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Review

Fungal Esophagitis: Molecular Insights Into Pathogenesis and Emerging Antifungal Strategies

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Abstract

Fungal esophagitis, predominantly caused by *Candida* species, remains the leading form of infectious esophagitis worldwide. Although historically linked to human immunodeficiency virus infection, its epidemiology has shifted over recent decades, with a growing incidence among oncology patients receiving immune checkpoint inhibitors, individuals with eosinophilic esophagitis on oral corticosteroids, and solid-organ transplant recipients. Increasing evidence highlights that disease pathogenesis extends beyond simple fungal overgrowth and involves intricate host–pathogen interactions. Pathogenic mechanisms such as adhesion, hyphal transition, and biofilm formation enhance fungal virulence, while mucosal immune dysfunction, particularly impaired T helper 17/interleukin 17 signaling and reduced antimicrobial peptide activity, predisposes to persistent infection. Antifungal resistance represents an emerging challenge, driven by efflux pump overexpression, *ERG11* mutations conferring azole resistance, and mutations of *FKS* genes leading to reduced echinocandin susceptibility. These molecular mechanisms underscore the complexity of treatment and have important implications for antifungal selection and clinical management. While fluconazole remains the first-line agent for most cases, the increasing prevalence of non-*albicans* *Candida* species and drug resistance underscore the importance of alternative medications with different molecular targets. Agents such as the recently approved rezafungin as well as compounds such as ibrexafungerp and fosmanogepix, represent promising options for the treatment of refractory disease. This review synthesizes current advances in the molecular pathogenesis of fungal esophagitis, with particular emphasis on host–fungal interactions, antifungal resistance mechanisms, and novel treatment strategies. A deeper understanding of these processes is essential to improve management and to guide the development of innovative immunomodulatory and antifungal therapies.

Keywords: fungal esophagitis; immunocompromised patients; host-fungal interactions; pathogenesis; antifungals; treatment strategies

1. Introduction

Fungal esophagitis (FE) is a potentially serious inflammatory condition of the esophagus which is attributed to infection by fungal pathogens, most commonly *Candida* species [1]. FE is a disease mainly associated with immunocompromised individuals, especially those infected with the human immunodeficiency virus (HIV) and experiencing acquired immunodeficiency syndrome (AIDS), where FE prevalence is high [2]. However, advances in antiretroviral treatment, which have limited the severity of HIV infection, together with the expanding use of newer immunosuppressive therapies, have reshaped the epidemiology of FE, with the increasing emergence of cases among other patient populations, such as organ transplant recipients, cancer patients receiving immunotherapy, diabetics and those with eosinophilic esophagitis [3,4]. These observations underscore the importance of investigating host–fungal interactions and the immune mechanisms that predispose individuals to fungal infection.

The pathogenesis of FE is complex. Many fungi are normally present in the oropharynx and esophagus of humans. The disruption of this symbiosis can occur due to events such as dysfunction of the host immune system, the use of medications such as antibiotics and corticosteroids, disruption of the esophageal anatomical barrier, and increased fungal virulence [5]. Molecular processes such as fungal adhesion, invasion, and evasion of the host immune responses are central to disease development and treatment resistance. Exploring these mechanisms can certainly aid in the development of novel therapeutic agents and provide further options in the treatment of these patients. Although traditional antifungal therapies have proven effective in most cases, the development of antifungal resistance and the lack of therapeutic options specific to FE make the treatment of this condition challenging [6].

In this review, we aim to explore the molecular mechanisms involved in the development of FE, with a focus on host–pathogen interactions and the role of the immune system in disease progression. We also examine current treatment strategies and highlight emerging therapeutic agents that show promise for advancing FE treatment in the future. Through this comprehensive review, we hope to of-

fer valuable insights for clinicians treating this challenging condition, improve overall patient care, and suggest future research directions.

2. Epidemiology and Risk Factors

Infectious esophagitis caused by fungal, viral, bacterial, and parasitic infections is the third most common etiology of esophagitis, after gastroesophageal reflux disease (GERD) and eosinophilic esophagitis (EoE) [7]. Among infectious causes, *Candida* esophagitis (CE) represents the most common cause of FE, while other fungal infections, such as *Aspergillus* and *Histoplasma*, remain rare, with few cases reported in the literature [8]. In the general endoscopic population, the prevalence of FE is approximately 1%, with substantial variation according to host immune status and comorbid risk factors. In a large Japanese endoscopic cohort comprising 80,219 patients from 2002 to 2014, the overall prevalence of CE was 1.7%; this increased to 9.8% among HIV-infected patients, while remaining at 1.6% in non-HIV-infected patients [3]. In a more recent multicenter retrospective case-control study in the United States, which included 1969 hospitalized and outpatient non-HIV patients between 2015 and 2020, the prevalence of CE reached 9% [9].

