Infectious Esophagitis

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Opinion statement

Infectious esophagitis can have significant implications in an impaired host. Described most commonly in immunocompromised patients, infectious esophagitis can also occasionally be discovered in immunocompetent individuals in several unique clinical settings. Evaluation of the typical presenting complaints, such as dysphagia or odynophagia, are especially important in immunocompetent patients, and therapy should be directed at the appropriate predisposing condition and resultant infectious agent. In immunocompromised patients, however, clinical experience supports the use of empiric therapy in patients without concomitant systemic complaints. Especially in AIDS patients or those with lymphoma or leukemia, the initial approach to infectious esophagitis complaints (*ie*, dysphagia or odynophagia) is to begin an empiric trial of oral systemic fluconazole for presumed candidal esophagitis. If the individual remains symptomatic after 3 to 7 days or has any associated systemic complaints or concerning clinical findings (*eg*, hematemesis), then upper endoscopy with biopsies is indicated. If an etiologic agent other than *Candida* is defined by histologic, immunohistochemical, or culture methods, then appropriate therapy can be initiated. There are many important and pathologic agents implicated in infectious esophagitis. Thus, directed therapy needs to be administered appropriately and in a timely fashion to avoid poor short-term problems or long-term sequelae.

Introduction

Infectious esophagitis is a relatively uncommon condition that is important because of its significant morbidity and mortality, if the condition is unrecognized. It can present in association with disparate clinical conditions but is most commonly diagnosed in immunocompromised patients, specifically those with AIDS, leukemia, lymphoma, or other tumors [1–3]. Other significant risk factors are generally iatrogenic, resulting from chemotherapy, broad-spectrum antibiotics, immunomodulators, and high-dose corticosteroid administration. Important infectious agents to consider include fungi (primarily *Candida albicans, Aspergillus, Blastomyces, Cryptococcus, Histoplasma*), viruses (herpes simplex [HSV], cytomegalovirus [CMV], varicella zoster virus [VZV], Epstein-Barr virus [EBV], human papillomavirus [HPV], or HIV), and bacteria (*eg*, *Staphylococcus aureus, Streptococcus epidermidis*, and *Bacillus* species). The likelihood of a specific infectious agent varies with the clinical situation, but *Candida* is generally the most common, especially in the modestly immunocompromised individual. In those individuals who are profoundly immunocompromised, the full spectrum of listed agents (and some not listed) can be the offending pathogens.

Infectious esophagitis may be symptomatic or asymptomatic. Symptoms can include dysphagia or odynophagia, pyrosis, nausea, chest pain, and even hematemesis. Pain or difficulty with swallowing is the most common complaint with candidal infection of the esophagus, although the majority of infected patients in one study were asymptomatic and a significant percentage of patients with AIDS were asymptomatic in another study [4,5]. In general, acute and severe odynopaghia is reported to be the typical presentation for HSV or VZV esophagitis, whereas more vague complaints (nausea and vomiting, epigastric discomfort, anorexia and fevers) are attributed to CMV esophagitis. However, one report suggested that CMV can frequently be associated with as odynophagia as well [6].

Infectious esophagitis may be uncovered incidentally (during routine endoscopy or post mortem autopsy [7]), it may be suspected owing to characteristic clinical complaints, or the etiologic agent may be diagnosed after careful clinical investigation. Therefore, diagnosis may be either clinical or histologic, with endoscopy being the optimal approach in cases of uncertainty. Barium swallow is generally inadequate for characterization of the infecting organism [8] (a so-called shaggy appearance has been reported with both *Candida* and HSV [9]), and biopsies are not possible with this diagnostic approach. However, blind brush cytology can be used in correspondence with or in lieu of other studies, with reasonable sensitivity and specificity for *Candida* [10,11]. On endoscopy, *Candida* is reported to present as isolated white or yellow plaques, with underlying mucosal erythema. HSV has isolated shallow ulcerations that can coalesce over time, whereas CMV is reported to have more linear or serpiginous superficial ulcerations (although these can also coalesce). Endoscopic appearance, however, is not diagnostic, and brushings or biopsies are required for definitive diagnosis. Notably, an individual may be infected with several organisms [12,13], so sending histologic specimens, viral cultures, and specimens for immunoperoxidase staining, even with clinical evidence suggesting *Candida*, is often appropriate.

Generally, patients do not undergo immediate endoscopy if there is significant suspicion for *Candida* of the esophagus (although some experts have advocated initial endoscopy in symptomatic HIV-infected patients [14]). An immunocompromised patient (especially a patient with AIDS) who presents with acute-onset dysphagia or odynophagia (especially if oropharyngeal thrush is present) generally is treated empirically with antifungal therapy. If the patient does not improve after several days to a week, then endoscopy with biopsies and brushings should be performed to ensure an accurate diagnosis.

Given that many of the pathogens imputed in infectious esophagitis are commensal organisms, there can be some blurring of the distinction between colonization and infection by a specific organism (especially with fungi). Bacteria, fungi, and viruses can be commonly found in the esophagus but only rarely become pathogenic. Determination of infection may require that specific endoscopic and histologic criteria be met. For example, a diagnosis of candidal infection would show intraesophageal plaques with associated esophagitis and biopsies demonstrating invasive hyphae and budding yeast. Simply demonstrating topical yeast does not rule out the possibility of swallowed orocutaneous *Candida* from thrush.

