Peptic ulcer disease: Epidemiology, etiology, and pathogenesis

AUTHOR: Nimish B Vakil, MD, AGAF, FACP, FACG, FASGE
SECTION EDITOR: Mark Feldman, MD, MACP, AGAF, FACG
DEPUTY EDITOR: Shilpa Grover, MD, MPH, AGAF

All topics are updated as new evidence becomes available and our peer review process is complete.

Literature review current through: **Sep 2023.**
This topic last updated: **Jul 20, 2022.**

INTRODUCTION

Peptic ulcers are defects in the gastric or duodenal mucosa that extend through the muscularis mucosae (picture 1). They develop and persist as a function of the acid-peptic activity in gastric juice. Peptic ulcer disease remains an important cause of morbidity and health care costs [1].

The natural history of peptic ulcer ranges from healing without intervention to the development of complications with the potential for significant morbidity and mortality, such as bleeding and perforation. This topic will review the epidemiology, etiology, and pathogenesis of peptic ulcer disease. The clinical manifestations, diagnosis, and management of peptic ulcer disease are discussed in detail, separately. (See "Overview of complications of peptic ulcer disease".)

EPIDEMIOLOGY

Incidence and prevalence — In a systematic review of 31 published studies, the pooled incidence of uncomplicated peptic ulcer disease (PUD) was approximately one case per 1000 person-years in the general population, and the incidence of ulcer complications was approximately 0.7 cases per 1000 person-years [2].

The incidence and prevalence of PUD varies based upon the presence of *Helicobacter pylori* (*H. pylori*). Higher rates are found in countries where *H. pylori* infection is higher [3-6]. The incidence of PUD in *H. pylori*-infected individuals is approximately 1 percent per year, a rate that is 6- to 10-fold higher than for uninfected individuals [7,8]. A systematic review of seven studies from developed countries indicated a population-based one-year prevalence of PUD of 0.1 to 1.5 percent based on physician diagnosis and 0.1 to 0.19 percent based on hospitalization data [9]. A study in the United States reported an endoscopic point prevalence for peptic ulcers in asymptomatic, *H. pylori*-positive adults of 2 percent [10]. Other studies, in presumably asymptomatic subjects in whom *H. pylori* status was unknown, have reported an endoscopic point prevalence ranging from 1 and 6 percent [5,11-13].

Ulcer incidence increases with age for both duodenal ulcers (DUs) and gastric ulcers (GUs), but the incidence of uncomplicated PUD reached a plateau with age, whereas for complicated PUD, the incidence increases with age [14]. DUs occur two decades earlier than GUs, particularly in males [14].

Time trends — PUD rates have been steadily falling over the past several decades [14-22]. In several regions, rates of DUs have fallen more dramatically than for GUs [16,20]. Age-adjusted hospitalization rates for peptic ulcer disease have also declined, suggesting that the decline in *H. pylori* infection has had a major impact on ulcer rates [23-25]. In developed countries, the prevalence of ulcer disease in young people has declined, while nonsteroidal anti-inflammatory drug (NSAID)-related ulcers in older adults have increased due both to increased life expectancy and frequent use of aspirin and NSAIDs [16,19-22,26-29]. PUD has shifted from being a male-predominant disease in western countries to one with a nearly equal prevalence in males and females [2,9].

ETIOLOGY

Peptic ulcer disease (PUD) is associated with two major factors: *Helicobacter pylori* (*H. pylori*) infection and the consumption of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAID use and *H. pylori* infection represent independent and also synergistic risk factors for uncomplicated and bleeding peptic ulcer disease. There are also a number of other defined mechanisms for peptic ulcer disease that are much less common but becoming more evident as the prevalence of *H. pylori* declines in developed countries (table 1). (See "Unusual causes of peptic ulcer disease".)

H. pylori — *H. pylori* affects a number of aspects of gastrointestinal physiology, including gastric acid secretion, and mucosal defense mechanisms leading to peptic ulcer disease. The

prevalence of *H. pylori* both in the general population and in peptic ulcer patients is decreasing rapidly in developed regions, presumably due to improved hygiene and decreased *H. pylori* transmission in early childhood. A systematic review of *H. pylori* prevalence around the world showed that the highest reported *H. pylori* prevalence areas were in Africa (70.1 percent), South America (69.4 percent), and Western Asia (66.6 percent). Regions with the lowest reported *H. pylori* prevalence were Oceania (24.4 percent), Western Europe (34.3 percent), and Northern America (37.1 percent) [30].

NSAIDs, including aspirin — NSAID use is associated with a fourfold increase in the risk of peptic ulcer disease [31]. In addition, NSAIDs are associated with an increase in risk of complications from peptic ulcer disease which include gastrointestinal bleeding, perforation, and pyloric obstruction. NSAID-induced ulcers may also be more refractory to conventional therapy [32]. However, up to 40 percent of patients may not report using NSAIDs [33]. (See "Nonselective NSAIDs: Overview of adverse effects", section on 'Gastrointestinal effects'.)

Other rare causes — Although some NSAID-negative, *H. pylori*-negative ulcers are due to specific causes, such as gastrinoma or viral infections, others remain in the idiopathic category (table 1). Unusual causes of peptic ulcer disease are discussed in detail separately. (See "Unusual causes of peptic ulcer disease".)

