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Acute Esophageal Necrosis: An In-depth Review of Pathogenesis, Diagnosis and Management

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Abstract

Introduction: Acute esophageal necrosis (AEN) is an uncommon but fatal cause of upper gastrointestinal bleeding. The complex pathophysiology of the disorder provides multiple points for intervention. Therefore, it is important to discuss the many multifaceted aspects of the disease.

Methods: A scoping review was performed using PubMed, Google Scholar, and [ClinicalTrials.gov](https://www.clinicaltrials.gov). We reviewed literature from 1990 to 2021. The keywords used were ‘acute esophageal necrosis’, ‘upper GI bleed’, ‘pathogenesis’, ‘EGD’, ‘prognosis’.

Results and conclusions: The review summarized findings of 46 studies. AEN usually targets older males who have underlying cardiovascular disease. The middle part of the esophagus is commonly involved. The pathogenesis of AEN depends on conditions that increase risk of mucosal damage such as ischemia, lack of mucosal protection and excessive gastric reflux. Some medications are also responsible for the disease. Esophagogastroduodenoscopy is usually the gold standard for diagnosis. Findings suggestive of AEN include darkened, sharply demarcated circumferential areas. Supportive measures, including bowel rest, fluid supplementation and proton pump inhibitors are the cornerstone of therapy. A high index of suspicion should be maintained in patients with chronic health problems presenting with signs and symptoms of upper gastrointestinal bleeding because AEN can carry an unfavorable prognosis in these patients.

Keywords: Acute esophageal necrosis, upper GI bleed, pathogenesis, EGD, prognosis

1. Introduction

Acute esophageal necrosis (AEN), also known as necrotizing esophagitis or “black esophagus”, was first described by Goldenberg et al., in 1990.¹ While uncommon, the associated mortality rate was as high as 32%.² It typically presented in elderly males with symptoms of upper gastrointestinal bleeding (UGB). Despite its alarmingly high mortality rate, the condition has been poorly understood due to low incidences described by various studies in the literature.^{3–8} The multifactorial etiology was attributed to a combination of esophageal ischemia, impaired mucosal barrier protection, and reflux esophagitis. Other risk factors included diabetes mellitus (particularly diabetic ketoacidosis),

hematologic and solid organ malignancies, malnutrition, gastric outlet obstruction, renal insufficiency, hemodynamic compromise and shock; the underlying pathogenesis was related to poor perfusion and nutritional states.⁹

Esophagogastroduodenoscopy is the gold standard modality for diagnosis.¹⁰ Biopsy, although not required for definitive diagnosis, might be helpful in excluding superimposed infections. Complications included esophageal stenosis or stricture formation in the distal esophagus, perforation and subsequent infection.⁹ The main focus of management was to correct the coexisting chronic medical conditions and provide supportive treatment in the form of fluid therapy, NPO restriction maintenance and IV Proton pump inhibitor therapy (PPI).¹⁰ Given the

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prevalence of its associated conditions, high mortality rate, and limited research data surrounding AEN, it is imperative to attain a more comprehensive understanding of this condition in order to achieve an early diagnosis and improve outcomes.

2. Methods

We screened PubMed, Web of Science, Google Scholar and [ClinicalTrials.gov](https://www.clinicaltrials.gov) databases for all articles about acute esophageal necrosis published from 1990 to 2021. The keywords used in the review were ‘acute esophageal necrosis’, ‘upper GI bleed’, ‘pathogenesis’, ‘EGD’, ‘prognosis’. After the initial search, duplicates were removed and imported all included search study into EndNote online software. Two independent reviewers screened remaining studies for the inclusion based on inclusion criteria, and researchers were blinded to each others' decisions. The inclusion criteria for the review were as follows: 1) Literature from 1990 to 2021 about acute esophageal necrosis 2) Articles discussing any aspect of acute esophageal necrosis 3) Fully retrievable articles. The exclusion criteria were as follows: 1) Articles not in English language 2) Articles that could not be retrieved. The screening was done via reading the abstract and if needed by reading full-text articles. Studies published in the English language or with English translation available, were included in the initial review.

Data was extracted from study documents, including information about epidemiology, etiology, pathogenesis, clinical symptoms and signs, differential diagnoses, management, prognosis, and complications. Data were cross-checked for accuracy and completeness. Publications that were not peer-reviewed were excluded from this study.