HOST FACTORS

Immunocompetent hosts For infectious esophagitis, there are risk factors other than immunosuppression. Recall that the prevention of esophageal pathogen adherence is an important aspect of host defense. Therefore, conditions in which the clearance of organisms is impaired can result in esophageal infection. Impairment in salivation, reduction in physiologic reflux or gastric acid production, injury to esophageal mucosa, alterations of esophageal motility, or defects in esophageal clearance can result in infection or colonization of the human esophagus. Illustrative clinical conditions include hypochlorhydria, progressive systemic sclerosis, or achalasia. Further, when the typical equilibrium amongst commensal organisms is disrupted (as with antibiotic therapy), organisms with pathogenic potential can result in opportunistic infections. Although they are not truly immunosuppressed, individuals with conditions like diabetes mellitus, alcoholism, and adrenal insufficiency may have alterations in their immune system that can increase the risk for infectious esophagitis, as well.

Immunocompromised hosts Although immunosuppression from any condition or therapy can potentially lead to esophageal infections, the individuals at highest risk for infectious esophagitis are those with HIV-infection (low CD4 counts) and leukemia or lymphoma (especially during chemotherapy). Chemotherapy and irradiation can increase the risk for immunosuppression and opportunistic infections of the esophagus, but they can also have a negative impact on the natural mucosal defenses of the esophagus. Hematologic more than solid tumor malignancy increases the risk of infectious esophagitis, but both are substantial risk factors [15]. Interestingly, immunosuppression for transplantation only modestly increases the risk for infectious esophagitis [16,17], whereas systemic and topical corticosteroids (administered for other conditions) appear to pose a significant risk for resultant infectious esophagitis [18,19•,20].

SPECIFIC PATHOGENS

Fungal pathogens *Candida albicans* is one the most common causes of infectious esophagitis in patients with AIDS, found in approximately 50% of symptomatic individuals. *Candida* is a commensal organism that is present as flora in the mouth, gastrointestinal tract, and vagina in normal individuals, and is easily found in the environment. There are numerous noncandidal fungal species that are less common inhabitants of the oropharynx and gastrointestinal tract (*eg*, *Candida glabrata*, *Candida krusei*, *Candida parapsilosis*, and *Candida tropicalis*), but they can be significant pathogens in the right clinical setting. For a fungal infection to take place, host defenses must be overcome, including impairment of the host's ability to clear the pathogenic organism and problems with cellular immunity, which allows fungal invasion. In patients with candidal infection of the esophagus, frequently there is an associated oral thrush (in >70% of patients) [21,22].

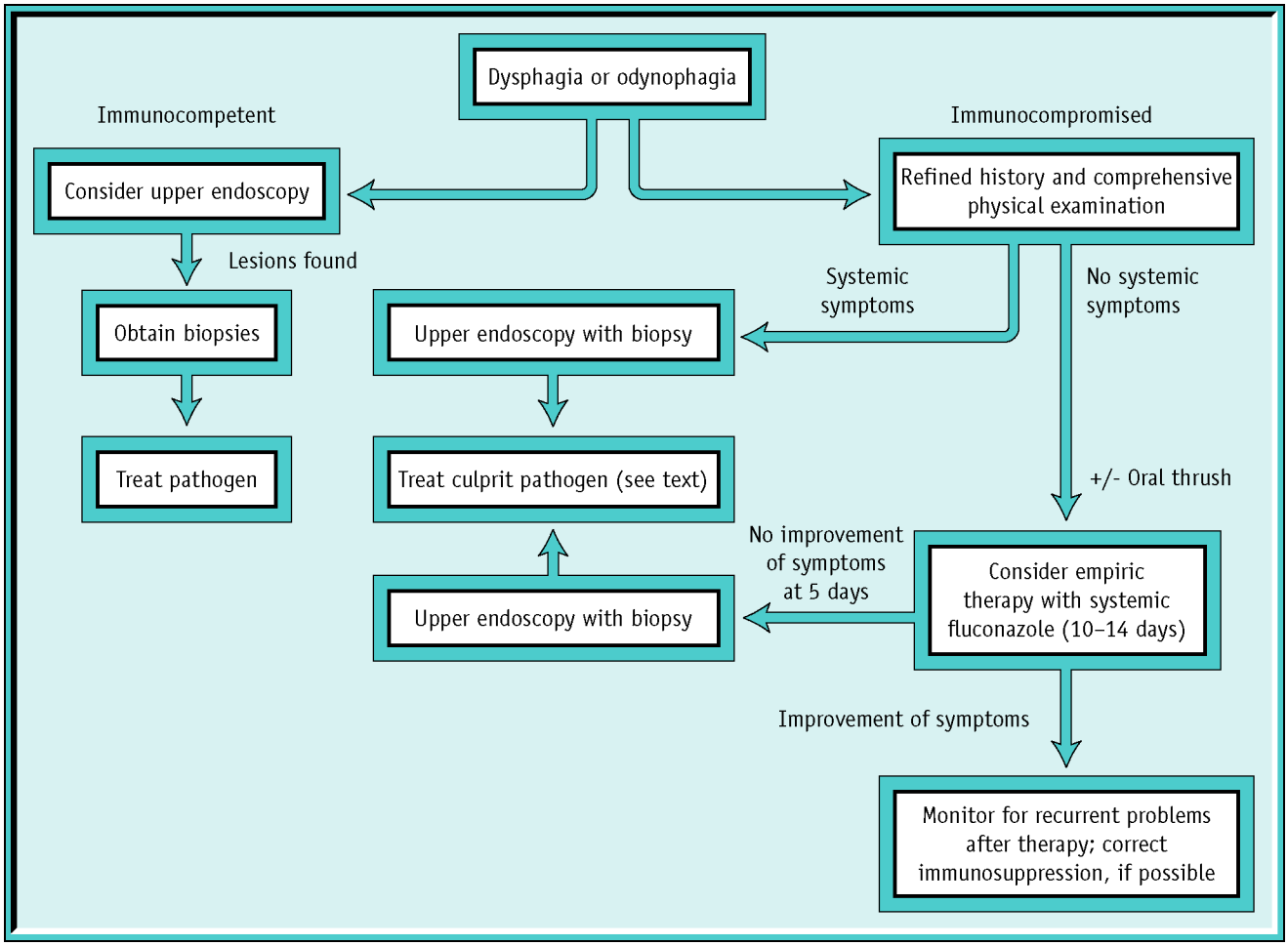

Figure 1. Algorithm for evaluation and treatment of infectious esophagitis.