RISK FACTORS

The presence of *Helicobacter pylori* (*H. pylori*) or use of nonsteroidal anti-inflammatory drugs (NSAIDs) alone is not likely to be sufficient for ulcer formation. Although gastritis is consistently observed with *H. pylori* infection and NSAIDs consistently inhibit mucosal prostaglandin production, the yearly incidence of clinical ulcer disease among subjects at risk is only approximately 1 percent for both categories of ulcer [7,8,34]. There are a number of risk factors for ulcer disease.

Smoking — Smoking is an independent risk factor for symptomatic and asymptomatic peptic ulcer disease (PUD) [35]. PUD risk progressively increases with increasing pack-years of cigarette smoking [36]. A population-based study found that the prevalence of ulcer disease in current and former smokers was almost twice as high as non-smokers [37]. Smoking more than 15 cigarettes per day compared with never smoking increased the risk of a perforated ulcer more than threefold [38]. In addition, ulcers in smokers appear to be more difficult to treat and may be associated with a higher rate of recurrence [39-42]. The deleterious effects of smoking may be due to its impact on the balance of mucosal aggressive and protective factors [43].

However, in patients with *H. pylori*, smoking does not appear to be a risk factor for ulcer relapse once *H. pylori* has been eradicated [44-46].

Alcohol — Alcohol in high concentrations damages the gastric mucosal barrier. Alcohol consumption is related to the development of complicated and uncomplicated ulcer disease. In a large population based study, heavy drinking (more than 42 drinks per week) increased the risk of a bleeding ulcer fourfold (RR = 4.4; 95% CI 2.3–8.3) compared with drinking less than one drink per week in high concentrations and also stimulates acid secretion [47]. In addition, contents of alcoholic beverages other than alcohol are also strong stimulants of acid secretion.

Genetic factors — Host genetic factors appear to be important in predisposing to *H. pylori* infection and to disease outcomes such as duodenal ulcers (DU) and gastric cancer. Genes that encode for cytokines account for the individual responses to *H. pylori* infection. Genetic variations in pro-inflammatory cytokines (eg, IL-1B, IL-6, IL-8, and tumor necrosis factor (TNF)-alpha) and anti-inflammatory cytokines (IL-10) are associated with PUD [48]. A genome-wide association study in Japan found that specific genetic variations in the Prostate Stem Cell Antigen are associated with gastric ulcer, duodenal ulcer, and gastric cancer [49]. Genetic polymorphism related to synergy between host (TNF-alpha promoter) and bacterial (induced by contact with epithelium, or the iceA1 gene) factors have been related to DU in children [50].

There is also evidence for a genetic predisposition to PUD that is independent of any predisposition to *H. pylori* infection [51,52]. An illustrative report found high concordance of a self-reported ulcer history in monozygotic compared with dizygotic twins regardless of whether they were reared apart or together [53]. Cross-twin, cross-trait correlations for monozygotic and dizygotic twins indicated that genetic effects for peptic ulcer were independent of genetic influences for *H. pylori*. Hyperpepsinogenemia linked to elevated serum pepsinogen group A has also been noted in patients with familial clustering of PUD [52]. Genetic predisposition due to a polymorphism of cytochrome P450 2C9 may delay the metabolism of several NSAIDs, with a prolonged duration of drug effect, enhancing the ulcerogenic effect [54].

Blood groups O and A, the Lewis phenotype Le (a + b-), and non-secretors of ABH in particular have been associated with an increased risk of peptic ulcers [55,56]. However, other studies have failed to find any association of blood group O with *H. pylori* infection or with peptic ulcer [57-59]. Studies suggest that strains of *H. pylori* from different areas of the world may have different binding affinities for gastric epithelium accounting for these seemingly contradictory results seen with blood group studies from different countries [60]. (See "Pathophysiology of and immune response to Helicobacter pylori infection".)

Other

- **Diet** – Dietary factors have been hypothesized to account for some of the regional variation of ulcer disease, possibly related to toxins generated with storage of certain foods or from protective effects of certain foods [61,62]. A prospective study of a cohort of 47,806 males found no association between the type or amount of fat intake and the risk of DU [63]. However, high consumption of fruits and vegetables, dietary fiber, and vitamin A were associated with a reduced risk of ulcer disease.

  Evidence to support the use of a bland diet or dietary restrictions to prevent PUD are lacking. Although certain foods, beverages, and spices cause dyspepsia, there are no convincing data that such specific foods cause, perpetuate, or reactivate peptic ulcers. There is no evidence that coffee consumption is a risk factor for ulcer disease, although increased consumption may be associated with a higher rate of infection with *H. pylori* [64-66]. In one series, coffee increased dyspepsia in subjects with nonulcer dyspepsia, but not in those with DU when compared with controls [67].

- **Psychologic factors** – Two lines of evidence suggest an association between psychosocial factors and ulcer pathogenesis. First, in prospective studies, poorly tolerated stress or depressive symptoms at baseline increase the risk of ulcer development over the next 9 to 15 years [68]. Other psychosocial factors, such as work-related stress, social problems, and post-traumatic stress disorder, are also predictive of subsequent ulcer disease [69-72]. Second, several studies have established that peptic ulcer complications become much more prevalent during periods of natural disaster or societal catastrophe [68,73,74].

