Review Article

Fungal esophagitis

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Abstract: The prevalence of fungal esophagitis (FE) has risen in various populations, with increased risk factors of the disease including HIV infection and the use of immunosuppressive agents. FE has been recognized increasingly over the last few decades. This article reviews the findings of recent studies and the conclusions of some mainstream guidelines to inform clinicians and researchers in this field.

Keywords: Fungal esophagitis (FE); incidence; risk factors; clinical manifestations; treatment

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Fungal esophagitis (FE) refers to an infection caused by a specific fungus in the esophageal mucosa. The disease can be caused either by Candida or filamentous fungi. Since the vast majority of FE cases are caused by Candida species, FE is often referred to as "Candida esophagitis (CE)". The disease has been recognized increasingly over the last few decades, and a series of studies have been carried out in this field. This article reviews this disease in terms of epidemiology, etiology, clinical manifestations, and diagnosis and treatment.

Epidemiology

The prevalence of FE has been reported in single medical centers in different time periods and countries, including Brazil, India, and Japan, with prevalence rates ranging between 0.5% and 1% pre-2010 (1-5). However, a report from Iran showed a prevalence rate of 5.3% among 398 patients who underwent gastroscopy between 2012 and 2014 (6). In addition, Kakati *et al.* found that the incidence of FE in patients who had received gastroscopy at one tertiary hospital in India between 2011 and 2013 was as high as 8.7% (163/1,868) (7). In both cases, the prevalence rate of FE was far higher than the rates reported in other regions. In addition to regional diversity, FE's gradually increasing prevalence over time should also be considered. In a 12-year [2002–2014] study, Takahashi *et al.* concluded that the prevalence of FE was 1.7% among 80,219 patients who had received endoscopy; further analysis showed that the prevalence rates in two periods (from 2002 to 2003 and from 2012 to 2014) were 0.6% and 2.5%, respectively, showing a rapid upward trend (4). In China, the prevalence rates of FE dramatically differ between regions. The reported prevalence of FE was about 0.463% in Shaoyang Central Hospital (in central China) from 2005 to 2007 (8) but reached 3.41% (and is still gradually rising) in the Jinyun mountainous areas of Zhejiang Province (in eastern China) (9). The prevalence of FE thus constantly differs according to geographic region and time period. According to currently available data, the prevalence of FE is increasing worldwide.

Although studies on pathogens showed diverse results in different regions, Candida remains the dominant pathogen, and Cryptococcus, Histoplasma capsulatum, Blastomyces, and Aspergillus have also been noted (10). In particular, Candida albicans accounts for about 60–90% of pathogens, and *Candida tropicalis*, *Candida glabrata*, and *Candida krusei* are not uncommon. *Candida parapsilosis* is less common (3,4,7), and *Candida guilliermondii* has only occasionally been reported (11). In a small number of cases, co-infections

of two Candida species have been reported (12). The proportions of fungal species also constantly vary according to alterations in overall population characteristics and disease spectra. According to statistics, although *Candida albicans* remains the most common pathogen, infections caused by non-*Candida albicans* fungal species are rising (13). Results from the ARTEMIS DISK Global Antifungal Surveillance Study performed in 142 centers in 41 countries have shown that the proportion of *Candida albicans* in Candida spp had dropped from 70.9% in 1997 to 62.9–65.0% in 2007, and the proportions of *Candida parapsilosis*, *Candida tropicalis*, and *Candida glabrata* had increased slightly (14). Considering the susceptibilities of different fungal strains to various antifungal drugs, we should pay adequate attention to such changes and adjust empirical antibacterial drug treatment protocols accordingly.

