Approach to refractory peptic ulcer disease

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INTRODUCTION

A peptic ulcer is an excavated defect in the gastric or duodenal mucosa that extends through the muscularis mucosa into the deeper layers of the wall. Most peptic ulcers respond to treatment with antimicrobial therapy for *Helicobacter pylori*, withdrawal of nonsteroidal antiinflammatory drugs, or treatment with antisecretory drugs. However, in some individuals, the ulcer is either refractory to conventional therapy or recurs following successful initial treatment.

This topic will review the factors associated with refractory ulcer disease, and their diagnosis and management. The clinical manifestations, diagnosis, and initial management of peptic ulcer disease are discussed in detail, separately. (See "Peptic ulcer disease: Clinical manifestations and diagnosis" and "Peptic ulcer disease: Treatment and secondary prevention".)

TERMINOLOGY

Refractory peptic ulcer — A refractory peptic ulcer is defined as an endoscopically proven ulcer greater than 5 mm in diameter that does not heal after 8 to 12 weeks of treatment with a proton pump inhibitor.

EPIDEMIOLOGY

In the absence of continued nonsteroidal antiinflammatory drug use, acid suppression heals >90 percent of peptic ulcers. However, approximately 5 to 10 percent of ulcers are refractory to 12 weeks of antisecretory therapy with a proton pump inhibitor (PPI). Even with continued PPI use, approximately 5 to 30 percent of peptic ulcers recur within the first year based on whether *Helicobacter pylori* has been successfully eradicated [1,2].

ETIOLOGY AND RISK FACTORS

There is significant overlap in the risk factors for refractory and recurrent peptic ulceration (table 1 and table 2) [3-6].

Persistent H. pylori infection — Persistent *Helicobacter pylori* can underlie refractory peptic ulceration because this infection was not initially considered, testing was falsely negative, or eradication therapy failed [7]. Failure of eradication therapy may be due to the selection of an inappropriate regimen, antibiotic resistance (particularly to clarithromycin), or poor patient compliance. (See "Treatment regimens for Helicobacter pylori in adults", section on 'Treatment failure'.)

Use of culprit medications

Continued nonsteroidal anti-inflammatory drug (NSAID) use — Continuing NSAID use is a leading cause of refractory peptic ulceration [7-9]. In an illustrative study that included 60 patients with refractory peptic ulcer and 54 non-refractory matched controls, NSAID and analgesic use was a significant predictor of ulcer refractoriness, present in 40 percent of those with nonhealing ulcers [10]. Forty-four percent of NSAID use was surreptitious and was detected by measuring platelet cyclooxygenase activity.

Other medications/substance use — Several medications can cause or exacerbate peptic ulcer disease when used alone or in combination with NSAIDs (eg, glucocorticoids, cytotoxic agents, alendronate, olmesartan) [11,12]. Substances (eg, cocaine) can cause peptic ulceration from ischemia due mucosal vasoconstriction [13,14]. (See "Unusual causes of peptic ulcer disease", section on 'Non-NSAID medications' and "Unusual causes of peptic ulcer disease", section on 'Non-occlusive ischemia'.)

Impaired healing

Ulcer characteristics — In a subset of patients, refractory ulcers may be caused by an intense inflammatory response, dense scarring, or low mucosal blood flow, which impair angiogenesis and tissue repair [15]. Ulcer size also impacts the healing time. Some studies suggest that large

and small gastric ulcers heal at the same rate of approximately 3 mm per week, and thus larger ulcers will require more time to heal [13]. However, another explanation for slow healing in patients with large ulcers is that they are often associated with fibrosis, which in turn adversely affects ulcer healing [14].

Comorbid diseases — Risk factors associated with impaired wound healing include uremia, respiratory failure, organ transplantation, cirrhosis, and a critical illness [16].

Smoking — Cigarette smoke and its active ingredients can suppress mucosal cell proliferation and induce apoptosis during ulceration and adversely affect the healing processes [17].

Ineffective antisecretory therapy

Limited adherence or rapid metabolism — Limited adherence with antisecretory therapy and tolerance to histamine 2 receptor antagonists can contribute to refractory peptic ulceration. Although tolerance does not develop with proton pump inhibitors (PPIs), rapid P450 mediated metabolism might account for incomplete inhibition of acid secretion and failure of PPI therapy in a small subset of patients. Other mechanisms of PPI resistance are rare and still poorly defined. (See "Proton pump inhibitors: Overview of use and adverse effects in the treatment of acid related disorders", section on 'Pharmacology'.)