  The pathophysiologic mechanisms accounting for the effects of stress on the ulcer formation have not been defined. These effects could be mediated by both altered behaviors and by altered physiology. A population-based prospective study in Denmark that included 3379 individuals demonstrated that psychological stress increased the incidence of peptic ulcer in part by influencing health risk behaviors [69]. Stress had similar effects on ulcers associated with *H. pylori* infection and those unrelated to *H. pylori* or NSAID use. Stress also increases acid secretion, but the effects are more prominent in patients with DU compared with controls [75]. As a result, one must consider not only the stressor, but the individual's physiological and psychosocial response to the stress; deleterious effects may only be evident in a subset of predisposed individuals. Stress, anxiety, and depression have also been observed to impair endoscopic healing and to promote relapse of endoscopically diagnosed ulcers [68,76,77]. The effects of stress seem to be reversible; patients who develop an ulcer following traumatic life events, but who are psychologically stable, tend to do well after the stress has resolved [68].

However, the finding a relationship between psychosocial factors and ulcer disease does not establish causality. One study found that anxiety and neuroticism were high in a group of DU patients at the outset, but normalized in relapse-free patients at the end of a 10-year follow-up period [78]. In some cases, psychological features may be the result and not the cause of the disease process.

- **Sleep and sleep apnea** – Disturbances in sleep may be a risk factor for ulcer disease, complications of peptic ulcer disease, and ulcer recurrence [79,80]. In a large retrospective study that included 7096 patients with sleep apnea and 28,384 age- and sex-matched controls, in adjusted analysis, patients with sleep apnea were twice as likely as controls to develop gastrointestinal bleeding during a follow-up period of four years [79]. In another study, females who slept more than nine hours a day by self-report had a lower incidence of ulcer disease than females who slept less than nine hours. A similar nonsignificant trend was seen in males [81].

- **COVID-19 infection** – Gastrointestinal bleeding is frequently reported in patients with COVID-19, and peptic ulcer disease is the most common cause of gastrointestinal bleeding [82]. The clinical presentation of patients is similar to those presenting without COVID-19 infections, and ulcers are found in one-half of the patients [83]. In a meta-analysis, overall mortality was high at 19.1 percent (95% CI 12.7-27.6 percent) and pooled mortality secondary to gastrointestinal hemorrhage was 3.5 percent (95% CI 1.3–9.1 percent). The risk of rebleeding was high at 11.3 percent (95% CI 6.8–18.4 percent). The majority of patients can be managed conservatively, and only one-third of patients undergoing upper endoscopy required therapeutic intervention to stop bleeding. Mortality from gastrointestinal bleeding was low in this population, and most deaths were unrelated to bleeding and were caused by other complications of the disease [83].

- **Checkpoint inhibitor-induced gastritis and ulcer disease –** Immune checkpoint inhibitors are increasingly used in oncology, and they have been associated with severe gastritis, gastric ulcers, and gastrointestinal bleeding. These ulcers and gastritis may not respond to proton pump inhibitor therapy, and corticosteroid therapy is needed in severe cases. The incidence and risk factors remain unclear.

PATHOPHYSIOLOGY

Considering the acid-peptic environment of the stomach and the noxious agents that are ingested, ulcers are surprisingly uncommon, reflecting the effectiveness of the protective mechanisms that govern gastric mucosal function and repair. Primary malfunction of these

secretory, defense, or repair mechanisms is a very uncommon cause of ulcer, if it occurs at all. Most ulcers occur when the normal mechanisms are disrupted by superimposed processes such as *Helicobacter pylori* (*H.* pylori) infection and the ingestion of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs, via inhibition of prostaglandin synthesis, affect the amount of gastric acid generated, the integrity of the mucosal barrier, the amount of bicarbonate and glutathione generated, and the rate of mucosal blood flow. (See "NSAIDs (including aspirin): Pathogenesis and risk factors for gastroduodenal toxicity".)

Gastric acid hypersecretion — Gastric ulcers involving the gastric body or distal antrum, and gastric ulcers associated with concurrent duodenal ulcers (DU) have normal or even increased levels of acid secretion. Although only a minority of DU subjects have true acid hypersecretion, high-normal or modestly elevated values appear to be a defining characteristic of patients with DU, whether or not they are infected with *H. pylori*.

The majority of patients infected with *H. pylori* develop pangastritis, which over time is associated with a reduction in gastric acid secretion. However, approximately, 10 to 15 percent of patients with the infection develop an antrum predominant gastritis which is associated with decreased antral somatostatin concentrations and increased basal and stimulated gastric acid secretion [84-86]. Somatostatin secretion by the antral D cells is a feedback mechanism by which gastrin secretion is regulated. Inhibition of somatostatin secretion may involve cytokines induced by *H. pylori* infection. Host genetic factors can also influence the cytokine response to *H. pylori* infection and predispose to ulcer disease [84,85,87-89].

Increased acid secretion is also an important factor in some patients with ulcer recurrences following successful *H. pylori* eradication. Abnormalities in gastrin and somatostatin secretion and most abnormalities of acid secretion usually normalize within one year of *H. pylori* eradication [84,89]. However, a small study found higher basal and pentagastrin-stimulated acid secretion in patients with recurrent ulcers following successful *H. pylori* eradication, as compared with patients without recurrent ulcers [90]. (See "Association between Helicobacter pylori infection and duodenal ulcer", section on 'Pathogenesis of ulcer formation'.)

Among *H. pylori*-negative subjects, a subset have acid hypersecretion without hypergastrinemia [88,91]. The mechanisms of acid hypersecretion in these patients have not been defined. One study of six patients with non-*H. pylori*, non-NSAID DU found increased gastrin response to a meal (but not fasting hypergastrinemia) and increased peak gastric acid secretion [92]. Some subjects with non-*H. pylori*, non-NSAID hypersecretion may have a component of muscarinic-dependent, vagal hyperactivity, although this element is difficult to quantify. In the absence of *H. pylori* or gastrinoma, fasting hypergastrinemia is only rarely found in hypersecretory DU patients, sometimes linked to antral G-cell hyperfunction [93].