Etiology and risk factors

A series of studies has demonstrated that HIV infection is the most significant risk factor for FE (15). A large number of studies have shown that the incidence of FE can be as high as 10–30% in HIV-positive patients, which is much higher than the average prevalence of this disease, and that HIV-positive patients also experience more severe symptoms (2,16). Further analysis found that CD4 T lymphocyte count is closely associated with the pathogenesis of FE, and a CD4 count of <200/μL has been found to be an independent risk factor for the disease (2,4,12,17). The Japanese "Guidelines for the Diagnosis and Treatment of Deep-seated Mycosis" has also identified a decreased CD4 count as the only cause of FE (18). Based on the introduction and use of highly active antiretroviral therapy (HAART), Nkuize *et al.* divided the patient cohort into three groups: a pre-HAART group (between January 1991 and December 1994), an early HAART group (between January 1999 and December 2002), and a recent HAART group (between January 2005 and December 2008). Parameters studied included CD4 cell counts and FE. With the development of HAART, the CD4 count increased and the incidence of FE decreased in HIV carriers (19), suggesting that a decline in the CD4 count promotes the pathogenesis of FE.

Since HIV infection is a major risk factor for FE, a decline in immune function has become a widely accepted cause of FE. Many case-control studies and multivariate analyses have found that there were significant differences between the case group and the control group in terms of the use of glucocorticoids and the co-existing risk factors for other tumors (1,4,5,15,20). Both of them may cause FE by affecting normal immune function. However, whether diabetes and some other factors cause immune abnormalities remains controversial (20). In addition, in multiple studies, the doses of glucocorticoids were poorly defined. Notably, Takahashi *et al.* investigated the prevalence of FE among patients using different doses of glucocorticoids and concluded that FE was significantly associated with a higher prednisone-equivalent dose (>20 mL) among corticosteroid users (4).

Meanwhile, analyses of the above studies have revealed that antibiotic use is another risk factor for FE (7,9,15,21), which may be because the use of antibiotics can change the normal flora in esophageal mucosa. However, it should also be noted that patients with FE are also susceptible to other infections and thus may use antibiotics, which can affect the statistical results.

Mimidis (22) and Underwood (23) found in their surveys that, in patients with Candida esophagitis, the proportion who had received acid suppression therapy was equivalent to and even higher than those who had received therapy for other known risk factors such as tumors. Other case-control studies have also found that acid suppression therapy is associated with FE (20,21). Daniell reviewed the possible mechanisms as follows (24): (I) a previous study compared the results of fungal smear and culture of the esophageal mucosa, taking into account various factors, and found that the positive rate of Candida culture in the patients using H2 receptor antagonists dramatically increased (25), which suggests that AST breaks the acidic barrier of the gastric mucosa, resulting in an increase in the number of Candida in the stomach and esophagus mucosa; (II) PPI increases the intensity and the frequency of episodes of non-acid gastroesophageal reflux (26), which may bring the increased Candida in the gastric fluid back to the esophagus; and (III) ketoconazole, posaconazole, and itraconazole are transported from the stomach into the blood through acid-related transport pathways, and their plasma concentrations can be decreased by AST by about 20% (27-29), which can lower the efficacy of antifungal drugs and aggravate fungal infections. This has been demonstrated in immunosuppressed patients after induction chemotherapy for systemic scleroderma and/or acute leukemia (30,31). However, some well-designed studies have yielded opposite conclusions (3,4,15). The same review article also pointed out that no article had concluded that AST withdrawal could reduce the incidence of FE and improve treatment

outcomes. Thus, to determine whether or not AST promotes the pathogenesis of FE, further investigation is required.

H. pylori infection (32), smoking, increasing age (4), and heavy drinking (5) have also been described in a few reports as risk factors, while reflux esophagitis (4,5,33), chronic kidney disease, cirrhosis (4), and oropharyngeal fungal infections (34,35) have also been proposed. However, no definite or well-recognized conclusions have been reached.

