Etiology, Treatment, and Outcome of Esophageal Ulcers: A 10-Year Experience in an Urban Emergency Hospital

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Esophageal ulcers are a rare cause of upper gastrointestinal bleeding. This report describes the etiology, treatment, complications, and outcome of esophageal ulcers. An esophageal ulcer is defined as a discrete break in the esophageal mucosa with a clearly circumscribed margin; esophageal ulcers were seen in 88 patients from a total of 7564 esophagogastroduodenoscopies done by one surgeon at an urban hospital from 1991 to 2001. All hospital reports were reviewed. The etiology of esophageal ulcers included the following: gastrointestinal reflux disease (GERD) (n = 58, 65.9%), drug induced (n = 20, 22.7%), candidal (n = 3, 3.4%), caustic injury (n = 2, 2.3%), and herpes simplex virus (HSV), human immunodeficiency virus (HIV), marginal ulcer, foreign body, and unknown etiology (n = 1 of each, 1.1%). The mean size of GERD-induced esophageal ulcers and drug-induced esophageal ulcers was 2.78 and 2.92 cm, respectively; 80.3% of GERD-induced esophageal ulcers and 13.8% of drug-induced esophageal ulcers were located in the lower thoracic esophagus. Morbidity (n = 44, 50%) included hemorrhage (n = 30, 34%), esophageal stricture (n = 11, 12.5%), and esophageal perforation (n = 3, 3.4%). Nonoperative therapy sufficed in 81 patients (92%). Three patients (3.4%) had a recurrence of esophageal ulcers. Fifteen patients (17.0%) required endoscopic intervention including esophageal dilatation for stricture in 11 patients and endoscopic hemostasis for esophageal bleeding in four patients. Surgery (n = 7, 8.0%) was reserved for esophageal stricture and perforation. Two patients (2.3%) died from complications of esophageal ulcers: hemorrhage in one and perforation in one. Three patients died of their primary disease. GERD and drug ingestion are common causes of esophageal ulcers. Midesophageal ulcers have a greater tendency to hemorrhage compared with ulcers at the gastroesophageal junction; this may reflect the etiology. Strictures complicate GERD-induced esophageal ulcers but not drug-induced esophageal ulcers. Esophageal dilatation is an effective treatment for most strictures associated with esophageal ulcers. Esophageal ulcers rarely cause death. (J GASTROINTEST SURG 2003;7:836–842)

KEY WORDS: Esophageal ulcers, etiology, treatment outcome

Esophageal ulcers most commonly occur as a result of gastroesophageal reflux disease (GERD) with a reported prevalence of 2% to 7%.[1,2] Because of the rarity of these ulcers, there is little comprehensive literature regarding etiology and clinical course. Tileston,[3] in 1906, identified the causes of esophageal ulcers—namely, peptic ulcer disease, carcinoma, corrosive substances, foreign body, infectious disease, aneurysm, catarrhal, traction diverticula, tuberculosis, syphilis, esophageal varices, and thrush. Since then, the etiology has changed reflecting differences in demographics, diagnostic modalities, and therapeutic interventions. Esophageal ulcers secondary to nonsteroidal anti-inflammatory drugs (NSAIDs), antibiotics, radiation therapy, Crohn's disease, and dermatologic diseases have also been reported.[1,2] More recently esophageal ulcers due to cytomegalovirus, herpes simplex virus, and human immunodeficiency virus have become more prevalent.[2,4,5] This report defines the incidence, etiology, treatment, and outcome of esophageal ulcers seen in a large urban medical center.

Presented at the Forty-Fourth Annual Meeting of The Society for Surgery of the Alimentary Tract, Orlando, Florida, May 18–21, 2003 (poster presentation).
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1091-255X/03/$—see front matter
doi:10.1016/S1091-255X(03)00138-0

METHODS

This study was performed at Detroit Receiving Hospital, a large urban teaching emergency trauma hospital. Review of 7564 consecutive esophagogastroduodenoscopies (EGDs) performed by a single surgical endoscopist from August 1991 to June 2001 identified 88 patients (1.2%) with esophageal ulcers. The records of all of these patients were reviewed. All 88 of these patients were part of a subgroup of 3520 patients who had endoscopically diagnosed esophagitis. Esophageal ulcer was defined as a discrete break in the esophageal mucosa with a clearly identifiable margin. The term erosion refers to a superficial lesion that remains confined to the lamina propria and muscularis mucosae. In contrast, necrosis, hemorrhage, and inflammation associated with ulcers extend deeper into the underlying submucosa or muscularis propria. Erosions or ulcers may appear isolated or confluent, and they commonly coexist with one another.[6] The etiology of esophageal ulcers was ascertained from clinical, endoscopic, and pathologic findings. Data recorded included: history of caustic ingestion, location of the ulcer, morphology of the ulcer, previous EGD findings and pictures, concurrent EGD findings and pictures, and comorbid conditions. Biopsy specimens were obtained from both the center and the margin of the ulcer. EGD examinations were performed with Olympus flexible video endoscopes. Esophageal ulcers after sclerotherapy and those associated with esophageal malignancy were excluded from this analysis.