Impaired duodenal bicarbonate secretion — The majority of DU patients have impaired duodenal bicarbonate secretion. The combination of increased gastric acid secretion and reduced duodenal bicarbonate secretion lowers the pH in the duodenum, which promotes the development of gastric metaplasia (ie, the presence of gastric epithelium in the first portion of the duodenum) [94]. Excess acid secretion in gastrinoma patients is also associated with marked gastric metaplasia in the duodenum.

INFORMATION FOR PATIENTS

UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the keyword(s) of interest.)

- Basics topics (see "Patient education: Peptic ulcers (The Basics)" and "Patient education: H. pylori infection (The Basics)" and "Patient education: Gastritis (The Basics)")
- Beyond the Basics topics (see "Patient education: Peptic ulcer disease (Beyond the Basics)" and "Patient education: Helicobacter pylori infection and treatment (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

- Estimates of the annual incidence of peptic ulcer disease (PUD) range from 0.1 to 0.3 percent. PUD incidence in *Helicobacter pylori* (*H. pylori*)-infected individuals is approximately 1 percent per year, a rate that is 6- to 10-fold higher than for uninfected subjects. The incidence of PUD increases with age for both duodenal and gastric ulcers. (See 'Incidence and prevalence' above.)
- Peptic ulcer disease is associated with two major factors: *H. pylori* infection and the consumption of nonsteroidal anti-inflammatory drugs (NSAIDs). NSAIDs are also

associated with an increase in risk of complications from peptic ulcer disease which include gastrointestinal bleeding, perforation, and gastric outlet obstruction. (See 'Etiology' above.)

- Smoking is a risk factor for PUD. Alcohol in high concentrations damages the gastric mucosal barrier. Host genetic factors appear to be important in predisposing to *H. pylori* infection but can also influence the risk of PUD through other mechanisms. Dietary factors have been hypothesized to account for some of the regional variation of ulcer disease, possibly related to toxins generated with storage of certain foods or from protective effects of certain foods. However, evidence to support the use of a bland diet or dietary restrictions to prevent PUD are lacking. (See 'Risk factors' above.)

- Most ulcers occur when the normal secretory, defense, or repair mechanisms of the stomach are disrupted by superimposed processes such as *H. pylori* infection and the ingestion of NSAIDs. (See 'Pathophysiology' above.)

ACKNOWLEDGMENT

The UpToDate editorial staff acknowledges Andrew H Soll, MD, who contributed to an earlier version of this topic review.

REFERENCES

1. Peery AF, Dellon ES, Lund J, et al. Burden of gastrointestinal disease in the United States: 2012 update. Gastroenterology 2012; 143:1179.
2. Lin KJ, García Rodríguez LA, Hernández-Díaz S. Systematic review of peptic ulcer disease incidence rates: do studies without validation provide reliable estimates? Pharmacoepidemiol Drug Saf 2011; 20:718.
3. Li Z, Zou D, Ma X, et al. Epidemiology of peptic ulcer disease: endoscopic results of the systematic investigation of gastrointestinal disease in China. Am J Gastroenterol 2010; 105:2570.
4. Wang FW, Tu MS, Mar GY, et al. Prevalence and risk factors of asymptomatic peptic ulcer disease in Taiwan. World J Gastroenterol 2011; 17:1199.
5. Aro P, Storskrubb T, Ronkainen J, et al. Peptic ulcer disease in a general adult population: the Kalixanda study: a random population-based study. Am J Epidemiol 2006; 163:1025.

6. Zagari RM, Law GR, Fuccio L, et al. Dyspeptic symptoms and endoscopic findings in the community: the Loiano-Monghidoro study. Am J Gastroenterol 2010; 105:565.
7. Kuipers EJ, Thijs JC, Festen HP. The prevalence of Helicobacter pylori in peptic ulcer disease. Aliment Pharmacol Ther 1995; 9 Suppl 2:59.
8. Sipponen P, Varis K, Fräki O, et al. Cumulative 10-year risk of symptomatic duodenal and gastric ulcer in patients with or without chronic gastritis. A clinical follow-up study of 454 outpatients. Scand J Gastroenterol 1990; 25:966.
9. Sung JJ, Kuipers EJ, El-Serag HB. Systematic review: the global incidence and prevalence of peptic ulcer disease. Aliment Pharmacol Ther 2009; 29:938.
10. Anand BS, Raed AK, Malaty HM, et al. Low point prevalence of peptic ulcer in normal individuals with Helicobacter pylori infection. Am J Gastroenterol 1996; 91:1112.
11. Akdamar K, Ertan A, Agrawal NM, et al. Upper gastrointestinal endoscopy in normal asymptomatic volunteers. Gastrointest Endosc 1986; 32:78.
12. Kaneko E, Ooi S, Ito G, Honda N. Natural history of duodenal ulcer detected by the gastric mass surveys in men over 40 years of age. Scand J Gastroenterol 1989; 24:165.
13. Bernersen B, Johnsen R, Straume B, et al. Towards a true prevalence of peptic ulcer: the Sørreisa gastrointestinal disorder study. Gut 1990; 31:989.
14. Sonnenberg A. Temporal trends and geographical variations of peptic ulcer disease. Aliment Pharmacol Ther 1995; 9 Suppl 2:3.
15. Sonnenberg A. Time trends of ulcer mortality in Europe. Gastroenterology 2007; 132:2320.
16. el-Serag HB, Sonnenberg A. Opposing time trends of peptic ulcer and reflux disease. Gut 1998; 43:327.
17. Nam K, Shin JE, Kim SE, et al. Prevalence and risk factors for upper gastrointestinal diseases in health check-up subjects: a nationwide multicenter study in Korea. Scand J Gastroenterol 2018; 53:910.
18. Kamdem J, Palmer D, Barrier C, et al. Diagnostic yield of gastrointestinal endoscopy in North West Region Cameroon and trends in diagnosis over time. Pan Afr Med J 2018; 29:178.
19. Cai S, García Rodríguez LA, Massó-González EL, Hernández-Díaz S. Uncomplicated peptic ulcer in the UK: trends from 1997 to 2005. Aliment Pharmacol Ther 2009; 30:1039.
20. Dutta AK, Chacko A, Balekuduru A, et al. Time trends in epidemiology of peptic ulcer disease in India over two decades. Indian J Gastroenterol 2012; 31:111.
21. Xia B, Xia HH, Ma CW, et al. Trends in the prevalence of peptic ulcer disease and Helicobacter pylori infection in family physician-referred uninvestigated dyspeptic patients

