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AGA Clinical Practice Update on Esophageal Dysfunction Due to Disordered Immunity and Infection: Expert Review

Chanakyaram A. Reddy,[1,*] Emily McGowan,[2,*] Rena Yadlapati,[3] and Kathryn Peterson[4]

[1]Center for Esophageal Diseases, Division of Gastroenterology, Baylor University Medical Center, Dallas, Texas; [2]Division of Allergy and Immunology, University of Virginia School of Medicine, Charlottesville, Virginia; [3]Division of Gastroenterology, UCSD Center for Esophageal Diseases, GI Motility Lab, University of California San Diego, GEODE Research Program, San Francisco, California; and [4]Division of Gastroenterology, University of Utah, Salt Lake City, Utah

METHODS: **This expert review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee (CPUC) and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the CPUC and external peer review through standard procedures of *Clinical Gastroenterology and Hepatology*. These Best Practice Advice (BPA) statements were drawn from a review of the published literature and from expert opinion. Since systematic reviews were not performed, these BPA statements do not carry formal ratings regarding the quality of evidence or strength of the presented considerations.**

DESCRIPTION: **Infectious and immune-mediated esophageal disorders are poorly understood and often underdiagnosed conditions that lead to esophageal dysfunction and health care costs due to repeated procedures and a lack of understanding of their etiology and pathogenesis. Without a high index of suspicion, these disorders may be overlooked. Esophageal dysfunction may arise from active, localized infection and immune-mediated disease (ie, candida, etc.) or from an organ-specific manifestation of a more diffuse immune-mediated disease or infection (ie, systemic sclerosis, connective tissue disease, neurologic disease). These conditions can sometimes lead to neuromuscular dysfunction and subsequent esophageal dysmotility. Awareness of local and systemic processes that lead to esophageal dysfunction will improve patient outcomes by focusing therapeutics and limiting unnecessary procedures. Therefore, the purpose of this AGA Clinical Practice Update Expert Review is to provide BPA on diagnostic considerations of immune-mediated disorders that should be considered when encountering patients with dysphagia, heartburn, and odynophagia.**

BEST PRACTICE ADVICE STATEMENTS:

BEST PRACTICE ADVICE 1: **Gastroenterologists should be aware of the esophageal manifestations of systemic immunologic and infectious diseases to reduce diagnostic delay. Clinicians should identify if there are risks for inflammatory or infectious possibilities for a patient's esophageal symptoms and investigate for these disorders as a potential cause of esophageal dysfunction.**

BEST PRACTICE ADVICE 2: **Once esophageal infection is identified, clinicians should identify whether accompanying signs/symptoms suggest immunocompromise leading to a more systemic infection. Consultation with an infectious disease expert will aid in guiding appropriate treatment.**

*Authors share co-first authorship.

Abbreviations used in this paper: AEC, absolute eosinophil count; ANCA, antineutrophil cytoplasmic antibody; CI, confidence interval; CMV, cytomegalovirus; DIF, direct immunofluorescence; EGPA, eosinophilic granulomatosis with polyangiitis; ELP, esophageal lichen planus; EoE, eosinophilic esophagitis; FDA, United States Food and Drug Administration; GI, gastrointestinal; HES, hypereosinophilic syndromes; HSV, herpes simplex virus; IL, interleukin; LP, lichen planus; LyE, lymphocytic esophagitis; MCTD, mixed connective tissue disease; OR, odds ratio; PV, pemphigus vulgaris; SLE, systemic lupus erythematosus; SSc, systemic sclerosis.

