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Article

Pathophysiology, Risk Factors, and Advances in the Management of Peptic Ulcers: A Comprehensive Review

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Abstract: Peptic ulcers, characterized by mucosal erosion in the stomach or duodenum, continue to pose significant health challenges worldwide. This comprehensive review explores the pathophysiology of peptic ulcers, including the roles of *Helicobacter pylori*, acid secretion, and mucosal defense mechanisms. We examine key risk factors such as NSAID use, smoking, alcohol consumption, and genetic predisposition. Advances in diagnostic techniques, including endoscopy, biopsy, and non-invasive tests like urea breath tests and stool antigen tests, are discussed, alongside recent improvements in molecular diagnostics and imaging. The review also covers current management strategies, focusing on pharmacological treatments like proton pump inhibitors (PPIs) and H₂ receptor antagonists, as well as surgical interventions for complicated cases. Emerging treatment modalities, such as novel drugs, probiotics, and minimally invasive surgical techniques, are highlighted. Additionally, the paper identifies future research directions, including the exploration of new therapeutic targets, enhanced diagnostic tools, and the impact of gut microbiota on ulcer formation. By integrating recent advancements and identifying gaps in current knowledge, this review aims to provide a comprehensive understanding of peptic ulcers and inform future research and clinical practice.

Keywords: peptic ulcer

Peptic ulcers, which are open sores that develop on the inner lining of the stomach, upper small intestine, or esophagus, are a significant global health concern. Historically, they were once believed to be primarily caused by lifestyle factors such as stress, spicy foods, and the consumption of acidic substances. This belief persisted until the late 20th century, when groundbreaking research revealed that a significant proportion of peptic ulcers were actually caused by a bacterial infection, specifically by *Helicobacter pylori* (*H. pylori*). This discovery dramatically shifted the understanding and treatment of peptic ulcers, highlighting the importance of antibiotics in managing the condition, alongside acid-suppressing medications.

The global prevalence of peptic ulcers varies widely, with studies indicating that up to 10% of the world's population will develop a peptic ulcer at some point in their lives. Regions with higher infection rates of *H. pylori*, such as parts of Asia, Africa, and Latin America, generally have a higher prevalence of peptic ulcers. Conversely, in many Western countries, the prevalence of peptic ulcers has been declining, largely due to improved hygiene, better medical treatments, and a reduction in *H. pylori* infection rates. However, non-steroidal anti-inflammatory drugs (NSAIDs) and other medications remain significant causes of peptic ulcers in these regions.

Historically, peptic ulcers were also associated with significant morbidity and mortality due to complications such as bleeding and perforation. Before the advent of modern diagnostic and therapeutic techniques, many cases were managed surgically, often with significant risks. The understanding of the pathophysiology of peptic ulcers has evolved significantly over time. Today, it

is recognized that peptic ulcers result from an imbalance between aggressive factors (like gastric acid and pepsin) and the mucosal defense mechanisms (such as mucus and bicarbonate secretion, and blood flow to the stomach lining). The discovery of *H. pylori* emphasized the role of bacterial infection in disrupting this balance by causing inflammation and weakening the protective mucosal barrier, leading to ulceration.

In summary, the global prevalence of peptic ulcers remains significant, though it varies by region and is influenced by factors such as *H. pylori* infection and the use of NSAIDs. Historically, the understanding of peptic ulcers has undergone a paradigm shift from lifestyle factors to recognizing the critical role of bacterial infection and other physiological imbalances.

The pathogenesis of peptic ulcers involves a complex interplay of factors that disturb the delicate balance between the aggressive forces in the gastrointestinal tract and the defensive mechanisms of the mucosal lining. Key contributors include *Helicobacter pylori* infection, the use of non-steroidal anti-inflammatory drugs (NSAIDs), the role of gastric acid and pepsin, genetic predisposition, and various environmental and lifestyle factors.