Comparisons between different studies show a shift in the epidemiological pattern of FE over the years. The Japanese endoscopic cohort demonstrated an increase in CE prevalence among non-HIV patients from 0.6% in 2002–2003 to 2.5% in 2012–2014 [3]. On the contrary, national U.S. hospitalization data showed that the need for hospitalization due to CE decreased from 17 per 100,000 in 2010 to 12.9 per 100,000 in 2020, with fewer cases attributed to HIV infection and an increasing contribution of comorbid conditions such as GERD, long-term steroid use, and diabetes [10].

The varying frequency of CE across population groups indicates the presence of multiple risk factors for FE. Impaired cellular immunity remains responsible for most FE cases, and the most commonly associated reason is HIV [10]. However, the relative impact of HIV has declined, while other forms of immunosuppression have become more prominent in recent years. Based on studies with outpatients and hospitalized patients, these include hematological malignancies, chemotherapy, the increasing use of immune checkpoint inhibitors (ICIs), and solid-organ transplantation [11,12,13]. Furthermore, non-*Candida* FE, including cases caused by *Aspergillus* or *Mucorales*, occurs more frequently in patients with severe immunosuppression, including those with prolonged neutropenia, uncontrolled diabetes, or those treated with high doses of corticosteroids [14]. Non-*albicans Candida* species, including *C. glabrata* and *C. auris*, have emerged as recognized pathogens, particularly in hospitalized patients and in patients with prior exposure to azoles [15,16].

In addition to immunosuppression, other non-immune patient factors appear to play a significant role. Eosinophilic esophagitis is a condition characterized by chronic inflammation, disruption of esophageal epithelial integrity, and the frequent need for treatment with agents that predispose to fungal infections. More specifically, proton pump inhibitors (PPIs) are a risk factor for FE development, probably due to alterations in gastric acidity and upper gastrointestinal microbiota [17], while corticosteroid use also impairs local antifungal immunity [12]. Achalasia, cirrhosis, and diabetes are other comorbidities that have been linked to CE among hospitalized patients [18].

3. Pathogenesis and Host–Pathogen Interactions

3.1 Candida Virulence Mechanisms

The virulence of *Candida* species, the leading cause of FE, follows patterns similar to those observed in mucosal models of the oropharynx and intestine. The pathogenic process begins with adhesion to the host epithelium. The Agglutinin-like sequence (Als) family of proteins plays a central role by mediating adherence to epithelial cells and abiotic surfaces, thereby enabling *Candida* to adapt and establish infection under different host conditions [19]. Additionally, Hyphal wall protein 1 (Hwp1) is an adhesion protein expressed in hyphae that facilitates strong attachment to epithelial surfaces and is associated with persistent infections in mucosal membranes, thereby contributing to the structure and stability of the biofilm [20]. The transition from yeast to hyphae is critical for virulence. The regulatory networks of morphogenesis, including the RAS1–cAMP–PKA pathway and other transcriptional regulators, adapt to pH, nutrients, oxygen, and host immune pressure, thereby facilitating invasion and mucosal damage and coordinating the expression of many co-expressed virulence factors [21].

The next step is the formation of biofilms on mucosal surfaces. Biofilms are associated with protection from immune clearance and increased resistance to antifungal agents. The quorum-sensing (QS) molecules of *Candida* are chemical signals that affect biofilm development. Biofilm formation is a major pathogenetic pathway in FE from non-*albicans Candida* species, such as *C. glabrata* and *C. auris*, contributing to enhanced antifungal resistance and evasion of host immune responses [16].

Some QS molecules, such as tyrosol at micromolar concentrations, induce the growth of biofilms through the acceleration of hyphal formation [22], while others, like farnesol, inhibit the growth of biofilms via inhibition of hyphal formation [23]. The final step involves mucosal damage mediated by secreted aspartyl proteinases (SAPs) and phospholipases. SAPs cause tissue damage by adhering to the mucosa and degrading structural and immune proteins.