Acid hypersecretory states — Acid hypersecretion is associated with refractory peptic ulceration in patients with Zollinger Ellison syndrome (gastrinoma) [18]. Increased acid production and ulcer disease have been described in patients with primary hyperparathyroidism [19]. (See "Zollinger-Ellison syndrome (gastrinoma): Clinical manifestations and diagnosis" and "Unusual causes of peptic ulcer disease", section on 'Acid hypersecretory states'.)

A small number of patients with acid hypersecretion have neither of these risk factors. Smoking and genetic factors may play an important role in the pathogenesis of these ulcers. A proportion of these patients have idiopathic acid hypersecretion. Idiopathic acid hypersecretion has been defined as a condition with a high basal acid output of 10 mEq/hour or more with a normal basal serum gastrin or a negative secretin test [20,21]. However, all refractory ulcers in these individuals subsequently heal with high-dose antisecretory therapy. (See "Zollinger-Ellison syndrome (gastrinoma): Clinical manifestations and diagnosis".)

Other underlying disease — Other rare causes of gastric and duodenal ulceration include Crohn disease, sarcoid, lymphoma, ischemia, eosinophilic gastroenteritis, tuberculosis, syphilis, cytomegalovirus, IgG4-related sclerosing disease, and mesenteric ischemia. (See "Unusual causes of peptic ulcer disease" and "Clinical manifestations, diagnosis, and prognosis of Crohn

disease in adults", section on 'Other gastrointestinal features' and "Eosinophilic gastrointestinal diseases", section on 'Clinical manifestations' and "Extrapulmonary manifestations of sarcoidosis", section on 'Gastrointestinal' and "Clinical presentation and diagnosis of primary gastrointestinal lymphomas", section on 'Gastric lymphoma' and "Abdominal tuberculosis", section on 'Intestinal tuberculosis' and "Epidemiology, clinical manifestations, and treatment of cytomegalovirus infection in immunocompetent adults", section on 'Gastrointestinal manifestations' and "Syphilis: Epidemiology, pathophysiology, and clinical manifestations in patients without HIV", section on 'Gastrointestinal findings'.)

DIAGNOSIS

Refractory ulcers are suspected in patients with peptic ulcer disease with persistent or recurrent dyspepsia. They are diagnosed at upper endoscopy performed for evaluation of symptoms or on routine endoscopic surveillance after initial therapy for peptic ulcer disease. (See "Peptic ulcer disease: Treatment and secondary prevention", section on 'Repeat upper endoscopy in selected patients'.)

Upper endoscopy in patients with refractory ulcers can also help determine the underlying etiology. Biopsies of gastric ulcers should be performed to exclude an underlying malignancy and other causes of ulceration (eg, Crohn disease, sarcoid, eosinophilic gastroenteritis). If possible, we obtain biopsies from four quadrants of the ulcer. If endoscopic features suspicious for malignancy (eg, nodularity at the edges of the ulcer or infiltration of the surrounding tissue creating a heaped up appearance at the edge of the ulcer), we obtain biopsies using jumbo forceps with more extensive sampling along the edges of the ulcer. In addition, we biopsy the gastric antrum and body for *Helicobacter pylori*. (See "Indications and diagnostic tests for Helicobacter pylori infection in adults", section on 'Endoscopic testing'.)

MANAGEMENT

Address the etiology and risk factors

- **Re-evaluate risk factors** – In patients with refractory ulcers, it is important to reevaluate the underlying etiology and risk factors for peptic ulcer disease. Key elements of the history include the following:

  - Compliance with antisecretory therapy
  - Continued nonsteroidal anti-inflammatory drug (NSAID) use

- Use of medications/substances associated with peptic ulcers or that may impact healing
- Risk factors associated with poor ulcer healing (smoking, co-morbid diseases) (see 'Comorbid diseases' above)

In patients for whom the etiology remains uncertain based on the history and biopsy results from the upper endoscopy that established their diagnosis, selected laboratory testing (fasting serum gastrin and serum calcium levels) may help elucidate the underlying etiology. (See 'Diagnosis' above and "Unusual causes of peptic ulcer disease", section on 'Evaluation of H. pylori and NSAID negative ulcers'.)

- **Eradicate *Helicobacter pylori* (*H. pylori*)** – Most patients with refractory ulceration have *H. pylori.* Eradication of *H. pylori* improves ulcer healing rates in patients with peptic ulcers [7,22-25]. In patients with refractory ulcers who do not have evidence of *H. pylori* on gastric biopsies, we perform immunohistochemistry routinely to confirm the negative result. In patients treated for *H. pylori*, eradication of infection should be confirmed four or more weeks after the completion of therapy. (See "Indications and diagnostic tests for Helicobacter pylori infection in adults", section on 'Confirm eradication in all patients'.)

