Risk Factor Modification in Patients with Peptic Ulcer Disease

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Introduction

A "peptic ulcer" refers to a defect in the gastric or duodenal mucosa and submucosa caused by an imbalance between injurious factors and defense mechanisms in the GI tract. Injury to the gastric or duodenal lining can be caused by a number of factors that alter the delicate acid equilibrium. These include infections, medications, acid hypersecretion, and environmental aggressors such as smoking, alcohol, and diet. Although the incidence of uncomplicated PUD is approximately 1 case per 1000 person-year [1], it accounted for nearly 4000 deaths in 2004 in the United States alone [2]. The economic impact of PUD reaches $6 billion per year in the United States [3]. The burden of disease is much higher globally than in the United States [4]. Unlike many other medical conditions, PUD has been very clearly linked to a limited number of causative factors. Prevention, early identification, and treatment of these injurious mechanisms can significantly decrease the morbidity and mortality in affected patients. In this chapter, we discuss the main risk factors that predispose to peptic ulcer disease and management of these conditions.

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J. Grams et al. (eds.), *The SAGES Manual of Foregut Surgery*,
https://doi.org/10.1007/978-3-319-96122-4_54

Pathophysiologic Risk Factors

Infection

Perhaps one of the most clearly elucidated causes of peptic ulcer disease is the infection with *Helicobacter pylori*, a Gram-negative microaerophilic bacterium that is nearly ubiquitous in the general population. The prevalence of infection depends on age, socioeconomic status, and country and is estimated to be anywhere from 20–50% in industrialized countries and 50–80% in developing countries [5]. The infection is transmitted via oral ingestion and clusters within families. *H. pylori* is thought to be responsible for 90% of PUD development and is the leading cause of chronic gastritis and gastric cancer [6]. While the acidic environment of the gastric mucosa allows protection from most bacterial infections, *H. pylori* has developed sophisticated mechanisms to avoid the host defense systems. These include specialized proteins that allow it to manipulate host signaling cascades, bind to gastric epithelial cells, and evade the immune system, while causing low-grade inflammation [7]. With time, and depending on a variety of host factors, this chronic inflammation can lead to metaplasia, dysplasia, and subsequently carcinoma. The World Health Organization classifies *H. pylori* as a class I carcinogen because of its strong association with gastric adenocarcinoma and lymphoma [8, 9].

While the pathogenesis of *H. pylori* infection is quite complex and beyond the scope of this textbook, there are several mechanisms that are clinically important to understand as they contribute to the development of gastric and duodenal ulcers. Chief among them is the production of the enzyme urease, which converts urea into bicarbonate and ammonia. This creates an alkaline buffer around the organism that protects it from the bactericidal activity of the stomach. The ammonia that is produced as a result is damaging to the mucosal lining. Furthermore, the bacterium has been shown to inhibit the secretion of somatostatin from the antral D-cells; somatostatin is an inhibitor of G-cell gastrin secretion. The result is hypergastrinemia and acid hypersecretion, leading to parietal cell hyperplasia and gastric metaplasia. Infection in the duodenum leads to a decrease in the normal bicarbonate secretion in response to acidic chyle, leading to duodenal metaplasia [7, 10].

Although a majority of the population is infected with *H. pylori*, only a small percentage will develop complications. As such, the American College of Gastroenterology recommends testing for *H. pylori* only in specific circumstances, arguing against routine screening for the population at large [11]. In general, all patients with PUD should be tested for *H. pylori.* Table 54.1 illustrates the current indications for diagnosis and treatment.

The diagnosis of *H. pylori* is relatively inexpensive and can be performed either via noninvasive methods or invasive tests, depending on the clinical scenario. The noninvasive methods include urea breath test, stool antigen assays, and serologic tests. These tests are ideal for detecting uncomplicated PUD. With a sensitivity and specificity of >90%, the urea breath test is a qualitative study that detects active infection and relies on high urease activity during active infection in the stomach. It is a good initial screen as well as an easy means of confirming eradication following

Table 54.1 Current indications for diagnosis and treatment of *H. pylori*

Established
Active peptic ulcer disease (gastric or duodenal ulcer)
Confirmed history of peptic ulcer disease (not previously treated for *H. pylori*)
Gastric MALT lymphoma (low grade)
After endoscopic resection of early gastric cancer
Uninvestigated dyspepsia (depending upon *H. pylori* prevalence)
Controversial
Nonulcer dyspepsia
Gastroesophageal reflux disease
Persons using nonsteroidal antiinflammatory drugs
Unexplained iron deficiency anemia
Populations at higher risk for gastric cancer