For the purposes of the review, 10 studies discussing epidemiology, 4 studies regarding etiology and pathogenesis respectively, 30 studies elaborating risk factors, 8 studies about clinical presentation, one study highlighting differential diagnoses, two studies discussing complications, 9 studies focusing on management and two studies about prognosis were included.

3. Review

3.1. Epidemiology

Five retrospective studies^{3–7} and one prospective study⁸ carried out between 1993 and 2011 have established the incidence of AEN to be approximately 0.01–0.28%. AEN predominantly targeted the 7th decade of life as evidenced by a mean age of

62–67 years, typically affecting males 4 times more than females.¹⁰ A pooled analysis of 114 diagnosed cases of AEN by Schizas et al. reported cardiovascular disease as the most common pre-existing condition (47.3%), followed by diabetes mellitus (36.4%) alcohol abuse (28.2%), liver disease (17.3%) and kidney disease (15.5%). The same study exhibited lower esophageal involvement to be almost universal (92.9%), with common disease progression to the middle esophagus (64.3%). Upper esophageal involvement was rare and seen in only 33.7% of cases.¹¹

3.2. Etiology

The etiology of AEN was believed to be multifactorial; local hypoperfusion, loss of protective mucosal barrier and reflex of gastric acid caused tissue damage, initiating a cascade of events that lead to tissue necrosis.¹⁰ The anatomy of the distal esophagus contributed to perfusion injury in states where circulatory volume is low. The distal esophagus receives its blood supply primarily from branches of the left gastric artery or left inferior phrenic artery and sometimes from small branches of the celiac, splenic, short gastric, or left hepatic arteries as additional or alternative anatomical variants.^{12,13} Compared to the well-vascularized proximal and middle parts of the organ, the distal esophagus has more “watershed areas” making it susceptible to ischemic injury. Overall, esophageal infarction was a rare phenomenon due to the complex vascular anastomosis present in the esophageal submucosa.¹³

3.3. Pathogenesis

The pathogenesis of AEN involved multiple underlying mechanisms working in tandem to cause esophageal mucosal damage. This might include a chronic condition that rendered the body susceptible to mucosal damage, followed by an acute event that triggered AEN. Chronic predisposing conditions include conditions that increased the risk of esophageal ischemia, or diminished the protective capabilities of the esophageal mucosa, and or lead to excessive gastric acid reflux into the distal esophagus.¹⁴

The scarcely supplied distal esophagus was predisposed to ischemia in such low-flow states, such as hypotension and hypoperfusion. Patients with vascular risk factors such as male sex, atherosclerosis, advanced age, diabetes mellitus, hypertension or chronic kidney disease were at a higher risk of developing esophageal ischemia.⁹

Loss of the mucosal barrier was another mechanism contributing to AEN. Commonly seen in patients with poor nutritional status and general debilitation, a weak protective barrier rendered the mucosa more susceptible to gastric acid and other irritants, impairing the mucosa's ability to withstand chemical insults.⁸ This loss could be seen in patients with chronic comorbidities including malignancy, alcohol abuse, cirrhosis, chronic kidney disease, congestive heart failure, chronic pulmonary disease, and postoperative status.¹⁰ Gastric acid reflux also played a role in the pathogenesis of this disease. An impaired lower esophageal sphincter mechanism or loss of peristalsis might result in acid reflux, which can cause mucosal damage and subsequent necrotic injury.¹⁴ In patients with a compromised mucosal barrier due to the aforementioned conditions, acid reflux could further exacerbate injury to the mucosal lining.

These mechanisms coupled with a sudden precipitator such as hemodynamic compromise, metabolic derangements such as diabetic ketoacidosis, infection, surgery, chemotherapy, certain medications and certain gastrointestinal procedures were implicated in the development of AEN.

3.4. Risk factors and associated conditions

There are many risk factors predisposing patients to AEN (Fig. 1). AEN had been reported in patients presenting with hemodynamic compromise, particularly in patients with significant vasculopathy secondary to diabetes mellitus, atherosclerosis,