RESULTS

Patient Profile

Of the 88 patients with esophageal ulcers, 56 were men (63.6%), and 32 were women (36.4%) with a mean age of 56.4 years (±16 years standard deviation [SD]). Comorbid conditions included: hypertension (n = 33, 37.5%), diabetes mellitus (n = 18, 20.5%), central nervous system disorders such as cerebrovascular accident and head trauma (n = 16, 18.2%), peptic ulcer disease including four patients with gastric ulcers, three patients with duodenal ulcers, and one patient with both gastric and duodenal ulcers (n = 8, 9.1%), congestive heart failure (n = 8, 9.1%), cirrhosis (n = 6, 6.8%), pneumonia (n = 5, 5.7%), asthma (n = 5, 5.7%), recurrent episodes of acute pancreatitis (n = 5, 5.7%), and renal failure (n = 4, 4.5%). Eight patients (9.1%) were bedridden. A history of chronic, moderate, daily drinking or heavy (more than 8 ounces of alcohol per day) alcohol consumption was given in 40 patients (45.5%), and recent heavy alcohol consumption within 24 hours of admission occurred in 32 patients (36.4%); 35 patients (39.8%) smoked cigarettes daily or used illicit street drugs such as cocaine or heroin mix daily (n = 4, 4.5%). Nonsteroidal anti-inflammatory agents or clycooxygenase-2 (COX-2) inhibitors had been recently used in 28 patients (31.8%). H_2 blockers or proton pump inhibitors had been used recently in 20 patients (22.7%).

Most patients (79, 89.8%) were initially seen in the emergency room for evaluation. Esophageal ulcers were found in 79 patients during the initial EGD. The esophageal ulcers in the remaining nine patients developed in the hospital while these patients were being treated for another condition. The duration of symptoms was less than 3 days in 43 patients, and more than 10 days in 20 patients. These signs and symptoms included the following: hematemesis (n = 36, 40.9%), nausea and vomiting with regurgitation (n = 35, 39.8%), epigastric (with or without substernal) pain (n = 27, 30.7%), melena (n = 22, 25%), dysphagia to solids (n = 16, 18.2%), "coffee ground" gastric aspirate (n = 15, 17.0%), and chest pain that was substernal with extension to the back (n = 10, 11.4%). The chest pain was thought to be a manifestation of heartburn due to regurgitation. Esophageal ulcers were found on the first endoscopic assessment in 79 patients, whereas esophageal ulcers were first seen on a follow-up endoscopy in nine patients. Most patients (n = 74, 84.1%) required in-hospital treatment at the time of the initial diagnostic EGD. Eight patients (9.1%) required repeat EGD evaluation for esophageal ulcers or their complications after discharge.

Etiology of Esophageal Ulcers

The etiology of esophageal ulcers (Table 1) was most commonly associated with GERD (n = 58). All patients with esophageal ulcers caused by GERD had a

Table 1. Etiology of esophageal ulcers

Etiology	No. of patients	%
GERD	58	65.9
Drug-induced	20	22.7
Candida	3	3.4
Caustic injury	2	2.3
AIDS	1	1.1
Herpes simplex virus	1	1.1
Marginal	1	1.1
Foreign body	1	1.1
Unknown	1	1.1
Total	88	100

GERD = gastrointestinal reflux disease; AIDS = acquired immune deficiency syndrome.