Endoscopy favors the diagnosis of candidal infection when mucosal plaques are found, especially with underlying esophagitis and mucosal hyperemia and friability (without ulcerations, generally). Diagnosis of infectious esophagitis related to *Candida* requires that biopsies demonstrate sloughing of epithelial cells with fungal invasion into the epithelium. Mycelia (hyphae), pseudomycelia, and budding yeasts are more characteristic of infection than colonization, and they should be demonstrated histologically to make the diagnosis of candidal infectious esophagitis.

Treatment for *Candida* infections can be topical, oral, or parenteral, depending on the clinical circumstances. Immunocompetent patients with odynophagia or dysphagia should generally undergo endoscopy before empiric therapy is administered [23]. Patients who are immunocompromised or who have increased symptoms (*ie*, fever, chills. nausea, or chest pain) require oral systemic therapy [24]. Those patients who are unable to take medications orally or with marked systemic toxicity generally require parenteral therapy for effective treatment. In this case, endoscopy with biopsies or brushings may be an appropriate first step.

Other fungal pathogens include *Aspergillus*, *Blastomyces*, *Cryptococcus*, and *Histoplasma* species [25]. These fungi are generally not commensal organisms, must be obtained from the environment, and are generally only acquired by the most significantly immunosuppressed individuals. Thus, historical and clinical clues can often help in suggesting the possibility of a noncandidal fungal infection. *Aspergillus* most commonly affects the esophagus after contiguous spread from, and infection in, the mediastinum. *Blastomyces* and *Histoplasma* can also infect the esophagus from mediastinal lymph nodes or, more commonly, concomitant pulmonary infection. Primary infectious esophagitis by one these several agents is possible but less likely.

Treatment of these noncandidal infections varies with the pathogenic organism (Fig. 1).

VIRAL PATHOGENS

Herpes simplex virus Herpes simplex virus generally infects the squamous epithelium of the skin and mucosal membranes. HSV esophagitis (from HSV I or, rarely, HSV II) can occur as a primary infection or as reactivation of previously latent HSV, especially in the immunocompromised

patient. Esophageal HSV is infrequently described in HIV-infected individuals [13,26] or immunocompetent individuals [27•], whereas it is commonly described in individuals undergoing immunosuppression for solid organ or marrow transplantation [28,29]. The condition can manifest with concomitant oropharyngeal or genital HSV or *Candida* in 25% of affected individuals [21]. Esophageal mucosa develops inflammation, forms 1- to 3-mm vesicles, and eventually presents with discrete (< 2-cm) ulcerations that can infrequently coalesce to involve the entire esophagus. As vesicles evolve to ulcerations, they can develop a distinct central ulceration with raised edges, described as the volcano lesion that is considered characteristic of HSV.

Given that HSV infects squamous epithelial cells, biopsies should be directed at the edge or periphery of ulcerations. Several biopsy specimens should be placed into appropriate HSV culture medium, then several should be submitted in formalin for histopathology, and the pathologist should be notified of the clinical suspicion [27•]. The classic appearance of HSV infection includes the intranuclear Cowdry type A inclusion bodies (eosinophilic material), ballooning degeneration of cells, multinucleated giant cells, ground glass–like nuclei, and margination of chromatin [30,31]. However, confirmation may require immunoperoxidase staining or positive viral culture.

Cytomegalovirus Cytomegalovirus is a distinct virus of the herpesvirus family that also causes infectious esophagitis. Like HSV, infectious esophagitis with CMV can either result from new exposures or reactivation of latent virus. Patients with CMV infection have esophageal (dysphagia or odynophagia) or nonspecific (nausea and vomiting, abdominal pain, anorexia and fevers) symptoms, perhaps owing to frequent systemic or multiorgan involvement. Endoscopic lesions are often described as superficial and longitudinal or serpiginous in the mid- to distal esophagus, but they can vary greatly in their appearance [6]. Ulcers can coalesce; diffuse ulceration has been described. Because CMV infects fibroblasts (not epithelial cells), it is important to take biopsies from the base of ulcers to evaluate for this pathogen [32]. As such, brushings are less likely to yield diagnostic information in CMV infections. Histologic specimens may demonstrate cytomegalic cells (with intranuclear eosinophilic inclusions and intracytoplasmic basophilic inclusions) and perinuclear halos [33,34], but macrophage aggregates may be the only clue [35]. The diagnosis should be confirmed with immunohistochemical stains for antigens at the various stages of infection or viral culture [32,36].

Varicella zoster virus Varicella zoster virus is a relatively uncommon cause of infectious esophagitis in adults. However, it can cause very severe infectious esophagitis in the most significantly immunocompromised. Infectious esophagitis associated with VZV may often be accompanied by other signs of systemic dissemination (*eg*, pneumonitis, hepatitis, and encephalitis). Presenting complaints of VZV infectious esophagitis include dysphagia and odynophagia, which are made distinct by the discovery of any concomitant VZV skin eruptions. The endoscopic appearance of the disease can vary from vesicles to necrotic ulcerations, without a characteristic appearance. Therefore, diagnosis requires mucosal biopsies. Histologic examination shows ballooning degeneration, multinucleated giant cells, and intranuclear inclusion bodies (eosinophilic), with some similarities to HSV. Viral cultures and immunohistochemical staining are required for definitive diagnosis. The disease is treated with acyclovir or famciclovir; foscarnet is given for resistant viruses.