Clinical features

The clinical manifestations of FE are diverse. While in mild cases there is no obvious discomfort, in more severe cases of FE, repeated gastrointestinal bleeding (36), esophageal atresia/tracheoesophageal fistula (EA/TEF) (37), and even death caused by fungal septicemia can occur. Similar to other esophageal diseases such as reflux esophagitis, FE patients can also suffer from upper gastrointestinal symptoms such as difficulty swallowing, pain during swallowing, heartburn, epigastric pain, and nausea/vomiting. In a meta-analysis of 57 articles, Baehr *et al.* found that the incidence of difficulty in swallowing (dysphagia) and pain while swallowing (odynophagia) was 63% in FE patients, which is much higher than the incidence of nausea/vomiting and other symptoms (38). Takahashi *et al.* investigated the incidence of FE in 6,011 patients undergoing gastroscopy and found that: "dysphagia" and "odynophagia" were predictive of FE in HIV patients; in contrast, no symptom was predictive for FE among HIV-infected patients, which may be because the persistent inflammatory response caused by fungal colonization on the esophageal mucosa weakens the sensitivity of the esophageal mucosa to its self-expansion and thus decreases the reactive peristalsis that should occur, resulting in dysphagia and odynophagia (2). However, in some patients, FE may manifest as posterior sternum pain, heartburn, and nausea/vomiting, although these symptoms are non-specific and their incidences have varied in different studies (1,12).

Endoscopic findings

FE manifests endoscopically as white plaques on the esophageal mucosa that are difficult to wash off and are also the main basis for an initial endoscopic diagnosis (39). The endoscopic severity of Kodsi's grading was as follows: grade I, a few raised white plaques up to 2 mm in size without edema or ulceration; grade II, multiple raised white plaques greater than 2 mm in size without edema or ulceration; grade III, confluent, linear, and nodular elevated plaques, along with mucosa edema and ulceration; grade IV, the finding of grade III with increased friability of the mucous membranes and occasional narrowing of the lumen (17).

The diffuse inflammatory edema, thickening of the esophageal mucosa and enlargement of the peripheral lymph nodes caused by FE (including the inflammatory response and the increased metabolism caused by fungal infection) have similar biological behaviors to glucose uptake in tumors in PET-CT (positron emission tomography-computed tomography), which results in an abnormal increase in the WT value. As a result, FE can easily be misdiagnosed as an esophageal malignancy (40-42).

Diagnosis

Similar to other infectious diseases, a diagnosis of FE requires etiological evidence in addition to medical history and symptoms. Endoscopy is valuable in the diagnosis of the disease. First, the endoscopic findings are often suggestive of the disease; and second, smears, biopsies, and pathogenic culture and identification of endoscopically abnormal mucosal tissues can be performed. If abnormal lesions such as white plaques are found during an endoscopic examination, a further biopsy of the mucosa at the lesion to look for the presence of (false) hyphae or spores under the microscope is extremely helpful for a definite diagnosis (43). If necessary, HE staining, PAS staining, or silver staining can be performed to increase the isolation rate of the fungi (44). According to guidelines released by the American Society for Gastrointestinal Endoscopy, cytologic brushings can be more sensitive than biopsies in detecting FE (45).

Microscopically, esophageal histopathology mainly manifests through the infiltration of inflammatory cells including neutrophils, lymphocytes, and eosinophils, and the proliferation of the lamina propria and basal cells and the enlarged intercellular space. Demir *et al.* observed endoscopic biopsy specimens collected from 67 patients with infectious esophagitis and found that although there was a large amount of eosinophils infiltration in FE patients, the proliferation of the lamina propria occurred only in patients with herpes esophagitis or FE; however, the changes of these pathological parameters are not statistically significant among different infectious esophagitis cases, and as such these cases cannot be directly distinguished based on pathological changes under the microscope alone (46).

Treatment

Guidelines for the diagnosis and treatment of fungal infections in the United States (47), Australia (48), Japan (49), and Taiwan Province (50) have recommended fluconazole as the drug of choice for the treatment of FE. According to the Chinese Expert Consensus on the Diagnosis and Treatment of Candidiasis (14) and Clinical Practice Guideline for the Management of Candidiasis: 2016 Update [released by the Infectious Diseases Society of America (IDSA)] (47), unlike the treatment of oropharyngeal candidiasis, the treatment of esophageal candidiasis requires systemic medications; for patients highly suspected of having esophageal candidiasis, empirical treatment can be performed before endoscopic examination.

