Pathophysiology of Peptic Ulcer Disease

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KEYWORDS
- PUD
- Helicobacter pylori
- Virulence factors
- Immune evasion
- Nonsteroidal antiinflammatory drugs

KEY POINTS
- Peptic ulcer disease (PUD) consists of 2 types of ulcers, gastric and duodenal ulcers.
- The 2 primary causes of PUD are mediated by the pathogen, Helicobacter pylori, and by nonsteroidal antiinflammatory drugs.
- H pylori has an arsenal of virulence factors that aid in colonization and persistence in the unfavorable environment to the stomach.
- H pylori also hijacks and evades host immune responses.
- Nonsteroidal antiinflammatory drugs damage gastroduodenal mucosa through the inhibition of the cyclooxygenase pathway.

INTRODUCTION

Peptic ulcer disease (PUD) is the result of defects in the gastroduodenal mucosa mediated by an imbalance of mucosal protective and mucosal damaging mechanisms, thus leading to ulcer formation. Ulcerations are primarily located in the stomach and duodenum but can also be found in the lower esophagus. Ulcerations vary in size and can be superficial but can cause more extensive disease by extending from the muscularis mucosa into the deeper layers of the mucosa. The cause of PUD was previously thought to be caused by increased gastric acid production, dietary factors, and/or stress. However, with the isolation and identification of the bacterium, H pylori, as well as the increased consumption of nonsteroidal antiinflammatory drugs (NSAIDs), evidence has shown that these are the main causes of PUD. However, these factors alone are likely not enough on their own to cause ulcer formation. Other risk factors, including smoking, alcohol use, poor dietary habits, low socioeconomic status, presence of anxiety and stress, cocaine use, exogenous steroid use, advanced age, and Zollinger-Ellison syndrome, may also aid in ulcer formation. Fortunately, most of the patients diagnosed with uncomplicated PUD can be treated successfully.
Epidemiology

PUD continues to cause significant morbidity and mortality worldwide, with more than half of the world population infected. It is thought to be responsible for high health care costs of greater than $3 billion annually. In the United States, PUD affects 4.6 million people annually. The lifetime prevalence of PUD is estimated as high as 10% and is less prevalent in developed countries. PUD is the most common cause of upper gastrointestinal bleeding in the Western world; a systematic review estimated the annual incidence of hemorrhage at approximately 19 to 57 cases per 100,000 individuals. Other sequelae of PUD includes abdominal pain, gastric outlet obstruction, and ulcer perforation. Together these complications result in approximately 150,000 hospitalizations annually in the United States.

Pathophysiology

The causes of most PUD cases are caused by H pylori infection and chronic NSAID use. Most often, infection begins early in childhood and persists for several decades. H pylori has 2 main mechanisms of transmission, oral-oral and fecal-oral. Oral-oral transmission is the primary mechanism by which this organism is transmitted and is seen predominantly in developed countries. Infection among members of the same family is common and sharing of utensils during meals seems to be the primary mode of transmission, specifically from an adult to a child. Fecal-oral transmission occurs by the ingestion of contaminated water that is commonly found in countries that have poor sanitation.

H pylori is a helical (spiral) gram-negative bacterium that colonizes the surface of gastric epithelial cells and elicits a deleterious inflammatory response and subsequent damage to host cells. Several bacterial virulence factors have been identified that play a role in the pathogenesis of PUD. H pylori infection can be categorized into 3 pathogenic processes: colonization, immune escape, and disease induction.

Colonization

The environment of the stomach was believed to be sterile and not conducive for bacterial colonization and growth. However, this was disproved when H pylori was isolated from patient stomach biopsies. Successful colonization and subsequent infection can occur for decades in its host and is aided by several virulence factors, including its shape, urease expression, flagella, urease, chemotaxis, adherence to the gastric epithelium, and manipulation of the host cell and evasion of the immune system. H pylori, a neutrophile or an organism that thrives at a neutral pH, must deploy virulence factors to survive the harsh acidic environment of the stomach. Its cork-screw shape, similar to how a screw passes through a cork, provides a mechanical advantage for penetrating the viscous layer of the stomach and allows for continuous mobility through the mucous layer of the stomach to reach the gastric epithelium.