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BEST PRACTICE ADVICE 3: **If symptoms do not improve after therapy for infectious esophagitis, evaluation for refractory infection or additional underlying sources of esophageal and immunologic dysfunction should be performed.**

BEST PRACTICE ADVICE 4: **In individuals with eosinophilic esophagitis (EoE) who continue to experience symptoms of esophageal dysfunction despite histologic and endoscopic disease remission, clinicians should be aware that some patients with EoE may develop motility disorders. Further evaluation of esophageal motility may be warranted.**

BEST PRACTICE ADVICE 5: **In individuals with histologic and endoscopic features of lymphocytic esophagitis, clinicians should consider treatment of lymphocytic-related inflammation with proton-pump inhibitor therapy or swallowed topical corticosteroids and as needed esophageal dilation.**

BEST PRACTICE ADVICE 6: **In patients who present with esophageal symptoms in the setting of hypereosinophilia (absolute eosinophil count [AEC] >1500 cells/uL), consider further work-up of non-EoE eosinophilic gastrointestinal (GI) disease, hypereosinophilic syndrome, and eosinophilic granulomatosis with polyangiitis (EGPA). Consultation with allergy/immunology may help guide further diagnostic work-up and treatment.**

BEST PRACTICE ADVICE 7: **In individuals with rheumatologic diseases of systemic sclerosis (SSc), mixed connective tissue disease (MCTD), systemic lupus erythematosus (SLE), or Sjogren's disease, clinicians should be aware that esophageal symptoms can occur due to involvement of the esophageal muscle layer, resulting in dysmotility and/or incompetence of the lower esophageal sphincter. The degree of dysfunction is often especially significant in those with SSc or MCTD.**

BEST PRACTICE ADVICE 8: **In individuals with Crohn's disease, clinicians should be aware that a minority of individuals can develop esophageal involvement from inflammatory, stricturing, or fistulizing changes with granulomas seen histologically. Esophageal manifestations of Crohn's disease tend to occur in individuals with active intestinal disease.**

BEST PRACTICE ADVICE 9: **In individuals with dermatologic diseases of lichen planus or bullous disorders, clinicians should be aware that dysphagia can occur due to endoscopically visible esophageal mucosal involvement. Esophageal lichen planus, in particular, can occur without skin involvement and can be difficult to define on esophageal histopathology.**

BEST PRACTICE ADVICE 10: **Clinicians should consider infectious and inflammatory causes of secondary achalasia during initial evaluation. One should query for any history of recent COVID infections, risks for Chagas disease, and symptoms or signs of eosinophilic disease.**

Keywords: Achalasia; Autoimmune Esophagitis; Infectious Esophagitis; Allergic Esophagitis.

Understanding the infectious and immune disease processes that result in esophageal dysfunction will expedite evaluations and diagnostic workup indicated when patients present with esophageal complaints.

The health care burden of esophageal dysfunction is substantial—especially in the elderly population.[1,2] Dysphagia, odynophagia, chest pain, and heartburn are all common symptoms of esophageal dysfunction. Esophageal dysfunction may arise as an organ-specific manifestation of a more diffuse immune-mediated disease or infection (ie, systemic sclerosis, connective tissue disease, neurologic disease).[3,4] These conditions can sometimes lead to neuromuscular dysfunction and subsequent esophageal dysmotility with variable endoscopic esophageal appearances. Without a high index of suspicion, these disorders may be overlooked.

Immune-mediated disorders may present endoscopically with esophageal rings, texture changes, or nonspecific mucosal appearances requiring a high index of suspicion for accurate diagnosis. Clinical awareness of varied esophageal manifestations of systemic disease enables efficient management (Figure 1).

Recent data has focused specifically on the potential for inflammatory and infectious etiologies to lead to dysmotility. Achalasia is a prime example of an esophageal motility disorder for which new evidence supports infectious and/or allergy associated etiologies for some.[5,6]

Herein, we attempt to deliver a high level overview of the potential infectious and immune etiologies of esophageal disease and summarize recent data expanding our understanding of the potential inflammatory etiologies which may mimic achalasia.

