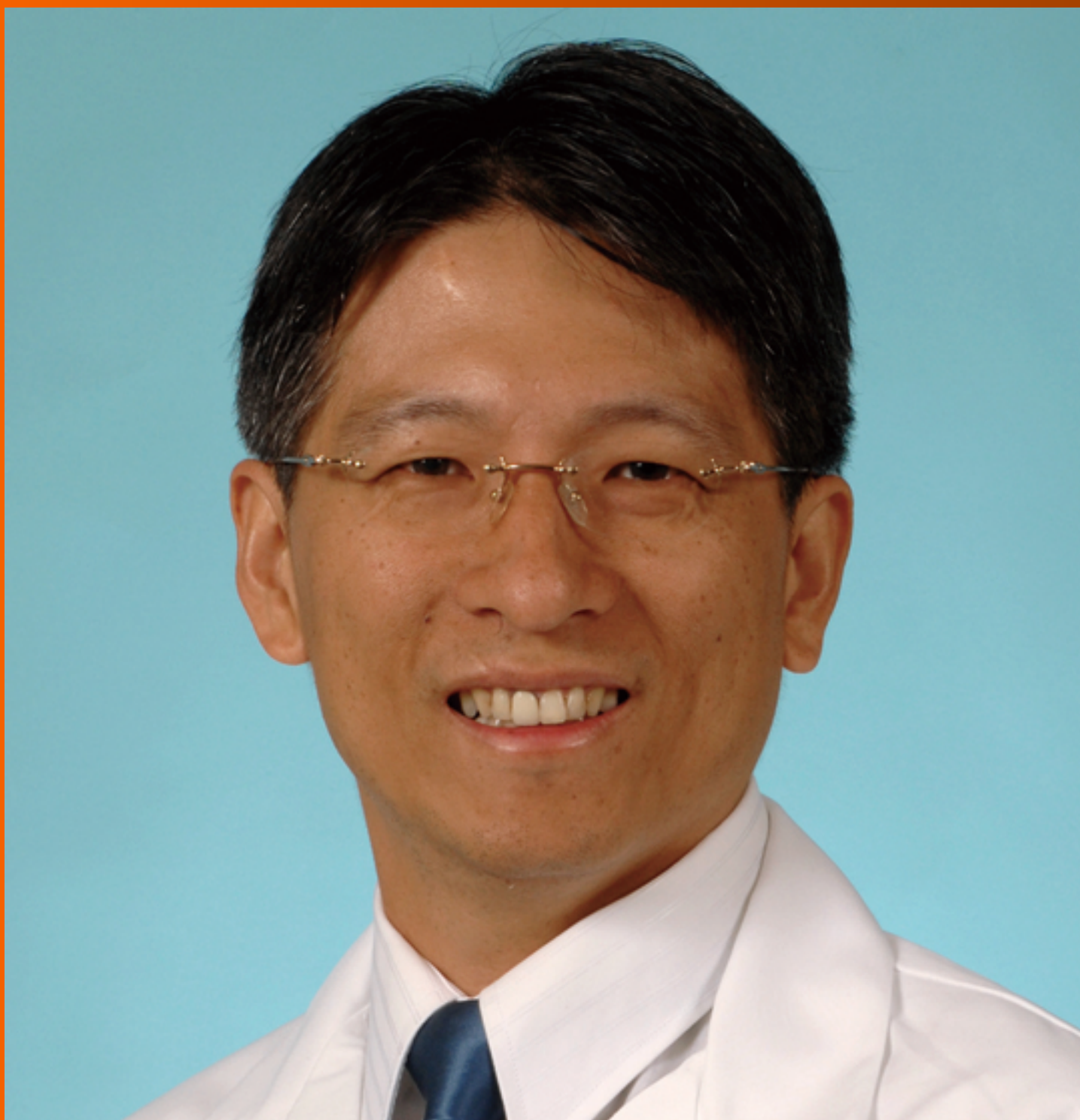


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Gastrointestinal amyloidosis: A focused review

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Abstract

Amyloidosis, a heterogeneous group of disorders, is characterized by the extracellular deposition of autologous, insoluble, fibrillar misfolded proteins. These extracellular proteins deposit in tissues aggregated in β -pleated sheets arranged in an antiparallel fashion and cause distortion to the tissue architecture and function. In the current literature, about 60 heterogeneous amyloidogenic proteins have been identified, out of which 27 have been associated with human disease. Classified as a rare disease, amyloidosis is known to have a wide range of possible etiologies and clinical manifestations. The exact incidence and prevalence of the disease is currently unknown. In both systemic and localized amyloidosis, there is infiltration of the abnormal proteins in the layers of the gastrointestinal (GI) tract or the liver parenchyma. The gold standard test for establishing a diagnosis is tissue biopsy followed by Congo Red staining and apple-green birefringence of the Congo Red-stained deposits under polarized light. However, not all patients may have a positive tissue confirmation of the disease. In these cases additional workup and referral to a gastroenterologist may be warranted. Along with symptomatic management, the treatment for GI amyloidosis consists of observation or localized surgical excision in patients with localized disease, and treatment of the underlying pathology in cases of systemic amyloidosis. In this review of the literature, we describe the subtypes of amyloidosis, with a primary focus on the epidemiology, pathogenesis, clinical features, diagnosis and treatment strategies available for GI amyloidosis.

Key Words: Gastroenterology; Hepatology; Amyloidosis; Dysmotility; Endoscopy; Therapeutics

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Core Tip: This manuscript focuses on a rare disease entity that can cause significant morbidity and mortality, especially amongst the elderly patient population. Lack of awareness regarding the possibility of gastrointestinal amyloidosis, which presents with vague symptoms common to a host of disorders, can lead to unnecessary testing and delays in diagnosis, contributing to poor outcomes. Physicians should consider the presence of gastrointestinal amyloidosis, especially in elderly patients with conditions predisposing them to the development of amyloid deposition.

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INTRODUCTION

In 1853, Rudolf Virchow first used the term “amyloid” to describe tissue deposits which showed close similarity to starch after they were dyed with iodine and sulphuric acid^[1]. Amyloidosis encompasses a heterogeneous group of disorders characterized by the extracellular deposition of autologous fibrillar proteins, which aggregate into a three-dimensional β -lamina disposition (β -pleated sheets aligned in an anti-parallel fashion) in tissues, disrupting normal tissue architecture and function^[2,3]. According to the Genetic and Rare Disease Information Center (GARD) of the National Institute of Health (NIH), amyloidosis is a rare disease. It is known to have a wide spectrum of possible etiologies and clinical manifestations, thereby making an accurate assessment of epidemiology extremely difficult. According to the data available from the NIH, AL (amyloid light chain) amyloidosis has an incidence of 1 case per 100000 person-years in Western countries^[4]. Systemic amyloidosis is more common than localized disease, and the annual incidence of primary systemic amyloidosis is 78% whereas that of secondary systemic amyloidosis is only 6% every year in the United States^[4]. In the literature, about 60 heterogeneous amyloidogenic proteins have been identified, out of which 27 are associated with known disease in humans^[5]. Based on the location of production of amyloidogenic precursor protein and its deposition within the tissues, it can be classified into two distinct subtypes: Systemic and localized amyloidosis^[6]. GI tract involvement may be a feature of both subtypes^[6]. Gastrointestinal (GI) amyloidosis is defined as the presence of GI signs and symptoms along with direct biopsy verification of the disease. However, as per the current literature, GI amyloidosis with direct biopsy verification from the GI tract may be a rare phenomenon. Hence, in this review, we describe the different subtypes of amyloidosis with associated amyloid precursor proteins deposited in tissues. We also describe the incidence rates of amyloidosis reported in different healthcare systems throughout the world. Additionally, we detail the pathogenesis, clinical presentations, methods to establish diagnosis, and the treatment strategies available for GI amyloidosis.

METHODS

A thorough literature search was performed to identify articles on amyloidosis of the GI tract and its clinical presentations. The authors used search engines such as PubMed, Google Scholar, and Ovid MEDLINE to search for published literature on GI amyloidosis between the years 1960 and 2020. A detailed literature search of the articles referenced in the identified publications was also performed. Furthermore, data and statistics available from national organizations such as the GARD were also researched. The keywords used in the literature search included, but are not limited to: “amyloidosis”, “gastrointestinal amyloidosis”, “localized amyloidosis”, “systemic amyloidosis”, “amyloid pathogenesis”, “hepatic amyloidosis”, “amyloidosis treatment”, “gastrointestinal amyloidosis treatment”, and “gastrointestinal

amyloidosis prognosis". The inclusion criteria set by the authors consisted of articles published between the years 1960 and 2020, published articles available in the English language, data and statistics available from national organizations such as the NIH, and published articles or guidelines related to the therapeutic options available for the management of GI amyloidosis in all clinical settings. The exclusion criteria consisted of duplicate articles or abstracts only, articles published before the year 1950, articles published in a language other than English, and unpublished research on GI amyloidosis. Application of the inclusion and exclusion criteria yielded a total of 3197 articles which were carefully reviewed by all the authors for this review of the literature. A total of 65 references ultimately were used for the purposes of drafting this narrative review.

DISCUSSION

As described earlier, amyloidosis refers to a heterogeneous group of disorders characterized by extracellular deposition of fibrillar proteins, which can disrupt tissue structure and function. On electron microscopy, amyloid fibrils are approximately 10 nm in diameter, and on polarized light microscopy after staining with Congo Red (CR) dye, they have the characteristic apple green-birefringence appearance^[5]. According to the 2010 recommendations from the Nomenclature Committee of the International Society of Amyloidosis, about 60 heterogeneous amyloidogenic proteins have been identified, out of which 27 have been found to be associated with known human disease^[7].

CLASSIFICATION

Amyloidosis can be classified into two main subtypes based on the location of production of the amyloidogenic precursor protein and its deposition within the tissues (Table 1)^[6]. The classification is as follows^[6,8].

Systemic amyloidosis

The most common subtype. It is characterized by the production of amyloidogenic precursor proteins at a site remote from the organ of amyloid deposition. It can either be due to acquired conditions such as plasma cell dyscrasias, or hereditary conditions due to modifications in the transthyretin (TTR) gene. Table 2 summarizes the common forms of systemic amyloidosis along with organ-specific involvement^[8].

Localized amyloidosis

It is characterized by the production of amyloidogenic precursor proteins at the same location as its deposition. It may commonly involve the respiratory tract, urinary bladder, breast, skin, or the GI tract. A single center retrospective analysis by Cowan *et al.*^[6] reported that out of the 3.3% of patients with biopsy proven amyloidosis, only 21% had amyloidosis restricted to the GI tract^[6]. Hence, localized amyloidosis is an uncommon entity.