In terms of treatment protocol, oral (PO) fluconazole is preferred [200–400 mg (3–6 mg/kg) daily for 2–3 weeks]. Intravenous (IV) formulations are useful when oral administration is not possible. IV can be switched to PO gradually when the patients can tolerate PO. The preferred IV formulation is fluconazole [400 mg daily (6 mg/kg body weight)] or echinocandins (micafungin 150 mg/d; caspofungin, 70 mg on day 1 followed by 50 mg daily; and anidulafungin, 200 mg/d). In addition, amphotericin B deoxycholate 0.3–0.7 mg/kg daily can also be used, but the level of evidence for this treatment is low. For fluconazole-refractory FE, itraconazole (PO, 200 mg/d) or voriconazole (IV or PO, 200mg bid for 14–21 days) is recommended. Alternative treatments include: (I) echinocandins (micafungin 150 mg/d; caspofungin, 70 mg on day 1 followed by 50 mg daily; and anidulafungin, 200 mg/d) for 14–21 days; (II) amphotericin B deoxycholate 0.3–0.7 mg/kg daily for 21 days; or (III) posaconazole suspension 400 mg bid (or, posaconazole sustained-release tablets 300 mg qd). For patients with recurrent esophagitis, the recommended long-term treatment regimen is fluconazole 100–200 mg, 3 times a week.

The Japanese Domestic Guidelines for Management of Deep-seated Mycosis 2014 proposed similar treatment protocols for FE, with only a few adjustments to drug doses: fluconazole PO 100–400 mg qd is preferred; itraconazole oral solution 200 mg qd is another option; if the above protocols fail, micafungin 150 mg/d or caspofungin 50 mg qd (initial dose 70 mg on day 1); or, amphotericin B deoxycholate 3–4 mg/kg qd; voriconazole PO 200 mg bid or IV 4 mg/kg bid.

In a randomized double-blind controlled study with a sample size of 128 patients, Villanueva *et al.* (51) compared the clinical symptoms, changes in endoscopic lesions, and side effects 14 days after treatment with different doses of caspofungin (50 and 80 mg qd) or amphotericin B (0.5 mg/kg body weight). The results showed no significant difference in the therapeutic effects of different doses of caspofungin and amphotericin B, although amphotericin B had a significantly higher incidence of toxicities.

The role of nystatin in treating FE is usually only seen in some case reports and expert comments. There is no strong evidence or well-designed case-control research to confirm the exact efficacy of nystatin or its relative efficacy when compared with fluconazole (52,53).

No guidelines have recommended the use of prophylactic anti-infective treatment. Some studies have pointed out that prophylactic use of fluconazole can lower the possibility of fungal colonization and infection in the esophagus of immunosuppressed individuals (e.g. HIV-positive patients), others argue that it will lead to the selection and colonization of non-albicans Candida species, resulting in drug-resistance and drug-dependence (54).

Candida albicans is still sensitive to fluconazole, and its drug resistance rate is about 3–6%. In contrast, *Candida glabrata* and *Candida krusei* are naturally resistant to fluconazole, and the drug resistance rates of other Candida species to fluconazole can reach 50% or higher. A study in India enrolled 163 cases of mycotic esophagitis and found that the total resistance rate to fluconazole reached 8.6%. Notably, the drug resistance rate of *Candida albicans*, the main pathogen type, was 3.5%, and the drug resistance rates of *Candida krusei* and *Candida glabrata* reached 50% and 45.4%, respectively. A Chinese study (33) found that the resistance rate of *Candida krusei* to fluconazole was 75%. Therefore, for patients who respond poorly to routine fluconazole treatment, pathogenic culture and identification tests and drug susceptibility tests are required.