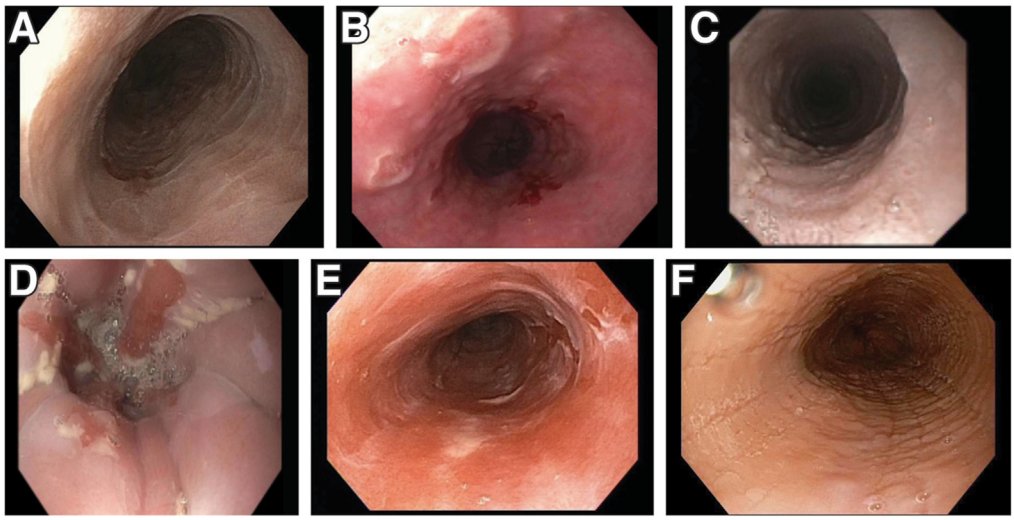

Figure 1. Examples of endoscopic findings in different infectious and immune-mediate esophageal disease. (*A*) Sjogren's esophagus with stricture; (*B*) Crohn's disease; (*C*) LP with edema and exudates; (*D*) candida esophagitis; (*E*) pemphigus with sloughing tissues; and (*F*) EoE with rings, furrows, edema, and exudates.

Infectious Etiologies of Esophageal Dysfunction

Most commonly, infectious etiologies for esophageal dysfunction include candida, herpes simplex virus (HSV), and cytomegalovirus (CMV). Although more common in immunosuppressed patients, infectious esophagitis may occur in immunocompetent hosts.[7–11]

Candida esophagitis is the most commonly encountered infectious esophagitis, presenting endoscopically with white nummular lesions, which in severe cases, may carpet the entire esophagus. Patients commonly complain of dysphagia or odynophagia. Diagnosis can be made with cytobrush or esophageal biopsies where fungal forms are identified.[12–15] Suggested risk factors for candida esophagitis include recent antibiotics, local or systemic steroids or immunosuppression, malignancy, proton pump inhibitor use, older age, chronic alcohol use, chronic kidney disease, diabetes, and motility disorders that lead to esophageal stasis.[16] Available guidelines recommend fluconazole as the preferred treatment.[14,17,18] Nystatin may be used as prophylaxis for patients at high risk of candida esophagitis or can be considered when it is unclear whether infection or colonization is present. Treatment of candida is not well-studied, and there is little guidance. Some studies suggest that candida may resolve on its own when the inciting risk is removed in immunocompetent hosts. It remains unclear whether treatment is warranted in asymptomatic individuals as one prior study demonstrated that asymptomatic candidiasis rarely becomes symptomatic. However, available guidelines recommend fluconazole as the preferred treatment (dosed at 200 to 400 mg per day for 14 to 21 days).[14,19,20]

Viral esophagitis commonly presents with dysphagia or severe odynophagia. HSV esophagitis presents as multiple small, shallow, well-circumscribed ulcers. CMV often results in a few large cratered ulcers.[21–23] HIV can also present with a few discrete esophageal ulcerations. HSV esophagitis displays intra-nuclear eosinophilic inclusions. HSV may be treated with up to 10 days (immunocompetent) or 21 days (immunosuppressed) of acyclovir, valacyclovir, or famciclovir. CMV is diagnosed on esophageal biopsies with histopathology demonstrating large eosinophilic or basophilic intranuclear inclusions. Up to 6 weeks of ganciclovir (or valganciclovir) may be needed to treat CMV.[24–26]

Immune Dysfunction of the Esophagus

Esophageal symptoms may also be a manifestation of immune dysfunction, which may be isolated to the esophagus or expanding to the esophagus from other organs.[27]

Localized Immune and Inflammatory Dysfunction

Eosinophilic esophagitis (EoE) and lymphocytic esophagitis involve local immune responses of the esophagus resulting in esophageal dysfunction.[28]