definite hiatal hernia. Hiatal hernia was diagnosed endoscopically when the squamocolumnar junction was more than 3 cm above the diaphragmatic impression.[7] In moderate-sized or large hiatal hernias, the gastric mucosal folds can be seen running proximally over the hiatal margin into the bulbous cavity of the distended hernia pouch. A hiatal hernia is also confirmed based on a retroflexed endoscopic view of the hernia pouch and the squamocolumnar junction from below.[7] All 58 patients with ulcer associated with hiatal hernia had moderate-sized or large hiatal hernias. The endoscopic grading of GERD depends on the endoscopist's interpretation of these visual images. Unfortunately there is no standard classification scheme for endoscopic findings.[7] Several classification systems have been devised to define or grade reflux changes by using characteristics seen at endoscopy. All 58 patients had grade III or IV esophagitis according to the Savary-Miller endoscopic grading system,[7,8] and also grade III or IV esophagitis according to the system devised by Hetzel et al.[7,8] Barrett's esophagus complicated GERD-induced esophageal ulcers in 10 patients and drug-induced esophageal ulcers in one patient. Other etiologies included drug-induced (n = 20), candidal (n = 3), and caustic injury (n = 2), in addition to acute human immunodeficiency virus (HIV), herpes simplex virus (HSV), marginal, foreign body, and obscure origin (n = 1 case of each). The offending medications of drug-induced esophageal ulcers included aspirin, ibuprophen, aspirin plus ibuprophen, ferrous sulfate, doxycycline, erythromycin, amoxicillin clavulanate, nifedipine, and cyclobenzaprine (Table 2).

Morphology of GERD-Induced and Drug-Induced Esophageal Ulcers

The mean size of all esophageal ulcers, GERD-induced esophageal ulcers, and drug-induced esophageal ulcers was 2.80 cm, 2.78 cm, and 2.92 cm, respectively (Table 3). Size was measured with the use of open biopsy forceps. The mean number of all esophageal ulcers, GERD-induced esophageal ulcers, and drug-induced esophageal ulcers was 2.48, 1.96, and 2.80, respectively (see Table 3). Most (91.4%) of the GERD-induced esophageal ulcers were located in the lower intrathoracic esophagus (35 to 40 cm from the incisors), whereas 80.0% of drug-induced esophageal ulcers were located in the middle intrathoracic esophagus (28 to 33 cm from the incisors).

Table 2. Drug-induced esophageal ulcers

Drug implicated	No.	%
NSAIDs	13	65
Aspirin only	7	35
Ibuprophen only	3	15
Aspirin + ibuprophen	3	15
Ferrous sulfate	2	10
Doxycycline	1	5
Erythromycin	1	5
Amoxicillin, clavulanate	1	5
Nifedipine	1	5
Cyclobenzaprine	1	5
Total	20	100

Table 3. Endoscopic morphology of esophageal ulcers

	GERD	Drug
Location		
Upper third	2 (3.4%)	9 (4.9%)
Middle third	11 (19.0%)	16 (80.0%)
Lower third	53 (91.4%)	4 (20.0%)
Total	66	29
Size		
Minimum	0.6 cm	0.6 cm
Maximum	10.0 cm	6.0 cm
Mean ± SD	2.78 cm ± 2.13	2.92 cm ± 1.98
Number		
Minimum	1	1
Maximum	12	16
Mean ± SD	1.96 ± 2.12	2.80 ± 4.19

SD = standard deviation.

Esophageal Ulcers: Inpatients

In-hospital esophageal ulcers developed in nine inpatients; this was due to GERD (n = 6), drugs (n = 1), Candida (n = 1), and AIDS (n = 1). Of the six patients with GERD, one had liver cirrhosis and five were bedridden because of a cerebral vascular occlusion (n = 4) or a right femoral neck fracture (n = 1). Concurrent diagnoses included pneumonia, decubitus ulcer, gas gangrene, seizure disorder and weakness, retroperitoneal mass, and tuberculosis peritonitis. Three patients died of primary disease, multisystem organ failure, and sepsis.

Esophageal Strictures

Eleven patients developed an esophageal stricture including 10 patients with GERD-induced esophageal ulcers and one of two patients with caustic injury. All esophageal strictures developed at the squamocolumnar junction on the distal esophagus and were associated with a hiatal hernia. Endoscopic dilatation was performed in all 11 of them; three patients underwent multiple endoscopic dilatations. Nissen fundoplication had been performed in four patients with esophageal stricture. Esophagectomy with colonic interposition was performed in one patient with caustic