Helicobacter pylori Infection

Helicobacter pylori is a spiral-shaped bacterium that colonizes the stomach lining, particularly in the antral region. It is the most common cause of peptic ulcers, responsible for about 70-90% of duodenal ulcers and 50-70% of gastric ulcers. The bacterium contributes to ulcer formation through several mechanisms:

1. **Inflammation:** *H. pylori* infection triggers a chronic inflammatory response in the stomach lining, leading to gastritis. The bacteria produce urease, which converts urea into ammonia, neutralizing the stomach acid and allowing the bacteria to survive. However, this ammonia, along with other bacterial toxins, damages the mucosal cells, weakening the stomach's defenses against acid and pepsin.
2. **Mucosal Damage:** The inflammation and direct bacterial damage compromise the mucosal barrier, allowing acid and pepsin to penetrate and damage the underlying tissues, leading to ulcer formation.
3. **Altered Gastric Physiology:** *H. pylori* infection can lead to increased acid secretion, particularly in the duodenum, further contributing to ulcer development.

NSAIDs

Non-steroidal anti-inflammatory drugs (NSAIDs) are another major cause of peptic ulcers, particularly in patients without *H. pylori* infection. NSAIDs cause ulcers through both systemic and local mechanisms:

1. **Inhibition of Prostaglandins:** NSAIDs inhibit cyclooxygenase (COX) enzymes, which are crucial for the production of prostaglandins. Prostaglandins play a protective role in the stomach by stimulating mucus and bicarbonate secretion, maintaining blood flow, and promoting cell repair. The inhibition of prostaglandins by NSAIDs reduces these protective factors, making the mucosa more susceptible to acid and pepsin.
2. **Direct Mucosal Irritation:** NSAIDs can cause direct damage to the stomach lining by disrupting the lipid layer of the gastric mucosa, leading to increased permeability and allowing acid to penetrate and cause injury.

Role of Gastric Acid and Pepsin

Gastric acid and pepsin are key aggressive factors in the development of peptic ulcers. Acid is secreted by parietal cells in the stomach and is necessary for the activation of pepsinogen to pepsin, a proteolytic enzyme that breaks down proteins. In normal conditions, the stomach mucosa is protected by a thick layer of mucus and bicarbonate, which neutralizes the acid. However, when the balance between these aggressive and protective factors is disrupted, acid and pepsin can erode the mucosa, leading to ulcer formation.

Genetic Predisposition and Environmental Factors

Genetic susceptibility plays a significant role in the development of peptic ulcers. Some individuals are genetically predisposed to increased acid secretion or have variations in genes involved in mucosal defense, making them more susceptible to ulcers. Specific genetic factors include:

1. **Blood Group:** Individuals with blood group O have been found to have a higher risk of developing duodenal ulcers. The exact mechanism is unclear, but it may be related to differences in mucosal glycoproteins or immune response.
2. **Family History:** A family history of peptic ulcers increases the risk, suggesting a hereditary component. This may be due to shared genetic factors or environmental influences within families.

Internal Factors

Other internal factors contributing to ulcer formation include:

1. **Hypersecretory States:** Conditions such as Zollinger-Ellison syndrome, where there is excessive production of gastric acid due to a gastrin-secreting tumor, significantly increase the risk of peptic ulcers.
2. **Comorbidities:** Conditions like chronic obstructive pulmonary disease (COPD) and chronic kidney disease (CKD) have been associated with an increased risk of ulcers, possibly due to impaired mucosal defense or other metabolic factors.

Lifestyle-Related Risk Factors

Several lifestyle factors have been associated with an increased risk of peptic ulcers:

1. **Smoking:** Smoking is a well-established risk factor for peptic ulcers. Nicotine increases gastric acid secretion, reduces bicarbonate production, and impairs blood flow to the gastric mucosa, making it more susceptible to injury. Smoking also interferes with ulcer healing and increases the risk of recurrence.
2. **Alcohol Consumption:** Excessive alcohol intake can damage the gastric mucosa directly and increase gastric acid secretion, contributing to ulcer formation. Chronic alcohol consumption also interferes with the mucosal healing process.
3. **Diet:** While specific foods have not been definitively linked to ulcer formation, diets high in irritants such as spicy foods, caffeine, and acidic foods can exacerbate symptoms in individuals with existing ulcers. Conversely, diets rich in fruits, vegetables, and fiber may offer some protective effects.
4. **Stress:** Psychological stress has long been associated with peptic ulcers, although its role is more complex and not as direct as previously believed. Stress may contribute to ulcer development by increasing acid secretion, impairing mucosal defense, and leading to behaviors that exacerbate ulcer risk, such as smoking and alcohol consumption.

