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Review Article

Infections of the esophagus: an update on risk factors, diagnosis, and management

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SUMMARY. **Infectious esophagitis is a leading cause of esophagitis worldwide. While esophageal infections have traditionally been associated with immunocompromised patients, these disorders are becoming increasingly recognized in immunocompetent individuals. The three most common etiologies of infectious esophagitis are Candida, herpes simplex virus, and cytomegalovirus. Human papilloma virus infection can also involve the esophagus in the form of ulcerative lesions and papillomas. Less common etiologies include various other fungal, bacterial, and viral organisms. This review provides a comprehensive update on risk factors, diagnosis, and management of both common and less common infections of the esophagus.**

KEYWORDS: **diagnosis, esophageal, esophagitis, infection, treatment.**

INTRODUCTION

Infectious esophagitis is the third leading cause of esophagitis behind gastroesophageal reflux disease (GERD) and eosinophilic esophagitis (EoE) and can be caused by bacterial, viral, fungal, and parasitic infections.[1] Much of the current research in infectious esophagitis relates to identification of new at-risk populations as well as development of targeted and effective approaches for prevention of infection in certain patient groups. It is of the utmost importance for clinicians to have appropriate suspicion for esophageal infections given the potential morbidity and mortality associated with these diseases, especially in the new generation of transplant recipients and other immunocompromised patient populations. Moreover, there is widespread availability of targeted and effective antimicrobial therapy that can readily be utilized if a prompt diagnosis is made. This article will serve to demonstrate the changing landscape of at-risk patient populations and review the latest recommendations for methods of diagnosis and considerations for selection of treatment approaches.

The most common cause of infectious esophagitis is *Candida* followed by herpes simplex virus (HSV) and cytomegalovirus (CMV).[2] Less common entities include human immunodeficiency virus (HIV),[3] tuberculosis,[4] varicella zoster virus (VZV),[5] human papilloma virus (HPV),[6] and various bacterial and parasitic organisms.[7] While infectious esophagitis most commonly occurs in immunocompromised patients, especially those with HIV/AIDs, diabetes, and those on immunosuppressive medications, it can also affect immunocompetent individuals.[8]

Candida esophagitis

Esophageal candidiasis (EC) is the most common cause of infectious esophagitis. Of all candida species, *Candida albicans* is the most common organism implicated in both colonization and infection.[7,9] Determination of specific *Candida* species can be clinically significant as *glabrata* species are more likely to have azole-resistance, which changes decision making in pharmacotherapy.[10] In addition, the use of prolonged antifungal therapy increases the rate of drug-resistant *C. albicans* species in the gastrointestinal tract and creates opportunities for non-*candida* fungal colonizers to proliferate.[11–13]

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Esophageal candidiasis has strong clinical significance with regard to patient mortality. In fact, one case-control study evaluating patients with EC 65 years of age or older found that patients with EC had a 6-month mortality rate of 47% compared to 5% in controls, and a 1-year survival of 38% compared to 93% in controls.[14] This finding was independent of the level of patient disability, suggesting that candida may be an independent risk factor as opposed to simply a marker of severe underlying medical comorbidities.

From an epidemiological standpoint, a recent large population based study from Japan evaluated the prevalence of EC among a cohort of 80,219 patients who underwent upper endoscopy between 2002 and 2014. The prevalence of EC was 1.7% in all patients, 9.8% in HIV patients, and 1.6% in non-HIV patients.[15] Other recent studies have demonstrated an overall decrease in the prevalence of EC in AIDS patients following the advent of highly active antiretroviral therapy (HAART).[16–18]

AIDS is the most commonly associated risk factor with development of EC, and AIDS patients with EC have lower CD4 counts than AIDS patients with limited oropharyngeal involvement.[19] However, there have been multiple recent studies aimed at identifying significant risk factors for development of EC in the non-HIV patient population where the prevalence of disease is increasing.[17] A summary of recent larger studies identifying these risk factors can be found in Table 1. Common risk factors identified include antibiotics, proton pump inhibitors (PPIs), H2 blockers,[20,21] alcohol, malignancy, topical and systemic corticosteroids,[22] and motility disorders, although the association of these risk factors is somewhat inconsistently demonstrated between studies.[14,15,23–27] Risk factors with the most consistent association between studies are antibiotics, corticosteroids, and malignancy. Medications can predispose patients to EC by altering the microenvironment of the esophageal mucosa and making it more favorable for candidal growth.[14,15,24–26] PPI and H2 blockers can result in hypochlorhydria, facilitating *Candida* colonization and infection of the esophageal mucosa.[25,21] Esophageal candidiasis is rarely present in patients without HIV or identifiable risk factors 0.[28]

A diagnosis of EC is made using a combination of characteristic endoscopic and histopathologic findings. Endoscopically, the esophageal mucosa displays thick, white plaques. Histopathology from biopsy or smear from brushings reveals budding yeast and pseudohyphae or hyphae with invasion of the epithelium (Fig. 1A).[29] While endoscopy is diagnostically necessary in the majority of EC cases, it may not be required in certain patient populations. One study evaluated 22 patients with known malignancy and oral candidiasis noted on physical exam. Of these 22 patients, 21 (95.5%) had endoscopic evidence of EC, suggesting routine endoscopy for this particular patient population may not always be necessary for diagnosis of EC.[30] The severity of esophagitis seen on endoscopy and classification using the Kodsi scoring system may be helpful in predicting the degree of gastrointestinal symptoms. Endoscopically, severe disease is found more often in patients with HIV infection. In contrast, patients with asymptomatic EC have endoscopic findings ranging from mild to severe esophagitis.[31]

Current guidelines recommend that EC in immunocompromised patients be treated with systemic antifungal therapy as opposed to local agents that are frequently used for oropharyngeal disease. Fluconazole is the mainstay of treatment.[32] Several randomized trials comparing fluconazole to other azole treatment regimens for EC were performed on severely immunocompromised patient populations including HIV-infected patients. A summary of these studies can be found in Table 2. Empiric fluconazole appears to be the most cost-effective strategy for management of HIV patients with esophageal symptoms when taking into consideration medication and procedure-related costs.[3] Echinocandins, amphotericin, and nonfluconazole azoles like posaconazole may be considered in patients refractory to fluconazole.[33–35]

