Upper endoscopy and basic procedural interventions

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Abstract: Upper endoscopy [esophagogastroduodenoscopy (EGD)] is one of the most common procedures performed by general surgeons and gastroenterologists. The list of indications for EGD is perpetually growing while few absolute contraindications exist. EGD is the only modality to allow direct visualization of the upper gastrointestinal tract with the added ability of obtaining a tissue biopsy and performing a variety of interventions. Completion of an EGD requires the fulfillment of several steps, including adequate pre-procedural preparation of the patient, preparation of the supporting staff and the procedure suite, a comprehensive endoscopic examination, and a detailed documentation. Indications, patient preparation and common EGD findings and their associated interventions are discussed in this article.

Keywords: Esophagogastroduodenoscopy (EGD); GERD; esophagitis; Barrett's esophagus (BE); hiatal hernia

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Learning objectives:
(I) applications of upper endoscopy [esophagogastroduodenoscopy (EGD)];
(II) indications for diagnostic EGD;
(III) pre-procedural preparation;
(IV) common findings and basic interventions of EGD;
(V) documentation of EGD.

Since it was first performed in the 1950s, EGD has been established as the primary modality for the diagnosis and treatment of many upper gastrointestinal conditions. An estimated 6.9 million EGDs were performed in 2009 with an estimated cost of $12.3 billion dollar (1). The practical use of the endoscope has expanded greatly over the past two decades. Patient preparation, procedural sedation and endoscopic equipment have become more standardized over the years. This has made it increasingly valuable to the general surgeon.

The indications for performing an EGD are numerous and the list continues to grow as more clinical applications are established through the development of new accessories and equipment for the flexible endoscope. The surgical endoscopist can not only perform a thorough mucosal evaluation but can also perform adequate tissue sampling, sclerotherapy, clipping for the control bleeding or for the closure of mucosal or full thickness defects, management of luminal obstructions and enteral access procedures. Surgical endoscopists also perform a variety of other advanced procedures including minimally invasive tumor resection via endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) (2). The flexible endoscope also allows us to treat surgical conditions that in the past were only achieved by a transabdominal or laparoscopic approach. These include per oral esophageal myotomy (POEM) for the treatment of achalasia and per oral pyloromyotomy (POP) for the treatment of adult onset pyloric stenosis and idiopathic refractory gastroparesis. Endoscopic suturing in the creation of an endoscopic sleeve gastroplasty as well and the endoscopic introduction of different gastric balloons have also been adopted by bariatric surgeons as options to patients who require less drastic weight loss, want to avoid surgery, or are poor surgical candidates (3). Mucosal ablation for Barrett’s esophagus
Table 1: Management of anticoagulants and antithrombotics during elective endoscopy

<table>
<thead>
<tr>
<th>CV risk</th>
<th>Bleeding risk</th>
<th>High risk</th>
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<tbody>
<tr>
<td>Low risk</td>
<td>(I) Continue warfarin, NOAC;</td>
<td>(I) Discontinue Warfarin, NOAC;</td>
</tr>
<tr>
<td></td>
<td>(II) Continue ASA/NSAIDs;</td>
<td>(II) Restart Warfarin day of procedure and NOAC when appropriate;</td>
</tr>
<tr>
<td></td>
<td>(III) Continue Thienopyridines</td>
<td>(III) Continue ASA/NSAIDs, hold thienopyridines 5 days/switch to ASA</td>
</tr>
<tr>
<td>High risk</td>
<td>(I) Continue warfarin, NOAC;</td>
<td>(I) Discontinue Warfarin, NOAC—Bridge therapy;</td>
</tr>
<tr>
<td></td>
<td>(II) Continue ASA/NSAIDs;</td>
<td>(II) Restart Warfarin day of procedure and NOAC when appropriate;</td>
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<tr>
<td></td>
<td>(III) Continue Thienopyridines</td>
<td>(III) Continue ASA/NSAIDs, hold thienopyridines 5 days/switch to ASA</td>
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NOAC, novel oral anticoagulant; ASA, Aspirin; NSAID, non-steroidal anti-inflammatory drug.

(BE) with BarrX (4), and endoscopic antireflux procedures by way of transoral incisionless fundoplication (TIF) (5) and the Stretta procedure (6) are also well established. This discussion will however focus on the indications, procedural preparation, and common EGD findings and associated interventions.

