

# Diarrhea — Differential Diagnoses and Treatment

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**Diarrheal diseases are a very common reason why patients consult their doctors. Acute diarrhea lasts no longer than 2 weeks and has usually a rather mild course; however, if diarrhea becomes more severe or is persistent, it can pose a serious health problem. Diarrheal diseases are most commonly due to infections. Chronic diarrhea represents a challenge to any doctor's diagnostic skills as there are a multitude of differential diagnoses. In the following article, we will present you with all the important information you might need for clinical exams and clinical practice.**



## Definition

### Diarrhea - an imbalance

Diarrhea is the result of an **imbalance between secretion and resorption in the intestines**, and it can have various causes. Every day, the gastrointestinal (GI) tract receives 10 L of fluid, of which 8.5 L is reabsorbed in the small intestine. In the colon, the stool becomes more condensed, reabsorbing up to 100 mL of fluid per day.

**Note:** Diarrhea is defined as having 3 or more loose stools per day, or an increased amount of stool (> 250 g/day), or a reduced consistency of the stool (water content > 75%).

**Steatorrhea** is the presence of excess fat in the feces (> 7 g/day). **Paradoxical diarrhea** refers to a type of diarrhea that is associated with constipation in the colon and

is characterized by a liquid consistency of the stool but normal amounts. The feces cannot pass the obstruction in the colon and is therefore decomposed by bacteria. This way, the liquefied, foul-smelling stool, can pass the obstruction.

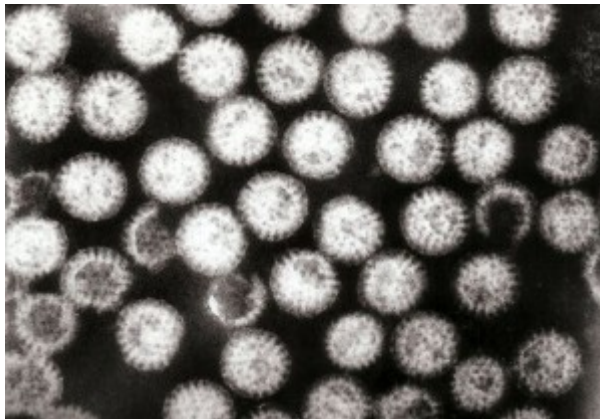
Diarrhea is clinically classified according to its duration into **acute diarrhea** (max. 2–3 weeks) and **chronic diarrhea** (more than 3 weeks).

## Pathogenesis

### Osmotic diarrhea

Osmotic diarrhea is the result of a **disturbance of the osmotic gradient between the intestinal lumen and the intestinal wall**. It is caused by the accumulation of a large amount of unabsorbable, osmotically active substrates in the intestinal lumen (e.g., unabsorbable sugar substitutes such as xylitol, sorbitol, and lactulose or lactose in the case of a lactase deficiency). Celiac disease (gluten intolerance) can also cause osmotic diarrhea.

### Secretory diarrhea



**Image:** "Transmission electron micrograph of multiple rotavirus particles. Each one is about 70 nanometers in meter" by Dr. Graham Beards, License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

Secretory diarrhea stems from increased secretion of electrolytes and water from the **crypts** into the intestinal lumen, while the integrity of the **enterocytes** remains intact. Possible causes are **laxatives** (e.g., anthraquinones, bisacodyl, and castor oil), **enterotoxins**, noroviruses, and rotaviruses, bile acids (chlorogenic diarrhea), or hormones (serotonin with carcinoid syndrome, gastrin with Zollinger-Ellison syndrome, and VIPoma).

### Exudative diarrhea

Exudative diarrhea develops as part of an inflammatory process and due to **ulcerations** caused by damage to the gastric mucosa. Increasing amounts of mucus, proteins, and blood are being exuded, which is often accompanied by abdominal pain, fever, and weight loss. Other causative factors include chronic inflammatory diseases of the intestines (**Crohn's disease and ulcerative colitis**), colorectal cancer, as well as bacterial or parasitic causes (e.g., *Salmonella*, *Shigella*, *Giardia lamblia*, and amoebas).