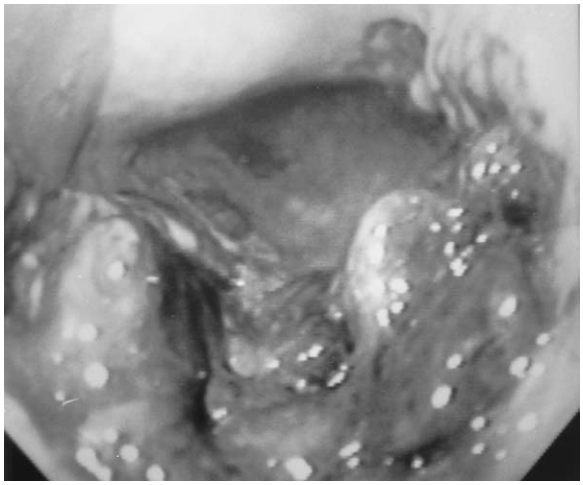

Fig. 1. A large ulcer with clot on the base is seen at midesophagus (25–30 cm from incisors). This patient had been taking 8–10 tablets of aspirin and Anacin daily for 3 weeks to treat her abdominal and chest pain. She chewed some pills before hematemesis. She did not have hiatal hernia or GERD.

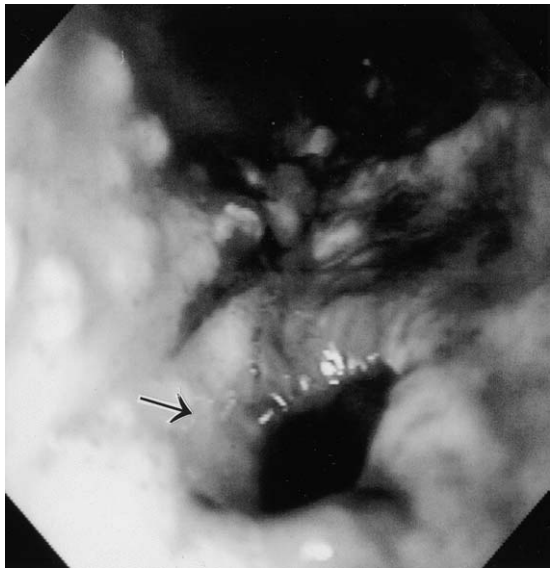

Fig. 2. A GERD-induced diffuse esophageal ulcer with perforation (see arrow).

injury. There were no complications related to dilatation. All five patients survived operative intervention.

Hemorrhage

Hemorrhage from esophageal ulcers was diagnosed by EGD in 30 patients including 17 with GERD, 10 with drug-induced esophageal ulcers (Fig. 1), and one patient each with HSV, idiopathic esophageal ulcers with HIV, and esophageal ulcers of unknown etiology. Twenty-one patients required blood transfusion including nine patients with GERD, nine patients with drug-induced esophageal ulcers, and one patient each with HSV, idiopathic esophageal ulcers of HIV, and esophageal ulcers of obscure origin. The mean amount of blood transfused was 5.38 ± 3.43 units (range 2 to 14 units). This included an average of 3.62 units in patients with GERD and 6.28 units in patients with drug-induced esophageal ulcers. Endoscopic hemostasis with epinephrine injection and heater probe application was required in three patients with drug-induced esophageal ulcers and in one patient with esophageal ulcers of unknown etiology. Endoscopic hemostasis was not necessary for bleeding from GERD-induced esophageal ulcers. No operative intervention was undertaken for esophageal bleeding secondary to esophageal ulcers.

Esophageal Perforation

Esophageal perforation occurred in three patients resulting in two deaths. One patient developed upper gastrointestinal bleeding 3 days after operative fixation of a right femoral neck fracture. EGD revealed GERD-induced diffuse esophageal ulcers and a 2×2 cm gastric polyp. A repeat EGD done 10 days later for recurrent bleeding showed esophageal perforation from the ulcer (Fig. 2). Emergency operation included cervical esophagostomy, gastrostomy, and feeding jejunostomy. This patient died of sepsis 3 weeks later. A second patient with drug-induced esophageal ulcers and an aneurysm of the thoracic aorta developed an esophagoaortic fistula and died rapidly from massive hemorrhage and aspiration. A third patient with GERD-induced esophageal ulcers diagnosed 3 months earlier was noncompliant with H_2 blocker therapy and developed a distal esophageal perforation, which was treated with segmental resection of the esophageal perforation, esophageal exclusion, cervical esophagostomy, feeding jejunostomy, and decompressive gastrostomy. The patient was discharged to a rehabilitation institute and eventually underwent esophageal reconstruction.