EPIDEMIOLOGY

According to the GARD, amyloidosis is a rare disease entity. It is known to have a wide spectrum of possible etiologies and clinical manifestations, thereby making an accurate assessment of epidemiology extremely difficult. Furthermore, regional variations in the environment *i.e.*, prevalence of local infections and autoimmune diseases which predispose to chronic inflammation, and genetic factors such as polymorphisms in the genes encoding for amyloid precursors may also contribute significantly to the likelihood of developing the disease^[9]. Studies, although limited, have been conducted to evaluate the epidemiology of the disease in the United States and worldwide. According to the latest statistics available from the NIH, AL amyloidosis has an incidence of 1 case per 100000 person-years in Western countries, and in the United States approximately 1275 to 3200 new cases are reported every year^[4]. Systemic amyloidosis is more common than localized amyloidosis, and the annual portion of new cases with primary systemic amyloidosis (AL) is 78% whereas secondary systemic amyloidosis (AA) represents only 6% of these cases every year in

Table 1 Differences in systemic and localized gastrointestinal amyloidosis

Systemic gastrointestinal amyloidosis	Localized gastrointestinal amyloidosis
More common subtype	Less common subtype
Amyloid production at a remote location with subsequent deposition in the GI tract	Amyloid production in the GI tract with subsequent deposition locally
Presence of amyloid precursor proteins in the blood	Amyloid precursor proteins absent in the blood
Associated with plasma cell dyscrasia, chronic inflammatory conditions, dialysis, or hereditary conditions	Not associated with an underlying disease pathology
Amyloid precursor protein deposited include AL, AA, A β 2M and ATTR	Amyloid precursor protein most deposited is AL
Management consists of symptomatic management and treatment of the underlying etiology	Management consists of observation or surgical excision of the localised deposition
Prognosis depends on the type and amount of amyloid deposition	Good prognosis. No transition to systemic type

AL: Monoclonal light chain; AA: Serum amyloid A; A β 2M: β 2-microglobulin amyloid; ATTR: Familial transthyretin-associated amyloidosis; GI: Gastrointestinal.

Table 2 The common forms of systemic amyloidosis with organ involvement

Type of systemic amyloidosis	Causative protein	Organ involvement
Primary systemic amyloidosis	Monoclonal light chain (AL)	Heart, Kidneys, Liver, Peripheral nervous system, Autonomic nervous system, and Gastrointestinal tract
Senile systemic amyloidosis	Wild-type transthyretin (ATTR)	Heart
Hereditary systemic amyloidosis	Mutant transthyretin (ATTR); Apolipoprotein 1 (AApoA1); Mutant fibrinogen A alpha (AFib); Lysozyme (ALys)	Heart; Heart, Kidneys, Liver, Peripheral nervous system, and Skin; Kidneys and Liver; Kidneys and Liver
Isolated Atrial Systemic Amyloidosis	Atrial natriuretic factor (AANF)	Heart
Secondary Systemic Amyloidosis	Serum amyloid A (AA)	Kidneys, Heart, and Gastrointestinal tract
Dialysis-Related Systemic Amyloidosis	β 2-microglobulin (A β 2M)	Osteoarticular tissue, Circulatory system, and Gastrointestinal tract
Finnish-type Systemic Amyloidosis	Gelsolin (AGel)	Lattice dystrophy of cornea, and Corneal neuropathy

the United States^[4]. Familial transthyretin-associated amyloidosis, believed to be less common and with a currently unknown incidence rate, constitutes approximately 10% to 20% of diagnosed cases at tertiary hospitals in the United States^[4]. Outside the United States, similar trends in incidence have been observed. In the United Kingdom, Pinney *et al*^[10] reported a global incidence of amyloidosis of 5 cases per million person-years, out of which 3 cases per million person-years were attributed to the AL amyloidosis and 1 case per million person-years to AA amyloidosis^[10]. Similarly, Hemminki *et al*^[11] estimated the incidence of amyloidosis to be 8 patients per million person-years in Sweden, from which 3 cases per million person-years were credited to AL amyloidosis and 2 cases per million person-years to AA amyloidosis^[11]. Typically, amyloidosis manifests later in life and more commonly affects the older demographic (mean age for the AL subtype is 63 years)^[12]. A higher incidence and prevalence of the disease has been reported in males as compared to females^[12]. In the United States, the literature also reported a substantial increase in amyloidosis-related mortality from 1.77 to 3.96 per million between 1979 and 2015, with the highest mortality rates noted in the African-American population^[13].

Involvement of the GI tract can be seen in both localized (limited only to the gut) and systemic (most commonly AL subtype) amyloidosis. GI amyloidosis is defined as the presence of GI signs and symptoms along with direct biopsy verification of the disease^[14]. It is more commonly seen in elderly males. Yen *et al*^[15] conducted a single center retrospective cohort study from 2008 to 2017 in 583 amyloid patients and observed that only 96 (16.8%) patients had GI signs and symptoms^[15]. Out of these 96

patients, 82 underwent esophagogastroduodenoscopy (EGD) or colonoscopy with biopsy, and it was reported that only 37 (45%) patients had biopsy proven GI amyloidosis, whereas 45 (55%) patients had absence of GI amyloidosis on biopsy^[15]. Similarly, another retrospective study which evaluated 2337 patients in a 13-year period using the Boston University Amyloid Treatment and Research Program database reported biopsy proven GI Amyloidosis in only 76 (3.3%) of the patients^[6]. Furthermore, on EGD or colonoscopy, the site of highest diagnostic yield from biopsy specimens was found to be the duodenum, followed by the stomach, colon and rectum, and esophagus^[6,15]. Hence, it can be concluded that GI amyloidosis with direct biopsy verification from the GI tract is a rare phenomenon. There is also a significant paucity of data on GI amyloidosis with most of it available either from small, retrospective single center studies, or isolated case reports. Therefore, we strongly advocate for the need for additional large multi-center prospective studies to capture the impact of GI amyloidosis globally and its burden on the healthcare system.

PATHOGENESIS

The basic pathogenic mechanism of amyloidosis involves the extracellular deposition of insoluble protein fibrils derived from amyloid precursor proteins in tissues^[16]. These are composed of low molecular weight subunits arranged in antiparallel β -pleated sheets^[16]. In GI amyloidosis, infiltration of extracellular misfolded proteins can be seen in the different layers of the GI tract.

Mucosal infiltration

The most common site of mucosal infiltration is the duodenum, followed by the stomach, colorectum and the esophagus^[17]. Furthermore, the subtype of amyloid protein deposited governs the clinical presentation^[18,19].

AL amyloid deposition is usually seen in the muscularis mucosa, submucosa and muscularis propria, often leading to the formation of protrusions. It may present with symptoms of bowel obstruction.

AA amyloid deposition is seen mainly in the mucosa, which may lead to increased friability and erosions in the involved area. It may present with diarrhea and clinical features of malabsorption.

β 2-microglobulin amyloid ($A\beta_2M$) deposition is usually seen in patients on hemodialysis and corresponds to increased mean time on dialysis. $A\beta_2M$ deposits can be seen in the blood vessels of the GI tract, mucosa, submucosa, and muscularis propria. It may present with features of mucosal ulceration.

Neuromuscular infiltration

It is characterized by the deposition of the amyloid proteins in the neuromuscular layer of the GI tract. This can affect the intrinsic nerve plexus (myenteric or submucosal nerve plexus) and the muscularis externa (longitudinal and circular muscles) leading to abnormal peristalsis, abnormal GI transit times and dysmotility^[20-22].

Hepatic amyloidosis, a manifestation of systemic amyloidosis, has a similar pathogenic mechanism and is characterized by the extracellular deposition of fibrillar amyloid protein (AL) in the hepatic parenchyma^[23]. It is a diagnostic challenge as it shares numerous clinical manifestations with other common chronic liver diseases, and has a poor prognosis particularly in patients with jaundice^[23].

CLINICAL MANIFESTATIONS

The clinical manifestations of GI amyloidosis depends on the amount and location of the amyloid deposits, irrespective of whether it is primary or secondary systemic amyloidosis^[17]. Patients with localized amyloidosis may have similar clinical features as those with systemic disease. All patients with amyloidosis share common presenting symptoms such as fatigue, light-headedness, anorexia, and weight loss^[24]. The common GI-specific abnormalities include.

Gastrointestinal bleeding

May occur from any site of amyloid deposition and can be seen in up to 57% of patients^[25]. The underlying cause is commonly mucosal lesions (amyloidoma ulcers,

erosions, polypoid lesions, hematomas or submucosal hemorrhage), vascular friability, or in some cases bowel ischemia^[25,26]. Massive occult bleeding from the GI tract is usually seen with dialysis-related amyloidosis^[27].

Malabsorption

May present with symptoms such as diarrhea, weight loss, steatorrhea, anorexia, or dizziness and is usually secondary to mucosal infiltration, pancreatic insufficiency, or bacterial overgrowth^[28,29].

Protein-losing gastroenteropathy

GI specific manifestations include diarrhea, edema, and ascites. It is secondary to mucosal lesions which may lead to abnormal protein loss from the GI tract^[30].

Chronic gastrointestinal dysmotility (Stasis syndrome)

May present with nausea, vomiting, dysphagia, gastroparesis, gastro-oesophageal reflux, loss of appetite, constipation, abdominal pain, bloating, or clinical features of chronic intestinal pseudo-obstruction^[20,21,25]. Dysmotility can be secondary to myopathic and neuropathic dysfunction^[25]. Some patients may present with persistent diarrhea due to rapid transit times secondary to dysmotility, intestinal inflammation and bacterial overgrowth^[25,31,32].

Hepatic amyloidosis

Has no clinical significance in most patients due to mild clinical manifestations^[33]. Hepatomegaly and mild elevations in alkaline phosphatase (ALP) are the most frequent findings^[34]. Other symptoms include weight loss (72%), fatigue (60%), abdominal discomfort (53%) and anorexia (26%)^[25]. Elevated direct serum bilirubin levels (> 2 mg/dL) are often associated with a poor prognosis^[25,34].

Uncommon symptoms

Some patients with GI Amyloidosis may have features of cholangitis, pneumatosis intestinalis (gas pockets within the bowel wall), or bowel perforation^[35-37].

The physical examination findings in patients with amyloidosis depend on the organ specific infiltration by abnormal proteins^[9]. However, from a purely GI perspective, physical examination may reveal macroglossia (enlarged tongue) in up to 50% of the cases^[25]. On abdominal examination, hepatosplenomegaly and ascites may be the most frequent findings^[34,38].

ESTABLISHING THE DIAGNOSIS

A high degree of clinical suspicion is necessary to establish a definitive diagnosis of GI amyloidosis. Due to the rarity of the condition coupled with non-specific signs and symptoms at the time of presentation, these patients usually undergo extensive and unnecessary testing to identify the cause of clinical presentation. GI amyloidosis should be high on the list of possible differential diagnoses in patients presenting with non-specific GI symptoms and a past medical history of disorders commonly associated with amyloidosis, such as plasma cell dyscrasia, chronic renal failure on hemodialysis, and other chronic inflammatory conditions (*e.g.* rheumatoid arthritis and inflammatory bowel disease). A positive family history of amyloidosis should also alert the provider to suspect GI amyloidosis^[9]. Laboratory investigations in these patients may reveal anaemia, mild elevations in ALP levels, elevations of acute phase reactants (due to the underlying chronic inflammatory condition) and deficiencies from malabsorption. Radiological investigations in GI amyloidosis are usually non-specific^[39]. Some common features seen on computer tomography (CT) or magnetic resonance imaging (MRI) include^[25,39-41]: (1) Diffuse or nodular wall thickening of the involved bowel segment; (2) Dilatation depending upon the degree of hypomotility; (3) Presence of fluid levels in dilated bowel loops; (4) Luminal narrowing secondary to amyloid infiltration or ischemia; (5) Attenuation due to cluster of calcifications or mucosal ulcerations; (6) Presence of polypoid protrusions or masses mimicking cancer; (7) Loss of haustrations; (8) Mesenteric thickening or adenopathy; and (9) Decreased hepatic attenuation with or without areas of calcification (Ultrasound may demonstrate heterogenic hepatic echotexture).