Source: American College of Gastroenterology guideline on the management of Helicobacter pylori infection [11]

treatment. Similarly, stool antigen testing has a sensitivity of 89–98% and specificity >90% [12]. This assay can also be used to confirm eradication, with the caveat that at least 8 weeks must pass between completion of treatment and retesting. Serologic testing for IgG against *H. pylori* is highly sensitive (90–100%) but not specific (76–96%), and the positive predictive is highly dependent on the prevalence of infection within a certain population [13]. This is not a practical test in countries such as the United States where the prevalence is relatively low, and a positive test would not be indicative of an active infection. One scenario in which serologic testing may be useful is to confirm eradication of infection by proving seroconversion from positive to negative serology [14]; however, at least 18 months must pass after completion of treatment and the sensitivity of detecting seroconversion was only 60%. Other testing modalities such as PCR, salivary assays, urinary assays, and ^{13}C-urea breath test exist, but none of them have been shown to be of particular value and are rarely used.

Invasive testing, such as endoscopy, is indicated in clinical scenarios where patients present with gastrointestinal bleeding or anemia. Active infection can be detected using a biopsy urease test, bacterial culture, or histology. The biopsy urease test relies on the bacterium's ability to secrete urease and create an alkaline buffer around itself. The sensitivity is 90–95% and specificity 95–100% [11]. Bacterial culture has not proven to be an initial test of choice because *H. pylori* is notoriously difficult to grow. However, it may be useful in patients with refractory infection, as there are reports of resistance to treatment. Lastly, histological diagnosis allows for detection of the bacteria as well as screening for secondary changes associated with infection such as dysplasia or metaplasia. Not surprisingly, any diagnostic testing that relies on biopsies is subject to sampling error; furthermore, the accuracy of these tests is decreased in patients taking proton pump inhibitors (PPIs). Lastly, it is important to recognize that repeat endoscopy is not recommended to test for eradication for simple peptic ulcers, and other noninvasive tests

can be used instead if necessary. However, in patients with refractory PUD, repeat endoscopy is warranted to increase sampling opportunities, document healing, or identify the presence of neoplasms.

Hormonal Factors

Any process that leads to a pathologic increase in acid secretion can predispose to ulcer formation. The most classic hormonal imbalance that contributes to PUD is caused by gastrinomas. As the name suggests, these are functional neuroendocrine tumors that secrete gastrin, which causes excessive amounts of acid to be secreted. This leads to damage to the GI mucosa as well as malabsorption secondary to inactivation of bicarb and other digestive enzymes. The constellation of symptoms associated with these tumors are also referred to as Zollinger-Ellison (ZE) syndrome. Suspicion for these tumors should be raised when patients present with weight loss, diarrhea, steatorrhea, multiple ulcers, ulcers in the setting of negative *H. pylori* and NSAID use, or a family history of multiple endocrine neoplasia type I (MEN I) [15].

Gastrinomas are typically located in the pancreas (60%) or the duodenum (30%) and represent an important cause of duodenal ulcers. The diagnosis can be made by measuring a fasting gastrin level that is typically tenfold the upper limit of normal [16]. If the gastrin level is normal but there is persistent high suspicion for gastrinoma, a secretin test can be performed. Whereas normal gastric G cells are inhibited by secretin, gastrinoma tumor cells have an exaggerated gastrin release that can be diagnostic in these patients [17]. There are rare conditions of gastric G-cell hyperplasia or retained antrum syndrome after surgical gastrectomy. Both conditions can present with hypergastrinemia and PUD, but in neither case would there be a significant response to secretin stimulation test. It is worth mentioning that the widespread use of PPIs has led both to a delay in diagnosis and an increase in false-positive rates during secretin stimulation [18]. Patients with mild symptoms can be temporarily transitioned to a high-dose H_2 receptor antagonist for one week prior to the secretin stimulation test; in patients with severe symptoms of Zollinger-Ellison syndrome, the risk of interrupting antacid medications and having a massive GI bleed or perforation from a duodenal ulcer is too great and not recommended [19].