- **Avoid culprit medications and tobacco** – Patients should be advised to avoid NSAIDs. We also advise cessation of tobacco use given that it affects gastric microcirculation adversely and impairs ulcer healing [26-30]. (See "Peptic ulcer disease: Epidemiology, etiology, and pathogenesis", section on 'Smoking'.)

- **Treat the underlying cause** – Patients with other causes of ulceration (eg, Crohn disease, sarcoidosis) require concurrent treatment to facilitate ulcer healing and prevent recurrence. (See "Unusual causes of peptic ulcer disease", section on 'Etiology'.)

Antisecretory therapy

Twice-daily dosing (eg, omeprazole 20 mg twice daily) is usually effective in inducing healing in patients with ulcers that were refractory to once-daily standard dose proton pump inhibitor (PPI) [3]. After 12 additional weeks of PPI therapy, we perform a repeat upper endoscopy to assess ulcer healing and obtain additional biopsies. Long-term maintenance acid inhibitory therapy (eg, omeprazole 20 mg daily) should be routinely offered to these patients once the ulcer has healed (see 'Repeat upper endoscopy' below). Some experts recommend changing the PPI when the initial treatment fails and a second course is being considered [6].

PPIs are the preferred therapy for refractory ulcer disease. Healing rates for duodenal ulcers, and to a lesser extent gastric ulcers, are associated with the degree of inhibition of acid

secretion [31,32]. In a report of patients with refractory ulcers after three months of histamine-2 receptor antagonist (H2RA) therapy, a 40 mg dose of omeprazole produced better healing than continued standard H2RA (96 versus 57 percent) [33]. With antisecretory therapy with a PPI, >90 percent of refractory ulcers heal with an additional eight weeks of treatment. Potassium competitive acid inhibitors are comparable to PPIs in preventing NSAID-related ulcer disease. Vonoprazan, a potassium competitive acid blocker, has been widely studied in Japan where idiopathic peptic ulcer disease is often refractory to conventional PPI therapy [34]. Vonoprazan may have high healing rates in this population (>80 percent healing), but is not available in many countries [35].

Repeat upper endoscopy — In patients with refractory ulcers, endoscopy should be performed after 12 weeks of additional treatment with a PPI. This endoscopy serves to document ulcer healing.

We biopsy the ulcer scar if the ulcer has healed as some neoplastic ulcers can heal with antisecretory therapy. If the ulcer has not healed, we obtain biopsies from four quadrants of the ulcer ideally using jumbo forceps with more extensive sampling along the edges of the ulcer. In addition, we biopsy the gastric antrum and body for *H. pylori*. (See "Indications and diagnostic tests for Helicobacter pylori infection in adults", section on 'Endoscopic testing'.)

Biopsies for culture and sensitivity should be performed to guide antibiotic therapy in patients with persistent *H. pylori* infection after two courses of antibiotic treatment. (See "Treatment regimens for Helicobacter pylori in adults", section on 'Confirm eradication in all patients'.)

Surgery in selected patients — Surgical management is rarely required and is reserved for the peptic ulcers that fail to heal after twice-daily antisecretory therapy with a PPI for 24 weeks in whom other correctable factors (eg, medication noncompliance, NSAID use, and *H. pylori* infection) have been addressed. Malignancy is rare in duodenal ulcer disease, but surgery may be indicated for chronic nonhealing gastric ulcers as they may harbor a malignancy that is sometimes not detected despite extensive endoscopic biopsy. Indications for surgical management of peptic ulcer disease and surgical treatment options are discussed in detail separately. (See "Surgical management of peptic ulcer disease", section on 'Indications for peptic ulcer surgery'.)

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Peptic ulcer disease".)