As the only modality to allow direct visualization of the upper gastrointestinal tract and obtain a tissue biopsy, EGD is routinely used as a primary tool to evaluate patients with suspected or established foregut pathology. The indications of performing a diagnostic EGD include but are not limited to the evaluation of chronic abdominal pain, dysphagia, reflux disease, anemia or to diagnose acute upper gastrointestinal bleeding, neoplasms, ulcers and a host of other foregut pathologies. There are few contraindications to EGD; namely functional symptoms whose courses will not be altered by EGD, bowel obstruction, coagulopathy, and some non-specific, asymptomatic radiographic findings.

Patient evaluation and preparation prior to any endoscopy is of utmost importance. Adequate preparation will help promote a better patient experience and will enhance the quality of the exam. Every patient should have a thorough history and physical exam to determine basic fitness and ability to undergo endoscopy in a way that will minimize adverse outcomes and complications. Several elements of the patient’s comprehensive history and physical exam will allow the endoscopist and anesthesiologist to make adequate preparations before the procedure. A review of the patient’s past medical history will reveal any potentially prohibitive cardiovascular or pulmonary disease. This will also account for obesity, obstructive sleep apnea and previously diagnosed upper gastrointestinal conditions that may affect the type of sedation, airway integrity and the technical aspects of the exam. These include esophageal strictures, diverticula, achalasia with a sigmoid esophagus, esophageal foreign bodies and prior caustic injury or radiation exposure. The past surgical history will reveal any prior neck, cervical spine, jaw, throat surgeries and any possible altered alimentary tract anatomy. A review of medications is crucial as it is important to be aware of any medications that may interact with sedatives and analgesics used during the procedure. The same goes for the patient’s social history and any ongoing substance abuse. Anticoagulants should be held for the appropriate recommended duration (Table 1) (7). Note that most diagnostic EGDs can be safely completed without stopping anticoagulants. This includes procedures with basic tissue removal with biopsy forceps. Procedures requiring advanced tissues removal (large polypectomy, EMR, ESD) however have a higher of bleeding. The patient should be made NPO prior to the procedure according to the ASGE guidelines (8). Appropriate prophylactic antibiotics should be administered depending on the procedure to be performed and the patient’s medical history (9-11). Finally, an informed consent should be obtained after a thorough discussion with the patient or their proxy regarding the risks and benefits of the procedure.

The risk of adverse events during diagnostic EGD is low and complications are rare however the risk is not zero. The most common complications—up to 60%—are anesthesia related from cardiac and respiratory suppression. These occur between 1 in 170 and 1 in 10,000 cases. Those related to the endoscopy include aspiration pneumonia, bleeding, infection, perforation and implant migration or impaction leading to injury (12). Clinically significant bleeding is exceedingly rare even in the thrombocytopenic or coagulopathic patients with endoscopic biopsy being safe in patients with platelet counts >20,000. Transient bacteremia is thought to occur in up to 8% of patients but is mostly asymptomatic. In large prospective studies, perforation occurs between 1 in 2,500 and 1 in 11,000 with an associated mortality rate between 2% and 36%.
The endoscopist can take several steps to limit those complications to a minimum. The patient is kept NPO prior to EGD to decrease the amount of stomach content during anesthesia and instrumentation and decrease the risk of aspiration. The patient is kept off anticoagulants, when appropriate, to decrease the risk of bleeding. Antibiotics are administered when necessary to decrease the risk of bacterial translocation. Specific maneuvers or patient positioning as well as adjuncts to endoscopy, including fluoroscopy, can be employed throughout the procedure to minimize the risk of perforation, implant malposition or migration.