Patient Comorbidities

"Stress ulcers" are essentially peptic ulcers that occur in critically ill patients. Traditionally, these are seen in patients with severe burns, trauma, sepsis, or multiorgan failure on mechanical ventilation. Recent data suggest that even stressors associated with hospital admissions can lead to GI mucosal injury. The relationship between critically ill patients and gastric erosions is determined by mucosal blood flow to the GI tract. Hypotension or inadequate perfusion leads to decreases in blood flow to areas of the gut that are important for maintaining the mucosal barrier and buffer

from the damaging effects of acid. Refluxed bile salts and uremic toxins can also contribute to gastrointestinal mucosal damage.

Inflammatory or infiltrative diseases such as sarcoidosis, Crohn's disease, eosinophilic gastroduodenitis, systemic mastocytosis, hypersecretory duodenal ulcer have also been associated with peptic ulcer development, although the mechanisms are not entirely clear. Similarly, organ transplantation, diabetes mellitus, cirrhosis, and renal disease have also been implicated as risk factors for gastroduodenal ulcer development. However, some of these associations may be confounded by the effects of medications used to treat these conditions. Radiation therapy has also been shown to cause both gastric and duodenal ulcerations. Lastly, there is a very small proportion of patients who present with "idiopathic ulcers," in which none of the abovementioned factors can be diagnosed.

Environmental Risk Factors

Medications

Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, represent 60% of the over-the-counter sales for analgesics in the United States. At least 70% of people over age 65 take NSAIDs, and half of them take at least 7 doses/week [20]. It has been shown that nearly half of patients who use these medications regularly have gastric erosions and that up to 30% of them have ulcers on endoscopy [21]. Despite this, the FDA accredits only 1–4% per year risk of a significant gastrointestinal event such as bleeding, perforation, or pyloric obstruction in patients who routinely use NSAIDs. Risk factors for developing PUD in patients who use NSAIDs include not only the dose, duration of action, and duration of therapy but also extrinsic elements such as age, concomitant treatment with other medications (e.g., steroids, anticoagulants, selective serotonin reuptake inhibitors, alendronate), comorbidities including *H. pylori* infection, and even genetic polymorphisms that predispose to ulcerogenic side effects [21].

NSAIDs lead to ulcer formation through several mechanisms, including direct damage to the mucosa, suppression of prostaglandin synthesis, reduction of gastric mucosal blood flow, inhibition of mucosal regeneration, and delay in healing [22].

Steroids alone have not been specifically shown to cause PUD. However, they do increase the risk of bleeding in patients with existing ulcers. Even a short 7-day course of glucocorticoids has been shown to increase the risk of bleeding in patients with existing ulcers [23]. This effect was even higher in patients taking NSAIDs or aspirin.

Smoking

Epidemiologically, the risk of PUD is twice as high in smokers compared to nonsmokers. The effects of nicotine on the development of gastroduodenal ulcers are

manyfold and include stimulation of gastric acid secretion via activation of H_2 receptors, decrease in gastric mucus production and defense mechanisms, oxidative stress, and inhibition of gastric cell renewal to name a few [24]. In addition, smoking potentiates the ulcerogenesis associated with the use of NSAIDs, as well as *H. pylori* infection, and alcohol. It is important to mention that although alcohol is often mentioned as a risk factor for peptic ulcer development, there is no confirmatory data to support this claim.

Other Risk Factors

There are many other risk factors associated with the development of peptic ulcer disease. These include mechanical causes such as magnet and battery ingestions. Vascular compromise caused by use of cocaine and methamphetamines has also been shown to be linked to gastric and duodenal erosions.

Management

H. pylori Treatment

It is important to remember that, despite its prevalence and pathogenicity, only 3% of people infected with *H. pylori* develop PUD [25]. The goal of therapy is eradication of the infection, although up to 20% of patients will likely redevelop ulcers in the future [26]. Because the antibiotic treatments are needed to work within highly acidic gastric mucosa and many of them are inactivated in this environment, antacids such as proton pump inhibitors and H_2 blockers are used to increase effectiveness of the treatment. In addition, in order to prevent the development of resistance in the versatile genome of *H. pylori*, two antibiotic regiments are typically used. Hence, the treatment of *H. pylori* is commonly referred to as "triple therapy," meaning two antibiotics and an antacid used together to effectively maximize therapeutic potential with minimal induction of bacterial resistance. Table 54.2 illustrates current treatment recommendations for *H. pylori* [27].