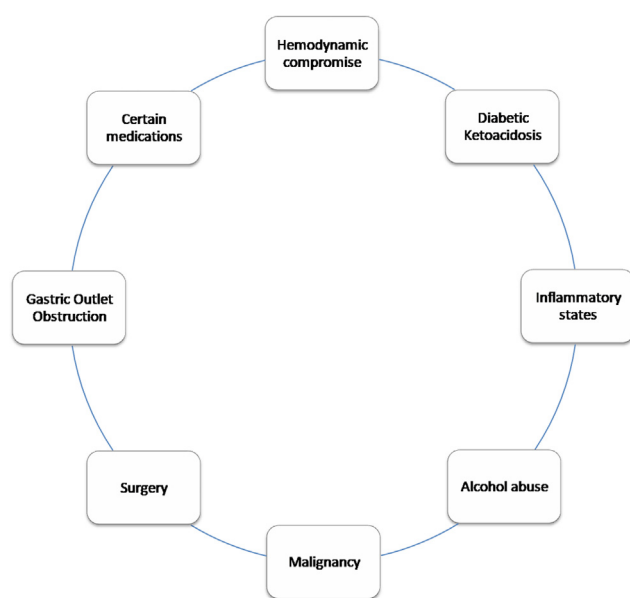


Fig. 1. Risk factors predisposing to development of acute esophageal necrosis.

cardiovascular and renal disease. In these patients, hypotension might result in significant hypoperfusion of the esophagus, eventually leading to ischemic necrosis.⁹

Hemodynamic compromise might occur with any type of shock. Cardiogenic shock leads to hypoperfusion that could cause ischemia of the esophagus. Septic shock following an infection causes generalized vasodilation resulting in a state of hypoperfusion. Both types of shock have poor prognosis due to progression to multi-organ failure.^{15–17} Hemorrhagic shock can also cause hemodynamic compromise secondary to blood loss due to causes such as variceal bleeding,¹⁸ aortic aneurysm rupture,^{19,20} blunt thoracic trauma resulting in transection of the aorta¹² and post-surgical bleeding.²¹ Hypovolemic shock may occur with substantial fluid loss secondary to diarrhea or vomiting.

Diabetic ketoacidosis (DKA) is a well-documented trigger of AEN.^{22–25} DKA leads to AEN through several mechanisms. Patients with DKA typically have a history of poor glycemic control which could accelerate the development of atherosclerosis, thus increasing the risk of developing ischemia in low volume states. In fact, DKA might cause a low circulatory volume in itself via osmotic diuresis resulting in profound fluid loss.²⁴ Furthermore, DKA could induce gastric stasis resulting in increased gastric reflux and subsequent mucosal damage.⁹ A retrospective analysis performed by Yasuda et al. demonstrated the association of DKA with 4 of the 16 analyzed cases of AEN.²⁶

Inflammatory states result in increased capillary permeability, causing increased third spacing of fluid and subsequent low circulatory volume. This could occur with infection and inflammation of various organs and tissues including the gallbladder, pancreas, lung, endocardium, peritoneum, subcutaneous tissue and bone. Malignancy could also predispose to AEN due to immune dysregulation, resulting in diminished regenerative capacity of the esophageal mucosal cells. There had been documented cases of AEN induced by chemotherapeutic agents such as tacrolimus²⁷ and atafinib.²⁸

Chronic alcohol abuse is another well documented predisposing factor, seen in as many as 25% of patients with AEN.² It might lead to AEN through increased gastric acid secretions, reduced lower esophageal sphincter pressure causing increased reflux and poor nutritional status.²⁹ Alcohol abuse might predispose to cirrhosis, another documented risk factor of AEN. Acute alcohol abuse in cases of binge drinking could cause AEN due to esophageal mucosal damage secondary to severe vomiting.³⁰

The resulting hypovolemia and lactic acidosis could trigger AEN.³¹

Surgery is a common precipitating factor for AEN, being a cause for physiologic stress. The immune system responds by increasing the amount of circulating cytokines, thereby affecting the regenerative capacity of the esophageal mucosa. Furthermore, blood loss associated with surgery can induce a hypovolemic state and hinder perfusion.²¹ AEN had been documented following cardiac procedures, including radiofrequency ablation for atrial fibrillation³² and percutaneous coronary intervention.³³ AEN might also be associated with certain endoscopic procedures, including percutaneous esophageal gastrostomy,³⁴ insertion of biodegradable esophageal stents³⁵ or photodynamic therapy for esophageal carcinoma.³⁶

Gastric outlet obstruction leads to prolonged exposure of gastric contents in the distal esophagus resulting in a breach of mucosal protective mechanisms. Such cases may occur secondary to gastric ulcers and edema in the duodenal bulb.³⁷ There was a documented case of AEN secondary to gastrostomy tube migration into the duodenal bulb resulting in obstruction at the gastric outlet.³⁷

Certain medications are also implicated in the development of AEN. Vasoconstrictors, such as terlipressin³⁸, could cause local ischemia whereas antihypertensive drugs might lead to a transient low-flow state causing hypoperfusion.³⁹ Drugs such as NSAIDs²⁶ and bisphosphonates⁴⁰ might cause direct mucosal damage.

