



The insidious presentation and challenging management of esophageal perforation following diagnostic and therapeutic interventions

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Abstract: Diagnostic and therapeutic interventions on the esophagus or adjacent organs are responsible for nearly half of all esophageal perforations. If not recognized at the time of the injury, iatrogenic esophageal perforations can present insidiously and lead to delay in diagnosis, thereby increasing morbidity and mortality. Acute clinical awareness is vital for prompt diagnosis, which is usually confirmed with contrast esophagography and contrast-enhanced computed tomography. After establishment of diagnosis, treatment should be promptly initiated and include fluid-volume resuscitation, cessation of oral intake, nasogastric tube insertion, broad-spectrum antibiotics and analgesia. Primary repair, when feasible, is the treatment of choice. Additional procedures beyond primary repair, such as relief of concomitant obstruction, may be necessary if there is underlying esophageal pathology. Drainage alone can be performed for perforations of the cervical esophagus that cannot be visualized. Esophageal T-tube placement or exclusion and diversion techniques are appropriate in clinically unstable patients and in cases where primary repair is precluded either due to preexisting esophageal disease or extensive esophageal damage. Esophagectomy should be performed in patients with malignancy, end-stage benign esophageal disease or extensive esophageal damage that precludes repair. Endoscopic techniques, including stenting, clipping or vacuum therapy, can be used in select cases. Finally, nonoperative management should be reserved for patients with contained esophageal perforations, limited extraluminal soilage and no evidence of systemic inflammation.

Keywords: Esophageal perforation; iatrogenic; esophagoscopy; esophagectomy; esophagus

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Introduction

Perforation of the esophagus can be defined as a transmural disruption of its continuity, which results in leakage of intraluminal contents into the surrounding tissues. Most esophageal perforations are caused by diagnostic and therapeutic interventions, followed by spontaneous rupture, foreign body ingestion, trauma and malignancy (1-3). Since its first description by Hermann Boerhaave nearly 300 years ago (4), esophageal perforation remains a potentially life-threatening condition. The mortality depends on the

etiology, part of the esophagus involved, presence of underlying pathology and time elapsed from symptom onset to diagnosis. Indeed, the reported mortality ranges from 10% to 25% when therapy is instigated within 24 hours but increases up to 60% when treatment is delayed beyond 48 hours (5). Unfortunately, the rarity of this pathological condition and its nonspecific presentation can lead to delay in diagnosis in more than 50% of patients (6). In these cases, the optimal therapy remains unclear. It becomes evident that esophageal perforation continues to present

diagnostic and therapeutic challenges. Therefore, clinicians must be aware of its potentially insidious presentation and knowledgeable regarding the management options of this highly morbid condition. The present article reviews solely iatrogenic esophageal perforations and aims to identify their incidence, aid their diagnosis and elucidate the controversial aspects of their treatment. This review does not include leaks from esophageal anastomoses, which represent a different clinical entity.

Etiology

Diagnostic and therapeutic interventions on the esophagus or adjacent organs are the leading cause of esophageal perforation, accounting for 46.5% of all cases in a systematic review of 40 studies that included 1,933 patients (7). Of these interventions, esophageal instrumentation is the commonest cause of perforation. When therapeutic procedures are performed at the time of diagnostic esophageal endoscopy, the risk of perforation increases even further. For instance, the estimated risk of perforation during diagnostic esophagoscopy is as little as 0.03% and 0.11% with flexible and rigid scope respectively (8,9). This risk, however, increases significantly after argon plasma coagulation of Barrett's esophagus, photodynamic therapy for palliation of esophageal cancer, stent placement for malignant dysphagia or stricture dilation (10-13). The risk is even higher after endoscopic mucosal resection or submucosal dissection, endoscopic variceal sclerotherapy, Nd:YAG laser therapy for palliation of esophageal cancer or pneumatic dilation for achalasia (11,14-21).