Although radiological investigations may provide a clue to the extent and area of involvement, the gold standard test to establish a diagnosis of GI amyloidosis is tissue

biopsy followed by CR staining and visualization under polarized light microscopy^[42]. Based on the patients presenting symptom, an EGD or colonoscopy should be performed to obtain the biopsy specimen. As mentioned earlier, the site of highest diagnostic yield from biopsy specimen in the GI tract has been found to be the duodenum, followed by the stomach, colorectum, and the esophagus^[6,15]. A liver biopsy may also be performed to confirm hepatic infiltration of the amyloid proteins; however, a transjugular route should be used to prevent fatal bleeding complications^[43,44]. Additionally, the study by Yen *et al*^[15] reported biopsy negative disease in 55% of the patients. However, these patients met the Rome IV criteria for several functional bowel disorders, but only 23.2% underwent additional diagnostic studies for functional assessment of the luminal gastrointestinal tract (such as esophageal or anorectal manometry, capsule endoscopy, or gastric emptying studies)^[6]. Hence, the authors recommend the need for additional diagnostic studies to evaluate for motility disorders in patients with clinical features of GI amyloidosis but a negative result on biopsy.

Amyloid fibrils appear as amorphous, eosinophilic deposits on routine hematoxylin-eosin stained preparations, which may sometimes be confused with hyaline changes or sclerosis^[45]. Hence, CR staining with the characteristic apple-green birefringence of CR-stained deposits under polarized light has been considered the gold standard for a definitive diagnosis since its inception^[45]. However, despite a high sensitivity and specificity of the CR-staining method, false negative results may be seen due to the quantity of amyloid deposition in the tissue, the age of the deposits, thickness of the sections for visualization, fixation of the tissues on the slide, or the staining procedure itself^[46]. Therefore, newer methods are being developed to act as an adjunct for diagnosis. Digitally reinforced hematoxylin-eosin polarization (DRHEP), a newly introduced technique which uses both routine light microscopy and digital photography, can detect weak birefringence which is not recognized through the microscope objective^[45]. Although the use of DRHEP is currently limited to kidney biopsies, its role for GI amyloidosis is currently under investigation^[45].

TREATMENT

Once the diagnosis of GI amyloidosis is established, the biopsy specimen needs further analysis to determine the subtype of amyloid deposition which can then help guide therapy^[47]. The management of GI Amyloidosis includes:

Symptomatic management

Symptom control in patients with GI amyloidosis is tailored to the clinical presentation. In patients with symptoms of dysmotility (stasis syndrome), dietary modifications, adequate hydration, and the use of pro-kinetic and anti-emetic agents is advised. Dietary modification consists of frequent, small-volume liquid or homogenized foods with low soluble fibre and fat content along with additional nutritional supplementation when necessary^[48]. Prokinetic agents such as metoclopramide, erythromycin or domperidone (if indicated) are the mainstay of therapy for dysmotility^[48]. Parenteral nutrition is indicated in severe cases of chronic GI dysmotility. Patients with dysphagia may be successfully treated with balloon dilation^[49]. For patients with diarrhea or bloating, anti-diarrheal agents such as loperamide should be initiated^[50]. Empiric antibiotic therapy should be considered in patients with diarrhea and suspected bacterial overgrowth. In patients with severe diarrhea associated with protein-losing enteropathy, literature reports good response to corticosteroid and octreotide therapy^[51,52]. The management for GI bleeding includes triage to appropriate settings, supportive measures, volume resuscitation if needed, and source control through ligation of the bleeding blood vessel. Surgical intervention may be necessary in cases of severe obstruction, uncontrolled GI hemorrhage or bowel ischemia^[8,53]. Patients with macroglossia causing airway obstruction or obstructive sleep apnea may need partial resection of the tongue to alleviate symptoms^[54].

Treatment of the underlying condition for systemic amyloidosis

No specific treatment protocols currently exist for the management of GI amyloidosis. Therapy varies significantly depending on the cause and type of amyloid protein deposited within the tissues (Table 3). The current management strategies based on the type of amyloid deposits available in literature include:

AL amyloidosis: The therapy is aimed at suppressing the production of monoclonal

Table 3 Management of gastrointestinal amyloidosis based on the amyloid protein

Gastrointestinal amyloidosis	AL amyloidosis	AA amyloidosis	Hereditary amyloidosis	Dialysis-related amyloidosis
Treatment strategy	Systemic: Eligible: Autologous stem cell transplantation (ASCT) for plasma cell dyscrasias. Non-eligible: No standard protocol; combination of Bortezomib, Melphalan and Dexamethasone has shown improved survival. Localized: Observation or localized surgical excision	Chronic inflammatory conditions: Biologics (anti-TNF antibodies, humanized anti-IL6 receptor antibody) and immunosuppressants. Familial mediterranean fever: Colchicine.	Liver production of transthyretin: Orthotopic liver transplantation (OLT). Disease modifying therapy: Transthyretin stabilizers (Tafamidis and Diflunisal), Doxycycline, Patisiran and Inotersen may be used on case-to-case basis	Prevention: Removal of plasmatic β_2 -microglobulin ($A\beta_2M$) through hemodialysis or peritoneal dialysis. Early renal transplant

immunoglobulin light chains through eradication of the malignant plasma cells^[55]. Autologous stem cell transplantation is the standard of care for plasma cell dyscrasias in eligible patients^[55]. For patients not eligible to receive autologous stem cell transplantation, the management guidelines are unclear; however, the use of combination therapy with Bortezomib, Melphalan and Dexamethasone has shown improved hematologic response rate and overall survival^[56]. The addition of Daratumumab (human monoclonal antibody against CD38) to bortezomib-based therapy has been evaluated but the results are yet to be published^[55]. Furthermore, a fully humanized monoclonal IgG1 anti-serum amyloid P component antibody (Dezamizumab) is also under evaluation for AL amyloidosis^[57].

AA Amyloidosis: Therapy is specifically directed at controlling the underlying disease which in turn helps reduce the acute phase response and production of serum amyloid A protein. Colchicine is used in the treatment of patients with Familial Mediterranean Fever^[58]. Biologic agents (activity against pro-inflammatory cytokines such as TNF- α , IL-1, and IL-6), cytotoxic agents and immunosuppressants have a key role to play in the management of underlying chronic inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, and psoriatic arthritis among others.

Hereditary amyloidosis: Therapy is aimed to eliminate the source of production of the genetically variant protein. The liver produces most of the circulating TTR in the body. Orthotopic liver transplantation can be used to significantly reduce the production of the mutant protein in patients where the liver is the culprit^[59]. Other disease modifying therapies such as TTR Stabilizers (Tafamidis and Diflunisal), Doxycycline, Patisiran and Inotersen may also be considered on a case-to-case basis^[59].

Dialysis-related amyloidosis: No medical or pharmacological therapy currently exists for dialysis-related amyloidosis^[60]. The prevention and treatment consists of removal of plasmatic $A\beta_2M$ through hemodialysis or peritoneal dialysis using ultrapure dialysate or with more biocompatible and high-flux membranes^[60]. Furthermore, early and successful renal transplantation leads to reduction in $A\beta_2M$ levels, which after a few years may lead to regression of the already deposited amyloid proteins^[61].

Treatment of localized amyloidosis: It is characterized by deposition of AL amyloid restricted to the GI tract. For patients who are asymptomatic, no intervention may be needed, and observation may be the key; however, patients with recurrent or severe symptoms may require localized surgical excision.

Moreover, the treatment strategies for GI amyloidosis are consistently evolving with a better understanding of the disease pathology and the development of newer agents with target specific actions. Clinical trials to assess the efficacy and the toxicity profile of newer agents are currently ongoing and available at clinicaltrials.gov^[62].

PROGNOSIS

The prognosis of GI amyloidosis depends on the extent of involvement of the GI tract, the quantity of deposition and the type of amyloid deposition. Literature reports that patients with AL amyloidosis and GI tract involvement had a worse prognosis than those without GI involvement^[63]. Additionally, patients with GI amyloidosis had involvement of additional organs, an increased number of poor prognostic factors, and

a more advanced disease than those without the involvement of the GI tract^[63]. Patients with AA amyloidosis were reported to have better median survival outcomes^[64]. Involvement of the liver was associated with poor prognosis and increased mortality, particularly in patients with jaundice at the time of initial presentation and those with elevated direct serum bilirubin levels (> 2 mg/dL)^[25,34].

CONCLUSION

Amyloidosis is characterised by the extracellular deposition of autologous fibrillar proteins aggregated into three-dimensional β -pleated sheets aligned in an anti-parallel fashion. Based on the location of production of amyloidogenic precursor protein and its deposition in tissues, it can be divided into two distinct subtypes, systemic and localized amyloidosis. Involvement of the GI tract (GI amyloidosis) may be seen with both subtypes. Patients with GI amyloidosis commonly present with fatigue, light-headedness, anorexia, weight loss, GI bleeding, features of malabsorption, protein-losing enteropathy, or chronic GI dysmotility. Infiltration of amyloid proteins in the liver may also be seen, often presenting with hepatomegaly and mild elevations of ALP. Presence of jaundice with liver involvement (elevated direct bilirubin levels > 2 mg/dL) is associated with a poor prognosis. Radiological investigations are usually non-specific, and a definitive diagnosis is established with a tissue biopsy followed by CR-staining. The characteristic apple-green birefringence of the CR-stained deposits under polarized light is diagnostic. In patients with a negative biopsy from the GI tract, the authors recommend for the need of additional investigations for motility disorders and referral to a gastroenterologist. The use of DRHEP, a newly introduced technique, is also being explored to aid in diagnosis. For all patients with localized GI amyloidosis, the management consists of observation or localized surgical excision; however, for those with systemic GI amyloidosis, therapy is directed towards the underlying disease pathology. Symptomatic management in these patients is tailored to the presenting symptoms. The overall survival outcome depends on the extent of involvement of the GI tract, the quantity, and type of amyloid deposition.

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Retrospective Study

Cost-effectiveness of endoscopic ultrasound-guided coils plus cyanoacrylate injection compared to endoscopic cyanoacrylate injection in the management of gastric varices

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Informed consent statement:

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Abstract

BACKGROUND

Cyanoacrylate (CYA) injection can be performed using a standard upper endoscopy technique or under endoscopic ultrasound (EUS) guidance alone or in combination with coils. There is little information available on the economic impact of these treatment methods.

AIM

To compare the cost-effectiveness of treating gastric varices by CYA injection *via* upper endoscopy *vs* coils plus CYA guided by EUS.

METHODS

This was an observational, descriptive, and retrospective study. Patients were allocated into two groups: A CYA group and coils plus CYA group. The baseline characteristics were compared, and a cost analysis was performed.

RESULTS

Overall, 36 patients were included (19 in the CYA group and 17 in the coils + CYA group). All patients in the CYA group had acute bleeding. They underwent a higher mean number of procedures (1.47 *vs* 1, $P = 0.025$), and the mean volume of glue used was 2.15 *vs* 1.65 mL, $P = 0.133$. The coils + CYA group showed a higher technical success rate (100% *vs* 84.2%), with a complication rate similar to the CYA group. The majority of CYA patients required hospitalization, and although the mean total per procedure cost was lower (United States \$ 1350.29 *vs* United States

Informed written consent was provided from all study participants or their legal guardians for attendance and research purposes.