There is limited literature to guide treatment of EC in non-HIV-infected patient populations. In fact, some recent studies suggest that not all patients with EC require treatment.[36,37] One study evaluated 142 immunocompetent patients with biopsy-proven EC who were asymptomatic and found no correlation between treatment with anti-fungal agents and endoscopic remission of EC on follow-up endoscopy.[36] These data suggest that antifungal treatment may not be necessary in the asymptomatic, immunocompetent EC patient population. In another recent study, Lee *et al*. retrospectively identified 79 patients with asymptomatic EC and described the natural history of the clinical course.[37] Of these 79 patients, 64 (81.0%) had resolved on repeat endoscopy and only 15 had recurrent EC on repeat endoscopy. In 10 of these 15 patients where EC persisted, none developed esophageal symptoms or had endoscopically worsening disease suggesting that asymptomatic EC could be a self-resolving disease in the majority of cases and even when it persists endoscopically, it is of little to no clinical significance.

Herpes simplex virus esophagitis

Much of the world's adult population is HSV seropositive, but often the virus remains latent and is not pathogenic. Primary infection or reactivation of latent virus can, however, result in clinically significant disease. HSV-1 causes herpes simplex esophagitis (HSE) far more commonly than HSV-2 in adults.[42]

Table 1. Summary to studies highlighting significant risk factors for development of EC.

Study	*N* (HIV/non-HIV)	PPIs	Antibiotics	Steroids	Diabetes	Cancer	Heavy alcohol use
Takahashi *et al.*[15]	211 (163/48)						
Martinez *et al.*[25]	51 (51/0)						
Weerasuriya *et al.*[14]	56 (unknown)						
Yokoob *et al.*[26]	51 (51/0)						
Choi *et al.* [27]	281 (281/0)						

Green, significant risk factor for EC; red, not significant risk factor for EC; gray, not assessed.

There are several known risk factors for the development of HSE, including hematologic malignancy, solid tumors, extensive burns, autoimmune disease, and HIV infection.[43] Interestingly, with increasing recognition of EoE, there is new data suggesting that HSE may be associated with EoE, especially in the pediatric patient population.[44–48] A recent study that performed a retrospective analysis of 16 pediatric patients with HSE from a single center found that 11 of the 16 were immunocompetent patients with 5 (45%) having biopsy-proven EoE following resolution of HSE. This suggests that clinical and endoscopic follow-up for EoE may be warranted in some children who develop HSE.[45] Similarly, a case series of three children with HSE found that they later developed EoE.[46] Given that the prevalence of HSE in immunocompetent children is rare and that EoE is relatively uncommon, there may be an association between these entities. Several case reports and series describe a similar association.[49–51] In a case series with five immunocompetent patients, four were found to have active EoE at the time of the HSE diagnosis.[50] Additional research is needed to further clarify the relationship between these two esophageal pathologies.

The diagnosis of HSV esophagitis is also made based using endoscopy and histopathology. The characteristic endoscopic appearance of HSV esophagitis includes multiple small, punched-out ulcers with or without raised margins, and fibrin exudate. Histological findings include multinucleated giant cells with nuclear molding and nuclear chromatin with ground glass appearance or Cowdry A inclusion bodies.[52,53] In the largest single center case series of HSE, 47 patients with HSE were identified. Thirty-five (74.5%) of the 47 patients had HSV ulcers located in the middle to lower one-third of the esophagus, and only 4.3% had ulcers isolated to the upper one third of the esophagus.[54] Immunocompromised hosts with HSE should receive treatment with acyclovir, famiciclovir, or valacyclovir. There is less evidence for treatment regimens for immunocompetent patient populations. Herpes simplex esophagitis is usually a self-resolving infection in immunocompetent adults with a natural history typically lasting 1 to 2 weeks. There are, however, case reports of treatment with acyclovir leading to a rapid symptomatic response in immunocompetent patients, suggesting that treatment with acyclovir may be beneficial even in immunocompetent patients.[42]

Cytomegalovirus esophagitis

Gastrointestinal CMV disease most frequently occurs in immunocompromised individuals such as those with AIDS, organ transplantation, long-term dialysis, and those on chemotherapy, corticosteroids, or immunosuppressive medications; however CMV esophagitis occurring in immunocompetent patients has been reported.[55–61] The most common gastrointestinal manifestations of CMV infection are colitis and esophagitis, respectively.[61]

The diagnosis of CMV esophagitis is made using a combination of clinical history, endoscopic findings, and histologic features. Cytomegalovirus esophagitis classically presents with odynophagia.[62] Other presenting symptoms include fever, nausea, emesis, dysphagia, epigastric pain, substernal chest pain, and gastrointestinal bleeding.[59,61–63] Systemic symptoms are common as more than one organ system may be involved. In general, the symptoms of CMV esophagitis tend to be more gradual than HSE.[7]

The endoscopic appearance of CMV esophagitis is variable. The majority of patients present with multiple ulcers located in the middle to distal esophagus.[62] Cytomegalovirus esophageal ulcers are typically either shallow or of intermediate depth with only a minority having deep depth or heaped up appearance.[62] The ulcers tend to be linear and discrete with normal intervening mucosa.[62,64] The size distribution of ulcers is variable with 43% less than 1 cm in size, 29% between 1 and 2 cm, and 28% greater than 2 cm in size.[62] Rarely, CMV esophagitis can be diffusely erosive and mimic HSV and reflux esophagitis.[62] Additionally, CMV esophagitis has also been associated with tissue necrosis and strictures.[65,66] There is significant overlap in the endoscopic findings between CMV and HSV esophagitis and histopathology may be required to differentiate these entities. In some patients, coinfection with CMV and HSV infection may be present.[67]