H pylori enters the body through the mouth and travels through the digestive system to infect the stomach where it must survive unfavorable conditions, such as a low pH and exposure to pepsin. The bacterium secretes large amounts of urease to counteract these conditions and to allow for its survival. This surface-bound enzyme provides a protective milieu by catalyzing the hydrolysis of urea to form ammonia and bicarbonate, which is then released into the cytoplasm and periplasm of the bacterium. This neutralizes the acidic environment inside and around the organism and decreases the viscosity of mucus, allowing for easier mobility of bacteria.
The ability of *H pylori* to dynamically modify the host environment and locate to the epithelium is essential to the initial steps of colonization. It must also avoid turnover of the gastric epithelium. To do this, *H pylori* uses a complex motility system and chemosensory-directed motility to efficiently swim through the gastric mucus toward the gastric epithelium. The motility system consists of a unipolar bundle of 4 to 8 flagella that rotate in unison to propel the bacterium toward the gastric epithelium and against the rhythmic contractions of the stomach.19 *H pylori*, in addition to flagella, must sense and integrate signals provided by the gastric epithelium for successful colonization. The ability for the organism to respond to environmental or chemical cues, termed chemotaxis, is orchestrated by core signaling proteins expressed both on the gastric epithelium as well as the bacterium.20,21

Under normal physiologic conditions, the epithelial barrier, which consists of gastric epithelial cells, prevents harmful elements in the gastric lumen from having direct access to the mucosa.22 It is regulated by cell shape, polarity, and intercellular junctions, including tight junctions and cellular interactions with the extracellular matrix. *H pylori*’s attachment to gastric epithelial cells leads to dismantling of the epithelial barrier and is mediated by outer membrane proteins (OMPs).23 OMPs also help the organism survive the harsh external environment and maintain the integrity of the bacterial cell membrane.24 OMPs’ physical interaction with gastric epithelial cells allows for long-term persistence in the host through gene expression of several bacterial genes.

One of OMPs’ essential functions is to provide anchorage of a type IV bacterial secretory system to the host cell membrane. The insertion of this system into the host membrane facilitates translocation of bacterial proteins, for example, cytotoxin-gene associated A (CagA), into the host cell.24,25 Once injected, CagA hijacks host cell machinery and alters several cellular functions leading to dysfunction of the cell.26 CagA affects cytoskeleton remodeling of the host cell, which leads to aberrant activation of intracellular signaling pathways and elongation of host cells. This may aid in tighter adhesion of the bacterium to gastric epithelial cells and disrupt the integrity of the epithelial barrier.27,28 CagA is also a potent immunogenic protein and induces the expression of inflammatory cytokines by gastric epithelial cells. The consequence of cytokine production leads to neutrophil migration, infiltration, and heightened inflammation.

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**Fig. 1. Pathogenesis of *H pylori***.
inflammation in the stomach, thus contributing to the pathogenesis of disease and ulcer formation.\textsuperscript{29–32}

\textit{H pylori} produces another virulence factor, vacuolating toxin A (VacA), that plays a key role in pathogenesis of disease. VacA, a pore-forming toxin, has diverse biological functions that affect the gastric epithelial cell directly and inhibit T lymphocyte proliferative responses, which will be discussed later. VacA forms pores in the host membrane of the gastric epithelial cell allowing for the transport of vital nutrients, for example, iron and nickel, between intercellular spaces of cells. This process permits \textit{H pylori} access to vital nutrients necessary for its survival within the host.\textsuperscript{33} VacA enters the host cell via a receptor-mediated dependent mechanism and induces multiple cellular responses. VacA can form vacuoles inside of the host cell and cause mitochondrial dysfunction, which can lead to apoptosis of the epithelial cell.\textsuperscript{34,35} These damaging mechanisms further potentiate a strong inflammatory response that leads to ulcer formation.