in Hong Kong. Aliment Pharmacol Ther 2005; 22:243.

22. Wu CY, Wu CH, Wu MS, et al. A nationwide population-based cohort study shows reduced hospitalization for peptic ulcer disease associated with H pylori eradication and proton pump inhibitor use. Clin Gastroenterol Hepatol 2009; 7:427.
23. Feinstein LB, Holman RC, Yorita Christensen KL, et al. Trends in hospitalizations for peptic ulcer disease, United States, 1998-2005. Emerg Infect Dis 2010; 16:1410.
24. Kanotra R, Ahmed M, Patel N, et al. Seasonal Variations and Trends in Hospitalization for Peptic Ulcer Disease in the United States: A 12-Year Analysis of the Nationwide Inpatient Sample. Cureus 2016; 8:e854.
25. Johnson CH, McLean RC, McCallum I, et al. An evaluation of the epidemiology, management and outcomes for perforated peptic ulcers across the North of England over 15 years: A retrospective cohort study. Int J Surg 2019; 64:24.
26. Ohmann C, Imhof M, Ruppert C, et al. Time-trends in the epidemiology of peptic ulcer bleeding. Scand J Gastroenterol 2005; 40:914.
27. Laine L, Yang H, Chang SC, Datto C. Trends for incidence of hospitalization and death due to GI complications in the United States from 2001 to 2009. Am J Gastroenterol 2012; 107:1190.
28. Bashinskaya B, Nahed BV, Redjal N, et al. Trends in Peptic Ulcer Disease and the Identification of Helicobacter Pylori as a Causative Organism: Population-based Estimates from the US Nationwide Inpatient Sample. J Glob Infect Dis 2011; 3:366.
29. Nagashima K, Tominaga K, Fukushi K, et al. Recent trends in the occurrence of bleeding gastric and duodenal ulcers under the Japanese evidence-based clinical practice guideline for peptic ulcer disease. JGH Open 2018; 2:255.
30. Hooi JKY, Lai WY, Ng WK, et al. Global Prevalence of Helicobacter pylori Infection: Systematic Review and Meta-Analysis. Gastroenterology 2017; 153:420.
31. Huang JQ, Sridhar S, Hunt RH. Role of Helicobacter pylori infection and non-steroidal anti-inflammatory drugs in peptic-ulcer disease: a meta-analysis. Lancet 2002; 359:14.
32. Hirschowitz BI, Lanas A. Atypical and aggressive upper gastrointestinal ulceration associated with aspirin abuse. J Clin Gastroenterol 2002; 34:523.
33. Lanas AI, Remacha B, Esteva F, Sáinz R. Risk factors associated with refractory peptic ulcers. Gastroenterology 1995; 109:1124.
34. Silverstein FE, Graham DY, Senior JR, et al. Misoprostol reduces serious gastrointestinal complications in patients with rheumatoid arthritis receiving nonsteroidal anti-

inflammatory drugs. A randomized, double-blind, placebo-controlled trial. Ann Intern Med 1995; 123:241.