Histopathology in CMV esophagitis demonstrates inflammation and nuclear and cytoplasmic inclusions.[68] Cytomegalic cells are also known as owl's eye cells because of their characteristic appearance

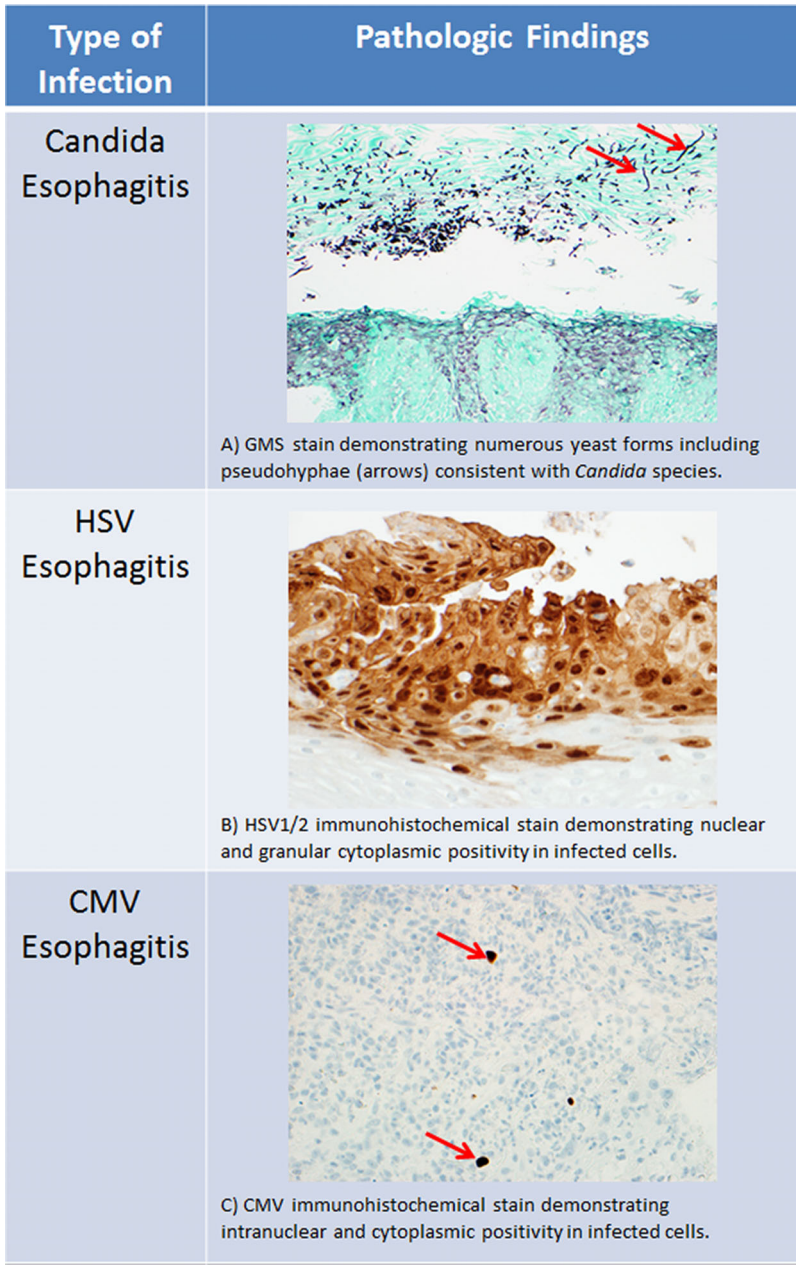

Figure 1. Histopathologic findings of Candida (A), HSV (B), and CMV (C) esophagitis.

of a basophilic intranuclear inclusion surrounded by a clear halo (owl's eyes) and intracytoplasmic inclusions.[55,69] The presence of owl's eye inclusion bodies is highly specific, albeit not sensitive, for the detection of CMV organ involvement.[70] Histologic evidence of CMV infection is common in patients with risk factors and suspicious lesions, although this is highly dependent on the number of biopsies taken and the diligence of pathologist.[55] Viral cultures and cytological brushings have little clinical benefit for diagnosis over multiple biopsy specimens with histology.[71]

In patients at high risk of developing CMV esophagitis (CD4 count < 50) who have severe clinical symptoms, treatment should be initiated while awaiting pathological confirmation. Treatment consists of induction therapy with or without maintenance therapy. Induction therapy consists of a 3- to 6-week course of ganciclovir or foscarnet.[72,73] While both antiviral agents have similar efficacy and are acceptable first-line agents,[74,75] ganciclovir is preferred due to cost and renal side effects associated with foscarnet. However, foscarnet is the preferred agent for patients with contraindications to ganciclovir such as moderate to severe thrombocytopenia or ganciclovir resistance.[68] Intravenous induction therapy is preferred for patients with severe clinical symptoms and inability to tolerate oral intake.[68] In patients with mild symptoms and no difficulty with oral intake,

Table 2. Randomized trials comparing fluconazole to other azole-based regimens for treatment of EC in immunocompromised patient populations.

Study	Comparison	Design and patient population	Results
Laine *et al.*[38]	Fluconazole versus ketoconazole with doubling of doses at week 1 and week 2 if no symptomatic improvement; total duration of treatment was for 2 weeks after time of symptom resolution.	169 patients with AIDS with symptomatic disease and endoscopic evidence with esophageal brushings or biopsies consistent with EC; Multicenter, randomized, double- blind study.	Fluconazole treatment led to 91% cure on repeat endoscopy. Ketoconazole led to 52% cure rate by endoscopy (95% CI, 24–52%, $p < 0.001$).
Wilcox *et al.* [39]	Fluconazole versus itraconazole for 2 weeks beyond symptom resolution.	126 immunocompromised patients with EC; Randomized, double-blind study.	Fluconazole led to clinical response in 91% of patients as opposed to itraconazole in 94% of patients.
Barbaro *et al.* [40]	Fluconazole versus itraconazole.	2213 HIV positive patients with first time diagnosis of symptomatic EC confirmed by biopsy or brushings were included; Multicenter randomized trial.	Fluconazole led to endoscopic cure after 2 weeks in 82.2% compared to 65.6% of patients who received itraconazole ($p < 0.001$). There was no difference in endoscopic and clinical cure rates at time of last follow up.
Ally *et al.* [41]	Fluconazole versus voriconazole.	391 immunocompromised patients with biopsy proven EC; Randomized, double blind, double dummy, multicenter trial.	High rates of endoscopic success in both groups (95.1% with fluconazole and 98.3% with voriconazole without statistically significant difference).