In addition to the fungus itself, exposure to antibacterial drugs is another mechanism by which fungal pathogens are able to develop resistance. The use of fluconazole is considered to be the major cause of drug resistance and dose-dependence (54). In a Brazilian study, fluconazole resistance was found in 14% of 40 FE patients, half of whom had previously used the drug (12). In addition, fluconazole is also related to drug-resistant mutations in specific gene loci of the pathogenic fungi: in a case report, the MIC value of the pathogenic *Candida albicans* increased 33 fold (baseline value: ≤0.06 mg/L) following six weeks of micafungin use, and the high MIC value lasted 7.5 months; further

analysis confirmed the mutations in the FKS1 gene (55). The FKS1 gene is an important subunit of β-(1,3)-D-glucan synthase, a target for echinomycins. Its mutations affect the binding of echinomycins to the enzyme. Y132H, T315A, A149V, D153E, E165Y, S279F, G465S, R467K, S405F and other site mutations in the CYP51 gene change the action site of lanosterol 14α-demethylase, a primary target for the azole class of antifungals, and thus reduce its binding to antifungals (56). Mutations in the MDR1 and MRR1 genes in Candida parapsilosis (57) and in the ERG11, CDR1 and CDR2 genes in *Candida glabrata* (58) are all related to drug resistance. It has also been proposed that younger (<50 years) HIV-positive patients and patients with a CD4 count <200 have higher risk of developing drug resistance (12).

In summary, FE, as an infectious disease, is mainly characterized by the abnormal growth of *Candida albicans* on the esophageal mucosa. While the prevalence of FE is increasing, the positive rates of classic pathogens are declining and the rates of non-specific pathogens such as *Candida glabrata* and *Candida krusei* have risen. Factors that contribute to such changes may include an increase of relevant risk factors (e.g., HIV infection) and the use of antifungal drugs, although the exact etiologies and pathogenic mechanisms warrant further investigation. The clinical symptoms of FE are generally similar to other esophageal diseases, and the diagnosis mainly depends on gastroscopy. When endoscopy reveals specific changes on the esophageal mucosa, further tissue biopsy, fungal culture and identification, and drug sensitivity tests are valuable for diagnosis and treatment. Guidelines suggest fluconazole is the preferred treatment for FE. For patients who respond poorly to fluconazole, the pathogen should be further examined and treatment should be adjusted according to the results of a drug sensitivity test.

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Footnote

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at http://dx.doi.org/10.21037/dmr.2019.12.07). The authors have no conflicts of interest to declare.

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References

1. Yakoob J. Candida esophagitis: Risk factors in non-HIV population in Pakistan. World J Gastroenterol 2003;9:2328-31.
2. Takahashi Y. Upper Gastrointestinal Symptoms Predictive of Candida Esophagitis and Erosive Esophagitis in HIV and Non-HIV Patients. Medicine 2015;94:e2138.
3. Kliemann DA. Candida Esophagitis: Species Distribution and Risk Factors For Infection. Rev Inst Med Trop Sao Paulo 2008;50:261-3.
4. Takahashi Y. 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.
5. Choi JH. Prevalence and Risk Factors of Esophageal Candidiasis in Healthy Individuals: A Single Center Experience in Korea. Yonsei Med J 2013;54:160-5.
6. Mohammadi R. Molecular identification of candida species isolated from gastro-oesophageal candidiasis in Tehran, Iran. Gastroenterol Hepatol Bed Bench 2015;8:288-93.
7. Kati BK. Fluconazole Resistant Candida Oesophagitis in Immunocompetent Patients: Is Empirical Therapy Justifiable? Clinical and Diagnostic Research 2015;9:16-8.
8. Zhu DL, Che ZP, Xv LB. Clinical analysis of 95 cases of fungal esophagitis. Chinese Journal of Clinical Gastroenterology 2008;21:56-8.
9. Zhu WQ, Su H, Chen LZ. Analysis of the incidence of mycotic esophagitis in 10 years. Contemporary Medicine 2008;140:72-3.
10. Rosołowski M. Etiology, diagnosis and treatment of infectious esophagitis. Prz Gastroenterol 2013;8:333-7.
11. Macêdo DP, Oliveira NT, Farias AM, et al. Esophagitis caused by Candida guilliermondii in diabetes mellitus: first