Preparation of the staff and the procedure room is equally important to ensure a seamless procedure and increase the chances of achieving the expected outcome of the procedure (13). Credentialing for sedation is hospital-specific and some institutions require that all sedation be administered by an anesthesia provider. At a minimum, ACLS certification is required. Our institution requires ACLS, BLS, as well as a hospital-administered cognitive exam prior to credentialing. Anesthesia-administered sedation provides the advantage of an otherwise unoccupied provider dedicated to the airway and cardiopulmonary assessment of the patient during the procedure. A review of 1.38 million procedures comparing anesthesia-directed vs. endoscopist-directed sedation suggested that use of anesthesia professionals during endoscopy had no apparent safety benefits in colonoscopy and may be related to more serious adverse events in ASA class I-III patients undergoing EGD (14). Thus, personal preference should ultimately guide the choice of sedation. In the case of endoscopist-administered sedation, the provider should have a discussion with the staff to verify that a suitable dose of medication, IV fluids and resuscitative equipment are available in the room prior to the start of the procedure. Verification of the availability of a working pulse oximeter, sphygmomanometer and heart rhythm monitors is essential. In the case of sedation by an anesthesia provider, the endoscopist should have a discussion with the anesthesia staff regarding the anticipated procedure including depth and duration of sedation, need for endotracheal intubation as would be appropriate for complete esophageal impaction or achalasia with megaesophagus. The endoscopist should also verify at this time that any equipment specific to the procedure, i.e., biopsy forceps, snares, baskets, clips, sclerotherapy needles, stents, etc. are available.

For a diagnostic EGD, the patient is typically placed in the left lateral decubitus position with the head slightly elevated or on a pillow (15). Patients can however be scoped in a supine reverse Trendelenburg position intraoperatively during a foregut/bariatric procedure, or during the establishment of feeding access requiring unrestricted access to the anterior abdominal wall. A mouth-piece or bite block is placed in the patient's mouth. The endoscopist will thoroughly test the scope ensure that all its functions are working properly. The small wheel is then placed in the neutral position and locked with the corresponding knob. The corresponding monitor is checked for adequate video transfer and quality. The patient’s information is verified, and a time-out is called. The time-out is a pause just prior to the start of the procedure where a checklist is followed to help prevent errors from occurring. This has become the standard in most places around the world as it helps prevent wrong site surgery or wrong endoscopic procedure, overdose of medication, patient misidentification and misplacement of implantable devices among other errors. The checklist follows a sequence of verifying the patient’s identity; followed by confirming the indication for the procedure and the consent. Next, any relevant comorbidities and factors affecting the procedure should be voiced, including any anticoagulants the patient may be taking and any antibiotics required for the procedure. Lastly, the equipment is noted to be in working condition and the availability of any other necessary equipment required for the procedure is confirmed (16). The scope is then inserted in the patient’s mouth and the procedure is performed.

Quality indicators for EGD suggest that the endoscopist should visualize all surfaces from the upper esophageal sphincter to the second portion of the duodenum. This would thus include evacuation of current stomach content to examine the entire mucosa as in the case of active upper gastrointestinal bleeding and the presence of clot (17). Once the upper endoscope is inserted into the patient’s mouth, the endoscopist should proceed with a controlled passage under direct visualization through the oropharynx. Careful inspection of the oropharynx and hypopharynx during esophageal intubation will not only decrease patient discomfort and the rate of tracheal intubation but will also aid in the identification of upper esophageal pathology. Common landmarks identified include base of tongue, palate, uvula, epiglottis, arytenoid cartilages and upper esophageal sphincter.

Beyond the upper esophageal sphincter, the lumen is distented with constant insufflation and a global survey of the esophagus is performed to rule out any mucosal
Table 2 The Los Angeles classification for esophagitis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
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<tr>
<td>Grade A</td>
<td>One (or more) mucosal break no longer than 5 mm, that does not extend between the tops two mucosal folds</td>
</tr>
<tr>
<td>Grade B</td>
<td>One (or more) mucosal break more than 5 mm long, that does not extend between the tops two mucosal folds</td>
</tr>
<tr>
<td>Grade C</td>
<td>One (or more) mucosal break that is continuous between the tops of two or more mucosal folds, but which involves less than 75% of the circumference</td>
</tr>
<tr>
<td>Grade D</td>
<td>One (or more) mucosal break which involves at least 75% of the esophageal circumference</td>
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abnormalities including fungal or reflux esophagitis, mucosal tears, ulcerations, webs, Schatzki’s rings or strictures and mucosal/submucosal lesions. Other pertinent findings include diverticula, varices, hiatal hernia and BE. Photo-documentation of a bird’s eye view of the esophagus and then of the Z line are obtained. The location of the Z line from the incisors is measured and noted.