induction with oral valganciclovir can be considered. When a patient fails treatment with either agent, combination therapy with both agents may be used although this increases the risk of pancytopenia.[76]

While CMV infection was previously considered a fatal disease in patients with AIDS, its prognosis has dramatically improved with the institution of HAART.[77] Consequently, at present, patients with severe manifestations of CMV infection are those who have AIDS but are not on HAART, are noncompliant with HAART, have intolerance or resistance to HAART, or are not on CMV prophylaxis when this is clinically indicated. Despite the response to antiviral agents, many patients with CMV esophagitis have a poor long-term prognosis due to their severe underlying immunosuppression.[78]

Human papilloma virus esophagitis

Human papilloma virus infection is classically associated with common and genital warts and cervical cancer.[79] Esophageal manifestations of HPV infection are less common and include ulcerative lesions, hyperkeratosis, and papillomas.[80–82] Rarely diffuse esophageal papillomatosis is observed involving the entire esophagus, which can be asymptomatic or symptomatic.[83,84] The relationship of esophageal papillomatosis to HPV is inconsistent but in one patient improvement occurred with administration of the HPV vaccine.[84] Diffuse esophageal papillomatosis has been successfully treated with a single treatment of liquid nitrogen cryotherapy.[85] The microscopic features associated with HPV lesions include the presence of koilocytosis, perinuclear clearing, and giant and multinucleated cells.[6] Patients from Asia and South Africa are more likely to have HPV-associated esophageal lesions compared to Western countries. While certain studies suggest an association between HPV and esophageal squamous cell carcinoma, literature on this topic remains conflicting and inconclusive.[82,86,87] HPV has been considered a risk factor for development of esophageal squamous papillomas (ESPs), which are uncommon, benign lesions of the esophagus. The presence of HPV infection in ESPs varies greatly among studies performed in various geographic regions. One study evaluated 19 cases of ESPs in Mexico and HPV was detected in 87.5% of ESPs.[88] In contrast, HPV was not detected in any of the 78 cases of ESPs from Northern France.[89] Overall, the reported prevalence of HPV detected in ESPs is highly variable in the available literature and larger prospective studies are needed to further characterize the natural history of ESPs and HPV infections role in esophageal carcinogenesis.

Other infectious esophagitis

While *Candida* species are a common cause of fungal esophagitis, other fungi can also cause infectious esophagitis including *Aspergillus* and *Histoplasma* species. Aspergillus-related disease most commonly occurs in immunocompromised patients with pre-existing pulmonary disease.[7] Disease spectrum can span from invasive aspergillosis, a leading cause of infection-related death in patients with acute leukemia and recipients of stem cell transplant, to allergic forms of the disease such as allergic bronchopulmonary aspergillosis.[90] The diagnosis of *Aspergillus* esophagitis can be made using cytologic brushings or biopsy.[91] Treatment for invasive aspergillosis typically

involves voriconazole and in refractory cases, amphotericin B.[92]

Histoplasma capsulatum is classically found in the Midwestern United States.[93] Histoplasmosis primarily manifests as a pulmonary infection and the disease activity depends on a host's immune system and the number of conidia inhaled.[93] In most healthy individuals, the disease causes mild to no symptoms; however, in immunocompromised hosts, disseminated disease can occur, which can potentially be life-threatening.[93] While primary esophageal involvement is rare, esophageal ulceration can occur with disseminated disease and esophageal narrowing can result from mediastinal lymph node involvement and compression.[94,95] Treatment depends on the severity of the disease with itraconazole as the drug of choice for mild to moderate disease and amphotericin B for severe disease.[93]

Bacterial esophagitis can occur due to organisms that constitute the normal oropharyngeal flora. This includes gram positive, gram-negative, and anaerobic organisms. The most frequent bacterial inhabitant of the esophagus is *Streptococcus* species.[96] However, in patients with longstanding reflux, inflammation can result in alterations to the normal microbiome, with an increase in gram-negative anaerobes.[97] Most commonly, bacterial esophagitis occurs in immunocompromised hosts with malignancy and neutropenia although case reports exist describing it in immunocompetent individuals.[98–100] Patients with bacterial esophagitis should be initiated on broad-spectrum antibiotics and narrowing of antibiotics should be guided by culture results. *Mycobacterial tuberculosis* can result in esophageal tuberculosis, particularly in patients with dysphagia from developing countries and immunocompromised status.[101–103] Esophageal involvement may manifest as a tracheoesophageal fistula, nodal invasion, or ulceration. Patients with esophageal tuberculosis respond well to standard antituberculosis treatment.[101] *Mycobacterium avium complex* esophagitis has also been described and requires treatment with multiple antimycobacterial agents for several months.[104]

Causes of viral esophagitis other than HPV include HIV, VZV, and Epstein-Barr virus (EBV).[105] Primary HIV ulceration is typically seen in patients with uncontrolled HIV and has become less common with the use of HAART. HIV-related esophagitis may develop during acute HIV seroconversion syndrome or in AIDS.[106] In a patient with HIV presenting with new esophageal symptoms, management often begins with a trial of systemic antifungal therapy. HIV-associated idiopathic esophageal ulcers should be considered in the differential if patients do not respond to antifungals or antivirals or without a more common cause identified on biopsy. Varicella zoster virus esophagitis is rare and should be suspected in ill patients with dermatological manifestations of the disease with pruritic vesicular lesions.[7] Patients may present with dysphagia secondary to multiple cranial nerve involvement or esophagitis due to esophagobronchial fistula.[107–109] Endoscopy may reveal vesicles and ulcers and biopsies may demonstrate multinucleated giant cells.[7,109] Treatment with acyclovir, valacyclovir, or famciclovir should be instituted within 72 hours for patients with or at-risk of complications from herpes zoster.[110] Epstein-Barr virus is the causative agent of infectious mononucleosis and can also cause esophagitis. Epstein-Barr virus has previously been associated with esophageal ulcerations in patients with AIDS.[111] Symptomatic EBV esophageal disease may require treatment with acyclovir.[7]