Eosinophilic esophagitis. EoE is a clinicopathologic condition characterized by symptoms of esophageal dysfunction and excessive accumulation of eosinophils in the esophageal tissue, in the absence of other causes.[29] EoE is triggered by exposure to food or aeroallergens, which induces a type-2 (allergic) response. Endoscopically, EoE can present with edema, rings, exudates, linear furrows, and strictures, or the esophagus can appear normal. It is advised to take multiple biopsies from 2 or more esophageal levels, as the inflammation can be located in a patchy distribution.[29]

EoE can affect both children and adults, and the presenting symptoms vary by age. Untreated transmural inflammation can lead to remodeling of the esophageal wall and smooth muscle hypertrophy, which leads to reduced esophageal wall compliance and contractility.[30,31] As a result, later presenting symptoms include

dysphagia, chest pain, and food impactions. Continued esophageal symptoms despite resolution of mucosal disease should prompt investigation for subtle esophageal strictures or motiity disorders. Recent data demonstrate increased risk for achalasia with EoE.[32–34]

Lymphocytic esophagitis. Lymphocytic esophagitis (LyE) has been characterized histologically as the finding of dense peripapillary lymphocytic infiltrate and peripapillary spongiosis involving the esophageal epithelium without significant eosinophilic or neutrophilic infiltrates.[35] In a 2012 study by Haque and Genta, the authors retrospectively reviewed histology of 129,252 adults who had undergone upper endoscopy with esophageal biopsy.[36] They found that 0.1% had histologic features of LyE on biopsy (compared with 2.8% with EoE). In the patients with LyE, a primary symptom of dysphagia (approximately two-thirds) occurred at similar frequency as those found to have EoE. EoE was endoscopically suspected in one-third of patients found to have LyE on histology. In contrast to the EoE demographic, LyE affected mostly women above the age of 60. However, the diagnosis of lymphocytic esophagitis should occur after one rules out EoE-like disease through biopsies obtained off proton pump inhibitor therapy for at least 2–4 weeks and even Crohn's disease, as these conditions may present in a similar manner histopathologically.

In retrospective single-center study of 81 patients diagnosed with LyE using similar definitions as described above, endoscopic findings were reviewed in more detail.[37] Abnormal endoscopic findings were described in approximately 70% to 75% of patients with rings, esophagitis, and stricture being the most common findings, respectively.

Overall, the etiology of LyE is thought to be unknown, and its status as a distinct clinical entity is unclear considering that lymphocytic esophageal recruitment seems to occur in response to a variety of scenarios where esophageal injury is taking place.[38]

Proton pump inhibitor therapy, swallowed topical corticosteroids, and esophageal dilations are therapeutic options for EoE and LyE, whereas elimination diets are effective therapies for EoE. Budesonide oral suspension is now United States Food and Drug Administration (FDA)-approved for EoE. Topical corticosteroids have not been well-studied in LyE. Dupilumab is a new monoclonal antibody to interleukin (IL-4) receptor alpha antibody FDA-approved for therapy of EoE.[39]

Esophageal Manifestations of Systemic Inflammation

Esophageal dysfunction from systemic inflammation/infection is poorly recognized, due to a paucity of knowledge surrounding esophageal involvement of disease.

Hypereosinophilic syndromes. Hypereosinophilic syndromes (HES) is an umbrella term for a group of rare and heterogeneous syndromes characterized by elevated eosinophils in the peripheral blood (absolute eosinophil count [AEC] >1500 cells/uL) and organ/tissue damage due to eosinophilic infiltration in the absence of other etiologies. Among patients with HES, up to 38% have gastrointestinal symptoms.[38,40] When HES affects the esophagus, the symptoms can mimic that seen in EoE.

HES can often be distinguished from EoE by the presence of peripheral eosinophilia (AEC >1500 cells/uL), which is rare in isolated EoE.[41] However, other eosinophilic gastrointestinal diseases such as eosinophilic gastritis and eosinophilic enteritis may be associated with peripheral eosinophilia, and these conditions can be accompanied by esophageal involvement.[42,43] In patients who present with esophageal symptoms in the setting of hypereosinophilia, further screening of upper and lower gastrointestinal (GI) involvement, and monitoring for other organ involvement (skin, lung, heart, neurologic) consistent with multisystem HES or eosinophilic granulomatosis with polyangiitis (EGPA), should be considered.