3.5. Clinical presentation and diagnosis

The characteristic presentation of AEN is an elderly man with multiple comorbidities demonstrating symptoms of UGB including hematemesis or melena.^{10,11} Other symptoms might include chest or epigastric pain, nausea, emesis, dysphagia, fever or syncope. On admission, patients with AEN commonly exhibited signs of hemodynamic compromise such as tachycardia and hypotension. Initial laboratory tests might show anemia secondary to blood loss, leukocytosis due to inflammation caused by esophageal necrosis and an elevated serum lactate due to tissue hypoperfusion.⁹

Esophagogastroduodenoscopy (EGD) is the diagnostic modality of choice for AEN. The characteristic appearance of EGD is a circumferentially and diffusely darkened esophagus, predominantly in the distal part of the organ with continuation proximally and sharply demarcated margins.¹⁰ The discoloration typically does not exceed beyond the gastroesophageal junction. This endoscopic finding is

sufficient for the diagnosis of AEN. Additional findings may include active bleeding or blood clots in the esophagus, or “coffee ground” material in the stomach, as well as esophageal or gastric ulcers.⁹

A lack of viable epithelium, necrotic debris, and necrotic changes in the mucosa with potential to extend into the submucosa and even deeper into the muscularis propria were important histological findings. Other findings might include dense leukocytic infiltrate, evident vascular thrombi, deranged muscle fibers, and alarming inflammatory changes.^{9,41} Though not required to establish diagnosis, a biopsy of the specimen might help exclude other differential diagnoses as well as infectious etiologies of AEN and help rule out superimposed infections.

Uncomplicated AEN follows a clinical course of well-documented phases. The initial diffuse black distal esophageal mucosa is followed by a healing phase dominated by residual black areas and thick white exudates composed of necrotic debris that cover pink friable mucosa.³⁷ Usually, esophageal mucosa acquires its normal endoscopic appearance in approximately 1–2 weeks. However, depending on the patient's general condition, the time to complete resolution might vary.⁹

3.6. Differential diagnosis

Due to the appearance of a darkened esophagus on endoscopy, differential diagnoses of AEN include malignant melanoma, acanthosis nigricans, pseudomelanosis, and melanosis of the esophagus. Esophageal erosion and necrosis is commonly seen in cases of corrosive chemical ingestion, hence it should be actively excluded in history. A biopsy of the specimen can help exclude other causes of similar appearance if there is uncertainty regarding the underlying cause.⁹ (Table 1).

3.7. Complications

Perforation, the most feared complication of AEN with an incidence of approximately 5–7%,² occurs due to transmural esophageal necrosis. Patients with perforation decompensate rapidly and have a poor prognosis. Since the esophagus lacks a serosa, perforation might result in rapid development of mediastinitis, mediastinal abscess formation or sepsis, eventually culminating in multiorgan failure and death.⁹ Other complications include esophageal stenosis and stricture formation which result from scar formation as AEN heals. Strictures were seen in about 10% of patients on follow up EGD and might cause dysphagia.² The necrosed area of the

Table 1. Differential diagnoses of acute esophageal necrosis.

	Clinical Features	Imaging (EGD unless otherwise stated)	Biopsy findings
Melanosis	<ul style="list-style-type: none"> • Acid reflux • Dysphagia • Heartburn • Indigestion • Epigastric pain 	Darkly pigmented desquamated patch in the esophagus	<ul style="list-style-type: none"> • Hyperpigmentation at the basal layer of the epithelium without atypia • immunohistochemistry stain positive for melanocytes
Pseudomelanosis	<ul style="list-style-type: none"> • Nausea • Vomiting • Melena 	Sharply demarcated dark pigmentation of the esophagus	<ul style="list-style-type: none"> • Hyperpigmentation of the lamina propria by macrophages laden with vesicles containing mostly iron sulfide
Acanthosis Nigricans	<ul style="list-style-type: none"> • History of gastric cancer • Epigastric pain • Dysphagia 	Thickened and finely granular esophageal mucosa with several larger elevations	<ul style="list-style-type: none"> • Papillomatous hyperplasia • Pigmentation • hyperkeratosis
Malignant Melanoma	<ul style="list-style-type: none"> • Dysphagia • Retrosternal or epigastric pain • Hematemesis • Melena • Weight loss 	<ul style="list-style-type: none"> • EGD: lobulated and darkly colored masses with intact mucosa or occasional ulceration • CT: bulky esophageal mass compressing the adjacent mediastinal structures 	<ul style="list-style-type: none"> • Melanin granules within the tumor cells • Melanocytes in the overlying epithelial layer • Areas of junctional activity within squamous mucosa and the adjacent epithelium

