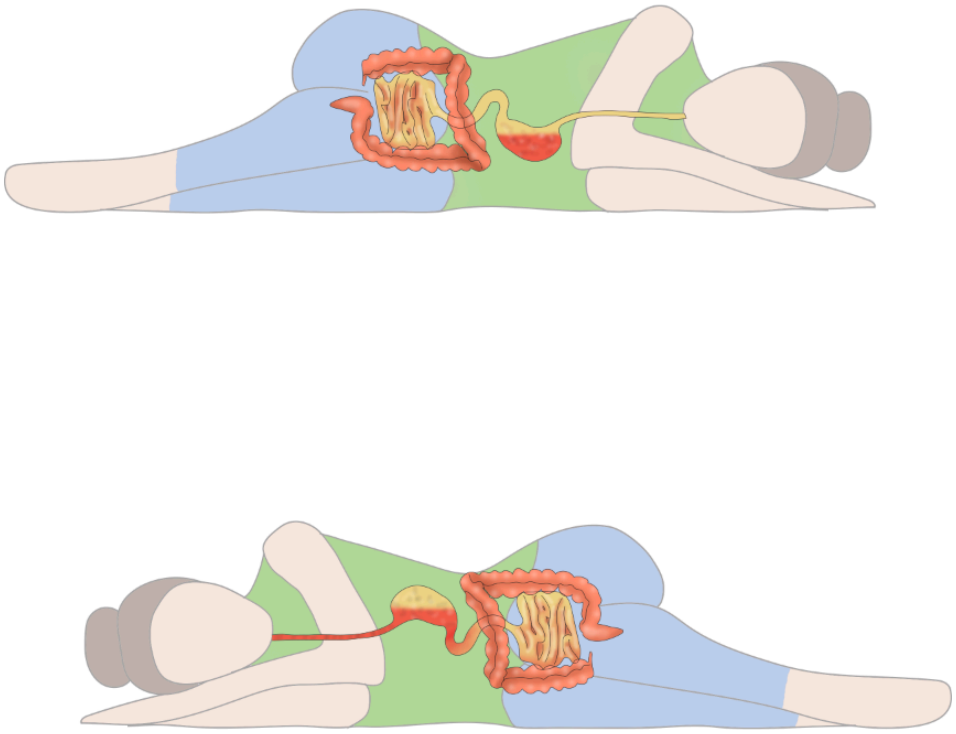
8.2.5

Gastroesophageal Reflux Disease (GERD)

Gastroesophageal reflux disease (GERD) is a digestive disorder where stomach acid flows up past the **lower esophageal sphincter (LES)** and irritates the lining of the esophagus. The most frequent symptom of GERD is heartburn. It is often worse when lying down, especially when lying on the right side due to the curvature of the stomach promoting more acid reflux. The pain associated with GERD may be confused with angina (heart pain). Common causes or contributors to GERD include inappropriate relaxation of the LES, overproduction of gastric acid, and large meals. Risk factors for development of GERD include hiatal hernia, conditions that put pressure on the stomach (like obesity and pregnancy), and foods or agents that decrease LES tone (like alcohol and other CNS depressants, smoking, cholinergic drugs, and foods like chocolate, onions, coffee, peppermint, spearmint, and fatty foods).



