

Pathophysiology of Diarrhea

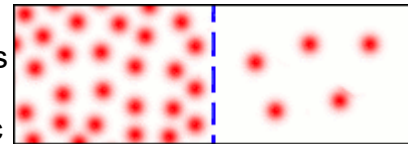
Diarrhea is **an increase in the volume of stool or frequency** of defecation. It is one of the most common **clinical signs of** gastrointestinal disease, but also can reflect primary disorders outside of the digestive system. Certainly, disorders affecting either the small or large bowel can lead to diarrhea.

For many people, diarrhea represents an occasional inconvenience or annoyance, yet at **least 2 million people** in the world, mostly children, die from the consequences of diarrhea each year.

There are **numerous causes** of diarrhea, but in almost all cases, this disorder is a manifestation of one of the four basic **mechanisms described below**. It is also common for more than one of the four mechanisms to be involved in the pathogenesis of a given case.

Osmotic Diarrhea

[Absorption of water in the intestines](#) is dependent on adequate absorption of solutes. If excessive amounts of **solutes are retained in the intestinal lumen**, water will not be absorbed and diarrhea will result. Osmotic diarrhea typically results from one of two situations:



- **Ingestion of a poorly absorbed substrate:** The offending molecule is usually a **carbohydrate or divalent ion**. Common examples include **mannitol** or sorbitol, **epson salt** (MgSO_4) and some antacids (MgOH_2).
- **Malabsorption:** Inability to absorb certain carbohydrates is the most **common deficit** in this category of diarrhea, but it can result virtually any type of malabsorption. A common example of malabsorption, afflicting many adults humans and pets is **lactose intolerance** resulting from a deficiency in the **brush border enzyme lactase**. In such cases, a moderate quantity of lactose is consumed (usually as milk), but the intestinal epithelium is deficient in lactase, and **lactose cannot be effectively hydrolyzed** into glucose and galactose for absorption. The osmotically-active lactose is retained in the intestinal lumen, where it **"holds" water**. To add insult to injury, the **unabsorbed lactose** passes into the large intestine where it is **fermented by colonic bacteria**, resulting in production **of excessive gas**.

A distinguishing feature of osmotic diarrhea is that it stops after the patient is fasted or **stops consuming the poorly absorbed solute**.

Secretory Diarrhea

Large volumes of **water are normally secreted** into the small intestinal lumen, but a large majority of this water is **efficiently absorbed** before reaching the large

intestine. Diarrhea occurs when secretion of water into the intestinal lumen exceeds absorption.



Many millions of people have died of the secretory diarrhea associated with cholera. The responsible organism, *Vibrio cholerae*, produces cholera toxin, which strongly activates [adenylyl cyclase](#), causing a prolonged increase in intracellular concentration of [cyclic AMP](#) within crypt [enterocytes](#). This change results in prolonged opening of the [chloride channels](#) that are instrumental in [secretion of water from the crypts](#), allowing [uncontrolled secretion](#) of water. Additionally, cholera toxin affects the [enteric nervous system](#), resulting in an [independent stimulus](#) of secretion.

Exposure to toxins from several other types of bacteria (e.g. *E. coli* heat-labile toxin) induce the same series of steps and massive secretory diarrhea that is often lethal unless the person or animal is aggressively treated to maintain hydration.

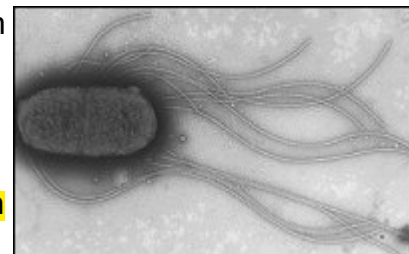
In addition to bacterial toxins, a large number of other agents can induce secretory diarrhea by turning on the intestinal secretory machinery, including:

- some [laxatives](#)
- hormones [secreted by](#) certain types of tumors (e.g. [vasoactive intestinal peptide](#))
- a broad range of [drugs](#) (e.g. some types of asthma medications, antidepressants, cardiac drugs)
- certain [metals](#), organic toxins, and plant [products](#) (e.g. arsenic, insecticides, mushroom toxins, caffeine)

In most cases, secretory diarrheas will [not resolve](#) during a 2-3 day [fast](#).

Inflammatory and Infectious Diarrhea

The [epithelium](#) of the digestive tube is protected from insult by a number of mechanisms constituting the [gastrointestinal barrier](#), but like [many barriers](#), it can be [breached](#). [Disruption](#) of the epithelium of the intestine due to [microbial or viral pathogens](#) is a very common cause of diarrhea in all species. [Destruction of the epithelium](#) results not only in [exudation of serum](#) and blood into the lumen but often is associated with widespread [destruction of absorptive epithelium](#). In such cases, [absorption of water](#) occurs very [inefficiently](#) and diarrhea results. Examples of pathogens frequently associated with infectious diarrhea include:



- Bacteria: *Salmonella*, *E. coli*, *Campylobacter*
- Viruses: [rotaviruses](#), [coronaviruses](#), [parvoviruses](#) (canine and feline), norovirus
- Protozoa: [coccidia species](#), *Cryptosporium*, *Giardia*

The immune response to inflammatory conditions in the bowel contributes substantively to development of diarrhea. Activation of white blood cells leads

them to secrete **inflammatory mediators** and **cytokines** which can stimulate secretion, in effect imposing a secretory component on top of an inflammatory diarrhea. Reactive **oxygen species from leukocytes can damage** or kill intestinal epithelial cells, which are replaced with immature cells that typically are **deficient in the brush border enzymes** and transporters necessary for absorption of nutrients and water. In this way, **components of an osmotic (malabsorption) diarrhea are added to the problem.**

Diarrhea Associated with **Deranged Motility**

In order for nutrients and water to be efficiently absorbed, the intestinal contents must be adequately exposed to the mucosal epithelium and retained long enough to allow absorption. **Disorders in motility** that **accelerate transit time** could **decrease absorption**, resulting **in diarrhea** even if the absorptive process per se was proceeding properly.



Alterations in intestinal motility (usually increased propulsion) are observed in many types of diarrhea. What is not usually clear, and very difficult to demonstrate, is whether primary **alterations in motility are** actually the cause of diarrhea or simply an effect.

Small Intestine: Introduction and Index

Small Intestine: Introduction and Index

Send comments to Richard.Bowen@colostate.edu