Intraoperative esophageal perforation accounts for nearly 2% of all cases and can occur at the time of neck, thoracic or abdominal surgery. Surgical procedures with risk of esophageal perforation include resection of lung cancer, pneumonectomy, pulmonary transplantation, mediastinoscopy, excision of mediastinal tumors, thoracic aortic aneurysm repair, left atrial radiofrequency ablation, hiatal hernia repair, antireflux surgery, vagotomy, thyroidectomy and operations on the cervical spine (22-30). In particular, the incidence of esophageal perforation after anterior osteosynthesis for cervical spine fracture can be as high as 3.4% (31). Lastly, esophageal perforation can be caused by various other procedures, including transesophageal echocardiography, endotracheal intubation, mini tracheostomy, transtracheal jet ventilation, Sengstaken-Blakemore or Minnesota tube placement, nasogastric tube insertion, bronchial artery embolization and radiotherapy

Table 1 Common causes of iatrogenic esophageal perforation

Esophageal endoscopy ^a
Diagnostic flexible esophagoscopy (0.03%)
Diagnostic rigid esophagoscopy (0.11%)
Argon plasma coagulation of Barrett's esophagus (2%)
Photodynamic therapy of esophageal cancer (2%)
Stent placement for malignant dysphagia (2%)
Dilation of simple rings or peptic strictures (0.09–2.2%)
Endoscopic mucosal resection (3%)
Endoscopic variceal sclerotherapy (0.5–5%)
Endoscopic submucosal dissection (6%)
Nd:YAG laser therapy of esophageal cancer (7%)
Dilation of complex strictures with Maloney dilator (2–10%)
Pneumatic dilation for achalasia (0.4–14%)
Neck, thoracic and abdominal surgery
Thyroidectomy, cervical spine surgery (e.g., anterior osteosynthesis), resection of lung cancer, pneumonectomy, pulmonary transplantation, mediastinoscopy, resection of mediastinal tumors, thoracic aortic aneurysm repair, left atrial radiofrequency ablation, hiatal hernia repair, antireflux surgery, vagotomy
Transesophageal echocardiography
Endotracheal intubation
Mini tracheostomy
Nasogastric tube insertion
Sengstaken-Blakemore or Minnesota tube placement
Bronchial artery embolization
Radiotherapy

^a, the risk of perforation for each esophageal endoscopic procedure is given in brackets.

(32-37). *Table 1* summarizes the commonest causes of iatrogenic esophageal perforation.

Clinical presentation

The clinical presentation of esophageal perforation is nonspecific and can mimic that of other, commoner disorders, such as pneumonia, angina, peptic ulcer disease and pancreatitis. Typical symptoms include pain in the neck, chest, back or epigastrium, as well as dysphagia, odynophagia, dysphonia and dyspnea (6,23,25,38-40).

Common clinical signs include subcutaneous emphysema, fever, tachypnoea, tachycardia and hypotension (6,22-25, 38-42). Any combination of the above signs and symptoms following instrumentation of the esophagus or surgery on neighboring organs should raise the suspicion of esophageal perforation.

The symptomatology mostly depends on the time interval from the iatrogenic injury to the diagnosis, as well as the site of the perforation. Cervical esophageal perforation presents with neck pain and stiffness, dysphagia, dysphonia and bloody regurgitation. Due to attachment of the esophagus to the prevertebral fascia, the spread of oropharyngeal soilage is limited, resulting in less severe clinical manifestations compared to thoracic and abdominal perforations. Thoracic esophageal perforation causes contamination of the mediastinum, which may extend into the pleural cavities, thereby leading to pleuritic, retrosternal or interscapular pain, odynophagia, dyspnea and cough. However, this clinical presentation may be less pronounced in the presence of an intercostal chest drain that has been inserted in the pleural cavity as part of a thoracic surgical procedure. Finally, abdominal esophageal perforation contaminates the peritoneal cavity and manifests with abdominal pain, nausea and vomiting. Abdominal pain may radiate to the back if there is collection in the lesser sac or may be referred to the shoulders due to diaphragmatic irritation.

Diagnostic investigations

A high level of suspicion is crucial for prompt diagnosis of iatrogenic esophageal perforation because early signs and symptoms may be subtle and misleading. Indeed, it is estimated that up to 50% of patients with esophageal perforation present with atypical clinical features leading to diagnostic delay (43).