Epstein-Barr virus Although the vast majority of individuals with infectious mononucleosis do not develop gastrointestinal manifestations (except pharyngeal discomfort), a small minority of even immunocompetent individuals can develop esophageal ulcerations. In an individual with a clinical picture consistent with infectious mononucleosis, presenting with nausea, dysphagia or hematemesis, the possibility of infectious esophagitis must be considered.

In immunocompromised individuals, EBV-related infectious esophagitis has been reported, with ulcerations [37] or an endoscopic appearance similar to that of hairy leukoplakia.

Although the benefits of therapy in EBV infectious esophagitis are unproven, it may be reasonable to treat the patient with oral acyclovir and provide close monitoring. Maintenance therapy may be required if symptoms recur with discontinuation of medication.

Human papillomavirus This virus, like HSV, generally infects squamous epithelial cells and has historically been associated with genital condylomata and skin warts. Although the condition is generally asymptomatic, endoscopic lesions have been described as white or yellow plaques, small macules or nodules, or patches of small villous projections. Diagnosis requires biopsy of the lesion, demonstrating multinucleated giant cells, koilocytosis, and cellular atypia on histology; confirmation requires immunohistochemical stains [38].

Treatment may be unnecessary given the benign nature of these generally asymptomatic lesions, although obstruction of the esophagus and airways is possible if lesions are exuberant. Such lesions could be débrided endoscopically. No proven pharmacologic therapy has been defined. It is still unclear if HPV might lead to esophageal squamous cell cancer; therefore, screening and surveillance cannot be recommended at this time.

Human immunodeficiency virus Though a risk factor for many of the other infections noted earlier, it is believed that HIV itself can lead to discrete esophageal ulcerations [39], although controversy remains [40]. Symptoms can

be variable but often appear during the viral prodrome of early HIV infection. Discrete lesions are aphthoid in appearance but can coalesce and deepen, leaving large areas of ulceration and predisposing the patient to secondary infection, esophageal bleeding, fistulae, or mucosal perforation. Biopsies may demonstrate HIV viral particles, but other pathogens may also be found.

Empiric therapy directed at HIV (highly active antiretroviral therapy [HAART]) or undiagnosed fungal pathogens have not been successful in resolving esophageal lesions, but one small trial suggested that short-term systemic corticosteroids could reduce symptoms, improve endoscopic appearance, and prevent long-term sequelae [41]. Therapy should continue for at least 4 to 6 weeks, so initial assurance that other pathogens are not present is essential, as is close monitoring for secondary infections. Topical agents such as dexamethasone and sucralfate can also be considered, as can thalidomide.

BACTERIA

Although they are frequently unrecognized, bacterial infections of the esophagus can have significant clinical impact. They are more commonly seen in patients undergoing chemotherapy, because granulocytopenia (especially in combination with hypochlorhydria or acid suppression) is the greatest risk factor. Infection is generally polymicrobial, consisting predominately of oral and upper respiratory flora (*eg*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Streptococcus viridans*, and *Bacillus*). Patients can present with dysphagia, odynophagia, nausea, and chest pain. Endoscopically, the esophageal mucosa can demonstrate ulcerations, discrete plaques, or pseudomembranes; diffuse mucosal friability is common. Diagnosis requires biopsies that show numerous bacteria on Gram's stain, with histologic evidence of bacterial invasion into the subepithelium without a significant neutrophilic response. Cultures of biopsies may not be informative given the high likelihood of growing nonpathologic bacteria as well, but they may help detect patterns of antibiotic resistance. The clinical course can be progressive and catastrophic, but more often, it is mild and asymptomatic.

Treatment is with broad-spectrum antibiotics, such as ampicillin-sulbactam or ticarcillin-clavulanic acid. For more systemically ill patients, combined therapy with a beta-lactam/aminoglycoside or monotherapy with a carbapenem should be considered. The course of therapy is variable.

Treatment

Diet and lifestyle

- Limit the use of antibiotics, corticosteroids, and other immunosuppressants as much as possible.
- Promote safe sexual practices; in immunocompromised patients, strive to reduce exposure to pathogens; limit contacts with persons with other illnesses.
- In patients with HIV, advocate appropriate therapy (HAART) to reduce the likelihood of developing AIDS; this measure has been proved to reduce the likelihood of developing oropharyngeal candidiasis or CMV in the gastrointestinal tract [42••,43].

Pharmacologic treatment—*Candida*

- Patients with mild or no symptoms but with findings thought to be consistent with oropharyngeal *Candida* can be given trial doses of topical therapy (clotrimazole or nystatin) or systemic therapy that might reduce the future risk of esophageal infection. For patients at risk for infectious esophagitis (especially patients with AIDS) presenting with dysphagia or odynophagia, oral systemic therapy is most appropriate. Initiation of fluconazole is the accepted standard in the United States and Europe [44,45]; itraconazole is a reasonable alternative [46,47•], especially in cases that demonstrate fluconazole resistance. Ketoconazole is less expensive, although it is associated with an increased risk of side effects and drug-drug interactions [48]. For patients with more significant systemic symptoms, granulocytopenia, or an inability to tolerate oral medications, parenteral therapy may be required. Intravenous amphotericin can be used at a low dose for 7 to 10 days, with close monitoring for toxicity. In life-threatening systemic fungal infections, flucytosine can be used in combination with amphotericin.

- Once a patient has AIDS or is significantly immunocompromised, prophylactic anticandidal therapy (fluconazole) has been shown to be effective in reducing the risk of infectious esophagitis. A case-by-case analysis helps to identify appropriate candidates without engendering an unnecessary risk of toxicity.
- There is evolving evidence for increasing azole resistance among *Candida* species, especially in those individuals who were treated previously with an azole [49,50]. Therefore, testing for patterns of resistance, especially in immunocompromised individuals, is becoming increasingly appropriate and necessary [51].