Multiple Presentations to the Hospital

One patient, a 63-year-old woman, was found to have drug (ibuprophen)–induced esophageal ulcers in the midesophagus with a moderate-sized hiatal hernia without GERD in 1991. Seven years later, at age 70, she developed GERD-induced esophageal ulcers with stricture at the squamocolumnar junction and a larger hiatal hernia than that previously seen. Another patient, a 41-year-old man with AIDS, presented with chest pain and melena and was diagnosed with an idiopathic esophageal ulcer in 1996. Three years later,

during hospitalization for AIDS encephalitis complicated by seizures, he developed coffee ground emesis and was diagnosed again with idiopathic esophageal ulcers. A third patient, 48 years of age, had been admitted for hematemesis in 1996 and was readmitted because of hematemesis 6 months later, despite taking proton pump inhibitors, and underwent a Nissen fundoplication. Four patients underwent multiple esophageal dilatations for esophageal stricture with esophageal ulcers; three were caused by GERD and one was due to caustic injury.

Treatment of Uncomplicated Esophageal Ulcers

Patients with uncomplicated esophageal ulcers were treated with H_2 blockers, proton pump inhibitors, or antifungal medication in the case of candidal esophageal ulcers. The mean length of stay for patients with uncomplicated esophageal ulcers (n = 50) was 6.08 ± 6.37 days (range 1 to 38 days). Endoscopically confirmed resolution of esophageal ulcers was seen in five patients with a mean resolution time of 49.8 days (range 4 to 150 days). This occurred in two patients with GERD-induced esophageal ulcers, two patients with drug-induced esophageal ulcers, and one patient with esophageal ulcers of unknown etiology. Long follow-up of these patients were not possible unless they returned to Detroit Receiving Hospital. Some patients with intractable esophageal ulcers or GERD may have had elective surgery at other hospitals.

Coexistent EGD Findings Associated With Esophageal Ulcers

Significant coexistent findings on EGD were noted in 50 (57%) of 88 patients with esophageal ulcers; these included: acute erosive gastritis (n = 29), doudenitis (n = 14), acute gastric ulcers (n = 12), and duodenal ulcers (n = 11). *Helicobacter pylori* testing was positive in 18 of 28 patients tested. Barrett's esophagus complicated GERD–induced esophageal ulcers in 10 patients and drug-induced esophageal ulcers in one patient. This latter patient developed a midesophageal ulcer surrounded by normal mucosa and had a strong history of NSAID use.

DISCUSSION

The EGD diagnosis of esophageal ulcers is rare; they were present in only 88 (1.2%) of 7564 patients undergoing upper endoscopic evaluation. The most common cause of esophageal ulcers in this series was GERD; esophageal ulcers complicated GERD in 2.5% (88 of 3520) of patients with endoscopically diagnosed esophagitis. The reported rate of esophageal ulcers in patients with esophagitis ranges from 2% to 7%.[2] All patients with GERD-induced esophageal ulcers will have esophagitis at the squamocolumnar junction.[9] Esophageal ulcers with no abnormality at the squamocolumnar juction are likely the result of a neoplasm because benign solitary esophageal ulcers related to acid reflux do not occur in normal squamous epithelium.[9]

The incidence of drug-induced esophageal ulcers has not been reported. Esophageal injury results from mucosal contact with the offending agent, thus the danger of administering known irritating agents by mouth to the bedridden patient.[10] Tablets and capsules may adhere to the esophageal wall and dissolve locally within the normal esophagus.[11–13] The characteristic appearance of NSAID-induced esophageal ulcers consists of large, shallow, discrete ulcers in the midesophagus near the aortic arch surrounded by normal mucosa.[10,12]

Differentiation between distal drug-induced esophageal ulcers and GERD-induced esophageal ulcers can be difficult. Patients with drug-induced esophageal ulcers may be more prone to develop GERD as a result of disorders of esophageal motility caused by the drug-induced esophageal ulcers. Five of 13 patients herein with NSAID-induced esophageal ulcers demonstrated GERD. One patient with a large NSAID-induced bleeding esophageal ulcer in the midesophagus developed a GERD-induced esophageal ulcer with esophageal stricture in the distal esophagus 7 years later. Possibly, drug-induced esophageal injuries are aggravated by GERD, and GERD-induced esophageal injuries progress with certain drugs.[14]

Complications of esophageal ulcers relate to etiology and include stricture, hemorrhage, and perforation. Esophageal stricture complicating GERD has been reported to occur in 4% to 20% of patients with GERD.[1,15] Esophageal stricture may occur in 2.6% to 7.0% of patients with NSAID-induced esophageal injury.[12,16] None of the patients in our study who developed stricture after drug-induced esophageal ulcers. Ten of the 11 patients diagnosed with stricture in this study had GERD-induced esophageal ulcers.