Findings in the esophagus should be managed with the appropriate procedural intervention. Esophagitis could be due to a variety of etiologies including infectious causes (candida, virus, tuberculosis), reflux, radiation and chemotherapy, eosinophilic causes and lastly, pills or other indwelling devices such as a nasogastric tube. The endoscopist should be familiar with the general types and classifications of esophagitis and the basic management and treatment plans. Mucosal samples should be obtained with biopsy forceps and sent to permanent pathology or culture to determine further treatment. For example, in the setting of a patient with suspected candida esophagitis, biopsies are sent to the lab for culture and subsequent antifungal treatment. Many classifications have been described for reflux esophagitis. Familiarity with one of those is important in documenting the extent of reflux and to monitor the evolution on subsequent EGDs. The Los Angeles Classification is a popular system with simple and well described findings (Table 2) (18). Patients should undergo repeat endoscopy after 8–12 weeks of PPI treatment in moderate to severe esophagitis.

BE is believed to be present in up to 15% of high-risk patients with chronic GERD symptoms undergoing EGD (19). There appears to be a correlation between the length of mucosal involvement and the risk of progression to dysplasia and cancer (20). The length of the Salmon-colored mucosa of BE should therefore be adequately documented. The Prague Classification is a proven system that assists in documenting the longitudinal and circumferential extent of BE. It uses Maximal (M) and Circumferential (C) attributes to designate the distance between the top of the gastric folds to the most proximal extent of a longitudinal tongue and circumferential BE respectively (17,21). The endoscopist will perform four quadrant biopsies every 1–2 cm according to the American College of Gastroenterology (ACG) guidelines to minimize sampling error and missed dysplasia (22). It is also important to clearly identify and note the endoscopic landmark during EGD as intestinal metaplasia of the Z line may occur in chronic GERD and does not put patient’s at higher risk of developing cancer. However, extension of columnar epithelium above the Z line should be adequately sampled for the presence of goblet cells, which confirms the diagnosis of BE. The pathologist will comment on the presence and grade of dysplasia, which will determine the surveillance intervals. Recommended surveillance intervals are 3–5 years for BE without dysplasia, 1 year for low grade dysplasia and 3–6 months with high grade dysplasia. High grade dysplasia also warrants further endoscopic procedures including radiofrequency ablation and/or EMR for nodular disease. Patients who have progressed to esophageal adenocarcinoma will require EMR or esophagectomy depending on the level of mucosal involvement (23).

Other disorders of the esophagus can be managed during EGD with basic procedural interventions. Esophageal strictures can occur as a result of prior esophageal surgery or resection, chronic GERD and other esophageal mucosal events from exposure to caustic material. Those strictures can be dilated with “through the scope” (TTS) controlled radial expansion (CRE) balloon dilators under direct visualization; or with partially blind dilation using Savary, Maloney or Hurst dilators with endoscopic assistance. Endoscopic pneumatic dilation (EPD) and botulinum toxin (Botox) injection have also become widely used as the treatment of choice in the patient with achalasia and failed relaxation of the lower esophageal sphincter. A recent meta-analysis reveals no difference at 2- and 5-year remission rates when pneumatic dilation was compared to laparoscopic Heller myotomy (LHM) (24). It was traditionally
hypothesized that LHM was superior to the EPD in the long treatment of the disease and therefore some surgeons and gastroenterologist will advocate for LHM in younger male patients (<40 years) (25). POEM has gained popularity over the past several years and has become well accepted as a treatment option as well.

Patients with luminal obstruction as a result of a foreign body are commonly treated with endoscopy. Impaction with food bolus can be retrieved with a combination of biopsy forceps, baskets, snares, tripod graspers, etc. They can also be gently forced into the stomach if minimal resistance is felt upon manipulation. The entire esophagus should then be examined for any underlying lesion, i.e., intraluminal masses, strictures or submucosal masses. Intraluminal lesions should be biopsied during the procedure. Other solid foreign bodies with potential for distal intestinal damage or obstruction will be retrieved in the same manner.