EGD-esophagogastroduodenoscopy, CT-computed tomography.

esophagus might also serve as a nidus for superimposed infections. A summary of the complications is presented in Fig. 2.

3.8. Management

The management of AEN focuses on counteracting the mechanisms that lead to its development and minimizing risk factors (Fig. 3). Supportive care and stabilization are the mainstay of therapy. Fluid resuscitation assists in enhancing perfusion and helps limit the damage caused by ischemia.¹⁴ Patients should be monitored and managed for anemia. Oral intake should be restricted for bowel rest and parenteral nutrition can be instated, especially in malnourished patients. Nasogastric tubes

increase the risk of perforation and should be avoided.⁹

The preferred medication for acid suppression is a PPI, which could be transitioned to oral formulation once clinical condition improves. Oral PPI therapy should be continued for several months after resolution of symptoms to prevent stricture formation.¹⁴

Biopsy specimens can help identify underlying infection. Appropriate antimicrobial therapy can be selected using the results of esophageal cultures, fungal stains or direct visualization of multinucleated giant cells or inclusion bodies. Empirical antibiotics might be initiated if perforation is suspected or if there is evidence of rapid clinical decompensation, unexplained fevers or immunosuppression. Otherwise, antibiotics are not recommended in the management of AEN.⁹

Active bleeding could be controlled with submucosal adrenaline injections.³⁹ Self-expanding metallic covered stents placed endoscopically could also help achieve hemostasis.⁴² Balloon tamponade with a Sengstaken-Blakemore tube should be avoided because of the risk of perforation.⁴³ In cases of perforation resulting in mediastinitis or abscess formation, surgical intervention is required. The usual procedure is an emergent esophagectomy followed by elective reconstruction using gastric or enteric tube.^{35,43}

A repeat endoscopy should be performed to ensure disease resolution and identify potential stricture formation 4 weeks after initial presentation. The first line treatment for strictures is endoscopic balloon dilation with a large proportion of patients

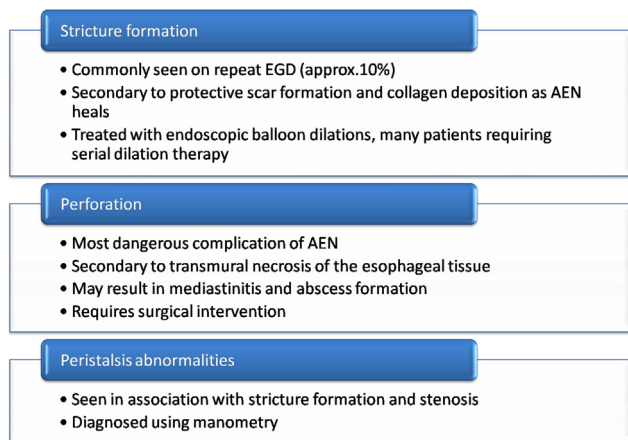


Fig. 2. Complications of acute esophageal necrosis.