Phospholipases disrupt epithelial membranes and increase permeability via pH-dependent activity, often in collaboration with other enzymes [24].

3.2 Host Defense Mechanisms

3.2.1 Epithelial Barrier

In FE, mainly in CE, host defense is initially mediated by the epithelial barrier. Maintaining the integrity of the stratified squamous epithelium is central to preventing the transition of *Candida* from a commensal to a pathogenic state. Epithelial cells recognize the hyphal form of *Candida* and activate signaling pathways that lead to the secretion of proinflammatory cytokines, such as members of the interleukin (IL)-1 family, IL-8/CXCL8, and CCL20, resulting in the rapid recruitment of neutrophils and other innate immune cells [25].

3.2.2 Dectin-1–Toll-Like-Receptors Axis

Innate immune recognition is further mediated through pattern recognition receptors (PRRs), including Toll-like receptors (TLRs) and C-type lectin receptors. Dectin-1 is a C-type lectin receptor that recognizes β-glucans in the fungal cell wall, signals through caspase recruitment domain-containing protein 9 (CARD9), and promotes protective T helper (Th) responses in mucosal tissues. Dysfunction of the Dectin-1–CARD9 axis has been associated with increased susceptibility to mucocutaneous candidiasis [26]. TLRs recognize other components of *Candida*, like mannans. Functional synergy between Dectin-1 and TLRs enhances cytokine production and induces effective antifungal inflammation.

3.2.3 Th17/IL-17/IL-22 Axis

Among adaptive immune pathways, the Th17/IL-17/IL-22 axis appears to have the greatest clinical impact on host defense against CE. The Th17/IL-17 immune response activates neutrophils and enhances epithelial antimicrobial responses [27]. IL-22 acts as a complementary tissue-protective cytokine by enhancing epithelial barrier integrity and inducing the production of antimicrobial molecules. Recent experimental data support the hypothesis that IL-17 and IL-22 act synergistically to reduce oral and, to a lesser extent, esophageal candidiasis [28]. Consistent with these findings, clinical observations show that autoantibodies against IL-17 (A/F) and IL-22 are associated with chronic mucosal candidiasis [29].

3.2.4 Epithelial Effector Molecules

In addition to cytokine-mediated immunity, direct epithelial effector molecules play a critical role in mucosal defense. Antimicrobial peptides such as β-defensins and cathelicidins exhibit antifungal activity. Human β-defensins contribute to fungal growth inhibition, while LL-37, an antimicrobial peptide stored in specific neutrophil granules, reduces *Candida* adhesion to epithelial surfaces and prevents the establishment of infection [30].

3.3 Immune Dysfunction in Fungal Esophagitis

3.3.1 HIV Infection

FE occurs when *Candida*, a commensal organism of the upper gastrointestinal tract, overcomes host immune control and disrupts mucosal integrity. This disruption can result from loss of mucosal Th17, combined with the exhaustion of *Candida*-specific $CD4^+$ T cells, particularly in the context of HIV disease. High viral load and advanced immunosuppression, defined by $CD4^+$ T-cell counts below 200 cells/μL, are associated with increased risk and severity of esophageal candidiasis [31].

3.3.2 Iatrogenic Immunosuppression

Corticosteroid therapy increases the risk of CE by suppressing neutrophil and macrophage activity and by disrupting mucosal cytokine networks [32]. Chemotherapy predisposes patients to FE through two synergistic mechanisms: neutropenia and mucosal damage, both of which impair epithelial barrier integrity [33]. Regarding biologic agents, IL-17 inhibitors increase the risk of CE by blocking the IL-17/IL-22 axis, whereas anti–tumor necrosis factor (TNF) agents impair macrophage and T-cell–mediated antifungal responses [34]. On the other hand, ICIs do not directly cause FE; however, their use is associated with immune-related adverse events (irAEs), which often require treatment with corticosteroids or anti-TNF agents, thereby indirectly increasing the risk of fungal infection [35].

3.3.3 Local Esophageal Disorders

Chronic inflammation from GERD-related reflux can weaken the epithelial barrier, facilitating colonization and surface infiltration by *Candida*. Gastric acid suppression, particularly PPI use, further reduces upper gastrointestinal antimicrobial defenses [18]. Another disorder strongly associated with CE is EoE, which is characterized by type 2 inflammation driven by IL-4 and IL-13. This process disrupts esophageal epithelial integrity by forming dilated intercellular spaces and may modify the esophageal microbiome, thus predisposing the esophagus to fungal colonization [36].