\textbf{Immune Escape}

The mammalian immune system consists of 2 tightly coordinated responses, the innate immune response and the adaptive immune response. The innate immune system is the initial response to pathogens and deployed within minutes of detecting a foreign pathogen. It consists of an army of specialized cells, for example, neutrophils, macrophages, and dendritic cells, that are effective at eradicating pathogens. Neutrophils are the first cell type to migrate to the site of infection and drive the inflammatory process, which is necessary to eliminate pathogens. When the innate immune response is unable to combat infection on its own, the adaptive immune response is activated.

The adaptive immune response is tightly regulated and is a highly organized, specific response directed against pathogens. It consists of 2 cell populations, B and T lymphocytes. B lymphocytes produce various antibody subtypes that serve various functions, including neutralizing pathogens, so they no longer have the ability to infect host cells, drive allergic responses, activate the complement system, and activate neutrophils and macrophages to become more efficient at killing pathogens.

T lymphocytes do not produce antibodies and consist of 2 types, CD4+ or T helper lymphocytes and CD8+ T lymphocytes or cytotoxic T lymphocytes (CTLs). T helper cells consist of many different subsets but the 3 most characterized subsets are T helper 1, 2, and 17. T helper 1 lymphocytes are efficient at killing intracellular pathogens, whereas T helper 2 lymphocytes shape B lymphocyte responses, eradicate helminth infections, and are chief contributors to allergic responses and inflammation. T helper 17 cells contribute to inflammation by secreting cytokines, are effective at eradication extracellular pathogens, and are essential in driving efficient mucosal immune responses.

A specialized type of CD4+ T lymphocyte, called regulatory T lymphocytes, police the immune system by suppressing immune responses and limiting the intensity of an immune response. This process is called tolerance and any breakdown in this process leads to the development of autoimmunity.

CTLs are responsible for killing cells infected with pathogens, such as viruses. T helper 1 and T helper 17 lymphocytes have been shown to be important in \textit{H pylori} infection as well as regulatory T lymphocytes. CTLs’ role against \textit{H pylori} seems to be minimal.

\textit{H pylori} has an arsenal of mechanisms to aid in its survival in the host. The bacterium hijacks gastric epithelial cell machinery as well as the immune system. It has also evolved mechanisms to avoid detection by the immune system. The initial defense
against *H pylori* infection is the mucus produced by the gastric epithelial cells and the response of the innate immune system present in the lamina propria of the stomach.\(^{36,37}\) In *H pylori* infection, gastric epithelial cells secrete the cytokine, interleukin-8, which elicits migration of neutrophils to the site of colonization. Neutrophils use a multitude of mechanisms to make them effective at eradicating pathogens.

Recognition of pathogens occurs through toll-like receptors (TLRs), which recognize conserved regions on many different pathogens and are expressed by innate immune cells; this ensures our innate immune system has the capability of recognizing many diverse pathogens. Engagement of these receptors elicits an inflammatory response necessary to eradicate pathogens by recruiting more immune cells to the site of infection. Many organisms, including *H pylori*, have evolved mechanisms to escape TLR recognition.\(^{38}\) Without engagement of TLRs, the innate immune response will not be able to initiate the appropriate immune response necessary to eradicate infection.

*H pylori* expresses many different proteins on its cell membrane that help the bacterium escape immune recognition by TLRs persistent in the host. For example, *H pylori* has flagella that rotate in unison to propel the organism toward the gastric epithelium. Flagella are also highly immunogenic; however, *H pylori* can modify its flagella to escape TLR recognition and evade the innate immune response.\(^{39}\)

*H pylori* not only has evolved to escape immune recognition by innate immune cells but also has the ability to reshape and avoid detection by the adaptive immune response. *H pylori* infection elicits T helper 1 and 17 responses that are thought to play an essential role in controlling infection; however, *H pylori* uses mechanisms to potentially suppress these responses when these cells migrate to the area of infection.\(^{40–42}\)