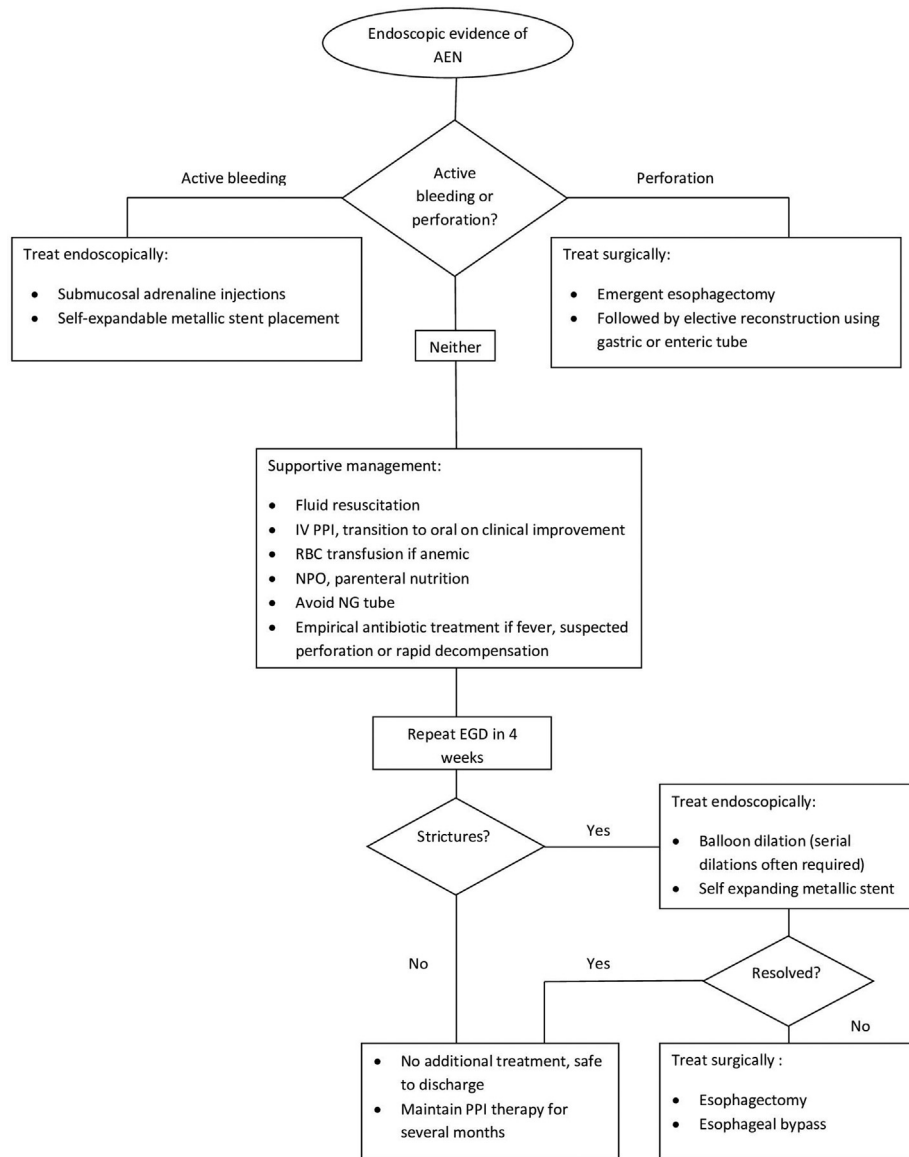


Fig. 3. An algorithm for managing acute esophageal necrosis.

requiring serial endoscopies with long term balloon dilation therapy.⁴⁴ If strictures persist despite serial dilations, surgery is recommended which consists of esophagectomy and esophageal bypass.⁴⁵

3.9. Prognosis

Prognosis of AEN is dependent on the extent of esophageal damage, the baseline medical conditions and health status of the patient. Other prognostic factors studied by Kim et al. include hemoglobin and albumin levels as well as age, pulse rate, and sepsis.⁴⁶

Overall, the mortality rate of AEN is high and was established as 32% in a study conducted by Abdullah et al.² However, this may likely be due to the

effect of simultaneous underlying critical illness. The same study observed a favorable outcome in more than 60% of patients who were treated appropriately. Gurvits et al. argue the mortality due to AEN itself is approximately 6%.¹⁰ Nonetheless, AEN remains a disease with life-threatening potential which should be suspected in elderly males with general debilitation and multiple medical conditions, who also exhibit symptoms of UGB and hemodynamic compromise.

4. Conclusion

AEN is a rare clinical syndrome occurring due to a combination of esophageal ischemia, increased acid

reflux, and reduced mucosal defenses. A high index of suspicion should be maintained in elderly male patients with chronic health problems presenting with signs and symptoms of UGB. EGD is diagnostic and demonstrates diffuse, circumferential darkening of the esophageal mucosa predominantly in the distal esophagus, extending as far as the GEJ. Treatment involves aggressive fluid resuscitation, NPO orders, IV proton pump inhibitors and red blood cell transfusions. AEN can carry an unfavorable prognosis, in most part due to the severity of underlying conditions present in most patients. However, early management and treatment are vital in reducing mortality, which can be achieved if clinicians have better understanding and awareness of this condition.

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Conflict of interest

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