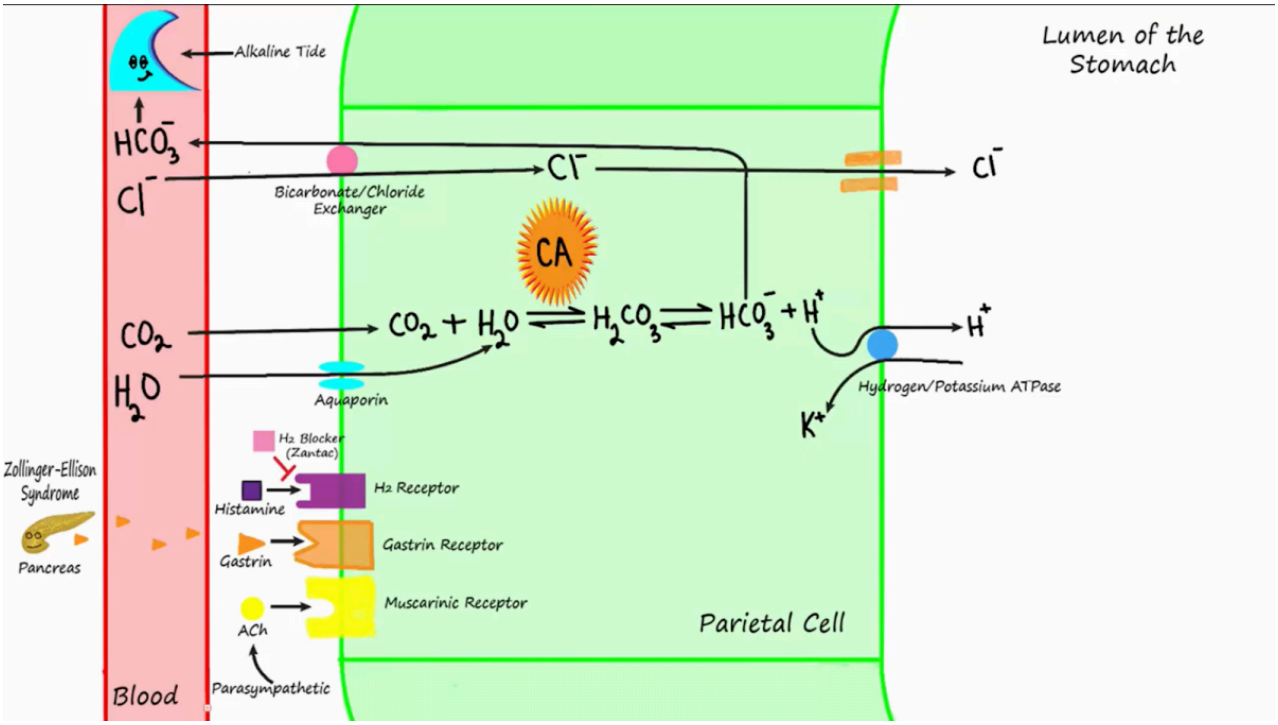
Influence of Stomach Curvature on Acid Reflux *Image by Becky T. BYU-I S20*

GERD can lead to the development of other complications:

- In some individuals, GERD may lead to a condition called **laryngopharyngeal reflux (LPR)** where stomach acid travels far up the esophagus and gets in the throat. LPR can cause sore throat, hoarseness, and affect the air passages to cause chronic cough. It may also lead to pharyngitis, laryngitis, tooth decay, gingivitis (gum inflammation), postnasal drip, and earache.
- **Esophageal strictures** are a common complication of GERD that occur when the esophagus tightens or narrows, leading to swallowing difficulties. Esophageal strictures can be diagnosed by taking an X-ray while a patient swallows barium. Sometimes, a surgeon may try to dilate the esophagus by placing a weighted tube down through the esophagus. Most often, esophageal strictures are treated with drugs to reduce GERD.
- GERD can also lead to a condition called **Barrett's esophagus**, which is when the normal squamous epithelial cells that line the esophagus are replaced by columnar epithelium cells. Barrett esophagus increases the risk of adenocarcinoma.

To understand how GERD is treated pharmaceutically, we need to understand how acid is made by the parietal cells of our stomach. As you have learned in your anatomy and physiology classes, parietal cells lining the stomach release **hydrochloric acid (HCl)** that is responsible for the low pH of the stomach.