*H pylori* avoids detection by these T lymphocyte populations by inhibiting T lymphocyte proliferation.\(^{43}\) VacA seems to play a major role in this inhibitory process by affecting actin rearrangement inside the T lymphocyte, thus inhibiting proliferative responses. VacA forms ion-specific channels, which leads to vacuole formation in T lymphocytes resulting in death. Furthermore, VacA can affect mitochondrial function by causing the release of mitochondrial proapoptotic enzymes in the cytoplasm of T lymphocytes.\(^{44}\) These mechanisms seem to be the primary mechanism by which *H pylori* mediates suppression of T lymphocyte responses. Without these responses, the bacterium continues to persist in the host and cause chronic infections that lead to peptic ulcer formation and other sequelae.

*H pylori* not only prevents proliferation of T lymphocytes through several mechanisms previously mentioned but also has the unique ability to skew T lymphocyte responses. Specifically, VacA indirectly drives the differentiation of T helper lymphocytes to regulatory T lymphocytes,\(^{45}\) and this prevents a robust T lymphocyte response, which allows for *H pylori* to persist in its host.

Bacterial virulence factors and evasion of immune responses permit *H pylori* to cause mucosal damage, thereby leading to an imbalance of mucosal protective and mucosal damaging mechanisms. These processes allow the organism to persist for decades in the host and lead to ulcer formation.

**Nonsteroidal Antiinflammatory Drugs**

NSAIDs are widely used therapeutics agents because they are effective antipyretics, antiinflammatories, and analgesics. Chronic NSAID use damages the gastroduodenal mucosa through the inhibition of the enzyme cyclooxygenase-1 (COX-1). COX-1 inhibition leads to decreased prostaglandin synthesis inside the cell. Prostaglandins or eicosanoids are a group of lipids derived from arachidonic acid. They regulate
homeostatic mechanisms, such as regulate blood flow, inflammation, and platelet aggregation. Reduced mucosal prostaglandin levels result in mucosal damage through decrease mucus and bicarbonate production, which mediate protective roles against the acidity in the stomach. Decreased levels of prostaglandins also result in decreased mucosal blood flow, which is essential in maintaining mucosal integrity. NSAIDs disrupt these homeostatic mechanisms and therefore lead to inflammation, erosions, ulcerations, and bleeding in the stomach.

SUMMARY

PUD continues to be one of the most common diseases worldwide. Various risk factors have been identified for the development of disease but \( H \) pylori and chronic NSAID use are the most important causes in pathogenesis of disease. \( H \) pylori is one of the most common infections worldwide and has evolved several mechanisms to persist in the host. Increasing antibiotic resistance will pose a problem for future treatment, and therefore, it is key to understand the pathogenesis of disease in order to design effective therapeutics and future vaccines.

CLINICS CARE POINTS

- Peptic ulcer disease is the result of ulcerations in the stomach or duodenum and two primary etiologies include nonsteroidal anti-inflammatory drug use and colonization by the bacterium, Helicobacter pylori.
- Though many patients with uncomplicated peptic ulcer disease may be asymptomatic, those with symptoms most commonly experience classic symptoms, epigastric or retrosternal pain and/or dyspepsia that is relieved or aggravated by consumption of certain liquids, foods, or antacids.
- Non-invasive diagnostic testing for Helicobacter pylori includes urea breath and stool antigen testing; however, patients must discontinue proton pump inhibitors two weeks prior to testing to eliminate the possibility of a false negative test.
- Management of Helicobacter pylori infection takes into account prior antibiotic exposure and first line therapies may include triple or quadruple therapy for 10-14 days.
- Development of resistance to antibiotics is a serious problem and therefore, understanding Helicobacter pylori’s virulence factors and the immune response against this organism will lead to the development of novel therapies, e.g., immune modulators, vaccines.

DISCLOSURE

The author has nothing to disclose.

REFERENCES


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