Oral thrush only

Nystatin

Standard dosage 25,000 units orally every 2 hours for 14 days.

Clotrimazole

Standard dosage 100-mg troche dissolved and taken orally three times daily for 14 days.

Moderate esophageal symptoms or immunocompromised patient

Fluconazole

Standard dosage 200 mg × 1 intravenously or orally, then 100 mg/d for 7 to 14 days.

Contraindications Hypersensitivity is possible. Use caution in individuals with underlying hepatic dysfunction.

Main side effects Side effects include nausea, headache, rash, abdominal pain, vomiting, diarrhea, transaminitis, and alopecia. These problems are more common in patients with HIV.

Drug interactions The following drugs have an impact on the availability of fluconazole (increases or decreases bioavailability): phenytoin (Dilantin; Parke-Davis, Morris Plains, NJ), phenytoin, rifampin. Fluconazole has an impact on the following drugs (increases or decreases bioavailability): amitriptyline, antihistamines, cisapride, cyclosporine, tacrolimus, phenytoin, Dilantin, midazolam/triazolam, anticoagulants, hypoglycemics, rifampin, tacrolimus, theophyllines, and zidovudine.

Special points Intravenous dosage equals oral dosage (good bioavailability). Monitor liver function tests. Consider organism resistance if there is a poor response.

Cost/cost effectiveness The drug costs $7.85 to $100 per day (oral 100 mg, $7.00; oral 200 mg, $12.00; 400 mg intravenous formulation, $129.00).

Itraconazole

Standard dosage 200 mg orally daily for 7 to 14 days. Oral dosage is greater than 200 mg daily for 7 to 14 days if the patient is refractory to fluconazole.

Contraindications Hypersensitivity. Use of cisapride, midazolam, pimozide, quinidine, triazolam, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors. Creatinine clearance is less than 30 mL/min. Use great caution in patients with cirrhosis, congestive heart failure, or cardiomyopathy.

Drug interactions The following drugs have an impact on the bioavailability of itraconazole: carbamazepine, didanosine, H_2 receptor agonists (H_2RAs), phenytoin (Dilantin), isoniazid, lovastatin/simvastatin, proton pump inhibitors, antacids, and rifampin. Itraconazole has an impact on the bioavailability of the following drugs: antihistamines, cisapride, cyclosporine, tacrolimus, phenytoin, Dilantin, midazolam/triazolam, anticoagulants, oral hypoglycemics, and rifampin.

Main side effects Nausea, diarrhea, vomiting, abdominal pain, allergic reactions, rash, hyperbilirubinemia, edema, and hepatitis.

Special points Itraconazole is more effective than ketoconazole. The oral solution is more effective than the tablet form. Take the tablet with acidic liquid and food to maximize absorption. Consider serum levels at 2 weeks. Monitor liver function tests.

Cost/cost effectiveness The drug costs $14.42 to $176 per day (100 mg oral preparation, $7.00; 200 mg intravenous preparation, $168.00).

Ketoconazole

Standard dosage	200 to 400 mg orally once daily for 14 to 21 days.
Contraindications	Hypersensitivity. Patients taking terfenadine, astemizole, or cisapride.
Main side effects	Nausea, vomiting; rarely hepatotoxicity, adrenal crisis. Testosterone and cortisol levels decline with doses greater than 800 mg/d.
Drug interactions	The following drugs have an impact on ketoconazole: didanosine, Dilantin, phenytoin, rifampin, proton pump inhibitors, H_2RAs, antacids, and isoniazid. Ketoconazole has an impact on the following drugs: antihistamines, cisapride, cyclosporine, tacrolimus, phenytoin, Dilantin, midazolam/triazolam, anti-coagulants, rifampin, tacrolimus, and theophyllines.
Special points	Achlorhydria, proton pump inhibitors, H_2RAs reduce absorption. Take with acidic drinks (like cola) to maximize absorption. Monitor liver function tests with prolonged therapy.
Cost/cost effectiveness	The drug costs $3.68 to $23.82/d. It is the cheapest.

Oral amphotericin B

Standard dosage	100 mg orally four times per day.
Contraindications	Hypersensitivity.
Main side effects	Fevers, chills, nausea and vomiting, anorexia, hypotension, usually with infusion.
Drug interactions	Antineoplastic drugs, digitalis, other nephrotoxins (*eg*, aminoglycosides, cyclosporine, foscarnet, and cidofovir).
Special points	Regimen is not proven.
Cost/cost effectiveness	The drug costs $10 to $25 per day; inexpensive.

Systemic symptoms

Intravenous amphotericin B

Standard dosage	0.3 to 0.7 mg/kg/d intravenously for 7 to 10 days. For details, see earlier.
Contraindications	Hypersensitivity. Caution in renal insufficiency, after recent leukocyte infusion or whole body irradiation.
Main side effects	Fever, chills, nausea and vomiting, anorexia, and hypotension with infusion.
Special points	Consider a 1-mL test dose for tolerability. Infuse over 4 hours or longer; pulmonary edema can be noted with rapid infusion. Premedication is controversial. Pre- and postinfusion with 500 mL saline can reduce the likelihood of nephrotoxicity. It is imperative to avoid other nephrotoxins.
Cost/cost effectiveness	The drug costs $10 to $25 per day.