4. Molecular Mechanisms of Antifungal Resistance

In addition to interactions between fungal pathogenesis and host immune dysfunction, molecular mechanisms of antifungal drug resistance contribute significantly to treatment failure and must be considered for the appropriate selection of antifungal therapy in FE (Fig. 1). Azole antifungals target lanosterol 14α-demethylase, an enzyme encoded by the *ERG11* gene, which is a key component of the ergosterol biosynthesis pathway. Mutations in *ERG11* can alter the conformation of 14α-demethylase, thereby reducing drug-binding affinity while maintaining catalytic activity. Moreover, it has been recently observed that increased

ERG11 expression confers antifungal resistance in many *C. albicans* and other *Candida* species, either in the presence or absence of concomitant *ERG11* mutations [37]. Additionally, gain-of-function mutations in *UPC*2, a transcriptional regulator of ergosterol genes, further promote overexpression of *ERG11* and result in azole resistance in *C. albicans* and *C. auris* [38].

A second important mechanism of azole resistance involves active drug efflux mediated by membrane transporters, including *Candida* drug resistance (CDR) transporters and multidrug resistance (MDR) transporters. Overexpression of CDR transporters reduces the intracellular concentration of azoles in resistant strains of *C. albicans*, *C. glabrata*, and *C. tropicalis*. MDR transporters are primarily associated with fluconazole resistance, leading to increased minimum inhibitory concentration (MIC) values in *C. albicans* and *C. tropicalis* [39]. Many clinical isolates exhibit a combination of resistance mechanisms, with upregulation of CDR and MDR transporters often leading to multi-azole resistance [39].

Azole resistance may also be mediated by altered sterol biosynthesis downstream of *ERG11* inhibition. While azole exposure typically leads to the accumulation of toxic 14-methylated sterols, mutations in *ERG2*, *ERG3*, *ERG6* and other ergosterol genes alter sterol composition and prevent the production of toxic intermediates, thus allowing fungal survival despite exposure to azoles [40]. Chromosomal rearrangements, such as the duplication of chromosome 5, where the *ERG11* gene is located, and activation of stress-response pathways, including the calcineurin pathway, may also enhance drug tolerance [40].

Echinocandins act as antifungals by inhibiting the catalytic subunits of β-(1,3)-D-glucan synthase, encoded by the *FKS* gene family. Point mutations in *FKS1* and *FKS2* hotspot regions in *C. albicans* and other *Candida* species are almost exclusively responsible for high-level resistance to echinocandins. Unlike azoles, efflux pumps do not play a significant direct role in determining echinocandin MICs [41]. Polyene antifungals bind to ergosterol in the fungal cell membrane, leading to pore formation and cell death. Clinical resistance to polyenes is relatively rare and usually associated with ergosterol disorders. Loss-of-function mutations in *ERG3* dysregulate the ergosterol pathway and reduce susceptibility to polyenes and azoles by altering the availability of ergosterol in the fungal membrane [42].

5. Endoscopic Appearance of Lesions and Correlation With Pathogenesis

Endoscopic lesions of FE have been better characterized in CE using Kodsi's classification. Kodsi's classification has been widely used in the literature and has been associated with symptom severity and $CD4^+$ T-cell counts in HIV patients [43]. In contrast, in non-*Candida* FE caused by organisms such as *Aspergillus* or *Mucorales*, the endoscopic lesions are more often ulcerative or necrotic rather than plaque-like and therefore do not conform to Kodsi's classification [44]. Given the epidemiological predominance of CE, this review focuses on Kodsi's classification.

Although no studies have systematically evaluated molecular or immunological characteristics across different Kodsi grades using esophageal biopsies, available data support a reasonable correlation between endoscopic severity and underlying pathogenic mechanisms. Established knowledge regarding *Candida* virulence factors, mucosal immune responses, and clinical observations demonstrates associations between higher Kodsi grades, lower $CD4^+$ T-cell counts, and advanced immunosuppression [45]. However, the correlations proposed in this section should be viewed as reasonable hypotheses rather than certain associations between endoscopic appearance and molecular alterations.