Esophageal varices represent another pathology that is commonly treated with endoscopy. Varices develop in patients with liver cirrhosis and portal hypertension and is the most common emergency in this patient population with a mortality of up to 20% (26). Several classification and grading systems have been described. In general, lower grade varices are less than 2 mm in diameter and only visible during Valsalva maneuver or by pressing the esophageal mucosa with the endoscope. Intermediate grades are in the range of 3–4 mm in diameter and tortuous. High grades have a grape-like appearance and may occlude the esophageal lumen (26). Varices are also classified based on their location in the esophagus or stomach. Sclerotherapy and band ligation are the mainstay of treatment for acute bleeding esophageal varices (27). These will be performed as adjuncts to pharmacotherapy and a shunting procedure prior to liver transplantation.

After a thorough examination of the esophagus, the scope is then advanced into the stomach. It is important to mention that hiatal hernias can also be observed in the esophagus however these are best visualized and described from within the stomach and will be discussed later. A complete survey of the stomach is performed. Masses, mucosal lesions or ulcerations, varices, retained gastric contents or bile reflux into the stomach would be noted at this time. The scope is methodically advanced through the body of the stomach towards the antrum and pylorus. Any identified pathology should be clearly documented with respect to size and location. Anterior/posterior gastric wall, lesser or greater curvature, and proximity to pylorus or gastroesophageal junction are common landmarks used to document the location of a lesion which would have a significant importance if surgical intervention is required. The antrum, a common location for gastritis and ulcerations should be meticulously examined. Photo-documentation of a bird’s eye-view of the stomach, the antrum, and the pylorus and any other positive findings should be obtained at this time.

The stomach is the site of the most common basic procedural intervention of an EGD, tissue sampling of the mucosa with biopsy forceps. This is performed in a variety of scenarios including not only obvious pathologic lesions but also benign appearing tissue in search of less obvious pathology. Biopsies will be obtained for mucosal erosions representing gastritis. Tissues will also be sampled for ulcers, polyps, gastric mucosal or submucosal growths, and normal mucosa for the diagnosis of Helicobacter Pylori. Many other interventions are applicable in the stomach and they can be used either alone with in combination with another depending on the encountered pathology.

Peptic ulcer disease (PUD) is quite common, though most PUD is uncomplicated without bleeding or perforation. EGD is commonly used in patient with PUD to confirm the diagnosis and rule out malignancy (28). Duodenal ulcers are at extremely low risk of harboring a malignancy and therefore are not typically biopsied. Gastric ulcers on the other hand carry a higher risk and therefore historically have been biopsied. The incidence of gastric ulcer is decreasing however and the decision to biopsy should be individualized (28). Features suspicious for a malignant ulcer include a punch out crater with raised, irregular borders, any associated mass or abnormal adjacent folds and a giant ulcer. Several other procedural interventions can be associated with complicated PUD with bleeding. A bleeding ulcer will usually require at least two hemostatic modalities to gain hemostasis at time of EGD. Injection of epinephrine with a sclerotherapy needle in the submucosa is extremely common. A bleeding vessel can also be clipped or cauterized. Non-bleeding ulcers can also be treated prophylactically based on the Forrest classification of ulcers which helps predict the likelihood of ulcer re-bleeding without treatment. An actively bleeding pulsatile vessel in an ulcer is classified as type Ia and has 100% chance of rebleeding if not treated at index endoscopy. Type Ib represents oozing within the ulcer and has a 30% chance of rebleeding. Type IIa carries up to a 50% chance of rebleeding and represents a non-bleeding, visible vessel in the ulcer base. An adherent clot is type IIb which carries a 30% chance. Hematin-covered flat spots (type IIc) and a
clean ulcer base (type III) carry less and 8% and less than 3% chance of rebleeding respectively (29).

The scope is passed through the pylorus into the duodenal bulb. A global survey of the bulb will reveal any mucosal or submucosal lesions, ulceration or diverticula. The duodenal bulb must be carefully evaluated upon initial scope insertion as visualization is usually limited on scope withdrawal. Duodenal ulcers are most commonly found in the duodenal bulb; however, one must also inspect for duodenitis, polyps as well as diverticula. The scope is then advanced to the second portion of the duodenum, where the area of the Ampulla of Vater will be identified. The ampulla may not be completely visible using a forward viewing gastroscope, but one should be able to identify periampullary diverticula as well as large ampullary lesions. The third portion of the duodenum is inspected for similar mucosal and submucosal abnormalities. It is usually reached by scope withdrawal causing a paradoxical effect of the scope tip advancing into the third portion of the duodenum. The fourth portion of the duodenum as well as proximal jejunum are not part of a diagnostic upper endoscopy. Further scope insertion is required to reach this area; thus, a longer endoscope is usually required. A pediatric colonoscope is typically used as it measures 133 to 168 cm in length, compared to an upper endoscope’s 103 cm, while having a more comparable scope diameter. Photo documentation of the duodenal bulb, periampullary region and second and third portion of the duodenum is obtained. Biopsy of any lesions or random biopsy to rule out Celiac disease and any other indicated therapeutic intervention can be performed at this time. The scope is withdrawn back into the stomach.