Eosinophilic granulomatosis with polyangiitis. EGPA, formerly known as Churg-Strauss syndrome, is a rare systemic eosinophilic vasculitis affecting small to medium-sized arteries. The clinical presentation of EGPA typically follows a pattern characterized by 3 stages: (1) prodromal (allergic rhinitis, nasal polyposis, asthma); (2) eosinophilic (peripheral blood eosinophilia and infiltration of eosinophils into tissues); and (3) vasculitic (necrotizing vasculitis that can lead to dysfunction of multiple organ systems). Although EGPA is considered to be an antineutrophil cytoplasmic antibody (ANCA)-associated vasculitis, only 30% to 40% of patients will have a positive ANCA.[44,45] Esophageal symptoms are rare, but may develop as a result of eosinophilic tissue infiltration, or as a result of neuropathy due to vasculitis.[46,47] Vasculitic changes are not always identified via histology,[47–49] so additional investigation to confirm the diagnosis may be required. Patients benefit from further consultation and discussion with allergy and/or rheumatology specialists.

Esophageal dysfunction associated with autoimmune disease. In adults, esophageal Crohn's disease is uncommonly encountered. It can be suspected in patients with active disease in multiple sites who complain of dysphagia and are found to have superficial or deep esophageal mucosal ulcerations.[48] Esophageal Crohn's disease has been described at a higher frequency in children, with one study reporting a rate of 20%.[49] Patients with esophageal involvement of Crohn's will require biologic therapy.

The esophageal manifestations of systemic sclerosis are common knowledge in gastroenterology and thought to be related to atrophy and fibrosis of the esophageal smooth muscle, resulting in severe hypomotility and an incompetent lower esophageal sphincter often appreciated on high-resolution manometry.[50] However, there are sparse literature discussing esophageal manifestations of mixed connective tissue disease (MCTD),

Sjogren's, systemic lupus erythematosus (SLE), and myositis.[3,50] MCTD is an overlap syndrome that can have features of systemic sclerosis (SSc), SLE, polymyositis, and/or rheumatoid arthritis. Esophageal involvement in patients with MCTD can resemble those with SSc. Esophageal involvement in MCTD can manifest proximally and distally due to its capability to affect both striated and smooth muscle, and involvement may be more variable and less severe as compared with SSc.[51]

Most clinicians are aware that Sjogren's syndrome manifests as secretory dysfunction due to exocrine lacrimal and salivary gland destruction. However, extraglandular manifestations are common, and up to 80% of patients may complain of dysphagia.[52] SLE is similar to Sjogren's in that dysmotility is thought to be the source of patients who complain of dysphagia, but also with unclear mechanism and variable findings on objective evaluation. Myositis affecting swallowing is typically attributed to polymyositis, dermatomyositis, or inclusion body myositis. These conditions affect proximal striated muscle with the cricopharyngeus (CP) often being involved.[53] Of patients with myositis, 30% to 80% will experience dysphagia, and CP-directed endoscopic therapy such as dilation, botulinum toxin injection, or myotomy often have important roles in management.[54–56]

Esophageal dysfunction due to esophageal involvement of dermatologic disease. Esophageal dysfunction may derive from esophageal involvement of dermatologic disease even without dermal manifestations.[57]

Pemphigus vulgaris (PV) is the most common bullous disorder affecting males and females equally, often between the ages of 40 and 60 years.[58] In a prospective study of 28 patients with oral PV, 18 had symptoms of dysphagia and were found to have objective esophageal involvement in setting of findings of erythema, red longitudinal lines, erosions, blisters, and/or ulcers, which all occurred at similar rates (except ulcers seen only in one patient).[59] Direct immunofluorescence (DIF), when positive for IgG and C3 deposition, is diagnostic for PV.[57] In a study of 26 patients with PV presenting with esophageal symptoms whose biopsies underwent DIF staining, 12 patients were found to be positive on DIF.[60] The described esophageal endoscopic findings in this study were non-specific, but commonly involved red longitudinal lines. Isolated esophageal involvement of PV has only been described in a few case reports.[61]