CONCLUSION

Esophagitis is a common condition worldwide, with reflux being the most common etiology. However, infectious esophagitis is important to recognize as early diagnosis is essential to guide appropriate management. Recent literature has identified new risk factors for development of infective esophagitis, especially in regards to candida esophagitis. A current and comprehensive understanding of persons at risk of the various forms of infectious esophagitis is important to correctly diagnose and treat them.

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References

1. Wilcox C M. Overview of infectious esophagitis. Gastroenterol Hepatol (N Y) 2013; 9: 517–9.
2. Wilcox C M, Karowe M W. Esophageal infections: etiology, diagnosis, and management. Gastroenterologist 1994; 2: 188–206.
3. Rabeneck L, Boyko W J, McLean D M, McLeod W A, Wong K K. Unusual esophageal ulcers containing enveloped virus-like particles in homosexual men. Gastroenterology 1986; 90: 1882–9.
4. Marshall J B. Tuberculosis of the gastrointestinal tract and peritoneum. Am J Gastroenterol 1993; 88: 989–99.
5. Gill R A, Gebhard R L, Dozeman R L, Sumner H W. Shingles esophagitis: endoscopic diagnosis in two patients. Gastrointest Endosc 1984; 30: 26–27.
6. Winkler B, Capo V, Reumann W *et al.* Human papillomavirus infection of the esophagus. A clinicopathologic study with demonstration of papillomavirus antigen by the immunoperoxidase technique. Cancer 1985; 55: 149–55.