## Diarrhea due to motility disorders

Diarrhea can also follow from increased intestinal motility and the subsequently reduced water resorption, or diminished motility of the small intestine with bacterial overgrowth and the subsequent malabsorption syndrome. Possible causes are, for instance, **hyperthyroidism**, **pheochromocytoma**, and **carcinoid syndrome**, or possibly sympathetic overstimulation (e.g., due to stress). **Irritable bowel syndrome** sometimes referred to as functional diarrhea, also causes diarrhea. Reduced intestinal motility can also be due to a prior **vagotomy**, a stomach resection, or a **diabetic enteropathy** (autonomic neuropathy).

## Diagnostic indicators for chronic diarrhea

Osmotic processes	<ul style="list-style-type: none"><li>• Reduced pH-level in the stool</li><li>• Increased osmotic gap (the difference between calculated and measured fecal osmolality)</li><li>• Fasting reduces the fecal volume; no nocturnal diarrhea</li></ul>
Secretory processes	<ul style="list-style-type: none"><li>• Increase in fecal volume (fecal weight &gt; 1,000 g/day) with an often liquid consistency<ul style="list-style-type: none"><li>• No osmotic gap</li></ul></li><li>• Fasting does not reduce fecal volume; nocturnal diarrhea</li></ul>
Inflammatory processes	<ul style="list-style-type: none"><li>• Blood and mucus in the stool; leucocytes in the stool</li><li>• Abdominal pain</li><li>• Possibly fever and weight loss</li></ul>
Motility disorders	<ul style="list-style-type: none"><li>• Systemic underlying disease such as <b>diabetes mellitus</b> or hyperthyroidism</li><li>• Prior abdominal surgery</li></ul>

## Etiology of acute diarrhea

More than 90% of acute diarrhea cases have an infectious origin. The most common cause of acute diarrhea is an infection with **enteropathogenic viruses** (e.g., noroviruses and rotaviruses). Bacterial pathogens (e.g., enteritis-inducing salmonella, *Campylobacter jejuni*, *Shigella*, and enterohemorrhagic *Escherichia coli* (EHEC)) can also cause acute diarrhea; enterotoxigenic *E. coli* (ETEC) and cholera have to be considered as pathogens of traveler's diarrhea. Diagnosis is made by the identification of the pathogenic agents in the stool.

Further causes of acute diarrhea include food poisoning (**enterotoxins**, especially *Staphylococcus aureus*), fungus poisoning, **uremia**, and medication (e.g., laxatives and cytostatic agents). A special case is **pseudomembranous colitis** (antibiotic-associated colitis): Dangerous infection with ***Clostridium difficile*** which may develop after a (usually iatrogenic) damage to the intestinal flora caused by antibiotics. If antibiotic-associated colitis is being suspected, a stool culture should be obtained and screened for *C. difficile*. In the case of bloody mucoid diarrhea, a colonoscopy is indicated.

## Diagnosis of Acute Diarrhea

In most cases, acute diarrhea has a mild and self-limiting course, which means that no further diagnostic measures have to be taken. The basic diagnostic process for acute diarrhea consists of a comprehensive history and physical examination.

## Important components of medical history

- Disease onset: How long have the symptoms been present? Are they connected to the ingestion of food? Have there been any stays abroad? Are other persons in the patient's environment also affected?
- Secondary symptoms (e.g., pain, vomiting, fever, and weight loss)
- Fecal analysis (appearance (watery, mucoid or bloody?), frequency, volume, and time of defecation (also at night?))
- Medication (e.g., antibiotics)

## Important components of physical examination

- Abdominal palpation (e.g., resistance and guarding)
- Hydration state (**dehydration?**)

Further diagnostic work-up should be ordered if patients present with a persistent or severe course of the disease (e.g., severe dehydration, abdominal pain, fever  $> 38.5^{\circ}\text{C}$ , and bloody diarrhea), if a malignancy or underlying disease is suspected, or if patients are immunosuppressed (chemotherapy, human immunodeficiency virus (HIV), or organ transplantation).