Lichen planus (LP) is capable of affecting the oral, esophageal, and genital mucosa as well.[57] LP represents a small fraction of all skin diseases yet is the most common disorder to affect the esophagus among all dermatologic conditions.[62] In contrast to PV, esophageal LP (ELP) has been described in isolation on a more frequent basis. Podboy et al noted that in a retrospective study of 40 patients with ELP, there were 13 (33%) who had esophageal involvement alone.[63] Coexisting cutaneous involvement was found in only 10%, and concomitant oral or genital involvement occurred in less than 50%. ELP has a very strong predilection towards Caucasian females who are typically middle or older aged.[63,64] Dysphagia is common in ELP.[62,63] Narrowed caliber of the majority of the esophagus, especially proximal and middle esophagus, along with multiple strictures are frequently seen.[64,65] In addition to strictures, classic ELP endoscopic findings consist of pale, edematous mucosa with peeling/sloughing often upon on contact with the endoscope, and the presence of thick white exudates.[62,65] Civatte bodies (necrosis of keratinocytes resulting in a vacuolated appearance) are the characteristic signs of LP on esophageal biopsies; however, less than 50% of biopsies are found to be diagnostic for ELP.[66] The role for DIF in ELP is primarily to rule out other dermatologic-related diseases that can involve the esophagus, such as PV. Although not diagnostic, the presence of fibrinogen deposition on DIF in the epithelial basement membrane is suggestive of ELP.[67]

In summary, esophageal manifestations of dermatologic diseases should be considered in patients with dysphagia who present with endoscopic abnormalities often thought to be atypical in nature. Obtaining tissue sample for DIF evaluation can sometimes clarify the diagnosis and should be obtained from both the involved and nearby uninvolved mucosa.[57,62] Biopsies for DIF can be placed directly onto saline-soaked non-woven gauze/sponge and put into containers for future processing in a suitable medium (ie, Michel's). In particular, clinicians should be aware of ELP being the most frequent esophageal manifestation of dermatologic disease, its unique endoscopic features, its increased risk for esophageal cancer, and its ability to manifest in the esophagus without other organ involvement.[68,69] Due to paucity in data, treatment algorithms are not fully defined. However, swallowed topical corticosteroids appear to result in benefit for >60% of patients diagnosed with ELP.[63] In the patients who do not respond to topical corticosteroids, systemic immunosuppressants will likely need to be considered, in which cases dermatologic consultation for further management is highly advisable.[62]

Achalasia (a specific disorder). Recent published literature reports unusual causes for some achalasia subsets: eosinophilic disease, mast cell disease, and infections such as Chagas disease. These data demand critical thinking when evaluating esophageal motility disorders.

A prevailing hypothesis is that achalasia is an autoimmune disease targeted at esophageal myenteric neurons.[34] In 2012, a study by Booy et al reported that, compared with the general population, patients with achalasia were more likely (odds ratio [OR], 3.6; 95% confidence interval [CI], 2.5-5.3) to have autoimmune conditions including type 1 diabetes mellitus, Sjogren's syndrome, and SLE.[70] In a more recent large claims database of 6769 achalasia cases compared with 27,076 non-achalasia controls, the presence of autoimmune conditions was associated with an increased odds (OR, 1.26; 95% CI, 1.11-1.42) of achalasia.[70,71] A follow-up

Table 1. Important Considerations When Evaluating Patients With Esophageal Dysfunction