reported case. Med Mycol 2010;48:862-5.
12. Wilheim AB. The Resistance To Fluconazole in Patients with Esophageal Candidiasis. Arq Gastroenterol 2009;46:32-7.
13. Wilson A. Candida Glabrata Esophagitis: Are We Seeing the Emergence of a New Azole-Resistant Pathogen? Int J Microbiol 2014;2014:371631.
14. Chinese Medical Association "Candidiasis Diagnosis and Treatment Strategy Summit " expert group. Diagnosis and treatment of candidiasis: expert consensus. Chinese Journal of Infection and Chemotherapy 2011;11:81-95.
15. Weerasuriya N. Oesophageal candidiasis in elderly patients: risk factors, prevention and management. Drugs Aging 2008;25:119-30.
16. Olmos MA, Araya V. Oesophageal candidiasis: clinical and mycological analysis. Acta Gastroenterol Latinoam 2005;35:211-8.
17. Asayama N, Nagata T, Shimbo S. Nishimura. Relationship between clinical factors and severity of esophageal candidiasis according to Kodsi's classification. Dis Esophagus 2014;27:214-9.
18. Kohno S. Executive Summary of Japanese Domestic Guidelines for Management of Deep-seated Mycosis. Med Mycol J 2016;57:E117-63.
19. Nkuize M. Upper gastrointestinal endoscopic findings in the era of highly active antiretroviral therapy. HIV Medicine 2010;11:412-7.
20. Kim KY, Jang JY. Acid suppression therapy as a risk factor for Candida esophagitis. Dig Dis Sci 2013;58:1282-6.
21. Chocarro Martínez A, Galindo Tobal F. Risk factors for esophageal candidiasis. Eur J Clin Microbiol Infect Dis 2000;19:96-100.
22. Mimidis K. Predisposing factors and clinical symptoms in HIV-negative patients with Candida esophagitis: are they always present? Int J Clin Pract 2005;59:210-3.
23. Underwood JA. Clinical findings and risk factors for Candida esophagitis in outpatients. Dis Esophagus 2003;16:66-9.
24. Daniell HW. Acid suppressing therapy as a risk factor for Candida esophagitis. Dis Esophagus 2016;29:479-83.
25. Vermeersch B. Fungal colonization of the esophagus. Am J Gastroenterol 1989;84:1079-83.
26. Clayton SB. Twice-daily proton pump inhibitor therapy does not decrease the frequency of reflux episodes during nocturnal recumbencyin patients with refractory GERD: analysis of 200 patientsusing multichannel intraluminal impedance-pH testing. Dis Esophagus 2012;25:682-6.
27. Fotaki N. Mechanistic understanding of the effect of the effect of PPIs and acidic carbonated beverages on the oral absorption of the itraconazole based on absorption modeling with appropriate in vitro data. Mol Pharm 2013;10:4016-23.
28. Lim SG. Short report: the absorption of fluconazole and itraconazole under conditions of low intragastric acidity. Aliment Pharmacol Ther 1993;7:317-21.
29. Dolton MJ. Multicenter study of voriconazole pharmacokinetics and therapeutic drug monitoring. Antimicrob Agents Chemother 2012;56:4793-9.
30. Hendel L. Esophageal candidasis in progressive systemic sclerosis: occurrence, significance and treatment with fluconazole. Scand J Gastroenterol 1988;23:1182-6.
31. Cojutti P, Candoni A, Simeone E, et al. Antifungal prophylaxis with posaconazole in patients with acute myeloid leukemia: dose intensification coupled with avoidance of proton pump inhibitors is beneficial in shortening time to effective concentrations. Antimicrob Agents Chemother 2013;57:6081-4.
32. Karczewska E. Assessment of co-existence of Helicobacter pylori and Candida fungi in diseases of the uppergastrointestinal tract. J Physiol Pharmacol 2009;60:33-9.
33. Xu DH. Drug sensitivity analysis and characteristics of pathogenic bacteria in patients with esophagitis complicated with fungal infections. Chinese Journal of Nosocomiology 2015;25:5335-7.
34. Samonis G, Skordilis P, Maraki S, et al. Oropharyngeal candidi-asis as a marker for esophageal candidiasis in patients with cancer. Clin Infect Dis 1998,27:283-6.
35. Kanda N, Yasuba H, Takahashi T, et al. Prevalence of esopha-geal candidiasis among patients treated with inhaled flutica-sone propionate. Am J Gastroenterol 2003,98:2146-8.
36. Zhang XW. Massive hematemesis caused by fungal esophagitis: one case report. Clinical Misdiagnosis & Mistherapy 2003;16:257.
37. Kanzaki R. Candida esophagitis complicated by an esophago-airway fistula: report of a case. Surg Today 2009;39:972-8.
38. Baehr PH. Esophageal infections: risk factors, presentation, diagnosis, and treatment. Gastroenterology 1994;106:509-32.
39. Longo DL. Harrison's Principles of Internal Medicine. 18th, America: The McGraw-Hill Companies, 2012.
40. Onur MR. Candida esophagitis mimicking esophageal carcinoma. Turk J Gastroenterol 2011;22:648-9.
41. Kuyumcu S. Candida esophagitis mimicking esophageal