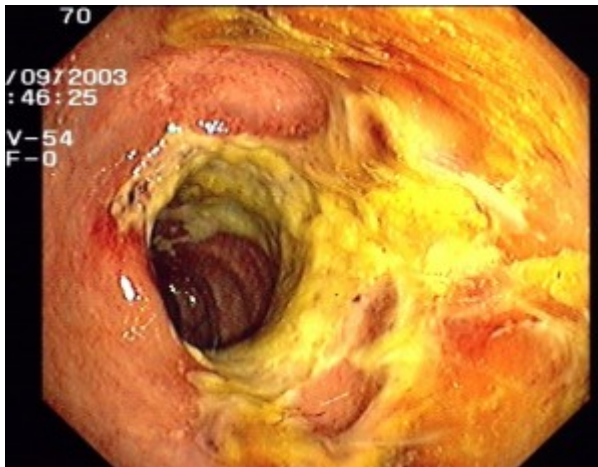


Image: "Colitis" by Joachim Guntau, License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

The general laboratory testing comprises erythrocyte sedimentation rate (ESR), a complete blood count (CBC), C-reactive protein (CRP), and an electrolyte panel. Microbiological stool examinations and possibly blood cultures can help find infectious pathogens/enterotoxins (common: **Campylobacter**, **C. difficile**, and **enteritis-inducing salmonella**). **Abdominal sonography** and maybe a **colonoscopy** can provide further diagnostic insight.

## Treatment of Acute Diarrhea

### Fluid and electrolyte replacement

Treatment approaches focus on **fluid replacement and electrolyte replacement**. In mild cases, salted soups and fruits, in combination with carbohydrates, will be sufficient. In more severe cases, a glucose-saline solution can be administered orally. In 1961, the World Health Organization (WHO) developed an oral rehydration solution for treating cholera.

## The WHO's oral rehydration solution (ORS)

- 3.5 g sodium chloride (NaCl)
- 2.5 g bicarbonate of soda (NaHCO<sub>3</sub>)
- 1.5 potassium chloride (KCl)
- 20 g glucose
- Dissolved in 1 L of drinking water

## Medication

An option for immunocompromised patients who have very severe intestinal infections with high fever and bloody stool is an antimicrobial treatment with **ciprofloxacin**. Patients with traveler's diarrhea can be symptomatically treated with **loperamide**; this is, however, contraindicated for cases with severe bacterial infections of the intestine.

## Prophylaxis

- Drinking water hygiene/food hygiene
- Vaccination (*Salmonella typhi* and *Vibrio cholera*)
- Sanitation

## Etiology of chronic diarrhea

The most important causes of chronic diarrhea at a glance:

- **Malassimilation syndromes:** maldigestion (e.g., due to chronic pancreatitis, bile acid malabsorption, or cystic fibrosis) and malabsorption ([celiac disease](#), [Whipple's disease](#), amyloidosis, or cardiovascular diseases), as well as [bacterial overgrowth of the small intestine](#), disorders of lymphatic circulation, and radiation enteritis.



▪ [Image: "Giardia lamblia"](#) by CDC, License: [Public Domain](#)

**Chronic infections of the intestines:** *Yersinia*, *Campylobacter enteritis*, *Giardia lamblia*, *Entamoeba histolytica* (amoebiasis, amoebic dysentery),

cyclospora, nematodes (roundworms); in patients with severe immunosuppression also microsporidia, *Mycobacterium avium*, cryptosporidium, *Isospora belli*, and cytomegalovirus

- **Chronic inflammatory diseases of the intestines** ([Crohn's disease and ulcerative colitis](#)): [diverticulosis and diverticulitis](#)
- **Food intolerances** (lactase deficiency): diarrhea occurs with colic and tympanism (flatulence); also as post-enteritis diarrhea after severe acute diarrheal diseases.
- **Obstructing tumors:** familial adenomatous polyposis (FAP), carcinoma
- **Endocrine causes:** [hyperthyroidism](#), carcinoid (serotonin-producing tumor), gastrinoma, VIPoma (Verner-Morrison syndrome), and diabetic enteropathy
- **Medication:** [laxative abuse](#) (→ measuring magnesium in the stool water), antibiotics, antacids containing magnesium, and digitalis
- **Short bowel syndrome:** after resection of the small intestine; post-gastrectomy syndrome (surgery in the patient's history)
- **Irritable bowel syndrome:** symptoms persist for years, alternating constipation and diarrhea, often no weight loss, diagnosis of exclusion

## Diagnosis of Chronic Diarrhea

There is a multitude of differential diagnoses for chronic diarrhea. The basis of any diagnosis is a comprehensive medical history, which already provides much important information for the further diagnostic process. Next to the patient's general condition, the onset, duration, and type of symptoms (fecal frequency and consistency, blood or mucus in the feces), you should watch out for signs of inflammatory diarrhea or a malignant disease: weight loss, fever, and fatigue. If the diarrhea is accompanied by **flush or asthma**, a possible [carcinoid syndrome](#) has to be considered. If the case involves chronic inflammation of the intestine, there might be a close connection to an inflammation of the joints (**arthritis**).