Pertinent medical history	Diagnostic considerations	Tests to consider	Supportive endoscopic findings
Recent antibiotics	Candidal esophagitis Medication-induced ulceration (ie, doxycycline)	Upper endoscopy with biopsies and brushings if nummular lesions identified	Whitish nummular lesions (Candida) 1–2 well marked ulcerations for pill-induced esophagitis
Immunosuppression	Candidal esophagitis HSV CMV	Upper endoscopy with biopsies/brushings Consider infectious disease consult if infection identified	Whitish nummular lesions (Candida) Shallow ulcers for HSV Deep ulceration(s) in CMV
Recent COVID infection	Post-COVID dysmotility/achalasia	Upper endoscopy to rule out other diagnoses High-resolution esophageal manometry Timed barium esophagram with pill	Most likely normal appearing esophagus
Bullous dermatoses • Pemphigoid • Pemphigus	Esophageal involvement of bullous dermatoses	Upper endoscopy with biopsies for routine H&E staining and additional biopsies for DIF sent to a pathology center of excellence (presence of dermatopathology expertise can be of value)	Sloughing/blistering of tissues, erythema, red longitudinal lines, erosions, sloughing with dislodgement of epithelium in pemphigus during biopsies similar to skin Nikolsky's sign
LP • Oral • Dermatologic • Genital • Middle-older age female	Esophageal involvement	Upper endoscopy with biopsies for routine H&E staining and additional biopsies for DIF sent to a pathology center of excellence (presence of dermatopathology expertise can be of value)	Narrowed caliber of the majority of the esophagus Pale, edematous mucosa with peeling/sloughing often upon on contact with the endoscope, and the presence of thick white exudates Non-specific short or pan-esophageal stenoses
Atopic dermatitis, asthma, or significant food allergy/atopy	EoE	Upper endoscopy with a minimum of 3–4 biopsies distal esophagus and 3–4 biopsies in proximal esophagus done: off PPI at least 2–4 weeks prior Consider further medical history to rule out HES or EGPA (below)	Edema, rings, exudates, furrows, some with stenoses (part or all of esophagus) - can appear normal
HES or EGPA	Esophageal involvement similar to EoE	Upper endoscopy with biopsies	Can be similar to EoE or may appear normal
Autoimmune disease • Crohn's • Scleroderma • Lupus • MCTD • Sjogren's disease • Polymyositis • Dermatomyositis • Inclusion body myositis	Esophageal involvement of extra-esophageal autoimmune disease (via inflammatory or dysmotility mechanisms)	Upper endoscopy with biopsies and High-resolution esophageal manometry	Varied presentations from ulcerations (Crohn's), dilation with reflux changes (Scleroderma), to nonspecific edema and crepe paper appearing tissue with non-specific stenoses (Sjogren's) Esophageal manometry in SSc frequently shows absent contractility with low amplitude lower esophageal sphincter Cricopharyngeal involvement common in myositis
Prior travel or exposures in Central/South America	Chagas disease with potential achalasia	Infectious disease consult if positive diagnosis Upper endoscopy with biopsies to rule out other diagnoses High-resoultion esophageal manometry	Normal mucosal appearance vs chronic stasis changes
Female >50 years old with dysphagia often mimicking EoE on endoscopy	LyE	Upper endoscopy with biopsies for routine H&E done: off PPI at least 2–4 weeks prior	Overlapping features seen in EoE, can be normal

CMV, Cytomegalovirus; DIF, direct immunofluorescence; EGD, esophagogastroduodenoscopy; EGPA, eosinophilic granulomatosis with polyangiitis; EoE, eosinophilic esophagitis; H&E, hematoxylin and eosin; HES, hypereosinophilic syndromes; HSV, herpes simplex virus; LP, lichen planus; LyE, lymphocytic esophagitis; MCTD, mixed connective tissue disease; PPI, proton pump inhibitor; SSc, systemic sclerosis.

retrospective case-control study in Germany of 1141 achalasia cases and 3423 matched controls without achalasia also reported an association between autoimmune conditions and achalasia (OR, 1.49; 95% CI, 1.23-1.80). In both these studies, the strongest associations were observed for SSc and Addison's disease.[72]