7. Baehr P H, McDonald G B. Esophageal infections: risk factors, presentation, diagnosis, and treatment. Gastroenterology 1994; 106: 509–32.
8. Hoversten P, Otaki F, Katzka D A. Course of esophageal candidiasis and outcomes of patients at a single center. Clin Gastroenterol Hepatol 2018. doi:10.1016/j.cgh.2018.04.035
9. McDonald G B, Sharma P, Hackman R C, Meyers J D, Thomas E D. Esophageal infections in immunosuppressed patients after marrow transplantation. Gastroenterology 1985; 88: 1111–7.
10. Wilson A, Delport J, Ponich T. Candida glabrata esophagitis: are we seeing the emergence of a new azole-resistant pathogen? Int J Microbiol 2014; 2014: 1–4.
11. Bluhm C S, Bickerstaff C A, Holt S. Refractory esophageal candidiasis in acquired immune deficiency syndrome (AIDS). Am J Gastroenterol 1990; 85: 479–80.
12. Kitchen V S, Savage M, Harris J R. Candida albicans resistance in AIDS. J Infect 1991; 22: 204–5.
13. Tavitian A, Raufman J P, Rosenthal L E, Weber J, Webber C A, Dincsoy H P. Ketoconazole-resistant Candida esophagitis in patients with acquired immunodeficiency syndrome. Gastroenterology 1986; 90: 443–5.
14. Weerasuriya N, Snape J. A study of candida esophagitis in elderly patients attending a district general hospital in the UK. Dis Esophagus 2006; 19: 189–92.
15. Takahashi Y, Nagata N, Shimbo T *et al.* Long-term trends in esophageal candidiasis prevalence and associated risk factors with or without HIV infection: lessons from an endoscopic study of 80,219 patients. PLoS One 2015; 10: e0133589.
16. Mocroft A, Oancea C, van Lunzen J *et al.* Decline in esophageal candidiasis and use of antimycotics in European patients with HIV. Am J Gastroenterol 2005; 100: 1446–54.
17. Alsomali M I, Arnold M A, Frankel W L *et al.* Challenges to "Classic" esophageal candidiasis. Am J Clin Pathol 2017; 147: 33–42.
18. Raufman J-P. Declining gastrointestinal opportunistic infections in HIV-infected persons: a triumph of science and a challenge for our HAARTs and minds. Am J Gastroenterol 2005; 100: 1455–8.
19. López-Dupla M, Mora S P, Pintado G V *et al.* Clinical, endoscopic, immunologic, and therapeutic aspects of oropharyngeal and esophageal candidiasis in HIV-infected patients: a survey of 114 cases. Am J Gastroenterol 1992; 87: 1771–6.
20. Kochhar R, Talwar P, Singh S, Mehta S K. Invasive candidiasis following cimetidine therapy. Am J Gastroenterol 1988; 83: 102–3.
21. Vermeersch B, Rysselaere M, Dekeyser K *et al.* Fungal colonization of the esophagus. Am J Gastroenterol 1989; 84: 1079–83.
22. Mullaoglu S, Turktas H, Kokturk N, Tuncer C, Kalkanci A, Kustimur S. Esophageal candidiasis and *Candida* colonization in asthma patients on inhaled steroids. Allergy Asthma Proc 2007; 28: 544–9.
23. Underwood J A, Williams J W, Keate R F. Clinical findings and risk factors for Candida esophagitis in outpatients. Dis Esophagus 2003; 16: 66–69.
24. Gundry S R, Borkon A M, McIntosh C L, Morrow A G. Candida esophagitis following cardiac operation and short-term antibiotic prophylaxis. J Thorac Cardiovasc Surg 1980; 80: 661–8.
25. Chocarro M A, Galindo T F, Ruiz-Irastorza G *et al.* Risk factors for esophageal candidiasis. Eur J Clin Microbiol Infect Dis 2000; 19: 96–100.
26. Yakoob J, Jafri W, Abid S *et al.* Candida esophagitis: risk factors in non-HIV population in Pakistan. World J Gastroenterol 2003; 9: 2328–31.
27. Choi J H, Lee C G, Lim Y J, Kang H W, Lim C Y, Choi J-S. Prevalence and risk factors of esophageal candidiasis in healthy individuals: a single center experience in Korea. Yonsei Med J 2013; 54: 160–5.
28. Mimidis K, Papadopoulos V, Margaritis V *et al.* Predisposing factors and clinical symptoms in HIV-negative patients with Candida oesophagitis: are they always present? Int J Clin Pract 2004; 59: 210–3.
29. Kodsi B E, Wickremesinghe C, Kozinn P J, Iswara K, Goldberg P K. Candida esophagitis: a prospective study of 27 cases. Gastroenterology 1976; 71: 715–9.
30. Samonis G, Skordilis P, Maraki S *et al.* Oropharyngeal candidiasis as a marker for esophageal candidiasis in patients with cancer. Clin Infect Dis 1998; 27: 283–6.
31. Asayama N, Nagata N, Shimbo T *et al.* Relationship between clinical factors and severity of esophageal candidiasis according to Kodsi's classification. Dis Esophagus 2014; 27: 214–9.
32. Pappas P G, Kauffman C A, Andes D R *et al.* Clinical practice guideline for the management of candidiasis: 2016 update by the infectious diseases society of America. Clin Infect Dis 2016; 62: e1–50.
33. Vazquez J A, Skiest D J, Nieto L *et al.* A multicenter randomized trial evaluating posaconazole versus fluconazole for the treatment of oropharyngeal candidiasis in subjects with HIV/AIDS. Clin Infect Dis 2006; 42: 1179–86.
34. Skiest D J, Vazquez J A, Anstead G M *et al.* Posaconazole for the treatment of azole-refractory oropharyngeal and esophageal candidiasis in subjects with HIV infection. Clin Infect Dis 2007; 44: 607–14.
35. Barbaro G, Barbarini G, Di Lorenzo G. Fluconazole vs. flucytosine in the treatment of esophageal candidiasis in AIDS patients: a double-blind, placebo-controlled study. Endoscopy 1995; 27: 377–83.
36. Min Y W, Kim E, Son H J, Kim J J, Rhee P-L. Antifungal treatment is not required for immunocompetent individuals with asymptomatic esophageal candidiasis. Medicine (Baltimore) 2015; 94: e1969.
37. Lee S P, Sung I K, Kim J H, Lee S Y, Park H S, Shim C S. The clinical course of asymptomatic esophageal candidiasis incidentally diagnosed in general health inspection. Scand J Gastroenterol 2015; 50: 1444–50.
38. Laine L, Dretler R H, Conteas C N *et al.* Fluconazole compared with ketoconazole for the treatment of candida esophagitis in AIDS. Ann Intern Med 1992; 117: 655–60.
39. Wilcox C M, Darouiche R O, Laine L, Moskovitz B L, Mallegol I, Wu J. A randomized, double-blind comparison of itraconazole oral solution and fluconazole tablets in the treatment of esophageal candidiasis. J Infect Dis 1997; 176: 227–32.
40. Barbaro G, Barbarini G, Calderon W, Grisorio B, Alcini P, Di Lorenzo G. Fluconazole versus itraconazole for candida esophagitis in acquired immunodeficiency syndrome. Candida Esophagitis. Gastroenterology 1996; 111: 1169–77.
41. Ally R, Schürmann D, Kreisel W *et al.* A randomized, double-blind, double-dummy, multicenter trial of voriconazole and fluconazole in the treatment of esophageal candidiasis in immunocompromised patients. Clin Infect Dis 2001; 33: 1447–54.
42. Kadayakkara D K, Candelaria A, Kwak Y E, Loeser C. Herpes simplex virus-2 esophagitis in a young immunocompetent adult. Case Rep Gastrointest Med. 2016; 2016: 1–3.
43. Généreau T, Rozenberg F, Bouchaud O, Marche C, Lortholary O. Herpes esophagitis: a comprehensive review. Clin Microbiol Infect 1997; 3: 397–407.
44. Žaja F O, Lesar T, Busic N, Tešović G. Herpes simplex primoinfection in an immunocompetent host with eosinophilic esophagitis. Pediatr Int 2013; 55: e38–41.
45. Fritz J, Lerner D, Suchi M. Herpes simplex virus esophagitis in immunocompetent children. J Pediatr Gastroenterol Nutr 2018; 66: 609–13.
46. Squires K A, Cameron D J, Oliver M, da Fonseca Junqueira J C. Herpes simplex and eosinophilic oesophagitis: the chicken or the egg? J Pediatr Gastroenterol Nutr 2009; 49: 246–50.
47. Monsanto P, Almeida N, Cipriano M A, Gouveia H, Sofia C. Concomitant herpetic and eosinophilic esophagitis—a causality dilemma. Acta Gastroenterol Belg 2012; 75: 361–3.
48. Sehgal S, Darbari A, Bader A. Herpes simplex virus and eosinophilic esophagitis. J Pediatr Gastroenterol Nutr 2013; 56: e1.
49. Lindberg G M, Van Eldik R, Saboorian M H. A case of herpes esophagitis after fluticasone propionate for eosinophilic esophagitis. Nat Rev Gastroenterol Hepatol 2008; 5: 527–30.
50. Zimmermann D, Criblez D H, Dellon E S *et al.* Acute herpes simplex viral esophagitis occurring in 5 immunocompetent