Usually performed after the duodenal inspection, the scope is retroflexed to examine the lesser curve of the stomach, the incisura, the gastric cardia and gastroesophageal junction. Pertinent pathology to be noted includes, hiatal or paraesophageal hernia, type I ulcers at incisura and well as other mucosal or submucosal lesions. Photo documentation of the incisura and gastroesophageal junction is obtained. The scope straightened and biopsies of the antrum, random gastric biopsies or any other indicated diagnostic or therapeutic procedures can be performed at this time. The endoscopist should avoid over distention of the stomach as this precludes adequate biopsy specimen from the stretched-out mucosa.

Hiatal hernias represent a subset of pathology where the stomach or other elements of the abdominal cavity are herniating through the esophageal hiatus into the mediastinum. Different classifications and grading systems exist to describe the type and size of hiatal hernias and the need for further intervention. Type 1 hiatal hernias are also called sliding hiatal hernias. They are the most common and represent circumferential displacement of the gastroesophageal junction (GEJ) into the mediastinum. In type 2 hiatal hernias, The GEJ remains at the level of the diaphragmatic hiatus, however part of the stomach is herniating up along the esophagus into the mediastinum. These are thus called paraesophageal hernias. Type 3 hiatal hernias are another type of paraesophageal hernias and are more of a mixed type where there is proximal displacement of the GEJ as well as herniation of stomach along the esophagus. Type 4 hiatal hernias are type 3 hernias but with herniation of other intra-abdominal organs which may include the transverse colon, pancreas, spleen and small intestine. Types 2-4 hiatal hernias represent at most 5–15% of all hiatal hernias (30). The role of endoscopy in hiatal hernia is to obtain an adequate assessment including the size of the hernia by measuring the distance between location of the GEJ or Z line and the diaphragmatic pinch; any associated pathology i.e., Cameron’s ulcers, esophagitis; and the type of hiatal hernia based on the portion of stomach seen herniating above the diaphragm. Endoscopy can also be important in the patient with large paraesophageal hernia and gastric volvulus to aid in the decompression and detorsion of the stomach as well determining mucosal compromise and the need for urgent operation.

Once all indicated procedures are performed, the stomach is decompressed, and the scope is withdrawn. The esophagus is again examined on the way out and suctioned only above the level of the upper esophageal sphincter to remove any excess saliva from the oropharynx prior to terminating the procedure. Limited evaluation of the external vocal cords may be performed quickly at this time without inciting the patient's gag reflex. The bite-block is removed, and the patient awoken from anesthesia.

The quality of endoscopic exam is inherently related to the quality of the post procedure documentation. Pertinent positive and negative findings should be noted, and photographs should be referenced when applicable. The endoscopist should provide a detailed description of positive findings. This will help other providers in the healthcare team better care for the patient by taking the appropriate next steps. It will also serve as a reference for future exams to monitor the progression or stability of findings. For example, when a hiatal hernia is encountered, it is important to note the location of the Z line and the diaphragmatic
pinch from the incisors. Adequate description of Barrett’s changes, esophagitis, ulcers, varices, etc. are equally important in dictating further management.

The indications for flexible endoscopy are broad and endoscopists continue to find more applications for it. An EGD allows us to directly visualize and promptly treat many conditions of the upper gastrointestinal tract. Though complications can arise from an upper endoscopy, a thorough understanding of how to prepare the ancillary staff, the patient, and a comprehensive handle on the maneuverability of the endoscope, the tools available for basic procedural interventions and how to use them, will limit adverse events. It is however essential that the endoscopist have direct communication with the surgeon when a complication does occur. It is also paramount that the general surgeon familiarizes themselves with the flexible endoscope as this will open many avenues for ways to care for patients in a minimally invasive fashion.

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Footnote
Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References