malignancy on 18FDG PET/CT. Turk J Gastroenterol 2015,26:63-4.
42. Seong M. Pancreatic Candidiasis That Mimics a Malignant Pancreatic Cystic Tumor on Magnetic Resonance Imaging: A Case Report in an Immunocompetent Patient. Korean J Radiol 2015;16:1253-6.
43. Patel NC. Esophageal infections: an update. Curr Opin Pediatr 2015;27:642-8.
44. Nishimura S. Factors Associated with Esophageal Candidiasis and Its Endoscopic Severity in the Era of Antiretroviral Therapy. PLoS One 2013;8:e58217.
45. Endoscopic mucosal tissue sampling. American Society for Gastrointestinal Endoscopy 2013.
46. Demir D. Is it possible to diagnose infectious oesophagitis without seeing the causative organism? A histopathological study. Turk J Gastroenterol 2014;25:481-7.
47. Pappas PG. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62:409-17.
48. Thursky KA. Recommendations for the treatment of established fungal infections. Intern Med J 2008;38:496-520.
49. Executive Summary of Japanese Domestic Guidelines for Management of Deep-seated Mycosis 2014. Med Mycol J 2016;57:E117-63.
50. Guidelines for the Use of Antifungal Agents in Patients with Invasive Fungal Infections in Taiwan — Revised 2009. J Microbiol Immunol Infect 2010;43:258-63.
51. Villanueva A. A randomized double-blind study of caspofungin versus amphotericin for the treatment of candidal esophagitis. Clinical Infectious Diseases 2001;33:1529-35.
52. Ebert S. Candida esophagitis as the cause of swallowing disturbances in an 85-year-old patient with myasthenia gravis. Z Gerontol Geriatr 2011;44:268-9.
53. Zhou YL. A clinical study of fungal esophagitis in 13 patients with hematologic malignancies. Chinese Journal of Hematology 2016;37:507-11.
54. Brion LP. Risk of resistance associated with fluconazole prophylaxis: systematic review. J Infect 2007;54:521-9.
55. Laverdière M, Lalonde RG, Baril JG, et al. Progressive loss of echinocandin activity following prolonged use for treatment of Candida albicans oesophagitis. J Antimicrob Chemother 2006;57:705-8.
56. He XY. Review on antifungal drug resistance mechanisms in Candida Spp. Chinese Journal of Mycology 2015;10:49-53.
57. Zhang L. Epidemiology, drug resistance, and azole drug resistance mechanism of Candida parapsilosis: a multicenter clinical study in China. Beijing: Peking Union Medical College Hospital. Chinese Academy of Medical Sciences, 2015.
58. Liu ZG. Mechanism of the resistance of Candida glabrata to fluconazole. Hebei: Hebei Medical University, 2011.

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