5.1 Grade I

Endoscopic findings consist of a few raised white plaques, each up to 2 mm in diameter, without surrounding redness, edema, or ulceration. The mucosal substrate is normal or slightly hyperemic [46]. At this stage, the proposed molecular profile is that *Candida* adhesion to the epithelium is dominated by the Als family and Hwp1 [19,20]. Early biofilm formation and limited hyphal development may be present, without extensive infiltration of hydrolytic enzymes [21]. The host mucosal defense may remain effective, so the infection is often mild and asymptomatic [27].

5.2 Grade II

Grade II lesions are characterized by multiple raised white plaques >2 mm without overt ulceration on an otherwise intact mucosa [46]. The potential molecular profile may include increased fungal load, more mature biofilm architecture, stronger Als/Hwp1 expression, and denser hyphal networks [19,20,21]. In this phase, innate immunity (TLRs, Dectin-1) may be activated. However, extensive mucosal destruction is not observed [39].

5.3 Grade III

Endoscopic findings in Grade III include confluent, continuous plaques, linear and/or nodular, extending along a large portion of the esophagus. Mucosal edema, superficial erosions, and bleeding upon contact with the endoscope are often seen [46]. The proposed molecular profile is that of a mature, thick biofilm with high hyphal density and the coexistence of yeast forms [21]. In this phase, increased SAP activation leads to microulcerations and mucosal fragility [24]. Additionally, in patients with immunodeficiency, the Th17/IL-17/IL-22 response is insufficient, allowing fungal-induced tissue damage to exceed regenerative capacity, often leading to macroscopically thickened plaques [47].

