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, 200 mg 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, 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 MDRI 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

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