Key learnings

- Although considered a 'nuisance' disease, diarrhoea can give rise to serious complications
- There are numerous potential causes for diarrhoea, exposure to infectious agents is the major risk factor for acute diarrhoea
- Conventional diagnostic testing is seldom used for patients with acute watery diarrhoea
- A thorough and directed history is essential to direct further investigations as to the cause of persistent diarrhoea not responding to empiric treatment
- Chronic diarrhoea requires a different diagnostic and therapeutic work-up than acute diarrhoea
- Of the anti-diarrhoeal agents, adsorbents and intestinal barrier modulators are safe to use adjunctive to ORT
- Anti-motility drugs may prolong infection by delaying elimination of the causative organisms and are not recommended for use in young children.

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