35. Lee SP, Sung IK, Kim JH, et al. Risk Factors for the Presence of Symptoms in Peptic Ulcer Disease. Clin Endosc 2017; 50:578.
36. Kato I, Nomura AM, Stemmermann GN, Chyou PH. A prospective study of gastric and duodenal ulcer and its relation to smoking, alcohol, and diet. Am J Epidemiol 1992; 135:521.
37. Garrow D, Delegge MH. Risk factors for gastrointestinal ulcer disease in the US population. Dig Dis Sci 2010; 55:66.
38. Andersen IB, Jørgensen T, Bonnevie O, et al. Smoking and alcohol intake as risk factors for bleeding and perforated peptic ulcers: a population-based cohort study. Epidemiology 2000; 11:434.
39. Martin DF, Montgomery E, Dobek AS, et al. Campylobacter pylori, NSAIDS, and smoking: risk factors for peptic ulcer disease. Am J Gastroenterol 1989; 84:1268.
40. Anda RF, Williamson DF, Escobedo LG, Remington PL. Smoking and the risk of peptic ulcer disease among women in the United States. Arch Intern Med 1990; 150:1437.
41. Korman MG, Hansky J, Eaves ER, Schmidt GT. Influence of cigarette smoking on healing and relapse in duodenal ulcer disease. Gastroenterology 1983; 85:871.
42. Rosenstock S, Jørgensen T, Bonnevie O, Andersen L. Risk factors for peptic ulcer disease: a population based prospective cohort study comprising 2416 Danish adults. Gut 2003; 52:186.
43. Maity P, Biswas K, Roy S, et al. Smoking and the pathogenesis of gastroduodenal ulcer--recent mechanistic update. Mol Cell Biochem 2003; 253:329.
44. Chan FK, Sung JJ, Lee YT, et al. Does smoking predispose to peptic ulcer relapse after eradication of Helicobacter pylori? Am J Gastroenterol 1997; 92:442.
45. Bardhan KD, Graham DY, Hunt RH, O'Morain CA. Effects of smoking on cure of Helicobacter pylori infection and duodenal ulcer recurrence in patients treated with clarithromycin and omeprazole. Helicobacter 1997; 2:27.
46. Kim JJ, Kim N, Lee BH, et al. [Risk factors for development and recurrence of peptic ulcer disease]. Korean J Gastroenterol 2010; 56:220.
47. Peterson WL, Barnett C, Walsh JH. Effect of intragastric infusions of ethanol and wine on serum gastrin concentration and gastric acid secretion. Gastroenterology 1986; 91:1390.
48. Miftahussurur M, Yamaoka Y. Helicobacter pylori virulence genes and host genetic polymorphisms as risk factors for peptic ulcer disease. Expert Rev Gastroenterol Hepatol 2015; 9:1535.

49. Tanikawa C, Urabe Y, Matsuo K, et al. A genome-wide association study identifies two susceptibility loci for duodenal ulcer in the Japanese population. Nat Genet 2012; 44:430.
50. Wilschanski M, Schlesinger Y, Faber J, et al. Combination of Helicobacter pylori strain and tumor necrosis factor-alpha polymorphism of the host increases the risk of peptic ulcer disease in children. J Pediatr Gastroenterol Nutr 2007; 45:199.
51. Räihä I, Kemppainen H, Kaprio J, et al. Lifestyle, stress, and genes in peptic ulcer disease: a nationwide twin cohort study. Arch Intern Med 1998; 158:698.
52. Del Bianco T, Borgoni R, Del Bianco P, et al. Peptic ulcer inheritance in patients with elevated serum pepsinogen group A levels and without infection of Helicobacter pylori. Dig Liver Dis 2000; 32:12.
53. Malaty HM, Graham DY, Isaksson I, et al. Are genetic influences on peptic ulcer dependent or independent of genetic influences for Helicobacter pylori infection? Arch Intern Med 2000; 160:105.
54. Pilotto A, Seripa D, Franceschi M, et al. Genetic susceptibility to nonsteroidal anti-inflammatory drug-related gastroduodenal bleeding: role of cytochrome P450 2C9 polymorphisms. Gastroenterology 2007; 133:465.
55. Nakajima T. Studies on factors affecting healing of gastric ulcer. A prospective, cooperative study in Japan. Am J Gastroenterol 1976; 66:150.
56. Edgren G, Hjalgrim H, Rostgaard K, et al. Risk of gastric cancer and peptic ulcers in relation to ABO blood type: a cohort study. Am J Epidemiol 2010; 172:1280.
57. Niv Y, Fraser G, Delpre G, et al. Helicobacter pylori infection and blood groups. Am J Gastroenterol 1996; 91:101.
58. Umlauft F, Keeffe EB, Offner F, et al. Helicobacter pylori infection and blood group antigens: lack of clinical association. Am J Gastroenterol 1996; 91:2135.
59. Keller R, Dinkel KC, Christl SU, Fischbach W. Interrelation between ABH blood group 0, Lewis(B) blood group antigen, Helicobacter pylori infection, and occurrence of peptic ulcer. Z Gastroenterol 2002; 40:273.
60. Anstee DJ. The relationship between blood groups and disease. Blood 2010; 115:4635.
61. Kang JY, Yeoh KG, Chia HP, et al. Chili--protective factor against peptic ulcer? Dig Dis Sci 1995; 40:576.
62. Tovey FI, Hobsley M, Kaushik SP, et al. Duodenal gastric metaplasia and Helicobacter pylori infection in high and low duodenal ulcer-prevalent areas in India. J Gastroenterol Hepatol 2004; 19:497.

63. Aldoori WH, Giovannucci EL, Stampfer MJ, et al. Prospective study of diet and the risk of duodenal ulcer in men. Am J Epidemiol 1997; 145:42.

64. Aldoori WH, Giovannucci EL, Stampfer MJ, et al. A prospective study of alcohol, smoking, caffeine, and the risk of duodenal ulcer in men. Epidemiology 1997; 8:420.

65. Shimamoto T, Yamamichi N, Kodashima S, et al. No association of coffee consumption with gastric ulcer, duodenal ulcer, reflux esophagitis, and non-erosive reflux disease: a cross-sectional study of 8,013 healthy subjects in Japan. PLoS One 2013; 8:e65996.

66. Brenner H, Rothenbacher D, Bode G, Adler G. Relation of smoking and alcohol and coffee consumption to active Helicobacter pylori infection: cross sectional study. BMJ 1997; 315:1489.

67. Elta GH, Behler EM, Colturi TJ. Comparison of coffee intake and coffee-induced symptoms in patients with duodenal ulcer, nonulcer dyspepsia, and normal controls. Am J Gastroenterol 1990; 85:1339.