First-line therapies include a PPI, such as omeprazole or lansoprazole, and two antibiotics such as amoxicillin and clarithromycin or metronidazole or a nitroimidazole and clarithromycin. Multiple randomized controlled trials have shown equivalence of any of the above regimens [28]. The recommended duration of therapy is 14 days to achieve 80% cure rate based on intention-to-treat analyses [28]. Ranitidine bismuth citrate with clarithromycin and bismuth with metronidazole and tetracycline are also valid options [13]. Persistence of infection despite initial treatment is due either to non-adherence or antibiotic resistance. The latter is problematic as cultures are not routinely performed, and, thus, susceptibility data is typically not available. As such, a second course of triple therapy can be prescribed, ideally using different antibiotics than in the initial regimen.

Table 54.2 2017 American College of Gastroenterology guidelines for treatment of *H. pylori* [27]

Clarithromycin, amoxicillin or metronidazole, PPI x 14 days*
- OR –
Bismuth, Tetracycline, nitroimidazole, PPI x 10-14 days**
- OR –
Clarithromycin, amoxicillin or nitroimidazole, PPI x 10-14 days
- OR –
Amoxicillin and PPI x 5-7 days, followed by clarithromycin, nitroimidazole, PPI x 5-7 days
- OR –
Amoxicillin and PPI x 7 days, followed by amoxicillin, clarithromycin, nitroimidazole and PPI x7 days
- OR –
Levofloxacin, amoxicillin, PPI x 10-14 days
- OR –
Amoxicillin and PPI x 5-7 days, followed by fluoroquinolone, nitroimidazole, PPI x 5-7 days
* if clarithromycin resistance <15%
** in patients allergic to penicillin

Managing Hormonal Causes of PUD

In patients who present with peptic ulcers caused by acid hypersecretion from an underlying gastrinoma, the treatment focuses on treating the underlying etiology. Acid suppression with proton pump inhibitors is paramount to preventing mortality and morbidity in patients with Zollinger-Ellison syndrome [15]. Surgical options are also available and should be considered in patients without metastases. Radiation therapy is available for those who are not surgical candidates.

Patient Comorbidities

With the advent of PPIs and H_2 blockers, stress ulcer prophylaxis has dramatically decreased the incidence of peptic ulcer disease in critically ill patients. The latest guidelines for prophylaxis in severe illness recommend the use of PPIs in the presence of a history of GI ulceration within the past year, mechanical ventilation × 48 h or more, coagulopathy (platelet count <50,000/m^3 [3], INR > 1.5 or PTT > 60), traumatic brain injury, spinal cord injury or burn injury, or two of the following: sepsis, ICU stay >7 days, GI bleeding, or use of steroids. Nevertheless, cautious use should be enforced as the latest data emphasize the risk of nosocomial pneumonia, *Clostridium difficile* infection, drug interactions, and thrombocytonemia associated with unnecessary use of antacids [29].

Medications Use

Patients with risk factors for development of peptic ulcer disease should avoid the use of NSAIDs. COX-2 inhibitors have been linked to a lower risk of PUD compared to NSAIDs, but the risk is still higher than placebo [30]. Furthermore, both classes of medications inhibit ulcer healing and therefore are contraindicated in patients with PUD. Ideally, the use of such medications should be paused during treatment of PUD to allow for adequate healing. The same is valid for antiplatelet agents such as clopidogrel and aspirin.

The interaction between NSAIDs and *H. pylori* in patients with PUD is complex and not yet fully elucidated. Numerous studies that investigated this relationship have shown correlation, but not causation of increased risk of PUD in this patient population. Nevertheless, the American College of Gastroenterology agrees that there is a potential synergy between NSAID use and *H. pylori* infection. The current recommendations are to test and treat the infection prior to initiation of long-term NSAID therapy, particularly in patients with other risk factors for PUD.

Environmental Risk Factor Management

The prevention of peptic ulcer disease caused by environmental factors focuses on avoidance of injurious insults. Smoking cessation, avoidance of mechanical

injurious entities, and abstinence from any drugs that can lead to vascular compromise can be equally important in prevention of PUD.

Conclusion

While the majority of peptic ulcers are caused by infection with *H. pylori* or NSAID use, there are many other risk factors that deserve consideration. Prophylaxis or treatment against these various injurious elements can significantly decrease morbidity and mortality in affected patients.

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