Conditions like Zollinger-Ellison syndrome (ZES) and Crohn's disease contribute to ulcer formation through distinct mechanisms related to abnormal physiological processes that affect the gastrointestinal tract.

Zollinger-Ellison Syndrome (ZES)

Zollinger-Ellison syndrome is a rare disorder characterized by one or more tumors called gastrinomas, usually found in the pancreas or duodenum. These tumors secrete excessive amounts of the hormone gastrin, which significantly increases gastric acid production.

Mechanism of Ulcer Formation in ZES:

1. **Hypergastrinemia:** The excessive secretion of gastrin leads to hypergastrinemia, which stimulates the parietal cells in the stomach to produce large amounts of hydrochloric acid (HCl).

2. Gastric Hyperacidity: The marked increase in gastric acid secretion overwhelms the protective mechanisms of the gastrointestinal mucosa. The elevated acid levels can cause severe damage to the lining of the stomach and duodenum, leading to the development of peptic ulcers.
3. Multiple and Atypical Ulcers: Unlike typical peptic ulcers, which are usually solitary, ZES often causes multiple ulcers that may be located in unusual parts of the gastrointestinal tract, such as the jejunum. These ulcers tend to be more resistant to standard treatments and have a higher risk of complications, such as bleeding or perforation.

In summary, the excessive gastric acid secretion in ZES overwhelms the mucosal defenses, leading to ulcer formation that is often severe and recurrent.

Crohn's Disease

Crohn's disease is a chronic inflammatory bowel disease (IBD) that can affect any part of the gastrointestinal tract, from the mouth to the anus, though it most commonly affects the ileum and colon. Unlike peptic ulcers, which are typically due to acid and pepsin, ulcers in Crohn's disease arise from chronic inflammation.

Mechanism of Ulcer Formation in Crohn's Disease:

1. Chronic Inflammation: Crohn's disease is characterized by transmural inflammation, meaning that it affects the entire thickness of the bowel wall. This inflammation leads to ulceration as the inflamed tissues become damaged over time.
2. Immune Response: The exact cause of Crohn's disease is not fully understood, but it involves an inappropriate immune response to intestinal microbes in genetically susceptible individuals. This abnormal immune response leads to persistent inflammation, causing ulcerations in the affected areas.
3. Granulomas and Fissures: In Crohn's disease, the inflammation can lead to the formation of granulomas, which are clusters of immune cells that form in response to chronic inflammation. Fissures, which are deep cracks or ulcers, can also develop in the intestinal wall. These fissures can progress to form fistulas, which are abnormal connections between different parts of the intestine or other organs.
4. Location and Severity: The ulcers in Crohn's disease can occur anywhere in the gastrointestinal tract but are most commonly found in the terminal ileum and colon. The severity of ulceration varies, and in severe cases, deep ulcers can lead to complications such as strictures (narrowing of the intestine), abscesses, or perforations.

In Crohn's disease, the ulceration is a direct result of chronic, immune-mediated inflammation rather than the action of gastric acid, as seen in peptic ulcers.

Diagnostic Techniques for Peptic Ulcers

Endoscopy

- Overview: Endoscopy is the gold standard for diagnosing peptic ulcers. It allows direct visualization of the mucosal surface of the gastrointestinal tract. During an endoscopy, a flexible tube with a camera (endoscope) is inserted through the mouth to examine the esophagus, stomach, and duodenum.
- Use in Diagnosis: Endoscopy can detect the presence of ulcers, identify their location, size, and depth, and assess any complications like bleeding or perforation.
- Advances: High-resolution endoscopy and chromoendoscopy provide enhanced imaging, allowing for better visualization and characterization of lesions. Narrow-band imaging (NBI) and confocal laser endomicroscopy (CLE) are also emerging as tools for detecting subtle mucosal changes.

Biopsy

- Overview: A biopsy involves taking small tissue samples during endoscopy for histopathological examination.
- Use in Diagnosis: Biopsies are essential for confirming the presence of *H. pylori* infection, which is a common cause of peptic ulcers. They can also help rule out malignancy in ulcerated lesions.
- Advances: Molecular methods, like PCR, can detect *H. pylori* DNA in biopsy samples, offering greater sensitivity than traditional staining techniques.