Esophageal perforation can initially be suspected with plain radiography. In perforation of the cervical esophagus, plain neck imaging may demonstrate subcutaneous emphysema, anterior displacement of the trachea and gas in the prevertebral fascial planes on lateral view (38). In thoracic esophageal perforation, a chest radiograph may demonstrate subcutaneous emphysema, pneumomediastinum, mediastinal air-fluid level, mediastinal widening, pleural effusion, pneumothorax or hydropneumothorax (44,45). Abnormal chest radiograph is developed within 12 hours of instrumental esophageal perforation in as many as 75% of patients (46). However,

these radiological findings are non-specific after intrathoracic surgical procedures and become subtler if an intercostal chest drain is *in situ*. In abdominal esophageal perforation, a chest radiograph may show subdiaphragmatic air.

Once esophageal perforation is suspected, contrast esophagography should promptly be performed to confirm the presence and demonstrate the site of the perforation. Iodinated water-soluble contrast agents, such as diatrizoate, have been widely recommended for the detection of esophageal perforation (47). However, the rapid transit of thin contrast media may yield negative results, especially in perforations of the upper esophagus (38). In these cases, contrast esophagography with dilute barium sulphate may be considered (6). This imaging technique can determine the precise location of the perforation and indicate whether it is confined to the mediastinum or freely communicates with the pleural or peritoneal cavities (5,47). Nevertheless, the use of barium sulphate, especially in high concentrations, can cause inflammatory response, most notably mediastinitis, and may interfere with the interpretation of subsequent imaging studies.

Contrast-enhanced computed tomography of the chest is a valuable investigation for confirming esophageal perforation and ruling out alternative diagnoses. Computed tomography is indispensable when contrast esophagography cannot be undertaken or is negative and the clinical suspicion for perforation is high (48,49). Moreover, computed tomography can provide important information for the subsequent management strategy and operative planning. Abnormal radiological findings include extraluminal contrast, mediastinal air, periesophageal fluid collection, pleural effusion, esophageal thickening and communication of the air-filled esophagus with a contiguous mediastinal air-fluid collection (49,50).

Flexible esophagoscopy allows direct visualization of the perforation. However, esophageal endoscopy is not recommended as primary diagnostic procedure because air insufflation can cause further dissection of the perforation (51). For the same reason, if there is suspicion of perforation during an endoscopic procedure, meticulous inspection of the esophagus should be undertaken without air insufflation prior to removal of the endoscope.

Pleural fluid analysis can confirm the diagnosis of esophageal perforation by revealing elevated salivary amylase, pH less than 6 or the presence of undigested food or liquids (52). *Table 2* summarizes the key diagnostic findings in iatrogenic esophageal perforation.

Table 2 Diagnosis of iatrogenic esophageal perforation

History: recent diagnostic or therapeutic intervention on the esophagus or adjacent organs

Clinical signs and symptoms: pain in the neck, chest, back or epigastrium, subcutaneous emphysema, fever, tachypnoea, tachycardia, hypotension, dysphagia, odynophagia, dysphonia, dyspnea, cough, nausea, vomiting

Lateral neck radiograph: subcutaneous emphysema, anterior displacement of the trachea, gas in the prevertebral fascial planes

Chest radiograph: subcutaneous emphysema, pneumomediastinum, mediastinal air-fluid level, mediastinal widening, pleural effusion, pneumothorax, hydropneumothorax, subdiaphragmatic air

Contrast esophagography: extraluminal contrast

Contrast-enhanced chest computed tomography: extraluminal contrast, mediastinal air, periesophageal fluid collection, pleural effusion, esophageal thickening, communication of the air-filled esophagus with a mediastinal air-fluid collection

Flexible esophagoscopy: visualization of esophageal defect

Pleural fluid analysis: elevated salivary amylase, pH <6, presence of undigested food or liquids

Treatment

The treatment of iatrogenic esophageal perforation is mainly determined by the site and extent of the injury. Additional factors include the time interval between perforation and treatment initiation, damage to surrounding tissues, overall condition of the patient and presence of concomitant esophageal pathology (53-55). A high incidence of underlying esophageal disease has been reported and represents a marker for the iatrogenic nature of esophageal perforation (3,25). The main goals of treatment are prevention of further contamination, eradication of the infection, establishment of nutritional support and restoration of the continuity of the gastrointestinal tract. Once the diagnosis is confirmed, treatment should be commenced immediately. The patient must be kept nil *per os* and a nasogastric tube should be inserted to clear gastric contents and limit further contamination. Due to the lack of randomized clinical trials, an empiric regime of intravenous broad-spectrum antibiotics should be initiated as early as possible. Antifungal coverage is warranted in patients who have been hospitalized or received broad-spectrum antimicrobial agents prior to the perforation, patients on long-term antacid therapy, patients who have received