Conflict-of-interest statement:

Carlos Robles-Medrandá is a key opinion leader and consultant for Pentax Medical, Boston Scientific, G-tech medical supply and MD consulting group. The other authors have nothing to disclose.

Data sharing statement:

All available data can be requested by contacting the corresponding author.

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\$ 2978), the mean total treatment cost was significantly different (United States \$ 11060.89 for CYA *vs* United States \$ 3007.13 for coils + CYA, $P = 0.03$).

CONCLUSION

The use of EUS-guided coils plus cyanoacrylate is more cost-effective than cyanoacrylate injection when the total costs are evaluated. Larger, randomized trials are needed to validate the cost-effectiveness of the EUS-guided approach to treat gastric varices.

Key Words: Cost-effectiveness; Endoscopic ultrasound-guided therapy; Gastric varices; Gastrointestinal bleeding; Hemostasis; Therapy

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Core Tip: There is little evidence regarding the economic impact of standard endoscopic cyanoacrylate therapy *vs* endoscopic ultrasound (EUS)-guided endovascular therapy in the management of gastric varices. In this retrospective study, we found that patients treated with endoscopic cyanoacrylate injection required hospitalization and had a significantly higher total treatment cost in comparison to those treated with an EUS-guided therapy. The incremental cost-effectiveness ratio analysis shows that in endoscopic therapy, each early rebleeding, adverse events, and day of hospitalization increased health-related costs on United States \$ 2670.80, United States \$ 8012.40, United States \$ 127.18 per presented event, respectively, when comparing with coils + cyanoacrylate group cost and presented events. Each inevitable death on the endoscopic group represented a health-related cost increase on United States \$ 8012.40 in comparison with EUS-guided therapy.

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INTRODUCTION

Variceal bleeding is the most expensive of all digestive diseases in terms of hospitalization charges^[1]. Although the prevalence of gastric varices (GV) is lower than esophageal varices (5% to 33%), and the risk of bleeding is also lower for GV than esophageal varices, the bleeding from GV can be severe, and the associated mortality rate is high^[1]. The incidence of bleeding was reported to be 25%, with re-bleeding rates as high as 40% and mortality rates of 50%^[2].

Endoscopy sclerotherapy with cyanoacrylate glue (CYA) has demonstrated higher hemostasis (> 90%) and lower rebleeding rates compared to band ligation or sclerotherapy with alcohol products for the management of GV^[3]. However, this procedure has been shown to be associated with significant adverse events. For example, pulmonary embolism due to CYA injection is a serious and sometimes fatal complication, which is seen in 4.3% of cases and is dependent on the volume of glue injected^[3]. Other related complications may include hemorrhage from post-injection ulcers, fever, abdominal pain, and needle impaction. In addition, the injection material can cause serious damage to the endoscope^[4].

Currently, endoscopic treatments with CYA injection can be performed under direct visualization using a standard gastroscope or under endoscopic ultrasound (EUS) guidance with the injection of CYA alone or in combination with coils^[5]. There is little information available in the current literature on the economic impact of these treatment methods for GV.

The aim of this study was to compare the cost-effectiveness of GV treatment with two different techniques, CYA glue injections using a standard gastroscope *vs* the use of coils plus CYA guided by EUS.

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MATERIALS AND METHODS

Study design

This was an observational, analytic, retrospective cohort study conducted in patients with cirrhosis and variceal bleeding, attended at an academic tertiary center in Guayaquil, Ecuador from November 2014 to March 2016 (Figure 1). The patients were categorized into two groups: One treated with only CYA injection by the standard upper endoscopy technique (CYA group) and the other treated by the EUS-guided insertion of coils + CYA injection (Coils + CYA group). The protocol of the study and consent form were approved by the Institutional Review Board, and the study was conducted according to the Declaration of Helsinki. All patients provided written informed consent for attendance purposes.

Population selection

For the study analysis, we considered ≥ 18 years old patients with gastroesophageal varices type II (GOV II, fundal varices communicating with esophageal varices) and isolated gastric varices type I (IGV I, fundal varices within a few centimeters of the gastric cardia) according to the classification described by Sarin and Kumar^[6]. The study included patients with acute bleeding or a history of previous bleeding due to GV (secondary prophylaxis).

We did not include patients with concurrent hepatorenal syndrome and/or multi-organ failure; esophageal stricture; splenic or portal vein thrombosis; a platelets count less than 50,000/mL or an international normalized ratio > 2 ; pregnancy^[7]; as well as patients with incomplete medical reports, or those without 6-mo follow-up.

General approach

One expert endoscopist (Robles-Medranda C) performed all endoscopic procedures in a hospital-based interventional endoscopy suite, where EUS and fluoroscopy were available. Endoscopic procedures were performed under general anesthesia and with antibiotic prophylaxis. After the procedure, the patients in both groups were observed for 2 h in the recovery room before being discharged. Patients were hospitalized if they had active bleeding or if they had early post-treatment bleeding according to the Baveno VI consensus^[8]. All patients with acute upper GI bleeding admitted to receive a standard assessment and were given resuscitation fluid, antibiotics, blood components if necessary, and intravenous octreotide (50 μ g bolus plus 50 μ g/h) for at least 72 h. Upper endoscopy was performed within 24 h of hospital admission.

Endoscopic technique

A 3.2-mm forward-view endoscope (EG29-i10 and EG 2990-I series, Pentax Medical, Hoya Corp, Japan) was used to perform the standard endoscopic technique. EUS was performed using a 3.8-mm working channel linear-array therapeutic echoendoscope (EG 3870UTK; Pentax Medical, Hoya Corp, Japan) attached to an ultrasound console (Avius Hitachi, Tokyo, Japan). Active flow within the GFV was confirmed by color Doppler and fine flow Doppler color before and after the treatment.

CYA injection by upper endoscopy: The 2-Octyl-CYA (Dermabond; Ethicon, Piscataway, NJ, United States) was injected through a 21 or 22 G needle. This type of CYA precludes the need for a diluent, such as lipiodol. After puncturing varix and injecting the CYA, the needle was rinsed with saline solution. A proper dosage has not been established, and it is usually decided by the endoscopist at the time of intervention, taking into account gastric varix size and the initial success in arresting bleeding, considering that larger doses can increase the risk of embolism to distal organs. However, no more than 2.5 mL of CYA was injected per session per our institution's protocol for this technique (Figure 2).

EUS-guided deployment of coil(s) plus CYA injection: First, a standard diagnostic upper endoscopy was performed to classify the varices according to the classification described by Sarin and Kumar^[6]. Then, an echoendoscope was positioned in the distal esophagus (anterograde transesophageal, transcrural approach) to endosonographically evaluate the gastric fundus, intramural varices, and gastric varices feeder vessels. Once positioned, water was instilled in order to fill the gastric fundus, improving the acoustic coupling and visualization of the GFV. EUS color Doppler imaging was used to allow direct visualization of the variceal flow. Then, a 19-gauge EUS-FNA needle (Expect flexible; Boston Scientific, United States) was used to puncture the vessel, the stylet was withdrawn, and a syringe with negative pressure was used to evaluate the blood return and therefore the intravascular location. Once

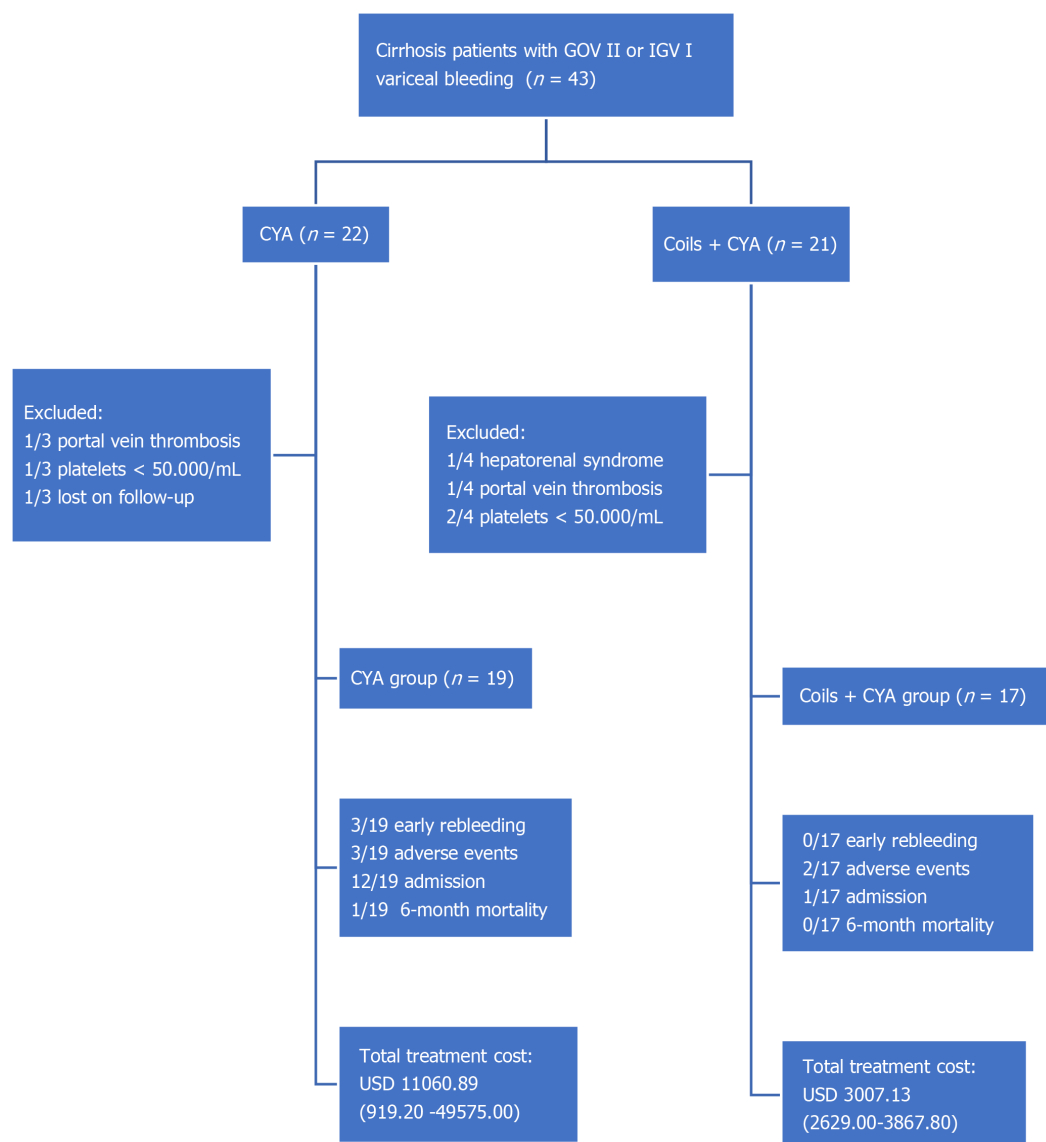


Figure 1 Study flowchart. CYA: Cyanoacrylate; GOV: Gastroesophageal varices; IGV: Isolated gastric varices; USD: United States dollar.