68. Levenstein S. The very model of a modern etiology: a biopsychosocial view of peptic ulcer. Psychosom Med 2000; 62:176.

69. Levenstein S, Rosenstock S, Jacobsen RK, Jorgensen T. Psychological stress increases risk for peptic ulcer, regardless of Helicobacter pylori infection or use of nonsteroidal anti-inflammatory drugs. Clin Gastroenterol Hepatol 2015; 13:498.

70. Goodwin RD, Talley NJ, Hotopf M, et al. A link between physician-diagnosed ulcer and anxiety disorders among adults. Ann Epidemiol 2013; 23:189.

71. Fuller-Thomson E, Bottoms J, Brennenstuhl S, Hurd M. Is childhood physical abuse associated with peptic ulcer disease? Findings from a population-based study. J Interpers Violence 2011; 26:3225.

72. Lee YB, Yu J, Choi HH, et al. The association between peptic ulcer diseases and mental health problems: A population-based study: a STROBE compliant article. Medicine (Baltimore) 2017; 96:e7828.

73. Spicer CC, Stewart DN, Winser DM. Perforated peptic ulcer during the period of heavy air raids. Lancet 1944; 1:14.

74. Kanno T, Iijima K, Abe Y, et al. Peptic ulcers after the Great East Japan earthquake and tsunami: possible existence of psychosocial stress ulcers in humans. J Gastroenterol 2013; 48:483.

75. Bresnick WH, Rask-Madsen C, Hogan DL, et al. The effect of acute emotional stress on gastric acid secretion in normal subjects and duodenal ulcer patients. J Clin Gastroenterol 1993; 17:117.

76. Armstrong D, Arnold R, Classen M, et al. RUDER--a prospective, two-year, multicenter study of risk factors for duodenal ulcer relapse during maintenance therapy with ranitidine. RUDER Study Group. Dig Dis Sci 1994; 39:1425.

77. Holtmann G, Armstrong D, Pöppel E, et al. Influence of stress on the healing and relapse of duodenal ulcers. A prospective, multicenter trial of 2109 patients with recurrent duodenal ulceration treated with ranitidine. RUDER Study Group. Scand J Gastroenterol 1992; 27:917.

78. Wilhelmsen I, Berstad A. Reduced relapse rate in duodenal ulcer disease leads to normalization of psychological distress: twelve-year follow-up. Scand J Gastroenterol 2004; 39:717.

79. Shiao TH, Liu CJ, Luo JC, et al. Sleep apnea and risk of peptic ulcer bleeding: a nationwide population-based study. Am J Med 2013; 126:249.

80. Fang B, Liu H, Yang S, et al. Effect of Subjective and Objective Sleep Quality on Subsequent Peptic Ulcer Recurrence in Older Adults. J Am Geriatr Soc 2019; 67:1454.

81. Ko SH, Baeg MK, Ko SY, Han KD. Women Who Sleep More Have Reduced Risk of Peptic Ulcer Disease; Korean National Health and Nutrition Examination Survey (2008-2009). Sci Rep 2016; 6:36925.

82. Zellmer S, Hanses F, Muzalyova A, et al. Gastrointestinal bleeding and endoscopic findings in critically and non-critically ill patients with corona virus disease 2019 (COVID-19): Results from Lean European Open Survey on SARS-CoV-2 (LEOSS) and COKA registries. United European Gastroenterol J 2021; 9:1081.

83. Iqbal U, Anwar H, Siddiqui HU, et al. Acute Gastrointestinal Bleeding in COVID-19 Patients: A Systematic Review and Meta-Analysis. Clin Endosc 2021; 54:534.

84. el-Omar EM, Penman ID, Ardill JE, et al. Helicobacter pylori infection and abnormalities of acid secretion in patients with duodenal ulcer disease. Gastroenterology 1995; 109:681.

85. Moss SF, Legon S, Bishop AE, et al. Effect of Helicobacter pylori on gastric somatostatin in duodenal ulcer disease. Lancet 1992; 340:930.

86. Gillen D, el-Omar EM, Wirz AA, et al. The acid response to gastrin distinguishes duodenal ulcer patients from Helicobacter pylori-infected healthy subjects. Gastroenterology 1998; 114:50.

87. Isenberg J, McQuaid K, Laine L, et al. Acid-peptic disorders. In: Textbook of Gastroenterology, 2nd ed, Yamada T (Ed), JB Lippincott, Philadelphia 1995. p.1347.

88. Hirschowitz BI, Simmons J, Mohnen J. Minor effects of Helicobacter pylori on gastric secretion and dose of lansoprazole during long-term treatment in ZE and non-ZE acid hypersecretors. Aliment Pharmacol Ther 2002; 16:303.

89. Olbe L, Hamlet A, Dalenbäck J, Fändriks L. A mechanism by which Helicobacter pylori infection of the antrum contributes to the development of duodenal ulcer. Gastroenterology 1996; 110:1386.

90. Harris AW, Gummett PA, Phull PS, et al. Recurrence of duodenal ulcer after Helicobacter pylori eradication is related to high acid output. Aliment Pharmacol Ther 1997; 11:331.

91. Collen MJ, Jensen RT. Idiopathic gastric acid hypersecretion. Comparison with Zollinger-Ellison syndrome. Dig Dis Sci 1994; 39:1434.

92. McColl KE, el-Nujumi AM, Chittajallu RS, et al. A study of the pathogenesis of Helicobacter pylori negative chronic duodenal ulceration. Gut 1993; 34:762.