steroids or other immunosuppressive therapy, patients with HIV infection and patients who fail to improve after several days of appropriate antibacterial therapy. Adequate analgesia should be provided to control pain or discomfort, but narcotic analgesics should be used cautiously in hypotensive patients. Total parenteral nutrition should be instigated if a prolonged fasting period is anticipated, while percutaneous endoscopic gastrostomy may also be considered. The patients may be transferred to a higher level of care for hemodynamic monitoring, fluid-volume resuscitation and stabilization as required. However, these preparations should not delay surgical assessment and management.

Surgical management includes drainage alone, primary closure, esophageal resection, T-tube placement, as well as exclusion and diversion techniques. The selection of surgical approach must be based on the site of the perforation. Cervical esophageal perforations that cannot be visualized and are well-contained down to the level of the carina can be managed with drainage alone through a cervical incision (3). Optimal surgical approach to perforations of the middle and lower third of the esophagus is achieved via a right thoracotomy in the sixth intercostal space and a left thoracotomy in the seventh intercostal space respectively. However, primary repair of esophageal perforation following instrumentation has also been performed successfully with video-assisted thoracoscopic surgery (56,57). Perforations of the abdominal esophagus are best approached via an upper midline laparotomy.

Primary repair has been traditionally advocated as the treatment of choice for esophageal perforations diagnosed within the first 24 hours (23,25,39,40,52). However, an increasing number of studies have identified high rates of delayed diagnosis and demonstrated improved survival rates with primary repair undertaken after the first 24 hours (3,58-60). Successful primary repair mandates debridement of necrotic tissue, drainage of the contaminated area, as well as full exposure and secure closure of the damaged mucosa to avoid leakage (58,59,61). The problem of leakage from the primary repair site led to the development of reinforcement techniques with various vascularized pedicle flaps, including parietal pleura (62), diaphragm (63), omentum (64), as well as intercostal, rhomboid and latissimus dorsi muscles (65).

Additional procedures beyond primary repair or esophagectomy may be necessary in perforation of an esophagus with underlying pathology. Relief of concomitant esophageal obstruction at the time of the repair has been

shown to significantly reduce mortality (66). In particular, when there is esophageal stricture distal to the perforation, adequate dilation should be performed intraoperatively (67). In case of a non-dilatable stricture, myotomy is indicated along with fundoplication to cover the defect (68). Esophageal perforation from pneumatic dilation for achalasia requires primary repair of the perforation site and myotomy on the contralateral side of the esophagus, with a partial fundoplication procedure to prevent reflux and buttress the repair (67). In perforation of an esophagus with end-stage achalasia, the surgeon may choose to proceed with esophagectomy and reconstruction with gastric conduit if there is minimal contamination and the patient is clinically stable. In the presence of malignancy, distal obstruction requires esophageal resection with immediate or delayed reconstruction (55), while disseminated carcinoma necessitates stent placement for symptom palliation (69-71).

Esophageal T-tube placement or exclusion and diversion techniques are appropriate in clinically unstable patients and in cases where primary repair is precluded either due to preexisting esophageal disease or extensive esophageal damage. Placement of a T-tube allows establishment of a controlled esophagocutaneous fistula, thereby preventing further contamination and promoting the healing process of surrounding tissues (72). The T-tube can be removed after 4-6 weeks and the fibrous tract that was formed around the tube will eventually obliterate. Successful management of esophageal perforations with this method has been reported in many studies (3,73,74). Exclusion and diversion techniques aim to adequately drain the perforation site, minimize further contamination and expedite healing (75-77). A diversion procedure comprises of cervical esophagostomy (creation of salivary fistula), resection of the remaining esophagus, gastric decompression with gastrostomy tube, feeding tube access with a jejunostomy and closure of the diaphragmatic hiatus to prevent hernia formation (78). In critically ill patients, a cervical esophagostomy is constructed, the distal esophagus is divided at the diaphragmatic hiatus to exclude the site of perforation and a gastric feeding tube is inserted. Restoration of alimentary tract continuity is typically performed six months to one year following the perforation and usually requires retrosternal colon interposition graft (79,80). Exclusion and diversion techniques can be rather complex, highly morbid and inconvenient for the patient (3,61,68). This resulted in the development of modifications, in which the esophagus is ligated with absorbable sutures or staples, thereby obviating the need for a second operation and providing improved clinical results (81,82).