Life-threatening or disseminated infection

Amphotericin B plus flucytosine

Standard dosage	Amphotericin B 0.6 mg/kg/d intravenously × 7 days, then 0.8 mg/kg every other day intravenously. Flucytosine 25 to 37.5 mg/kg orally four times a day (or every 6 hours).
Contraindications	Hypersensitivity. Use cautiously in patients with renal insufficiency, bone marrow suppression and hyperkalemia.
Main side effects	Diarrhea, nausea, vomiting, leukopenia, thrombocytopenia, hepatotoxicity, rash, and anemia.
Drug interactions	Cytosine arabinoside; amphotericin B, drugs affecting glomerular filtration.
Special points	The drug can falsely elevate creatinine in certain analyzers. If the patient shows no improvement with therapy in 3 to 7 days, consider esophagogastroduodenoscopy with biopsies [52].
Cost/cost effectiveness	Amphotericin B 40 to 50 mg/d intravenous preparation is $10.00 to $36.00 a day. Flucytosine 500 mg is $7.00; four tablets four times a day is $112.00 a day.

Chronic suppressive therapy

Fluconazole

Standard dosage 100 to 200 mg orally once daily to once weekly [53].

Pharmacologic treatment—*Aspergillus, Histoplasma capsulatum*

- The accepted standard therapy is parenteral amphotericin, although oral itraconazole, fluconazole, and ketoconazole have been used successfully for other types of aspergillosis and histoplasma (not specifically for esophagitis).

Amphotericin B

Standard dosage 0.3 mg/kg/d intravenously for 7 to 10 days. For further details, see the section on *Candida*.

Itraconazole

Standard dosage 200 mg orally three times daily for 4 days, then 200 mg twice daily. For further details, see the section on *Candida*.

Pharmacologic treatment—herpes virus

- Patients with herpetic esophagitis should be considered for treatment with acyclovir. Data have shown that immediate treatment of labial HSV with acyclovir shortened the duration of symptoms and healing [54]. Comparable results have not been demonstrated specific to esophageal HSV. However, the use of acyclovir, with its limited side effect profile, appears warranted in symptomatic individuals [55]. Parenteral acyclovir should be initiated until the patient can be converted to oral therapy (when dysphagia or odynophagia is resolved).
- Generally, patients are treated with acyclovir for 7 to 10 days. Because resistance to acyclovir has been reported, therapy with foscarnet must be considered if there is limited improvement with acyclovir (monitor renal function) [56]. Famciclovir and valacyclovir are especially promising as replacements for acyclovir, as well.
- Prophylaxis for at-risk individuals should be considered.

Acyclovir

Standard dosage 250 mg/m^2 intravenously (or 5 mg/kg) every 8 hours for 7 to 14 days, or 400 mg orally five times daily for 14 to 21 days.
Contraindications Hypersensitivity. Use with caution in patients with renal insufficiency.
Main side effects With oral administration: diarrhea, vertigo, arthralgias, rash, insomnia, and acne. With intravenous administration: phlebitis, lethargy, tremors, confusion, delirium, coma, renal insufficiency, hematuria, transaminitis, rash, hypotension, and nausea.
Drug interactions Nephrotoxins.
Special points The risk of renal insufficiency is reduced with adequate prehydration.
Cost/cost effectiveness The drug costs $15 per day for the oral preparation; it costs $60 to $150 per day for the intravenous form.

Famciclovir

Standard dosage 500 mg orally twice daily for 7 days.
Contraindications Hypersensitivity. Use with caution in patients with renal insufficiency.

Main side effects	Similar to those for acyclovir.
Drug interactions	None defined.
Special points	Limited experience in infectious esophagitis; consider in acyclovir resistance. Penciclovir is the active metabolite. Dose should be reduced with creatinine clearance less than 60 mL/min.
Cost/cost effectiveness	The drug costs $15 per day.

Valacyclovir

Standard dosage	1000 mg orally three times daily for 7 days.
Contraindications	Hypersensitivity. Dose should be reduces in patients with renal insufficiency.
Main side effects	Similar to acyclovir. Thrombotic thrombocytopenic purpura and hemolytic uremic syndrome noted in HIV/transplant patients at 8 g/d (at doses exceeding recommendations).
Drug interactions	None defined.
Special points	Limited experience in infectious esophagitis. Improved bioavailability over acyclovir.
Cost/cost effectiveness	The drug costs $21 per day.

Foscarnet

Standard dosage	40 mg/kg intravenously three times daily for 10 to 24 days.
Contraindications	Hypersensitivity. Concomitant use of other nephrotoxins.
Main side effects	Renal impairment, nephrogenic diabetes insipidus, electrolyte abnormalities, headache, fever, nausea, fatigue, anemia, leukopenia, transaminitis, penile ulcerations.
Drug interactions	Amphotericin B, aminoglycosides, and pentamidine.
Special points	Consider with acyclovir resistance; lesions may recur after medication discontinuation. Risk of renal insufficiency reduced with adequate prehydration. Monitor renal function.
Cost/cost effectiveness	The drug costs $30 to $60 per day.

Pharmacologic treatment—cytomegalovirus

- In CMV infection of the esophagus, parenteral therapy with ganciclovir or foscarnet is warranted [57]. Both regimens may require maintenance therapy until immunosuppression resolves or indefinitely.
- Prophylaxis against CMV infection is accepted practice for those patients undergoing immunosuppression for organ transplantation. It should be considered in the appropriate setting for all individuals who are immunosuppressed and at risk for CMV infection.

Ganciclovir

Standard dosage	5 mg/kg intravenously twice daily for 14 to 42 days, then once daily.
Contraindications	Hypersensitivity. Neutropenia. Use with caution in patients with anemia.
Main side effects	Neutropenia, thrombocytopenia, anemia, fever, nausea, vomiting, diarrhea, rash, retinal detachment, headaches, and seizures.
Drug interactions	Azathioprine, zidovudine, imipenem, and probenecid.
Special points	Not proven to be efficacious in this setting. Must monitor for bone marrow suppression; increased likelihood with azathioprine and zidovudine. May be a teratogen; inhibits spermatogenesis.
Cost/cost effectiveness	The drug costs $40 to $80 per day.