individuals with eosinophilic esophagitis. ACGCR 2016; 3: 165–8.
51. Machicado J D, Younes M, Wolf D S. An unusual cause of odynophagia in a patient with eosinophilic esophagitis. Gastroenterology 2014; 147: 37–38.
52. Wong R C K, Abdul-Karim F W. Atypical herpes simplex esophagitis. Gastrointest Endosc 2005; 61: 291–2.
53. McBane R D, Gross J B. Herpes esophagitis: clinical syndrome, endoscopic appearance, and diagnosis in 23 patients. Gastrointest Endosc 1991, 37: 600–3.
54. Wang H-W, Kuo C-J, Lin W-R *et al.* Clinical characteristics and manifestation of herpes esophagitis. Medicine (Baltimore) 2016; 95: e3187.
55. Goodgame R W, Genta R M, Estrada R, Demmler G, Buffone G. Frequency of positive tests for cytomegalovirus in AIDS patients: endoscopic lesions compared with normal mucosa. Am J Gastroenterol 1993; 88: 338–43.
56. Weile J, Streeck B, Muck J *et al.* Severe cytomegalovirus-associated esophagitis in an immunocompetent patient after short-term steroid therapy. J Clin Microbiol 2009; 47: 3031–3.
57. Galiatsatos P, Shrier I, Lamoureux E, Szilagyi A. Meta-analysis of outcome of cytomegalovirus colitis in immunocompetent hosts. Dig Dis Sci 2005; 50: 609–16.
58. Umemoto K, Kojima Y, Nagata N *et al.* Cytomegalovirus esophagitis developing during chemoradiotherapy for esophageal cancer: two case reports. J Med Case Reports 2016; 10: 259.
59. Marques S, Carmo J, Pinto D, Bispo M, Ramos S, Chagas C. Cytomegalovirus disease of the upper gastrointestinal tract: a 10-year retrospective study. GE Port J Gastroenterol 2017; 24: 262–8.
60. Ozaki T, Yamashita H, Kaneko S *et al.* Cytomegalovirus disease of the upper gastrointestinal tract in patients with rheumatic diseases: a case series and literature review. Clin Rheumatol 2013; 32: 1683–90.
61. Wang H W, Kuo C J, Lin W R *et al.* The clinical characteristics and manifestations of cytomegalovirus esophagitis. Dis Esophagus 2016; 29: 392–9.
62. Wilcox C M, Straub R F, Schwartz D A. Prospective endoscopic characterization of cytomegalovirus esophagitis in AIDS. Gastrointest Endosc 1994; 40: 481–4.
63. Kanda K, Kume K, Yoshikawa I *et al.* Cytomegalovirus esophagitis with massive upper-GI hemorrhage. Gastrointest Endosc 2004; 59: 741–3.
64. Rosołowski M, Kierzkiewicz M. Etiology, diagnosis and treatment of infectious esophagitis. Prz Gastroenterol 2013; 8: 333–7.
65. Barjas E, Pires S, Lopes J *et al.* Cytomegalovirus acute necrotizing esophagitis. Endoscopy 2001; 33: 735.
66. Olmos M, Sanchez Basso A, Battaglia M, Concetti H, Magnanini F. Esophageal strictures complicating cytomegalovirus ulcers in patients with AIDS. Endoscopy 2001; 33: 822.
67. Albuquerque A, Cardoso H, Ribeiro A *et al.* Herpes and cytomegalovirus esophagitis. Endoscopy 2012; 44:E242–3.
68. Whitley R J, Jacobson M A, Friedberg D N *et al.* Guidelines for the treatment of cytomegalovirus diseases in patients with AIDS in the era of potent antiretroviral therapy: recommendations of an international panel. International AIDS Society-USA. Arch Intern Med 1998; 158: 957–69.
69. Herriot R, Gray E S. Images in clinical medicine. Owl's-eye cells. N Engl J Med 1994; 331: 649.
70. Mattes F M, Mclaughlin J E, Emery V C, Clark D A, Griyths P D. Histopathological detection of owl's eye inclusions is still specific for cytomegalovirus in the era of human herpesviruses 6 and 7. J Clin Pathol 2000; 53: 612–4.
71. Wilcox C M, Rodgers W, Lazenby A. Prospective comparison of brush cytology, viral culture, and histology for the diagnosis of ulcerative esophagitis in AIDS. Clin Gastroenterol Hepatol 2004; 2: 564–7.
72. Dieterich D T, Kotler D P, Busch D F *et al.* Ganciclovir treatment of cytomegalovirus colitis in AIDS: a randomized, double-blind, placebo-controlled multicenter study. J Infect Dis 1993; 167: 278–82.
73. Nelson M R, Connolly G M, Hawkins D A, Gazzard B G. Foscarnet in the treatment of cytomegalovirus infection of the esophagus and colon in patients with the acquired immune deficiency syndrome. Am J Gastroenterol 1991; 86: 876–81.
74. Blanshard C, Benhamou Y, Dohin E, Lernestedt J O, Gazzard B G, Katlama C. Treatment of AIDS-associated gastrointestinal cytomegalovirus infection with foscarnet and ganciclovir: a randomized comparison. J Infect Dis 1995; 172: 622–8.
75. Parente F, Bianchi Porro G. Treatment of cytomegalovirus esophagitis in patients with acquired immune deficiency syndrome: a randomized controlled study of foscarnet versus ganciclovir. Am J Gastroenterol 1998; 93: 317–22.
76. Dieterich D T, Poles M A, Lew E A *et al.* Concurrent use of ganciclovir and foscarnet to treat cytomegalovirus infection in AIDS patients. J Infect Dis 1993; 167: 1184–8.
77. Salzberger B, Hartmann P, Hanses F *et al.* Incidence and prognosis of CMV disease in HIV-infected patients before and after introduction of combination antiretroviral therapy. Infection 2005; 33: 345–9.
78. Mel Wilcox C, Straub R F, Schwartz D A. Cytomegalovirus esophagitis in AIDS: a prospective evaluation of clinical response to ganciclovir therapy, relapse rate, and long-term outcome. Am J Med 1995; 98: 169–76.
79. Muñoz N, Bosch F X, de Sanjosé S *et al.* Epidemiologic classification of human papillomavirus types associated with cervical cancer. N Engl J Med 2003; 348: 518–27.
80. Bohn OL, Navarro L, Saldivar J, Sanchez-Sosa S. Identification of human papillomavirus in esophageal squamous papillomas. World J Gastroenterol 2008; 14: 7107.
81. Quarto G, Sivero L, Somma P *et al.* A case of infectious esophagitis caused by human papilloma virus. Minerva Gastroenterol Dietol 2008; 54: 317–21.
82. Lavergne D, de Villiers E-M. Papillomavirus in esophageal papillomas and carcinomas. Int J Cancer 1999; 80: 681–4.
83. Lee K, Lee O, Lee S. Gastrointestinal: diffuse esophageal papillomatosis involving the entire esophagus. J Gastroenterol Hepatol 2014; 29: 1951.
84. Gençdal G, Degirmencioglu S, Akyıldız M. Diffuse esophageal squamous papillomatosis covering the entire esophagus. Clin Gastroenterol Hepatol 2018; 16: A28.
85. McDonald N M, Amateau S K. Treatment of diffuse esophageal squamous papillomatosis with cryotherapy. Am J Gastroenterol 2016; 111: 1378.
86. Li X, Gao C, Yang Y *et al.* Systematic review with meta-analysis: the association between human papillomavirus infection and oesophageal cancer. Aliment Pharmacol Ther 2014; 39: 270–81.
87. Petrick J L, Wyss A B, Butler A M *et al.* Prevalence of human papillomavirus among oesophageal squamous cell carcinoma cases: systematic review and meta-analysis. Br J Cancer 2014; 110: 2369–77.
88. Bohn O-L, Navarro L, Saldivar J, Sanchez-Sosa S. Identification of human papillomavirus in esophageal squamous papillomas. World J Gastroenterol 2008; 14: 7107–11.
89. d'Huart M-C, Chevaux J, Bressenot A *et al.* Prevalence of esophageal squamous papilloma (ESP) and associated cancer in northeastern France. Endosc Int Open 2015; 3: E101–6.
90. Segal B H. Aspergillosis. N Engl J Med 2009; 360: 1870–84.
91. Bergman S, Geisinger KR. Esophageal aspergillosis in cytologic brushings: report of two cases associated with acute myelogenous leukemia. Diagn Cytopathol 2004; 30: 347–9.
92. Herbrecht R, Denning D W, Patterson T F *et al.* Voriconazole versus amphotericin B for primary therapy of invasive aspergillosis. N Engl J Med. 2002; 347: 408–15.
93. Kauffman C A. Histoplasmosis: a clinical and laboratory update. Clin Microbiol Rev 2007; 20: 115–32.
94. Marshall J B, Singh R, Demmy T L, Bickel J T, Everett E D. Mediastinal histoplasmosis presenting with esophageal involvement and dysphagia: case study. Dysphagia 1995; 10: 53–58.
95. Sandkovsky U, Ali K F, VanSchooneveld T C, Radio S J, Swindells S. Disseminated histoplasmosis presenting as esophageal ulceration in an HIV-infected man. Infect Dis Clin Pract 2013; 21: 383–5.
96. Norder Grusell E, Dahlén G, Ruth M *et al.* Bacterial flora of the human oral cavity, and the upper and lower esophagus. Dis Esophagus 2013; 26: 84–90.