Endoscopic techniques have been recently used for the treatment of iatrogenic esophageal perforations. Endoscopic placement of covered stents aims to restore luminal integrity and prevent further extraluminal soilage (83-88). However, the effectiveness of this method depends on adequate control and drainage of the extraluminal contamination. Esophageal stenting may be appropriate in patients with extensive comorbidities, advanced mediastinal sepsis or large esophageal defects (89). Complications of this procedure include stent malposition and migration, especially when used near the gastroesophageal junction, which may cause gastric outlet obstruction. Moreover, endoscopic clipping has recently emerged as an alternative means of managing iatrogenic esophageal perforations with minimal extraluminal contamination (90). This treatment modality is generally best suited for small defects with healthy, compliant surrounding mucosa that can be approximated with minimal tension. Failure, however, to adequately control extraluminal soilage significantly increases the risk of fistula formation. Finally, topical negative-pressure therapy with an endoscopically placed vacuum sponge is a relatively new technique for the treatment of esophageal perforation. Clinical outcomes from small, retrospective studies are comparable to those of more traditional treatments; however, its safety profile is yet to be fully determined (91).

Nonoperative treatment should be reserved for patients with contained esophageal perforations, limited extraluminal soilage and no evidence of systemic inflammation. The first successful nonoperative management was described in 1965, with only 1 death in 18 patients treated for instrumental perforation of the thoracic esophagus (92). Since then, the role of nonoperative management has rapidly evolved (93-96), probably due to the increasing incidence of iatrogenic esophageal injuries, which are often associated with less extraluminal contamination. Perforation of the thoracic or abdominal esophagus can represent a relative contraindication to nonoperative management because of the difficulty in controlling spillage of intraluminal contents in the pleural or peritoneal cavities. Conversely, cervical esophageal perforation is considered suitable for nonoperative treatment due to the anatomic confinement of the esophagus by surrounding structures. Similarly, it is appropriate to consider nonoperative management if the injury is not in neoplastic tissue or proximal to an obstruction. Additional criteria include accessibility to contrast imaging studies at any time of the day and availability of an experienced surgeon if the patient