Figure 2 Endoscopic view of actively bleeding type II gastroesophageal varices treated with endoscopic cyanoacrylate injection.

the location was confirmed, 1 mL of saline solution was instilled to prevent blood clotting in the needle lumen, and then 2 mL of water-soluble contrast agent (Ultravist, Bayer, Ecuador) was injected under fluoroscopic evaluation to further ensure the intravascular location and to determine varix flow direction (afferent or efferent), as has been reported in a previous study^[9]. Then, coils were delivered, and the 2-Octyl-CYA was injected. The coils used were intravascular embolization coils (10–16 mm coiled diameter, 12–20 cm straight lengths, 0.035 inches in diameter, Nester Embolization Coil; Cook Medical) and were delivered into the vessel through the FNA needle using the stylet as a pusher. Special attention was paid to not place the needle tip at the counter wall because of the risk of perforation, bleeding, and coil extrusion and to allow enough space for the coil to curl. The 2-Octyl-CYA (Dermabond; Ethicon, Piscataway, NJ, United States) was injected using the same needle, and then 1 mL of normal saline solution was injected to rinse the needle. The diameter and number of coils (10 to 16 mm) and the volume of 2-Octyl-CYA injected were calculated according to the diameter of the vessel measured on EUS. After 90 to 120 s, the CYA was solidified, the risk of bleeding due to the puncture decreased, and the needle was withdrawn. The final obliteration of the vessel was evaluated using Doppler imaging 5 min after withdrawal (Figure 3).

Patients follow-up and data abstraction

Efficacy was measured by technical success, defined as successful technique performance, and functional success, defined as the complete obliteration of varix by endoscopy and/or by the absence of Doppler flow on EUS. Safety was determined based on the development of adverse events related to the procedure within and 30 d after the procedure.

Follow-up was performed in accordance with our institution's protocol for these kinds of procedures by standard endoscopy in the CYA group and by EUS and upper endoscopy at 1, 3, and 6 mo post-procedure. Hemostasis, early post-treatment bleeding, and late post-treatment bleeding were considered according to the Baveno VI consensus^[7].

Demographic data, endoscopic procedure records, cost variables [both endoscopic procedure and hospitalization; currency: United States of America dollar, United States dollar (USD); ISO 4217 code: USD] and clinical follow-up were obtained from institutional database register (SIAM V2.0, MD Consulting Group, Guayaquil, Ecuador). A 6-mo mortality was confirmed through the Ecuadorian Civil Registration database.

Statistical analysis

Technical considerations: The data analysis was reviewed by the institutional biostatistician (M.P.-T.). Statistical analysis was performed using R v3.6.3 (R Foundation for Statistical Computing; Vienna, Austria). A *P* value < 0.05 was considered to be statistically significant.

Sample size: A sample of 15 participants per study group was calculated using corresponding formula to compare two means (two-samples, one-sided), on the basis of a 5% α error, a 20% β error, $\kappa = 2$, and a 3-mo post-bleeding mean charges (standard deviation, \pm SD) between CYA-treated cases (USD: 42.450 \pm 43.916) and controls (USD: 78.165 \pm 47.857), as described by Greenwald *et al*^[10].

Baseline characteristics: Demographic and clinical data were described by mean \pm SD or median (minimum–maximum range) in accordance with statistical distribution (Shapiro–Wilk test), for quantitative variables, and frequency (percentage) for qualitative variables. Hospitalization length was described in a range of days. Cost variables were described as means considering it properly for economic data in terms of further cost analyses^[10] but using the maximum–minimum range for easier comprehension of corresponding distribution. Data were also compared among CYA *vs* coils + CYA groups using Welch Two Sample *t*-test for normal-distributed and cost data, Mann–Whitney *U* test for skewed-distributed data, Pearson's Chi-squared or Fisher's Exact test for qualitative data, and Gray's test for the length of hospitalization.

Cost analysis: The incremental cost-effectiveness ratio (ICER) is a proportion of the difference in the mean cost of procedures between groups and the number of episodes of a specific outcome between groups, such as the number of deaths, adverse events, or days of hospitalization. This ratio represents the amount of money saved to prevent the aforementioned outcomes^[11]. The ICER in the present study was established in terms of the following efficacy outcomes: Early re-bleeding, adverse effects, length of

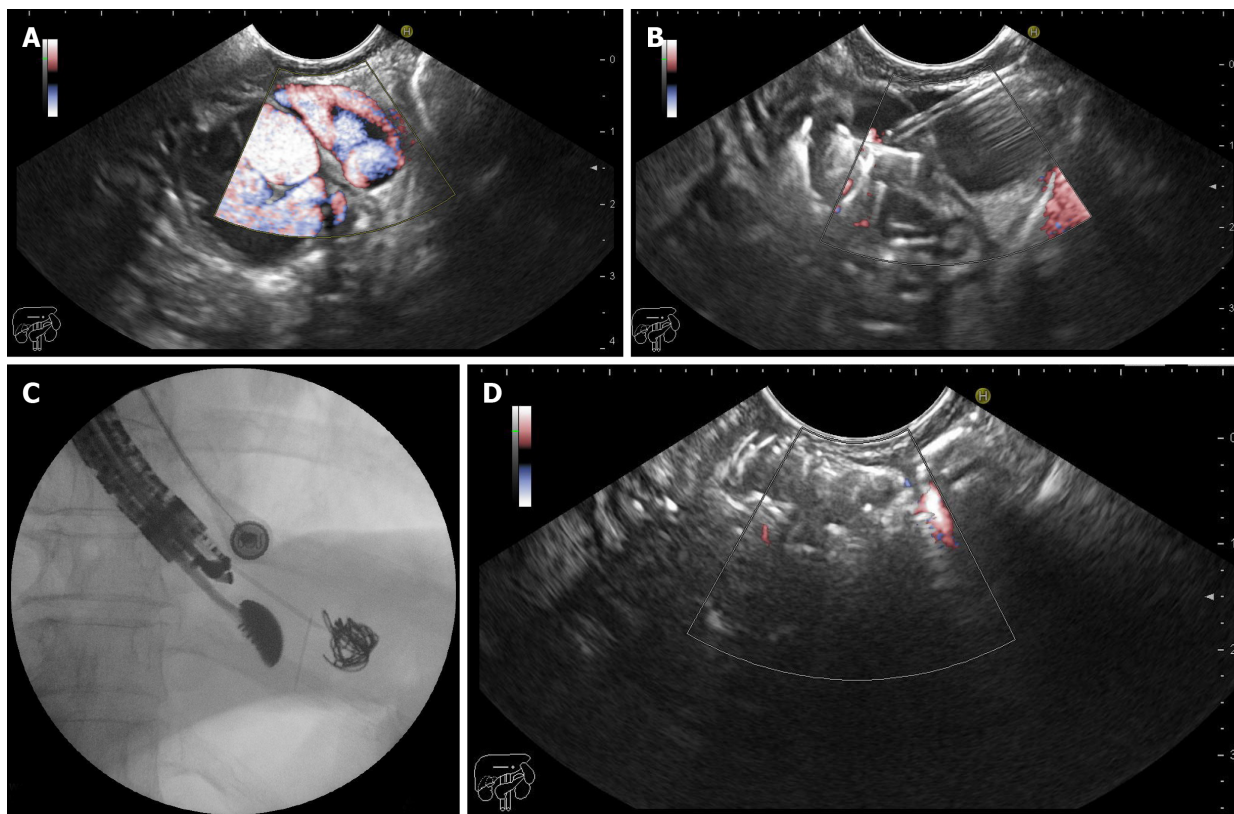


Figure 3 Endoscopic ultrasound-guided coiling plus cyanoacrylate injection for the management of gastric varices. A: Endoscopic ultrasound (EUS)-Doppler evaluation of the gastric varix feeder vessel; B: EUS-guided fine-needle puncture and cyanoacrylate injection; C: Fluoroscopic view of EUS-guided coiling of gastric varices; D: EUS-Doppler demonstrating absence of flow after combined therapy.

hospitalization, and 6-mo mortality. This corresponded to the difference between CYA *vs* coils + CYA in terms of the mean total treatment cost, divided by the difference between the numbers of events in each efficacy outcome, per the corresponding study group (Figure 4).

RESULTS

We enrolled 36 patients in the study (19 in the CYA group and 17 in the coils + CYA group). The overall mean age was 63.06 years old, and 20 (55.5%) patients were men. The baseline data are shown in Table 1.

Regarding the indications for the procedure, all 19 (100%) patients in the CYA group had a history of acute bleeding, while in the coils + CYA group, ten (58.8%) patients underwent the procedure for secondary prophylaxis.

GOV II type varices were predominant in both groups, being present in 12 (63.1%) and 12 (70.5%) patients in the CYA group and coils + CYA group, respectively. The mean varix size was 21.1 ± 8.7 mm in the CYA group and 22.6 ± 6.8 in the coils + CYA group.

The patients in the CYA group underwent a total of 28 procedures, with a mean of 1.47 procedures per patient. In this group, the mean volume of CYA used was 2.15 (0.6-2.4) mL. Conversely, in the coils + CYA, 17 procedures were performed (with a mean of 1 procedure per patient) using a mean volume of 1.65 (1.2-2.4) mL CYA and a mean of 2.1 (1-3) coils per patient. Technical success was achieved in 16 of the 19 (84.2%) patients in the CYA group, with 3 (15.8%) patients showing early rebleeding and with 3 (15.8%) adverse events, represented by 2 cases of pulmonary embolism and one death. In the coils + CYA group, technical success was achieved in all 17 (100%) patients, with no cases of early rebleeding and 2 (7.1%) adverse events (1 episode of fever and 1 of transient abdominal pain).

In relation to treatment modality, 13 (68.4%) patients in the CYA group were hospitalized for a mean of 3.36 (0-14) d, with most of the time spent in the Intensive Care Unit. Nevertheless, only 1 (5.9%) patient was hospitalized in the coils + CYA

Table 1 Baseline characteristics and cost description per intervention

	Total (n = 36)	CYA (n = 19)	Coils + CYA (n = 17)	P value
Age (yr), mean ± SD	63.06 ± 10.1	62.83 ± 11.5	63.29 ± 8.8	0.895 ¹
Gender (female), n (%)	16 (44.4)	9 (47.4)	7 (41.2)	0.970 ²
Indication, n (%)				< 0.001 ²
Acute bleeding	26 (72.2)	19 (100.0)	7 (41.2)	
Secondary prophylaxis	10 (27.7)	-	10 (58.8)	
Type of GV, n (%)				0.906 ²
GOV II	24 (66.7)	12 (63.1)	12 (70.5)	
IGV I	12 (33.3)	7 (36.9)	5 (29.5)	
Varix size (mm), mean ± SD	21.8 ± 7.8	21.1 ± 8.7	22.6 ± 6.8	0.578 ¹
Technical success (n of events), n (%)	33/36 (91.6)	16/19 (84.2)	17/17 (100)	0.231 ³
Volume of CYA (mL), median (range)	1.8 (0.6–6.6)	1.8 (0.6–6.6)	1.8 (1.2–2.4)	0.136
No of coils, median (range)	2 (1–3)	0	2 (1–3)	N/A

¹Welch Two Sample *t*-test.²Pearson's Chi-squared test with Yates' continuity correction.³Fisher's Exact Test for Count Data. CYA: Cyanoacrylate; SD: Standard deviation; GV: Gastric varix; GOV: Gastroesophageal varices; IGV: Isolated gastric varices; USD: United States dollar; N/A: Not available.

$$ICER = \frac{\text{mean cost Coils + CYA}_{(USD)} - \text{mean cost CYA}_{(USD)}}{\text{efficacy outcome Coils + CYA}_{(n)} - \text{efficacy outcome CYA}_{(n)}}$$

Figure 4 The Incremental Cost-Effective ratio equation.

group, and this patient remained in the Emergency Department.