Valganciclovir

Standard dosage	900 mg orally twice daily for 21 days, then 900 mg once daily.
Contraindications	See the section on ganciclovir.
Main side effects	Similar to those of ganciclovir.

Drug interactions See the section on ganciclovir.
Special points A prodrug of ganciclovir with improved bioavailability.
Cost/cost effectiveness The drug costs $120 per day.

Foscarnet

Standard dosage 90 mg/kg intravenously twice daily (or 60 mg three times daily) for 14 to 21 days, then once daily thereafter. For further details, see the section on HSV.

Pharmacologic treatment—varicella zoster virus

- If histologic and immunohistochemical studies suggest VZV infection, acyclovir or famciclovir therapy is appropriate. In rare instances, the virus is resistant to these agents and foscarnet will have to be chosen.
- For details on the following drugs, see the sections on HSV and CMV.

Acyclovir

Standard dosage 800 mg orally four to five times daily for 5 to 7 days.

For significantly immunocompromised patients

Acyclovir

Standard dosage 10 to 12 mg/kg intravenously (infuse over 1 hour) three times a day for 7 days.

Valacyclovir

Standard dosage 1000 mg orally three times daily for 7 days.

Famciclovir

Standard dosage 500 mg orally three times daily for 7 days.

Foscarnet

Standard dosage 40 to 60 mg orally three times daily for 10 days or more.

Pharmacologic treatment—Epstein-Barr virus

- Patients who are symptomatic or who have endoscopic findings consistent with EBV infection (suggestive esophageal lesions with histologic or immunohistochemical confirmation) can be considered for treatment with acyclovir. There are no studies demonstrating improvement in outcome with acyclovir therapy, but therapy does shorten the duration of oral lesions.

Acyclovir

Standard dosage 800 mg orally four times daily for 5 days. For further details, see the section on HSV.

Pharmacologic treatment—human papillomavirus

- There is no proven effective pharmacologic therapy.

Pharmacologic treatment—human immunodeficiency virus

- When infection with other pathogens has been excluded and esophageal lesions are consistent with HIV alone, therapy with oral corticosteroids may be warranted [41,58]. If this therapy fails or other comorbidities dictate, oral dexamethasone, sucralfate, or thalidomide can be tried [59].

Viscous lidocaine

Standard dosage 2% orally as needed; less than 0.1 mL/lb to avoid toxicity.

Prednisone

Standard dosage 40 mg orally for 7 days; taper 10 mg per week over 4 weeks.

Dexamethasone

Standard dosage Elixir 0.5 mg/mL orally, one-half teaspoon up to six times daily.

Sucralfate

Standard dosage 1 g orally four times daily for seven times for 14 days.

Thalidomide

Standard dosage 100 to 200 mg orally for 14 days.
Contraindications Hypersensitivity. Women in childbearing years.
Main side effects Birth defects. Drowsiness, somnolence, neuropathy, dizziness, neutropenia, bradycardia, seizures, Stevens-Johnson syndrome.
Drug interactions Increased sedation with barbiturates, alcohol, chlorpromazine, and reserpine.
Special points Avoid in women in childbearing years, because the drug can cause birth defects. Male patients must wear condoms when having sex with women of childbearing age. Drug is available only through a restricted distribution system (*ie*, the System for Thalidomide Education and Prescribing Safety [STEPS] program).
Cost/cost effectiveness The drug costs $16 to $20 per day.

Pharmacologic treatment—bacteria

- Often in treating patients with polymicrobial infections, appropriate therapy must be broad spectrum. If resistant organisms are discovered, these findings should help refine therapy. Otherwise, broad-spectrum monotherapy or combination therapy should be initiated.

General therapy

Ampicillin-sulbactam

Standard dosage 1.5 to 3 g intravenously every 6 to 8 hours.
Contraindications Hypersensitivity. Penicillin allergy.
Main side effects Pain at injection site, thrombophlebitis, and diarrhea.
Drug interactions Probenecid, allopurinol.
Special points Reasonable broad-spectrum coverage. The drug is not antipseudomonal.
Cost/cost effectiveness The drug costs $25 to $50 per day.

Ticarcillin-clavulanic acid

Standard dosage	3.1 g intravenously every 4 to 6 hours.
Contraindications	Hypersensitivity.
Main side effects	Diarrhea; rare cholestatic hepatitis. The side effects are similar to those of penicillin.
Drug interactions	Probenecid; can inactivate aminoglycosides.
Special points	Reasonable broad-spectrum coverage.
Cost/cost effectiveness	The drug costs $100 per day.

For systemically ill patients

Ampicillin (plus gentamicin)

Standard dosage	150 to 250 mg/kg/d intravenously divided into equal doses given every 3 to 4 hours.
Contraindications	Hypersensitivity.
Main side effects	Mild, systemic typical of penicillins.
Drug interactions	Allopurinol, probenecid.
Special points	For systemically ill patients, use with aminoglycoside.
Cost/cost effectiveness	The drug costs less than $20 per day.

Gentamicin

Standard dosage	2 to 2.5 mg/kg/dose (ideal body weight) intravenously every 8 hours.
Contraindications	Hypersensitivity. Pregnancy. Use with caution in patients with renal impairment, neuromuscular disorders, and other neurologic conditions.
Main side effects	Nephrotoxicity and ototoxicity, neuropathies and other neurologic disorders, transaminitis, Fanconi-like syndrome.
Drug interactions	Nephrotoxins; amphotericin B, *cis*-platinum, cyclosporine, neuromuscular blocking agents, loop diuretics, nonsteroidal anti-inflammatory agents, nonpolarizing muscle relaxants, radiographic contrast, and vancomycin.
Special points	Adjust dosing interval for renal impairment. Dose according to ideal body weight. Consider monitoring serum levels.
Cost/cost effectiveness	The drug costs $10 to $40 per day.