Nocturnal diarrhea points to an organic cause, while the absence of nocturnal symptoms suggests osmotic diarrhea or diarrhea caused by a motility disorder; for instance, a **malassimilation syndrome or irritable bowel syndrome** (functional diarrhea).

**Note:** In cases of osmotic or motility-related diarrhea, fasting often alleviates the symptoms, whereas fasting does not have much of an influence on fecal volume in cases of secretory or exudative diarrhea.

Another indication of irritable bowel syndrome is alternating constipation and diarrhea; however, this can also be a sign of **diabetic neuropathy, diverticulitis, carcinoma or intestinal stenosis**.

Symptoms that fluctuate subject to the intake of food point to food intolerance, e.g., lactose or fructose. If there have been any stays abroad, an infection with e.g., [protozoa](#) or **salmonella** can be suspected, or **tropical sprue**. If symptoms have persisted since childhood, **celiac disease** is a likely suspect, possibly even [cystic fibrosis](#).

Furthermore, diarrhea can occur as a consequence of radiation therapy (radiation enteritis, radiation colitis) or surgeries (resection of the stomach or small intestine, vagotomy).

## Fecal examination

The differential diagnosis of chronic diarrhea should include a stool examination. The diagnostic information that can be derived from an examination of the stool is summarized in the following table.

### Stool consistency in non-infectious chronic diarrhea

Watery diarrhea	<ul style="list-style-type: none"><li>• Functional diarrhea, VIPoma, and villous adenoma</li></ul>
Mucoid diarrhea	<ul style="list-style-type: none"><li>• With spasmodic pain during defecation (tenesmus): <a href="#">irritable bowel syndrome</a>, <a href="#">Crohn's disease</a></li></ul>
Bloody mucoid diarrhea	<ul style="list-style-type: none"><li>• With fever, leukocytosis, and tenesmus: <a href="#">ulcerative colitis and diverticulitis</a></li><li>• Occasional blood in the stool: familial adenomatous polyposis (FAP), colorectal carcinoma</li></ul>
Steatorrhea (fecal fat content > 7 g/day)	<ul style="list-style-type: none"><li>• With abdominal pain: chronic pancreatitis, pancreatic carcinoma, and <a href="#">Crohn's disease</a></li><li>• Without pain: lymphangiectasia, malign lymphoma, <a href="#">celiac disease</a>, <a href="#">Whipple's disease</a>, <a href="#">diabetes mellitus</a>, and <a href="#">cystic fibrosis</a></li><li>• Alcoholic diarrhea: obstructive jaundice, intrahepatic cholestasis, and biliary cirrhosis</li></ul>
Uncharacteristic stool	<ul style="list-style-type: none"><li>• With colic and tympanism (flatulence): <a href="#">lactose intolerance</a></li><li>• Medication-induced: laxatives, antibiotics, cholestyramine, and cytostatics</li></ul>

Further examinations depend on the suspected diagnosis; they may include blood tests (e.g., CBC, ESR, CRP, protein levels, electrolyte panel, alkaline phosphatase level, serum iron test, free T3, and free T4), lactose and fructose intolerance tests, abdominal sonography, upper gastrointestinal series, endoscopy with biopsy, stool tests (e.g., for **chymotrypsin and elastase** in the stool, especially in cases of chronic pancreatitis), and stool culture.

## Irritable Bowel Syndrome

**Irritable bowel syndrome** is a chronic condition characterized by recurrent abdominal pain and altered bowel habits in the absence of any detectable organic disease. Often, an abnormal stool frequency and form is accompanied by the disturbing passage of stool (straining, urgency, or sense of incomplete evacuation), evacuation of mucus, and gassiness or bloated abdomen.

Fifty percent of patients with gastrointestinal complaints suffer from irritable bowel syndrome. The diagnosis is led by the modified **Rome criteria**. This constitutes a diagnosis of exclusion, meaning that any indication of an organic cause (blood in the stool, weight loss, nocturnal diarrhea, and fever) rules out the diagnosis of irritable bowel syndrome until proven otherwise.

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