Concerning the financial aspects of the procedures, the cost per procedure with endoscopic CYA injection was USD 816.70 [mean of 1 203.56 (816.70-3266.80)], while it was USD 2247.00 (mean of 2247.00) with the EUS-guided approach. The mean total procedure costs were USD 1350.29 (857.70-3717.80) in the CYA group and USD 2978.00 (2629.00-3270.00) in the coils + CYA group. The hospitalization and mean total treatment costs were much higher in the CYA group, in which patients spent USD 9 710.60 (0-45857.20) and USD 11060.89 (912.20-49575.00), respectively. ICERs analysis lets us to estimate that in CYA group, each early rebleeding, adverse events, and day of hospitalization increased health-related costs on USD 2670.80, USD 8012.40, USD 127.18 per presented event, respectively, when comparing with coils + CYA group cost and presented events (Table 2). Each inevitable death on CYA group represented a health-related cost increase on USD 8012.40 in comparison with coils + CYA group (Table 3).

DISCUSSION

Despite advances in endoscopic techniques and devices, the treatment of gastric varices, particularly bleeding varices, is still a challenging issue. Several previous studies on this subject showed that there were advantages for the standard endoscopic injection of cyanoacrylate in the treatment of gastric variceal bleeding, with high success and low rebleeding rates^[1,2]. Thus, cyanoacrylate injection became the first choice of treatment worldwide. Nevertheless, this approach carries a huge risk of adverse events, notably, systemic embolization^[8]. To overcome this problem, recent studies suggested a new approach to gastric variceal bleeding using EUS-guided technique with coils deployment plus cyanoacrylate injection in the feeding vessels, with excellent short-term results^[8].

Overall, the two groups in the present analysis did not differ in age or gender, although there were slightly more males, which is common for GV^[1]. With regard to

Table 2 Study outcomes

	Total (n = 36)	CYA (n = 19)	Coils + CYA (n = 17)	P value
Early rebleeding (n of events), n (%)	3/36 (8.3)	3/19 (15.8)	0	0.231 ¹
Adverse events (n of events), n (%)	5/36 (13.8)	3/19 (15.8)	2/17 (11.8)	1.000 ¹
Treatment modality, n (%)				0.001 ²
Ambulatory	23 (63.1)	7 (36.8)	16 (94.1)	
Hospitalization	13 (36.1)	12 (63.2)	1 (5.9)	
No of endoscopic procedures, total	45	28	17	N/A
No. of endoscopic procedures per patient, median (range)	1 (1-4)	1 (1-4)	1	0.014 ³
Length of hospitalization (d), range	0-14	0-14	0-1	< 0.001 ⁴
Intensive care unit	0-11	0-11	-	0.012 ⁴
Intermediate care unit	0-14	0-14	-	0.001 ⁴
Emergency Department	0-1	-	0-1	0.303 ⁴
Cost per procedure (USD)	N/A	816.70	2247.00	N/A
Cost per procedure (USD), mean (range)	1696.29 (816.70-3266.80)	1203.56 (816.70-3266.80)	2247.00	< 0.001 ⁵
Coil cost (1 coil = \$ 300, USD), mean (range)	291.67 (0-900.00)	0	617.65 (300.00-900.00)	< 0.001 ⁵
CYA cost (1 vial × 0.3 mL = \$ 20.5, USD), mean (range)	130.97.00 (41.00-451.00)	146.74 (41.00-451.00)	113.35 (82.00-164.00)	0.141 ⁵
Total procedure cost (USD), mean (range)	2118.93 (857.70-3717.80)	1350.29 (857.70-3717.80)	2978.00 (2629.00-3270.00)	< 0.001 ⁵
Hospitalization cost (USD), mean (range)	5158.31 (0-45857.20)	9710.60 (0-45857.20)	70.46 (0-1197.80)	0.010 ⁵
Total treatment cost (procedure + hospitalization, USD) mean (range)	7277.20 (919.20-49575.00)	11060.89 (919.20-49575.00)	3007.13 (2629.00-3867.80)	0.030 ⁵

¹Fisher's Exact Test for Count Data.²Pearson's Chi-squared test with Yates' continuity correction.³Mann-Whitney U test.⁴Gray's test.⁵Welch Two Sample *t*-test. CYA: Cyanoacrylate; SD: Standard deviation; GV: Gastric varix; GOV: Gastroesophageal varices; IGV: Isolated gastric varices, USD: United States dollar; N/A: Not available.**Table 3 Incremental Cost Effectiveness Ratio analysis**

Efficacy outcome	ICER analysis
Early rebleeding (n of events)	(USD 3048.50) - (USD 11060.90)/(0) - (3) = US\$ 2670.80
Adverse events (n of events)	(USD 3048.50) - (USD 11060.90)/(2) - (3) = US\$ 8012.40
Length of hospitalization (total days)	(USD 3048.50) - (USD 11060.90)/(1) - (64) = US\$ 127.18
6-mo mortality (n of events)	(USD 3048.50) - (USD 11060.90)/(0) - (1) = US\$ 8012.40

ICER: Incremental Cost-Effectiveness Ratio; USD: United States of America dollar.

the indications for the procedure, ten (58.8%) patients in the coils + CYA group underwent the procedure for secondary prophylaxis, while all 19 (100%) patients in the CYA group had acute bleeding. In this retrospective analysis from our unit, the use of EUS-guided coils plus CYA was the preferred technique for the prevention of rebleeding.

Only fundal GOV II and IGV I varices were included in the present work because it is generally accepted that GOV I varices are best treated with endoscopic band ligation. Currently, there is no established treatment for IGV II vessels. We observed that the patients in the CYA group required significantly more procedures and a significantly larger mean amount of CYA to achieve hemostasis and variceal remission. Moreover, with the EUS approach, the coils work as a frame that retains

CYA within varix, with a fewer amount of cyanoacrylate needed to achieve obliteration, thus reducing the risk of adverse events, including embolism^[5]. In our study, a mean of 1.65 (1.2-2.4) mL of CYA was used in the coils + CYA group, with two adverse events, one episode of fever and one transient abdominal pain, neither requiring hospitalization.

Technical success with the EUS coils + CYA method was achieved in all 17 (100%) patients (in one session), a much better performance compared with the CYA group. The EUS-guided technique used in this trial targets the perforating vessel instead of depending on direct variceal puncturing. Perforating vessels are thought to be the source of varix, and blocking the feeder, thus effectively decreasing the blood flow in gastric varix. Moreover, the use of EUS permits direct variceal visualization, which contributes to technical success, since the visual field with the standard endoscopic method can be obscured by blood and residue in the stomach. Despite this advantage, there were no differences in the numbers of patients with early rebleeding between the two groups in this study.

Although the cost per procedure and mean total procedure cost were higher for the EUS-guided approach, the total treatment costs were much higher in the CYA group, in which patients spent USD 11060.89 (912.20-49575.00). The later may be related to the fact that most patients in the latter group were hospitalized, and most of their time was spent in the Intensive Care Unit, which greatly increased the costs.

Overall, the use of EUS-guided coils plus CYA technique was more cost-effective than the current standard endoscopic therapy. The ICER demonstrated that the EUS-guided approach was advantageous in terms of cost savings. By performing this technique, we saved USD 2670.80 by preventing one early rebleed episode and USD 8012.40 by avoiding one death.

However, this study has some limitations. First, the patients who underwent the endoscopic CYA injection were all in an acute stage, and thus had a more severe clinical impairment, which naturally required more interventions, increased the length of hospitalization, and raised costs. Second, only adverse events in patients who were already hospitalized or returned to our facility after an exam were counted. Adverse events that occurred at home probably also generate costs and should be considered in future cost analyses. Finally, this study was designed retrospectively and conducted in a single center institution with a relatively small number of patients.

In a recent study, Romero-Castro *et al*^[7] performed a thorax computed tomography (CT) scan on all patients who underwent an EUS-guided CYA injection, and they reported a very high incidence of asymptomatic pulmonary embolism that could have been missed by a clinical evaluation after the procedure. If a thorax CT was added to our EUS technique, the final treatment costs would significantly increase.

It is important to recognize that using hospital charges to estimate the costs of treatment poses a problem, because charges are different among institutions, and the treatment costs remain unknown for other institutions.

CONCLUSION

In conclusion, this preliminary analysis showed that the use of EUS-guided coils plus cyanoacrylate injection is more cost-effective than cyanoacrylate injection when the total costs are evaluated. Larger, multi-center studies are needed to address the cost effects of the EUS-guided approach of gastric varices.

ARTICLE HIGHLIGHTS

Research background

Bleeding gastric varices implies high morbidity and mortality in cirrhotic and noncirrhotic patients. Bleeding and rebleeding episodes, as well as their management, have a high health-related cost impact.

Research motivation

Currently, there is insufficient data about the cost-effectiveness of available therapies, mainly endoscopic cyanoacrylate injection and endoscopic ultrasound (EUS)-guided therapy for the management of gastric varices.

Research objectives

The study's main objective was to evaluate the cost-effectiveness of treating gastric varices, whether by the standard endoscopic cyanoacrylate injection or by the novel EUS-guided combined coiling and cyanoacrylate injection technique.

Research methods

This was an observational, descriptive, and retrospective study conducted in a single tertiary center. Patients with actively bleeding gastric varices and those with a history of bleeding were treated with either one of the two modalities. We evaluated the technical success and adverse event rates and the procedure and overall treatment costs.

Research results

We described a significantly higher number of procedures needed to achieve obliteration of gastric varices in the endoscopic cyanoacrylate group, with a higher number of admissions in this cohort. Technical and adverse events rates were not significantly different in the two groups. In terms of cost, endoscopic cyanoacrylate injection has a significantly higher mean total treatment cost, probably explained by a higher reintervention rate and hospitalization cost.

Research conclusions

In our study, EUS-guided combined therapy with coiling and cyanoacrylate injection proved to be more cost-effective than endoscopic cyanoacrylate injection in terms of the overall treatment cost.

Research perspectives

We encourage researchers to conduct a multicenter, randomized trial with a long-term follow-up comparing the endoscopic cyanoacrylate therapy *vs* the EUS-guided combined therapy with coiling and cyanoacrylate injection, in order to define formal therapeutical guidelines.

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Histoplasmosis and inflammatory bowel disease: A case report

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Abstract

BACKGROUND

Infection with *Histoplasma capsulatum* can lead to a disseminated disease involving the gastrointestinal tract presenting as diffuse abdominal pain and inflammatory diarrhea which may mimic inflammatory bowel disease (IBD).

CASE SUMMARY

In the current report, we discuss the case of a 41-year old male who presented to the emergency department with complaints of high-grade intermittent fevers and severe abdominal pain with associated diarrhea and hematochezia. Laboratory results demonstrated transaminitis and elevated erythrocyte sedimentation rate, C-reactive protein and ferritin levels. The patient's presentation was thought to be an exacerbation of his underlying IBD, but further investigations revealed a positive *Histoplasma* antigen in the urine. The patient was offered a colonoscopy and biopsy to confirm the diagnosis; however, he refused. He was treated with itraconazole and showed significant improvement of his symptoms, thereby confirming the diagnosis of gastrointestinal histoplasmosis.