Imipenem-cilastatin

Standard dosage	500 mg intravenously every 6 hours.
Contraindications	Hypersensitivity. Use with caution in patients with known renal insufficiency (especially in elderly patients) or previous seizure disorders.
Main side effects	Confusion, myoclonic activity, seizures, especially at doses above those recommended.
Drug interactions	Probenecid; ganciclovir (associated with seizures).
Special points	Cross-reactivity in half of patient with penicillin allergy.
Cost/cost effectiveness	The drug costs $120 per day.

Endoscopic treatment

- Endoscopy may be vital in defining the pathogen for appropriate therapy [60].
- Endoscopy may be required for esophageal bleeding or identification of complications of severe infectious esophagitis, such as fistulas, strictures, and perforation.
- Endoscopy may be required for débridement of obstructive HPV.

Emerging therapies

For *Candida* infection

- Lipid-based amphotericin B preparations are available, and they show comparable efficacy with improved tolerability (compared with amphotericin B), especially when there is baseline renal insufficiency, a high-risk for nephrotoxicity due to concomitant use of other nephrotoxic agents, rising creatinine level with amphotericin B, or failed therapy with amphotericin B. These agents have not been specifically evaluated for efficacy in the setting of infectious esophagitis. Although data are starting to support their use for invasive candidiasis, amphotericin B preparations are still considered second-line agents by many experts.

Amphotericin B lipid complex (Abelcet; The Liposome Company, Inc., Princeton, NJ)

Standard dosage	5 mg/kg/day intravenously; infuse at 2.5 mg/h.
Contraindications	Hypersensitivity. Use with caution in patients with renal insufficiency.
Main side effects	Fever, chills, nausea, vomiting, increased creatinine level, renal failure, hypokalemia, and rash.
Drug interactions	None defined; use caution with nephrotoxins and other drugs that interact with amphotericin B.
Special points	Approved agent for use in patients with proven candidiasis. Larger volume of distribution, rapid blood clearance, and high tissue concentration. Do not mix with other drugs or electrolytes or use an in-line filter.
Cost/cost effectiveness	The drug costs $600 to $800 per day.

Amphotericin B colloidal dispersion (Amphotec; Sequus Pharmaceuticals, Inc., Menlo Park, CA)

Standard dosage	3 to 6 mg/kg/d intravenously.
Contraindications	Hypersensitivity. Use with caution in patients with renal insufficiency.
Main side effects	Chills, fevers, increased creatinine, hypocalcemia, and hypokalemia.
Drug interactions	See the section on Abelcet.
Special points	Approved agent for use in patients with proven Candidiasis. Infuse at 1 mg/kg/h, dilute in D5W.
Cost/cost effectiveness	The drug costs $300 to $800 per day.

Liposomal amphotericin B (AmBisome; Fujisawa Healthcare, Inc., Deerfield, IL)

Standard dosage	3 to 5 mg/kg/d intravenously.
Contraindications	Hypersensitivity. Use with caution in patients with renal insufficiency.
Main side effects	Nephrotoxicity, chills, nausea, vomiting, rash, hypocalcemia, hypokalemia, and hypomagnesemia.
Drug interactions	See the section on Abelcet.
Special points	Approved for empiric treatment of fungal infections. Infuse over 120 minutes for the first infusion; if tolerated, can reduce to 60 minutes thereafter.
Cost/cost effectiveness	The drug costs $600 to $1400 per day.

For cytomegalovirus infection

- The US Food and Drug Administration has approved a new oral formulation of ganciclovir. Valganciclovir is biotransformed into ganciclovir and appears to have similar efficacy in several studies. It has not specifically been evaluated in infectious esophagitis, but its excellent oral bioavailability and evidence of comparability to ganciclovir suggests that this may be a reasonable alternative in the future [61–63]. The duration of therapy or need for maintenance therapy has not been defined.

- For patients in whom traditional therapy has failed, cidofovir may be another promising alternative therapy [64]. In vitro studies have demonstrated 100-fold greater activity against CMV than ganciclovir (it also has promise for HSV and HPV). It has not been tested clinically for outcomes in infectious esophagitis.

Valganciclovir

Standard dosage	900 mg orally once daily for 14 days to indefinitely. For further details, see the section on CMV.

Cidofovir

Standard dosage	5 mg/kg intravenously once weekly × 2, then every other week.
Contraindications	Hypersensitivity. Pregnancy. Use with caution in patients with renal impairment, neutropenia, and baseline metabolic acidosis.
Main side effects	Nephrotoxicity, Fanconi-like syndrome, nausea, fever, alopecia, myalgia, and neutropenia. Embryotoxicity; hypospermia.
Drug interactions	Nephrotoxins: amphotericin B, aminoglycosides, foscarnet, and intravenous pentamidine; agents that interact with probenecid.
Special points	Prehydrate before each dose; probenecid must be administered orally with each cidofovir dose. Two grams must be given 3 hours before the cidofovir dose and 1 g given at 2 and 8 hours after completion of the 1-hour cidofovir infusion (a total of 4 g). Monitor renal function and reduce dose according to creatinine clearance. Monitor neutrophil count.
Cost/cost effectiveness	The intravenous form of the drug costs $800 per week.

For varicella zoster virus infection

- Sorivudine has demonstrated 1000-fold increased activity over acyclovir in vitro against VZV [65] but appears unlikely to make it to US markets owing to concerns of toxicity with concomitant use with 5-fluorouracil. Several other new drugs are under investigation, such as ABT-606, an acyclic guanosine analog that inhibits viral DNA polymerase. Lobucavir, another guanosine nucleoside analog, also has in vitro activity against VZV [66]. Clinical studies are ongoing.

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