The reported rate of esophageal bleeding from GERD- and NSAID-induced esophageal injury is less than 2% and 30.1%, respectively.[2,16] Silverstein et al.[17] reported 1.7% of acute upper gastrointestinal hemorrhage is due to esophageal ulcers. The present study noted bleeding in 17 (29.3%) of 58 patients with GERD-induced esophageal ulcers and in 10 (50%) of 20 patients with drug-induced esophageal ulcers. Active bleeding of esophageal ulcers during EGD

was noted in 13.8% of patients with GERD-induced esophageal ulcers and in 45.0% of patients with drug-induced esophageal ulcers. Bleeding from drug-induced esophageal ulcers is always from the midesophagus and is more likely to be active bleeding than GERD-related bleeding (45.0% vs. 13.8%); patients with this bleeding require blood transfusions (45.0% vs. 13.8%) and endoscopic hemostasis (15.0% vs. 0%).

Anatomically there is a rich arterial and venous network at the level of the mucosa and submucosa throughout the esophagus, especially near the gastroesophageal junction.[18] Thus the bleeding tendency associated with drug-induced esophageal ulcers seems to be determined by factors other than vascular anatomy. Superficial ulceration of the squamous epithelium is typical of reflux esophagitis.[19] In some patients with GERD-induced esophageal ulcers, esophageal ulceration stimulates fibrous tissue production with collagen deposition and stricture formation.[1] The chronic nature of GERD, which is due to intermittent regurgitation of acid, may reduce the bleeding tendency of the epithelium lining the gastroesophageal junction. In contrast, the acute nature of drug-induced esophageal ulcers resulting from continuous contact of a caustic agent with previously normal mucosa may increase the bleeding tendency, particularly with NSAID-induced esophageal ulcers.[10]

NSAIDs are strikingly more likely to cause hemorrhage than other pill classes when they injure the esophagus.[10,16] Kikendall[16] noted that 22 of 154 NSAID-induced esophageal injuries were complicated by hemorrhage. In contrast, only 25 of 796 esophageal injuries induced by other medications resulted in hemorrhage. Furthermore, 8 of 19 esophageal injuries induced by aspirin were complicated by hemorrhage, compared to only one of five esophageal injuries caused by ibuprophen.[16]

The reported rate of esophageal perforation complicating GERD is less than 0.2%.[2] The rate of perforation of GERD-induced esophageal ulcers has not been previously reported. In the present study, two patients with perforation were seen in 58 patients with GERD induced esophageal ulcers (5.1%). In a review of 22 esophageal perforations reported by Nesbitt and Sawyers,[20] the etiology was barogenic transmural disruption (Boerhaave's syndrome) in 20 patients and distal esophageal ulcers in two.

No perforation complicated the 154 NSAID-induced esophageal injuries identified in Kikendall's series.[16] One of our patients subsequently died of hemorrhage from an aortoesophageal fistula through an underlying thoracic aortic aneurysm; this patient had been taking aspirin and ibuprophen for 2 years.

Approximately 70% of patients with GERD-induced esophageal ulcers show complete healing within several months with H_2 receptor–blocking agents administered in conventional doses.[1] Most ulcerations refractory to conventional treatment will heal with the intensive suppression of gastric acid secretion achieved by administering high doses of H_2 receptor–blocking agents or proton pump inhibitors.[1] The role of antireflux surgery in the treatment of esophageal ulcers is limited to those few patients with GERD-induced esophageal ulcers refractory to high-dose medical therapy.

The clinical course of hospitalized patients who develop esophageal ulcers is unique. The development of esophageal ulcers is influenced by organ failure, recumbency, and underlying disease. Five of the nine patients who developed esophageal ulcers while hospitalized for other diagnoses had an infectious process including pneumonia, decubitus ulceration, gas gangrene, infected retroperitoneal mass, and tuberculous peritonitis. Three of these five patients died of sepsis or multiple organ failure. Likewise, the patient who died after fixation of a right femoral neck fracture developed upper gastrointestinal bleeding from GERD-induced esophageal ulcers and a later perforation that caused his death.

CONCLUSION

GERD and drug ingestion are the most common causes of esophageal ulcers. Midesophageal ulcers caused by NSAIDs have a greater tendency toward hemorrhage that requires blood transfusion and endoscopic hemostasis. Stricture formation is very likely with GERD-induced esophageal ulcers and is effectively treated with dilatation in most patients. Esophageal ulcers rarely cause death.

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