Watch the video Parietal Cell Acid Production



Parietal Cell Acid Production *Image by Nate S. F17*

The three main ingredients necessary for hydrochloric acid production by parietal cells are Cl^-, CO_2, and H_2O. CO_2 is hydrophobic, so it freely diffuses into the parietal cell from the blood. H_2O enters the parietal cells from the blood through aquaporin channels in the basolateral membrane. Inside the parietal cell, carbonic anhydrase makes H_2CO_3 (carbonic acid) from H_2O and CO_2. Carbonic acid then dissociates into HCO_3^- (bicarbonate ion) and H^+. The H^+ is then pumped into the lumen of the stomach in exchange for K^+ by the hydrogen/potassium ATPase . Another name for the hydrogen/potassium ATPase is the "proton pump" because hydrogen ions are simply protons. The movement of lots of hydrogen ions in the stomach lumen is what makes it highly acidic (aka low pH). Bicarbonate ions leave the parietal cell and enter the blood utilizing a transporter that exchanges bicarbonate with Cl^-. Because bicarbonate is basic, its influx into the blood from the stomach is called the "alkaline tide." The Cl^- that has come into the cell by way of the bicarbonate/chloride exchanger then crosses the apical membrane of the parietal cell and into the stomach lumen by way of facilitated diffusion. In this manner, parietal cells move H^+ and Cl^- into the stomach lumen to make HCl.

The parietal cell has receptors for acetylcholine (muscarinic receptor), histamine (called the H-2 receptor), and gastrin. When any of these receptors are activated, it increases the activity of the hydrogen/potassium ATPase and thus increases acidity in the stomach. Conditions that cause an increase in the ligands for these receptors can cause excessive acid production. Examples include systemic mastocytosis and Zollinger-Ellison syndrome. In **systemic mastocytosis**, mast cells accumulate in the body (including in organs of the GI tract) and produce excess amounts of histamine. This histamine then stimulates H-2 receptors on parietal cells to produce large amounts of stomach acid. Patients with **Zollinger-Ellison syndrome** produce excess amounts of gastrin, most commonly from their pancreas, generally because of a tumor. These patients have a higher risk for peptic ulcers because of the excessive amounts of stomach acid that is released into the duodenum.

Two drug classes that can be used to decrease acid production are **H-2 blockers** and **proton pump inhibitors (PPI's)**. H-2 blockers prevent histamine from activating H-2 receptors on parietal cells and thus decrease the production of stomach acid. Two commonly used H-2 blockers are famotidine (Pepcid) and ranitidine (Zantac). Proton pump inhibitors (PPIs) directly inhibit the hydrogen/potassium ATPase or "proton pump" of the parietal cells to also decrease stomach acid production. The generic names for the PPIs end in "prazole." Three commonly used PPIs are omeprazole (Prilosec), lansoprazole (Prevacid) and esomeprazole (Nexium). These medications are useful for conditions like GERD, ulcers, Zollinger-Ellison syndrome, and systemic mastocytosis.

Some lifestyle modifications that are important in the treatment and prevention of GERD include eating smaller meals, eliminating offending foods, weight loss, elevating the head when sleeping, and not eating within 3 hours of bedtime.

The treatment of GERD is most commonly carried out by taking antacids to neutralize stomach acid and provide rapid relief. The disadvantage of antacids is that their effect is not long lasting because the stomach compensates by increasing the production of acid in what is known as "acid rebound." Aluminum and calcium containing antacids tend to cause constipation, while magnesium containing antacids tend to cause diarrhea. It appears that magnesium salts are not well absorbed in the gut and thus increase the osmotic pressure of GI contents so more water enters the gut lumen. Increased calcium can decrease the sensitivity of voltage-gated sodium channels. Their decreased responsiveness can make the neural controls of smooth muscle more sluggish and cause constipation. The mechanism that explains how aluminum can cause constipation is not understood, but it is known that aluminum can somehow inhibit smooth muscle contraction. This would slow movement of intestinal contents. It is important to note that excessive use of calcium containing antacids like calcium carbonate (Tums) increases the risk for the development of calcium-containing kidney stones.