Further, there is growing evidence supporting an association between allergy mediated eosinophilic disease and achalasia. Esophagectomy specimens and esophageal muscle biopsies have demonstrated dense accumulation of eosinophils in the muscularis propria.[34,73] At the same time, recent studies report an association between EoE and achalasia.[34,74] In a recent study of 844 patients with achalasia, the estimated relative risk of EoE was 32.9 (95% CI, 24.8-42.8), and higher in patients with achalasia 40 years or younger. Furthermore, the relative risk was also increased for atopic/allergic disorders among those with achalasia.[34] In EoE, eosinophils and mast cells produce neuroactive and myoactive substances and proinflammatory and cytotoxic products that have potential to cause motility disturbances and/or neuronal destruction characteristic of achalasia.[75] Although esophageal eosinophilia may also occur due to stasis of food in the esophagus, it is prudent to consider eradication of the eosinophilic infiltration of the esophagus in patients if clinical suspicion is high for comorbid EoE, as this may improve esophageal function.

Achalasia has been reported as a paraneplastic phenomena in some malignancies. The most common malignancies associated with secondary achalasia other than adenocarcinoma of the esophagus are lymphoma, lung cancer, and breast cancer.[76–81]

Infectious etiologies of achalasia are also well-described. In Chagas disease, *Trypanosoma cruzi* can cause esophageal dysfunction through immune cross-reactivity of the flagellar antigen of *T.* cruzi and the myenteric plexus. The degeneration of the myenteric plexus results in loss of esophageal peristalsis and impaired lower esophageal sphincter relaxation.[75] Gastrointestinal manifestations of Chagas disease (eg, mega-esophagus, mega-colon) are seen in 10% to 15% of chronically infected individuals.[82] Chagas has become an increasing problem in the United States, affecting an estimated 300,00 individuals.[83] In suspected Chagas disease, serologic tests can reliably diagnose *T. cruzi* infection and exclude an idiopathic achalasia.[84]

More recently, acute-onset achalasia following COVID-19 infection has been reported.[85–88] It is hypothesized that SARS-CoV-2, with an affinity for neuronally expressed ACE2 receptors, has potential to trigger inflammation with ganglionic cell destruction within the esophagus, leading to achalasia.[89] One study comparing esophageal muscle tissue from 4 patients with SARS-CoV-2 infection from patients with sudden onset post-COVID-19 achalasia vs 8 patients with longstanding type 2 achalasia without sudden onset post-COVID 19 achalasia identified 625-fold higher N protein as well as higher levels of S protein in patients with achalasia following SARS-CoV-2 infection. The presence of SARS-CoV-2 mRNA correlated with increase in inflammatory markers NLRP3 and TNF. It is not yet known whether observation is indicated in these patients, as it is unclear whether the motility disturbance is reversible. A case series of patients with acute onset of achalasia following COVID 19 had favorable short-term outcomes following myotomy.

Conclusion

Approaching the clinical evaluation for esophageal dysfunction with awareness of potential infectious and inflammatory etiologies increases the likelihood of diagnosing underlying disease states contributing to esophageal disease (Figure 1; Table 1).

Initial evaluation of patients complaining of esophageal symptoms should include a broad history and physical exam specifically geared toward identifying concurrent autoimmune or allergic disease, as well as risks for immunosuppression, which would increase one's risk for infection.

Guidelines regarding appropriate evaluation for extra-esophageal or systemic etiologies of esophageal dysfunction are lacking.[8,19,90] The knowledge surrounding how many biopsies and when/how to perform these biopsies remains lacking in the management of these conditions,[91–93] but awareness of their existence will empower gastroenterologists to perform appropriate biopsies and subsequent testing.

It is important for a gastroenterologist to have a high index of suspicion for immune-mediated or inflammatory disease in patients who present with esophageal dysfunction and to recognize the potential sources of atypical endoscopic esophageal manifestations as well as the histopathologic findings of atypical disease. Collaboration with associated disciplines (ie, rheumatology, dermatology, allergy/immunology, or infectious diseases) improves understanding and treatment of disease. Recognition of underlying disease states can dramatically improve the health care burden to patients and payors and more rapidly alleviate patient discomfort.

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Correspondence
Address correspondence to: Kathryn Peterson, MD, Professor of Medicine, Gastroenterology Division, University of Utah, 50 Medical Dr N, Salt Lake City, UT 84132. e-mail: kathryn.peterson@hsc.utah.edu.

Conflicts of interest
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