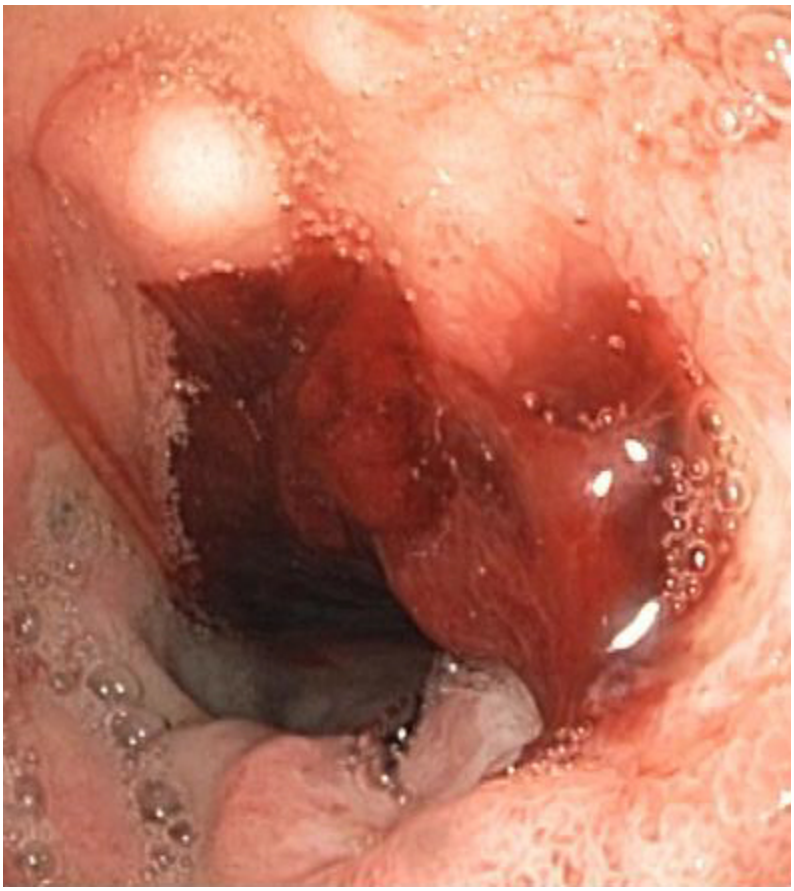
93. Annibale B, De Magistris L, Corleto V, et al. Zollinger-Ellison syndrome and antral G-cell hyperfunction in patients with resistant duodenal ulcer disease. Aliment Pharmacol Ther 1994; 8:87.

94. Wyatt JI, Rathbone BJ, Dixon MF, Heatley RV. Campylobacter pyloridis and acid induced gastric metaplasia in the pathogenesis of duodenitis. J Clin Pathol 1987; 40:841.

Topic 22 Version 23.0

GRAPHICS

Duodenal ulcer



Duodenal ulcer with a small amount of fresh blood oozing from the edge.

Courtesy of Nimish Vakil, MD.

Graphic 63114 Version 4.0

Etiologies and disease associations for peptic ulcer

Ulcers due to defined mechanisms
Infection
Helicobacter pylori
HSV
CMV
Helicobacter heilmannii
Other rare infections: TB, syphilis, mucormycosis, etc
Drug exposure (all probably worse when combined with NSAIDs or in high risk subjects)
NSAIDs and aspirin including low dose aspirin
Bisphosphonates (probably when combined with NSAIDs)
Clopidogrel (when combined with NSAIDs or in high risk subjects)
Corticosteroids (when combined with NSAIDs)
Sirolimus
Spironolactone (probable, no data with NSAID cotherapy)
Mycophenolate mofetil
Potassium chloride
Chemotherapy (eg, hepatic infusion with 5-fluorouracil), molecular targeted therapy, immune checkpoint inhibitors
Hormonal or mediator-induced, including acid hypersecretory states
Gastrinoma (Zollinger-Ellison syndrome)
Systemic mastocytosis
Basophilia in myeloproliferative disease
Antral G cell hyperfunction (existence independent of H. pylori is debatable)
Post surgical
Antral exclusion
Post-gastric bypass
Vascular insufficiency including crack cocaine use
Mechanical: Duodenal obstruction (eg, annular pancreas)
Radiation therapy
Infiltrating disease

Sarcoidosis
Crohn disease
Idiopathic peptic ulcer
Non-Helicobacter pylori, non-NSAID peptic ulcer
Comorbid ulcers associated with decompensated chronic disease or acute multisystem failure
Stress intensive care unit ulcers
Cirrhosis
Organ transplantation
Renal failure
Chronic obstructive pulmonary disease (secondary to smoking)

HSV: herpes simplex virus; CMV: cytomegalovirus; NSAID: nonsteroidal anti-inflammatory drug; TB: tuberculosis.

Courtesy of Andrew H Soll, MD.

Graphic 79691 Version 5.0

Contributor Disclosures

Nimish B Vakil, MD, AGAF, FACP, FACG, FASGE Consultant/Advisory Boards: Isothrive [GERD]; Phathom [GERD]; Redhill Biopharma [H pylori]. Other Financial Interest: Merck [Authorship of Merck Manual articles regarding gastritis]. All of the relevant financial relationships listed have been mitigated. **Mark Feldman, MD, MACP, AGAF, FACG** No relevant financial relationship(s) with ineligible companies to disclose. **Shilpa Grover, MD, MPH, AGAF** No relevant financial relationship(s) with ineligible companies to disclose.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

Conflict of interest policy

→