CONCLUSION

Here within, we provide a review of IBD, evaluation of chronic diarrhea, and gastrointestinal histoplasmosis.

Key Words: Histoplasmosis; Inflammatory bowel disease; Intestine; Endoscopy; Gastroenterology; Case report

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Core Tip: Histoplasmosis can lead to a disseminating disease state affecting a large number of organ systems, leading to a wide range of pathology. This includes the gastrointestinal tract. We present herein, a case of gastrointestinal histoplasmosis in a patient with long standing ulcerative colitis that presented in a manner very similar to acute exacerbation of inflammatory bowel disease. This case highlights the importance of keeping gastrointestinal histoplasmosis amongst the differential diagnoses in cases that present similarly to acute exacerbation of inflammatory bowel disease in order to prevent inappropriate delays in diagnosis, unnecessary procedures, and increased morbidity and mortality.

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INTRODUCTION

Histoplasma capsulatum (*H. capsulatum*) var. *capsulatum* is a dimorphic fungus that is known to have prevalence throughout the world. In the United States, *Histoplasma capsulatum* is mainly endemic in the Ohio and Mississippi valley regions^[1]. In the environment, it exists in its hyphal form, producing spores which are inhaled by humans initiating the infection^[2]. In the body, the spores transform into the yeast phase, evading intercellular killing and being transported by macrophages to any organ in the body. This leads to disseminated histoplasmosis (DH). Dissemination to the gastrointestinal (GI) tract, known as gastrointestinal histoplasmosis (GIH), most commonly involves the colon and terminal ileum^[3]. The most common presenting symptoms in patients with GIH are abdominal pain and inflammatory diarrhea^[4]. Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the intestinal mucosa through a complex immune mediated mechanism. The 2 main subtypes of IBD, Crohn's disease and ulcerative colitis (UC), are based on the histological involvement of the bowel. Common symptoms of IBD include diarrhea or constipation, hematochezia, severe diffuse abdominal pain, unintentional weight loss, significantly reduced appetite, fatigue and fever. Inflammatory diarrhea is a common feature seen both in GIH and IBD. The similarities in presentation, the pattern of the involvement of the gastrointestinal (GI) tract and the associated inflammation is the reason GIH is considered an IBD mimic. However, it is not commonly considered as one of the differential diagnoses in these patients. In patients with diagnosed IBD, GIH may be mistaken for an acute exacerbation of the underlying pathology. Our case report and review of the literature provides a step by step approach regarding IBD, GIH, and evaluating patients with chronic diarrhea. We strongly advocate and urge physicians to test patients with inflammatory diarrhea for *H. capsulatum*, particularly in endemic regions and those diagnosed with IBD presenting with a clinical picture suggesting exacerbation. Early diagnosis of GIH prevents inappropriate or delayed therapy, unnecessary surgical interventions and adverse outcomes.

CASE PRESENTATION

Chief complaints

A 41-year old male presented to the emergency department (ED) with chief complaints of high-grade intermittent fevers and severe abdominal pain.

History of present illness

The patient described the fever as episodic, high grade (maximum temperature of 103°F), without chills or rigors, and associated with a non-productive cough for one week. He also complained of severe, intermittent, diffuse abdominal pain associated with diarrhea and hematochezia for 2 d prior to this ED visit. He did not have a sore throat, rhinorrhea, abdominal pain, joint pain or rash.

History of past illness

The patient had a past medical history significant for UC. The patient had lived in the Great Lakes region for his entire life, worked in construction for many years and had no history of recent travel. He lived with 3 young children who all had recently suffered from a viral respiratory tract infection lasting approximately 1 wk. He had pets at home including a gecko, a rabbit and 2 dogs. 10 mo prior, he had presented to the ED with similar complaints of diffuse abdominal pain and diarrhea associated with haematochezia for 6 wk. Investigation for common conditions such as gastrointestinal infections, endocrine disorders, food allergies and medication changes were ruled out, and a decision was made to perform a colonoscopy with tissue biopsy. Biopsy from the colon revealed non-specific histological findings *i.e.* crypt abscess, mild architectural distortion of the lamina propria and chronic inflammation. Markers of acute inflammation such as erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) were also found to be elevated, suggesting a diagnosis of UC. The patient was started on prednisolone 40 mg daily which lead to resolution of his symptoms. A decision was made to have the patient continue on prednisolone 40 mg daily after failed attempts to switch the regimen to mesalamine lead to mesalamine-induced pancreatitis, and treatment with Vedolizumab lead to an allergic reaction after the second dose.

Personal and family history

Family history was significant for IBD in his mother. The patient had no other significant past medical history.

Physical examination

On examination, he was febrile with a temperature of 103F, heart rate 112 beats/min, and blood pressure 124/74 mmHg. On abdominal examination, no tenderness was noted but mild splenomegaly was appreciated. The working diagnosis of the patient's presentation at this time was believed to be an acute exacerbation of his underlying UC.

Laboratory examinations

Laboratory investigations were ordered, and infectious disease was consulted, with recommendations to start broad spectrum antibiotics until a definite cause could be established. Laboratory investigations revealed a Hemoglobin of 11.8 g/dL, white blood cell (WBC) count of 4.1×10^9 cells/L with 70% granulocytes, 22% lymphocytes and 0.1% eosinophils. Procalcitonin was elevated at 0.39 and elevations in the liver enzymes were also noted with alanine aminotransferase 232 U/L, Alkaline phosphatase 266 U/L and aspartate transaminase 79 U/L. Blood cultures showed no growth, and stool analysis was negative for *Clostridium difficile* (*C. diff*) and parasites. Interestingly, *H. capsulatum* antigen was detected in the urine. Hence, the working diagnosis was changed from an acute exacerbation of UC to GIH.

Imaging examinations

To confirm the diagnosis of GIH, the patient was offered a colonoscopy with biopsy, however he refused this stating that he preferred treatment for *H. capsulatum* based on the high specificity of the urine antigen testing.

FINAL DIAGNOSIS

Based on the positive urine antigen for *H. capsulatum*, and the patients refusal to have repeat colonoscopy with biopsy, the presumed diagnosis was GIH.

TREATMENT

The patient was started on oral itraconazole 200 mg twice daily for presumed GIH infection.

OUTCOME AND FOLLOW-UP

Over the next several days, the patient experienced significant improvement of his symptoms confirming our diagnosis of GIH. He was subsequently discharged home on oral itraconazole for 6 mo, oral corticosteroids for his UC and an appointment to follow-up with his gastroenterologist within 6 wk.

DISCUSSION

This case report and brief review of the literature places great emphasis on keeping *H. capsulatum* as one of the differential diagnoses in patients with IBD presenting to the hospital with a clinical picture of an acute exacerbation of their underlying disease. In patients presenting to the ED with complaints of diffuse abdominal pain and chronic diarrhea with hematochezia, it is standard clinical practice to obtain a stool analysis and rule out *C. diff* and parasitic infection. However, specific tests for *H. capsulatum* are not usually performed. In this article, we discuss the presentation and management of patients with IBD. We also review the classification of specific subtypes of chronic diarrhea and further investigations that might be necessary to investigate the underlying pathology. Furthermore, we discuss the presentation and management of GIH, a subtype of DH, and advocate for the importance of considering *H. capsulatum* infection as a differential diagnosis in patients with IBD.

Diarrhea in IBD

IBD is a disease characterized by chronic inflammation of the intestinal mucosa through a complex immune mediated mechanism. The exact cause of IBD is currently unknown, but it is believed to be due to an abnormal intestinal mucosal immune response to environmental triggers leading to inflammation of the epithelial lining of the GI mucosa^[5]. The immune system of the GI tract plays a vital role in providing an appropriate immune response to harmful pathogens, while inducing an immune tolerance to harmless food materials and commensal flora^[6]. Literature reports a rise in incidence and prevalence of IBD in the adult and pediatric populations^[7]. Although the exact reason for this increase is not clear, it is believed that an alteration in lifestyle and nutritional habits may play a significant role^[8]. The Rochester epidemiology project noted an increase in the incidence and prevalence of IBD between 2001 and 2011, but this was attributed to an increase in overall life expectancy^[9]. In light of increasing westernization and industrialization, Asian countries such as India, China and Iran are reporting significantly increased numbers of cases of IBD^[10].

IBD can be classified into 2 major subtypes based on the clinical picture and distinct pathological characteristics^[11]:

Ulcerative colitis: A chronic inflammatory condition characterized by relapsing and remitting episodes of inflammation limited only to the mucosal layer of the colon. The mucosa is involved in a continuous fashion with almost all cases reporting involvement of the rectum.

Crohn's disease: A chronic inflammatory condition characterized by a full thickness (transmural) involvement of the bowel and the presence of skip lesions (areas of disease between normal appearing bowel). It most commonly involves the ileum and the proximal part of the colon; however, any part of the GI tract may be involved.

The spectrum of symptoms in patients with IBD depend on the severity of the inflammation and can range from very mild to severe. The common symptoms of IBD include diarrhea or constipation, hematochezia, severe diffuse abdominal pain, unintentional weight loss, significantly reduced appetite, fatigue, and fever.

The initial step in the evaluation of a patient with IBD includes a detailed history and physical examination. The history may be critical in differentiating patients with IBD from other organic and functional causes. A thorough physical examination in patients with IBD may reveal mild to moderate abdominal tenderness without distention. Initial laboratory investigations may reveal an elevation of the markers of inflammation *i.e.* ESR and CRP. In patients with acute diarrhea as the presenting symptom, stool studies to rule out infectious etiologies such as *C. diff* and parasites should also be performed. Fecal calprotectin, a stool marker for inflammation, can also be used to determine the presence of intestinal inflammation in patients with clinical suspicion of IBD^[12]. If the fecal calprotectin value is above the reference range (50 mcg/g), ileocolonoscopy with biopsy and/or small bowel imaging can be used to diagnose IBD and assess the degree of mucosal inflammation^[13]. Although

ileocolonoscopy with biopsy is the preferred method to establish a definitive diagnosis and assess the degree of inflammation, radiological imaging modalities such as computed tomography (CT) enterography, magnetic resonance enterography (preferred over CT enterography), capsule endoscopy, or GI Ultrasound can also be used in certain situations^[14]. The management of IBD is primarily focused on providing symptomatic relief, rapid induction of steroid-free remission, and prevention of complications of the disease and its treatment^[15]. The choice of therapy is based on the extent and degree of the severity of the disease, its responsiveness to previous therapy, and the individual patient characteristics^[15]. Some agents used in the treatment of IBD include Sulfasalazine, Mesalamine, Olsalazine, Balsalazide, Corticosteroids, Azathioprine, 6-Mercaptopurine, Methotrexate, Infliximab, Adalimumab and Tacrolimus.

Due to the chronic inflammation in IBD, patients can present with multiple complications. These complications are usually associated with a specific subtype of IBD due to the pattern of the inflammation, but some may be shared between the two. The complications include^[16]:

Common complications: Colon cancer, Arthritis, Uveitis, Primary Sclerosing Cholangitis and hypercoagulable states.

Ulcerative colitis: Toxic Megacolon, perforation of the colon and severe dehydration.

Crohn's disease: Bowel obstruction, ulcers, fistulas and anal fissures.