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)")
- 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

- A refractory peptic ulcer is defined as an endoscopically proven ulcer greater than 5 mm in diameter that does not heal after 12 weeks of treatment with a proton pump inhibitor (PPI). (See 'Terminology' above.)
- In the absence of continued nonsteroidal anti-inflammatory drug (NSAID) use, acid suppression heals >90 percent of peptic ulcers. However, approximately 5 to 10 percent of ulcers are refractory to 12 weeks of antisecretory therapy with a PPI. Even with continued PPI use, approximately 5 to 30 percent of peptic ulcers recur within the first year. While there are several factors that are associated with refractory gastric/duodenal ulceration, persistent *Helicobacter pylori* (*H. pylori*) infection and NSAID use are the two main causes. (See 'Epidemiology' above.)
- Refractory ulcers are suspected in patients with peptic ulcer disease with persistent or recurrent dyspepsia. They are diagnosed at upper endoscopy performed for evaluation of symptoms or on routine endoscopic surveillance after initial therapy for peptic ulcer

disease. Biopsies of the ulcer to exclude an underlying malignancy and other causes of ulceration (eg, Crohn disease, sarcoid). In addition, we obtain biopsies of the antrum and body to diagnose or ex*clude H. pylori*. In patients with refractory ulcers who do not have eviden*ce of H. pylori* on gastric biopsies, we perform additional testing to confirm the negative result. (See 'Diagnosis' above.)

- Patients with refractory ulcers should be evaluated for continued NSAID use, the use of other medications associated with peptic ulcers, and comorbidities and other factors that may contribute to poor ulcer healing and recurrence. Fasting serum gastrin and total calcium levels should be measured to exclude Zollinger-Ellison syndrome and hyperparathyroidism, respectively. (See 'Epidemiology' above.)

- Patients should be advised to avoid NSAIDs and tobacco. Patients with *H. pylori* should be treated with a goal of eradication of *H. pylori* infection. Eradication of infection should be confirmed after the completion of therapy. (See 'Management' above.)

- In patients with refractory peptic ulcer disease, the mainstay of therapy is additional antisecretory therapy. For patients who fail to respond to standard doses of PPI (eg, omeprazole 40 mg daily), twice-daily dosing is usually effective in inducing healing. We perform a repeat endoscopy to document ulcer healing following 12 additional weeks of PPI therapy. Surgical management is reserved for the gastric ulcers that fail to heal after twice-daily antisecretory therapy with a PPI for 24 weeks in whom other correctable factors (eg, medication noncompliance, NSAID use, and *H. pylori* infection) have been addressed. (See 'Management' above.)

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GRAPHICS

Causes of refractory gastric/duodenal ulcers

Persisting *H. pylori* infection
Poor compliance with treatment
Resistant organism
Inadequate *H. pylori* regimen
Unrecognized *H. pylori* infection:
False negative *H. pylori* testing
Skipped or inadequate testing
Ulcers related to nonsteroidal anti-inflammatory drugs (NSAIDs)
Continued NSAID use
Undiscovered NSAID use
Poor response to co-therapy with a proton pump inhibitor (PPI) or histamine 2 receptor antagonist (H2RA)
Other mechanisms
Impaired healing:
Cigarette smoking
Inadequate inhibition of acid secretion:
Poor compliance with treatment
Pharmacologic resistance or tolerance to H2RAs
Pharmacologic resistance to PPIs
Rapid metabolism (inactivation) of PPIs
Hypersecretory states:
Gastrinoma
Antral G cell hyperfunction
Idiopathic hypersecretory duodenal ulcer
Co-therapies:
Glucocorticoids (especially when given with NSAIDs)
Cytotoxic drugs
Other drugs, such as methamphetamine or cocaine use

Uncommon causes:
Cancer
Crohn disease
Infections other than *H. pylori*
Eosinophilic, inflammatory, infiltrative conditions, mesenteric ischemia

H. pylori: *Helicobacter pylori.*

Graphic 76314 Version 9.0

Causes of recurrent peptic ulcer disease

Persisting *H. pylori* infection
Poor compliance with treatment
Resistant organism
Inadequate *H. pylori* regimen
Unrecognized *H. pylori* infection:
False negative *H. pylori* testing
Skipped or inadequate testing
Ulcers related to nonsteroidal anti-inflammatory drugs (NSAIDs)
Continued NSAID use
Undiscovered NSAID use
Poor response to co-therapy with a proton pump inhibitor (PPI) or histamine 2 receptor antagonist (H2RA)
Other mechanisms
Hypersecretory states:
Gastrinoma
Antral G cell hyperfunction
Idiopathic hypersecretory duodenal ulcer
Co-therapies:
Glucocorticoids (especially when given with NSAIDs)
Cytotoxic drugs
Other drugs, such as methamphetamine or cocaine use
Uncommon causes:
Cancer
Crohn disease
Infections other than *H. pylori*
Eosinophilic, inflammatory, infiltrative conditions

H. pylori: *Helicobacter pylori*.

Graphic 101181 Version 2.0

Contributor Disclosures

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