Non-Invasive Tests

- Urea Breath Test: This test detects *H. pylori* infection by measuring labeled carbon dioxide in the breath after ingestion of a urea solution. The presence of *H. pylori* breaks down urea, releasing labeled carbon dioxide.
- Stool Antigen Test: This test detects *H. pylori* antigens in the stool, providing a non-invasive method for diagnosis and monitoring treatment effectiveness.

Advances in Diagnostics

- Molecular Methods: Techniques like PCR and next-generation sequencing (NGS) are being utilized to identify *H. pylori* strains and their resistance patterns, guiding targeted therapy.
- Imaging Techniques: Advanced imaging technologies like PET/CT and MRI can be used in specific cases to detect complications such as perforation or malignancy. Artificial intelligence (AI) is increasingly being integrated into imaging diagnostics to improve accuracy and predictive capabilities.

7. Management and Treatment of Peptic Ulcers

Pharmacological Treatments

- Proton Pump Inhibitors (PPIs): PPIs like omeprazole, pantoprazole, and esomeprazole reduce gastric acid secretion, promoting ulcer healing and providing symptom relief.
- H2 Receptor Antagonists: Drugs like ranitidine and famotidine block histamine receptors on gastric parietal cells, reducing acid production.
- Antibiotics for *H. pylori* Eradication: Common regimens include a combination of clarithromycin, amoxicillin, or metronidazole with PPIs, forming the standard triple therapy.

Surgical Interventions

- Indications: Surgery is considered when there are complications like bleeding, perforation, or obstruction, or when medical therapy fails.
- Procedures:
 - Vagotomy: Involves cutting the vagus nerve to reduce acid secretion.
 - Antrectomy: The removal of the antrum (lower part of the stomach) which produces a significant amount of gastric acid.
 - Pyloroplasty: Surgery to widen the opening of the pylorus to help the stomach contents empty more easily into the small intestine.

Recent Advances

- Novel Drugs: Research is ongoing into new PPIs with improved safety profiles, and potassium-competitive acid blockers (P-CABs) like vonoprazan, which offer faster and more sustained acid suppression.
- Probiotics: There's growing interest in using probiotics as adjunct therapy to improve *H. pylori* eradication rates and reduce antibiotic-associated side effects.

- Minimally Invasive Surgical Techniques: Laparoscopic procedures are increasingly preferred for their reduced recovery times and lower complication rates compared to traditional open surgeries. Advances in robotic surgery are also being explored for precision and control in complex cases.

8. Complications of Peptic Ulcers

Peptic ulcers can lead to several serious complications, particularly if they are left untreated or if treatment is inadequate. Here's an analysis of the most common complications:

1. Bleeding

- Overview: Gastrointestinal bleeding is the most common complication of peptic ulcers and can range from occult bleeding to life-threatening hemorrhage.
- Clinical Presentation: Symptoms may include hematemesis (vomiting blood), melena (black, tarry stools), or anemia. Patients with significant blood loss may present with hypotension, tachycardia, and shock.
- Pathophysiology: Ulcers can erode into blood vessels within the stomach or duodenal wall, leading to bleeding. This can occur in any ulcer but is more common in those located in the posterior wall of the duodenum.

2. Perforation

- Overview: Perforation occurs when an ulcer erodes through the full thickness of the stomach or duodenal wall, creating an opening into the peritoneal cavity.
- Clinical Presentation: Patients typically present with sudden, severe abdominal pain, often described as a "knife-like" or "stabbing" pain. Signs of peritonitis, such as a rigid abdomen and rebound tenderness, may be present.
- Pathophysiology: Perforation allows gastric or duodenal contents to spill into the peritoneal cavity, leading to chemical and bacterial peritonitis, which can rapidly become life-threatening without prompt intervention.

3. Gastric Outlet Obstruction

- Overview: Gastric outlet obstruction (GOO) occurs when the pyloric channel or duodenum becomes narrowed or blocked, typically due to inflammation, edema, or scarring from chronic ulcers.
- Clinical Presentation: Symptoms include persistent vomiting, often with undigested food, early satiety, bloating, and weight loss. In severe cases, dehydration and electrolyte imbalances may occur.
- Pathophysiology: Chronic inflammation and scarring from repeated ulceration can cause stenosis of the pylorus or duodenum, impeding the passage of gastric contents into the small intestine.