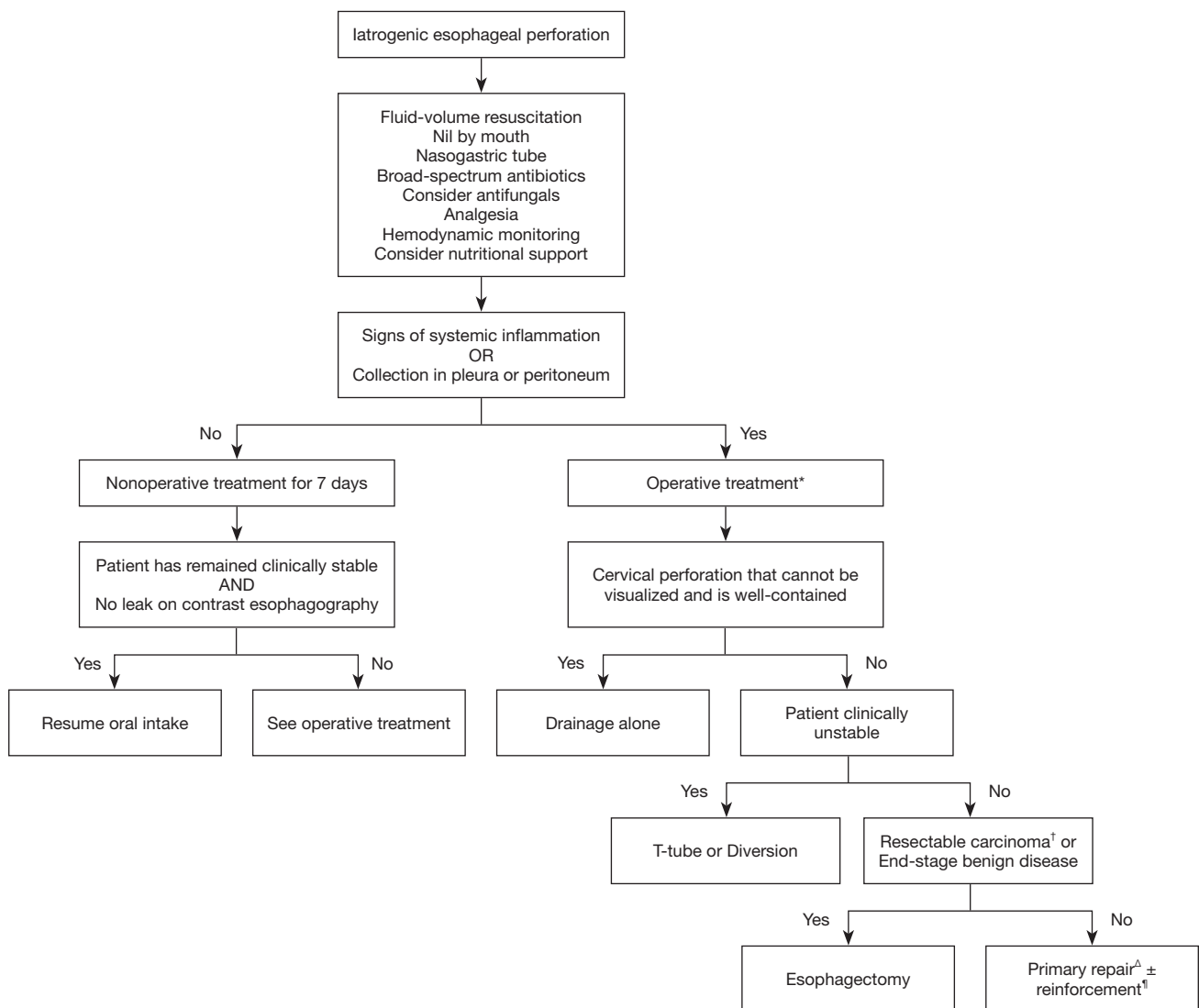


Figure 1 Treatment of iatrogenic esophageal perforation. *, endoscopic techniques, including stenting, clipping or vacuum therapy, can be used in select cases. †, disseminated carcinoma is best treated with stent placement. ^, additional procedures beyond primary repair are needed in cases of underlying esophageal pathology, including dilation of a stricture distal to the perforation, myotomy with fundoplication to cover the defect for non-dilatable strictures, myotomy on the contralateral side of the primary repair and partial fundoplication for achalasia. ‡, reinforcement can be performed with various vascularized pedicle flaps, including intercostal, rhomboid and latissimus dorsi muscles, parietal pleura, diaphragm and omentum.

deteriorates (6,93,95). Careful selection of patients with esophageal perforation for nonoperative management has achieved 100% survival rates (93,96,97).

Nonoperative treatment includes avoidance of oral intake, parenteral nutrition support, intravenous broad-spectrum antibiotics and drainage of fluid collections. If the patient remains clinically stable, a barium esophagram

should be obtained after 7 days and resumption of oral intake under observation may be considered depending on the results. If the patient demonstrates any evidence of clinical deterioration, with signs and symptoms of infection, surgical intervention is required to control extraluminal contamination and restore continuity of the digestive tract. *Figure 1* presents a simplified algorithm for the treatment of

iatrogenic esophageal perforation.

Prognosis

The mortality of iatrogenic esophageal perforation ranges between 7% and 33% (5). Regarding the injury site, thoracic esophageal perforations have the highest mortality, followed by abdominal and cervical perforations (25,52). Nonoperative management of esophageal perforation has been associated with higher mortality compared to surgical treatment (98). The most frequently reported postoperative complications include persistent leak, mediastinitis, empyema, fistula formation, esophageal stricture, pneumonia, abscess and sepsis (23,99-102).

Conclusions

Iatrogenic esophageal perforation is a serious complication of various diagnostic and therapeutic interventions that can be challenging to diagnose and difficult to treat. As a result, its morbidity and mortality remain high. To provide improved clinical outcomes, an individualized surgical treatment is vital. In a select group of patients, however, nonoperative management can be successful. In any case, increased clinical awareness, expeditious diagnosis and optimal supportive treatment are essential.

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Footnote

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