97. Yang L, Lu X, Nossa C W, Francois F, Peek R M, Pei Z. Inflammation and intestinal metaplasia of the distal esophagus are associated with alterations in the microbiome. Gastroenterology 2009; 137: 588–97.
98. Walsh T J, Belitsos N J, Hamilton S R. Bacterial esophagitis in immunocompromised patients. Arch Intern Med 1986; 146: 1345–8.
99. Radhi J M, Schweiger F. Bacterial oesophagitis in an immunocompromised patient. Postgrad Med J 1994; 70: 233–4.
100. Shin J A, Lee Y B, Yoon I C, Jeong H J, Kwon T, Lee H S. Bacterial ulcerative esophagitis in an immunocompetent patient. Case Rep Gastroenterol 2017; 11: 162–7.
101. Jain S K, Jain S, Jain M, Yaduvanshi A. Esophageal tuberculosis: is it so rare? Report of 12 cases and review of the literature. Am J Gastroenterol. 2002; 97: 287–91.
102. Gomes J, Antunes A, Carvalho A, Duarte R. Dysphagia as a manifestation of esophageal tuberculosis: a report of two cases. J Med Case Rep 2011; 5: 447.
103. Welzel T M, Kawan T, Bohle W, Richter G M, Bosse A, Zoller W G. An unusual cause of dysphagia: esophageal tuberculosis. J Gastrointestin Liver Dis 2010; 19: 321–4.
104. El-Serag H B, Johnston D E. Mycobacterium avium complex esophagitis. Am J Gastroenterol 1997; 92: 1561–3.
105. Wilcox C M. Esophageal disease in the acquired immunodeficiency syndrome: etiology, diagnosis, and management. Am J Med 1992; 92: 412–21.
106. Rabeneck L, Popovic M, Gartner S *et al.* Acute HIV infection presenting with painful swallowing and esophageal ulcers. JAMA 1990; 263: 2318.
107. Nishioka K, Fujishima K, Kobayashi H, Mizuno Y, Okuma Y. An extremely unusual presentation of varicella zoster viral infection of cranial nerves mimicking Garcin syndrome. Clin Neurol Neurosurg 2006; 108: 772–4.
108. Paliwal M, Prasanna K S, Saraswat V A, Misra A, Krishnani N, Ghoshal U C. Varicella zoster cranial polyneuropathy presenting with dysphagia, esophagitis and gastroparesis. J Neurogastroenterol Motil 2011; 17: 192–4.
109. Moretti F, Uberti-Foppa C, Quiros-Roldan E, Fanti L, Lillo F, Lazzarin A. Oesophagobronchial fistula caused by varicella zoster virus in a patient with AIDS: a unique case. J Clin Pathol 2002; 55: 397–8.
110. Cohen J I. Herpes zoster. N Engl J Med 2013; 369: 255–63.
111. Kitchen V S, Helbert M, Francis N D *et al.* Epstein-Barr virus associated oesophageal ulcers in AIDS. Gut 1990; 31: 1223–5.