Management of Complications

1. Management of Bleeding

- Endoscopic Treatment: Endoscopy is the first-line intervention, where techniques such as thermal coagulation, hemoclipping, and injection of epinephrine are used to control bleeding.
- Pharmacological Therapy: IV proton pump inhibitors (PPIs) are administered to reduce gastric acidity and promote clot stability. Blood transfusions and fluid resuscitation may be necessary for significant blood loss.
- Surgical Intervention: Surgery may be required if bleeding cannot be controlled endoscopically, especially in cases of recurrent or massive hemorrhage. Options include oversewing of the bleeding vessel or, in severe cases, resection of the ulcerated area.

2. Management of Perforation

- Immediate Medical Management: Patients should be made nil per os (NPO), and broad-spectrum IV antibiotics are initiated to cover both aerobic and anaerobic bacteria. Nasogastric (NG) tube placement is typically done for decompression.
- Surgical Treatment: Surgery is the definitive treatment, usually involving closure of the perforation with omental patch (Graham patch). In stable patients with localized perforation, laparoscopic repair may be considered.
- Postoperative Care: Post-surgery, patients are monitored for sepsis and other complications. Acid suppression therapy is continued to prevent recurrence.

3. Management of Gastric Outlet Obstruction

- Initial Management: Patients should be NPO with NG tube decompression to relieve vomiting and gastric distention. IV fluids and electrolyte correction are essential to manage dehydration.
- Endoscopic Dilatation: Endoscopic balloon dilatation may be attempted as a less invasive method to relieve obstruction.
- Surgical Intervention: If endoscopic treatment fails, surgery such as pyloroplasty, antrectomy, or gastrojejunostomy may be required to bypass or remove the obstructed area.

9. Prevention

1. Primary Prevention

- Lifestyle Modifications:
 - Dietary Adjustments: Reducing the intake of irritants such as NSAIDs, alcohol, and spicy foods can lower the risk of ulcer development. Smoking cessation is also crucial as smoking increases gastric acid secretion and reduces mucosal blood flow.
 - Stress Management: Managing stress through techniques such as mindfulness, yoga, or regular physical activity may help prevent stress-related ulcers.
- Prophylactic Medication:
 - PPIs and H2 Receptor Antagonists: These can be prescribed prophylactically in individuals at high risk for ulcers, such as those on long-term NSAIDs or corticosteroids.
 - Misoprostol: This prostaglandin analog can be used in patients at risk of NSAID-induced ulcers, particularly in those who cannot tolerate PPIs.

2. Secondary Prevention

- Eradication of *H. pylori*: After initial treatment, ensuring complete eradication of *H. pylori* is vital. This may require follow-up testing, such as urea breath tests or stool antigen tests, to confirm eradication.
- Maintenance Therapy: Long-term maintenance therapy with low-dose PPIs or H2 blockers may be necessary in patients with recurrent ulcers, particularly those who require ongoing NSAID therapy.
- Regular Monitoring: Patients with a history of peptic ulcers should have regular follow-ups, including endoscopic surveillance if they are at high risk of recurrence or have a history of complications.

Future research in the field of peptic ulcers could explore several promising areas that have the potential to revolutionize both treatment and diagnosis. One significant avenue for investigation is the development of new treatment targets beyond the traditional focus on acid suppression and *H. pylori* eradication. This could involve identifying novel molecular pathways involved in ulcer formation and healing, such as those related to the immune response or epithelial regeneration, and developing therapies that modulate these pathways to enhance healing or prevent ulcer recurrence.

Another critical area is the improvement of diagnostic methods. While endoscopy remains the gold standard, it is invasive and may not be readily accessible in all settings. Research into non-invasive biomarkers that could reliably indicate the presence of an ulcer or its complications could make diagnosis easier and more widespread. Advances in imaging technology, including AI-enhanced imaging, could also provide more precise and earlier detection of ulcers and their potential complications, leading to better patient outcomes.

The role of gut microbiota in ulcer formation is an emerging field that could offer new insights into the pathogenesis of peptic ulcers. The gut microbiome is known to influence various aspects of gastrointestinal health, and imbalances in microbial populations could contribute to ulcer development or impact the effectiveness of current treatments. Research exploring how modifying the gut microbiota, through probiotics, diet, or other interventions, could prevent ulcers or enhance healing is a promising area that could lead to innovative therapies.

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