Evaluation of patients with chronic diarrhea

Diarrhea is objectively defined as passing a stool weight or volume greater than 200 g or 200 mL per 24 h^[17]. According to the Centers for Disease Control and Prevention, chronic diarrhea is defined as diarrhea that lasts for longer than 2-4 wk^[18]. The initial investigation into the evaluation of chronic diarrhea starts with an extensive history and examination to formulate a preliminary differential diagnosis. The appearance of the stool can be categorized into one of the three major subtypes for further diagnostic investigations^[19]:

Fatty (Malabsorptive) diarrhea: The initial investigations in patients with malabsorptive diarrhea are aimed at ruling out anatomic defects. Radiological investigations of the abdomen, and sigmoidoscopy or colonoscopy with or without biopsy may help to diagnose the specific underlying etiology. A positive stool chymotrypsin level confirmed with a positive secretin test is diagnostic for pancreatic insufficiency.

Inflammatory diarrhea: In patients with a suspected inflammatory cause of their diarrhea, stool analysis is always the initial investigation of choice. Stool analysis positive for blood, WBC, and fecal calprotectin points toward a diagnosis of IBD. This can be confirmed with a colonoscopy and biopsy of the involved bowel. In patients with absence of WBC in the stool and a negative stool analysis, additional investigations are needed to identify the underlying cause. Testing for *C. diff* has become standard practice in patients with inflammatory diarrhea. We strongly advocate and urge physicians to test for *H. capsulatum*, particularly for patients in endemic regions and in those with IBD, as literature reports a high prevalence of GIH in autopsy specimens.

Watery diarrhea: The initial investigation of choice is the measurement of the fecal osmotic gap. A high fecal osmotic gap (> 125 mOsm per kg) along with a history of increased diarrhea on consumption of dairy products and a positive hydrogen breath test confirms the diagnosis of lactose intolerance. A normal fecal osmotic gap with improvement in the symptoms on dietary modification is usually seen in patients with irritable bowel syndrome. However, patients with a normal fecal osmotic gap and no improvement with dietary modifications may require further workup for Celiac disease, which includes a celiac panel. Patients with low osmolar gap (< 50 mOsm per kg) may need additional imaging, blood, and urine testing to investigate other possible etiologies.

It is important to recognize that diarrhea is not a disease but rather a symptom of the underlying pathology. Patients with ulcerative colitis will have inflammatory diarrhea with the presence of pus and blood on stool analysis. Furthermore, mimics of IBD such as GIH may also present with inflammatory diarrhea such as that in our case report. Therefore, it becomes extremely important to differentiate an acute exacerbation of UC from other causes in order to initiate appropriate therapy early and

prevent adverse outcomes.

***H. capsulatum* and the gastrointestinal tract**

Histoplasmosis is an endemic mycosis caused by a dimorphic fungus called *H. capsulatum*. The two distinct varieties of *Histoplasma* that are pathogenic to humans include *H. capsulatum* var. *capsulatum* which is prevalent worldwide in endemic areas, and *H. capsulatum* var. *duboisii* which is restricted to the Sub-Saharan Africa region^[1]. In the United States, endemic regions with a high prevalence of histoplasmosis include areas centered in the Ohio and Mississippi river valleys. An analysis of the data from hospital records in 2002 revealed 3370 inpatient stays and 254 deaths associated with histoplasmosis with almost 90% of these hospitalizations in the midwestern and southern regions of the United States^[20]. *H. capsulatum* var. *capsulatum* is dimorphic meaning that it exists in two distinct forms. It grows in its hyphal form in soil, and bird and bat guano, but upon inhalation of the spores, it transforms into the pathogenic yeast form, replicating inside the macrophages^[2]. These macrophages can transport the yeast to virtually any organ in the body leading to DH^[2]. Although *H. capsulatum* is non-contagious and humans are the dead-end or accidental hosts for fungal replication, it appears to be specifically well adapted to the mammalian host cells. The pathogenic yeast phase is equipped to evade intercellular killing by macrophages with mechanisms to degrade reactive oxygen species, regulate lysosomal pH and capture essential nutrients that might otherwise be deprived^[2]. Human infections by *H. capsulatum* usually present as acute pulmonary histoplasmosis, chronic pulmonary histoplasmosis, cutaneous histoplasmosis, rheumatologic histoplasmosis, ocular histoplasmosis, mediastinal histoplasmosis, broncholithiasis, and progressive disseminated histoplasmosis extending to the brain^[21]. DH is commonly seen in immunocompromised states with low CD4 cell counts (< 200 cells/mm³), such as in acquired immune deficiency syndrome patients and also rarely in patients with human T-lymphotropic virus 1 infection.

DH to the GI tract, also known as GIH, is a rare entity. Involvement of the GI tract in DH is very non-specific, may involve any area of the GI tract and is usually seen in immunocompromised patients. However, the most common sites of involvement are the terminal ileum and the colon due to abundance of lymphoid tissue^[3]. The involvement becomes less common more proximally in the intestine^[3]. Literature reports high rates of GIH in autopsy specimens, indicating a higher prevalence of asymptomatic disease^[22]. The most common presenting symptoms in patients with GIH are abdominal pain and diarrhea^[4]. This diarrhea could be intermittent and typical of that seen in other diseases, or could be unremitting and associated with malabsorption^[23]. Bloody diarrhea may also be present in a subset of patients with GIH and often mimics IBD, thereby making it difficult to differentiate between IBD and GIH, such as that in our case^[24]. Other symptoms associated with GIH may include irregular fevers with or without chills and night sweats, anorexia, weight loss of varying degrees, and abdominal distention^[25]. On physical examination, patients may have hepatosplenomegaly, peripheral lymphadenectasis, abdominal tenderness and rebound tenderness concerning for peritonitis^[25]. The similarities in presentation, the pattern of the involvement of the GI tract and the associated inflammation is the reason as to why GIH is considered a mimic of IBD.

Laboratory investigations in patients with GIH may reveal an elevation in the alkaline phosphatase levels, lactate dehydrogenase, and increased levels of markers of inflammation such as ESR, CRP and serum ferritin levels^[26]. In our case, elevations in all of the liver enzymes were noted along with elevations in the ESR and CRP. Pancytopenia may indicate an underlying immunocompromised state. Although none of these investigations are diagnostic for *H. capsulatum*, they direct the physician to consider an infectious etiology as a differential diagnosis for the presenting symptoms. For patients with suspected DH, Histoplasma antigen enzyme immunoassay of the serum and urine should be performed. Urine antigen-enzyme immunoassay has a high sensitivity (89.47%) and specificity (100%) in the detection of *H. capsulatum*^[27]. Radiological investigations such as CT scan and magnetic resonance imaging may also help point physicians towards a diagnosis of GIH, while ruling out other etiologies of bloody diarrhea. The radiological findings with GIH may include^[28]: Bowel wall thickening; Mass-like lesions in the bowel; Signs suggesting small bowel obstruction; Bowel perforations, although rare, may show free intraperitoneal air; Hepatosplenomegaly; Generalized lymphadenopathy.

The most common endoscopic findings in patients with GIH are unifocal or multifocal mucosal ulcerations^[28]. Polypoid lesions, strictures, and obstructing masses may also be noted^[29]. The definitive diagnosis of GIH is always established with colonoscopy and biopsy of the lesions which may reveal the typical 2 to 4-micron yeast

structure of *H. capsulatum*. Although the histopathology specimens of the fungus can be stained with hematoxylin and eosin, it is better visualized using the methenamine silver or periodic acid-schiff stain. It is also always preferable to have culture evidence of *H. capsulatum* for diagnosis. However, in our case, a colonoscopy with biopsy was offered to the patient, who refused the procedure as he had a colonoscopy with biopsy 10 mo prior to establish a diagnosis of UC and did not wish to undergo the procedure again. After learning about the positive results of the urine antigen testing for *H. capsulatum* and that GIH can be a mimic for an acute exacerbation of UC, the patient wanted to proceed with the treatment for GIH and deferred the procedure to a later date if there was no improvement in his symptoms.

The treatment of DH and the selection of the appropriate agent for therapy depends primarily on the severity of the disease. The treatment strategy (summarized in Table 1) can be classified as^[30]:

Severe disease: Liposomal Amphotericin B 3 mg/kg daily, or Amphotericin lipid complex 5 mg/kg daily, or Amphotericin deoxycholate 0.7 to 1 mg/kg daily for one to two weeks followed by itraconazole 200 mg twice daily for a minimum of 2 mo.

Mild to moderate disease: Itraconazole 200 mg twice daily for a minimum of 2 mo.

CNS histoplasmosis: Liposomal Amphotericin 5 mg/kg daily for four to six weeks followed by itraconazole 200 mg two to three times daily for a minimum of 2 mo.

Most patients with disseminated Histoplasmosis respond well to antifungal therapy. Early diagnosis and treatment of the GIH is essential to prevent serious adverse outcomes. Perforation of the bowel and hemorrhage are two of the most serious complications reported in patients with GIH.

The clinical manifestations of GIH may mimic other GI diseases such as IBD, including UC and Crohn's disease, tuberculosis, carcinomas and lymphomas. However, it is commonly not considered as one of the differential diagnoses in patients presenting with abdominal pain and chronic diarrhea with hematochezia^[4]. This usually leads to inappropriate or delayed therapy, unnecessary surgical interventions and adverse outcomes. Our article places great emphasis on the importance of testing in order to rule out GIH in patients who present with clinical characteristics of a sudden onset acute exacerbations of IBD without an underlying cause.

CONCLUSION

H. capsulatum is a dimorphic fungus endemic in the Ohio and Mississippi valley regions. *H. capsulatum* var. *capsulatum* is prevalent worldwide and is seen in the United States. *H. capsulatum* exists in its hyphal form in the environment and inhalation of the spores produced by this form are infectious to humans. After infection of the host, it transforms into the pathogenic yeast form which replicates inside the macrophages and evades intracellular killing. Macrophages can disseminate the fungus to any organ in the body leading to DH. In the gastrointestinal tract, most common sites of involvement are the terminal ileum and the colon due to abundance of lymphoid tissue. The most common presenting symptoms in patients with GIH are abdominal pain and diarrhea. GIH often mimics IBD due to similarities in presentation, the pattern of the involvement of the GI tract and the associated inflammation. Hence, for patients with inflammatory diarrhea, or those with diagnosed IBD with clinical characteristics of a possible acute exacerbation without an underlying cause, GIH should be among the differential diagnoses. The diagnosis of GIH is confirmed with colonoscopy and biopsy of the involved region of the GI tract. The treatment of DH depends on the severity of the disease.

Table 1 Treatment strategies based on the severity of disseminated histoplasmosis

Disseminated histoplasmosis	Mild disease	Moderate disease	Severe disease	CNS histoplasmosis
Treatment	Itraconazole 200 mg twice daily (minimum of 2 mo)	Itraconazole 200 mg twice daily (minimum of 2 mo)	Liposomal Amphotericin B 3 mg/kg daily for 1-2 wk or Amphotericin lipid complex 5 mg/kg daily for 1-2 wk or Amphotericin deoxycholate 0.7 to 1 mg/kg daily for 1-2 wk followed by Itraconazole 200 mg twice daily (minimum of 2 mo)	Liposomal Amphotericin 5 mg/kg daily for 4-6 wk followed by Itraconazole 200 mg 2-3 times daily (minimum of 2 mo)

CNS: Central nervous system.

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