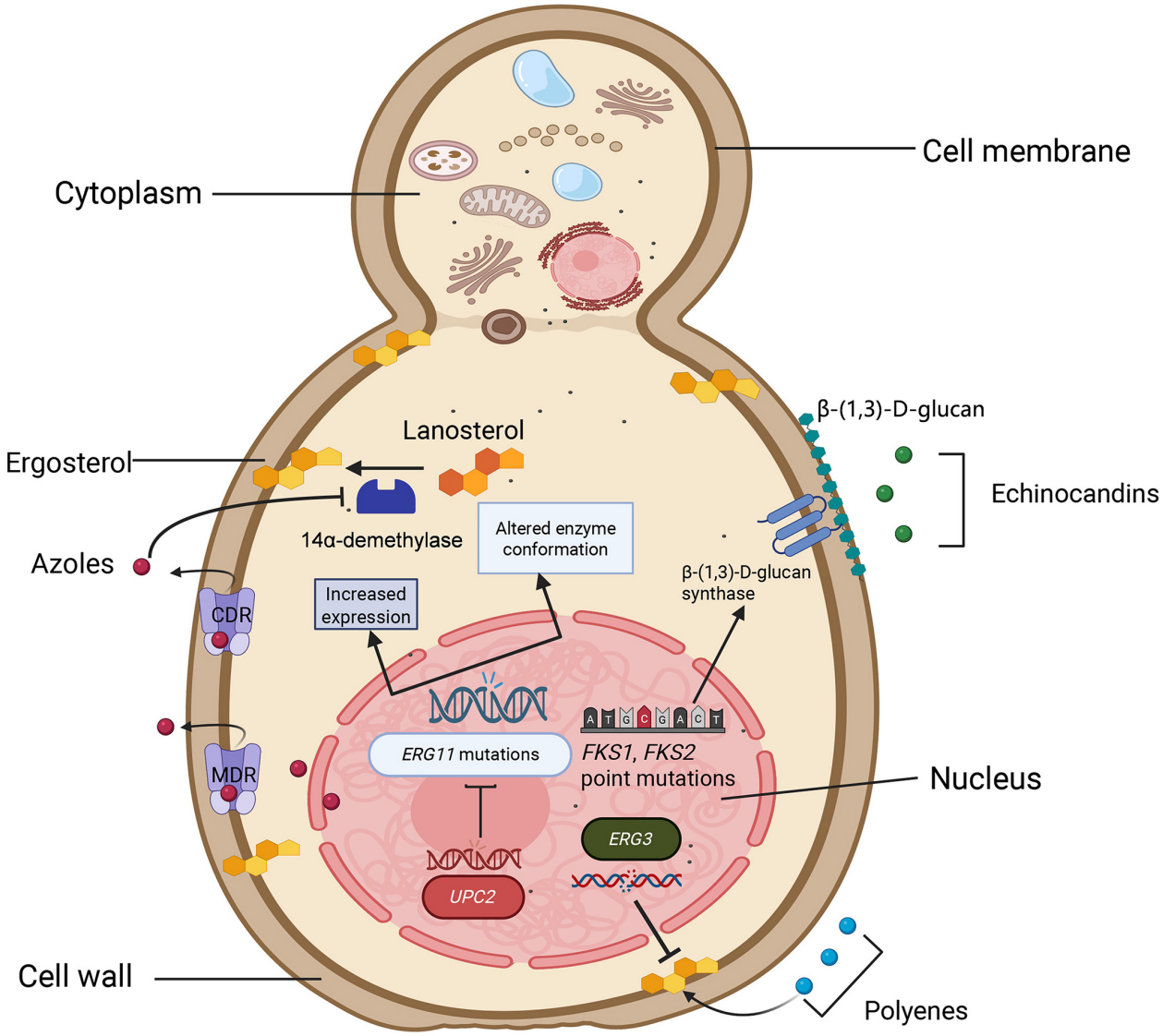

Fig. 1. Molecular mechanisms of antifungal resistance in fungal esophagitis. Resistance to azoles arises through *ERG11* mutations, *ERG11* overexpression mediated by *UPC2* activation, increased drug efflux through CDR and MDR transporters, and alterations in downstream sterol biosynthesis genes. Echinocandin resistance is mainly associated with mutations in *FKS1* and *FKS2* genes encoding β-(1,3)-D-glucan synthase. Polyene resistance is rare and typically involves alterations in ergosterol biosynthesis, particularly due to *ERG3* mutations. Abbreviations: CDR, Candida drug resistance transporters; MDR, multidrug resistance transporters. Created in BioRender. Tsounis, E. (2026) https://BioRender.com/ypmcbg4.

5.4 Grade IV

Grade IV lesions resemble those of Grade III but with increased mucosal fragility or bleeding, stenosis, or partial luminal obstruction. They may coexist with extensive ulceration, deeper erosive esophagitis, and rarely necrotic areas [46]. At this stage, the fungal burden is presumed to be maximal, characterized by very dense biofilms, high metabolic activity, and strong expression of all major virulence modules [20]. The continuous production of hydrolytic enzymes results in severe disruption of epithelial integrity. From the host perspective, severe disease may be associated with very low $CD4^+$ T-cell counts and a severe IL-17/Th17 deficit, as well as profound immunosuppression [47]. In this phase, the formation of a pseudomembrane and the development of strictures or fistulae may be observed [43].

5.5 Advanced Disease Beyond Kodsi Classification

Although not included in Kodsi's original classification, a fifth stage, named "white carpet" or extreme grade IV, has been proposed in some extended adaptations. The endoscopic findings at this stage include a thick, white pseudomembrane covering the mucosa circumferentially, severe luminal narrowing, extreme friability, and pronounced bleeding. In prolonged or severe CE,

complications such as stenosis, annular scars, hemorrhage, and esophagobronchial fistulas or infiltrative necrosis have been reported [46]. The proposed molecular and immunological features of Grade V and its complications may be similar to those at Grade IV, reflecting sustained fungal overgrowth, persistent virulence factor expression, and profound failure of mucosal immune defense.

6. Current Treatment Choices

The management of FE has evolved in recent years due to the rising incidence of resistant infections and the growing population of immunocompromised patients. The efficacy of antifungal agents is influenced by their interaction with specific molecular targets and fungal adaptive responses. Fluconazole is still considered the first-line choice for FE and is generally effective when initiated promptly. Other azoles, echinocandins, amphotericin B and emerging therapies should be considered in refractory or resistant cases. Fig. 2 shows an algorithm which suggests a stepwise approach for clinicians who treat these patients in everyday practice.

6.1 Azoles

Azoles exert their antifungal effect by inhibiting lanosterol 14α-demethylase, an enzyme that catalyzes the conversion of lanosterol to ergosterol within the cytochrome P450 pathway. This process disrupts the integrity of the fungal cell membrane and impairs its protective function, causing a reduction in fungal growth [48]. Among them, fluconazole is an agent with proven efficacy in the treatment of most *C. albicans* isolates [49,50]. Current international guidelines recommend fluconazole as the first-line treatment for uncomplicated FE due to its efficacy, favorable safety profile, good tolerability and oral availability [6].

Despite its widespread use, the rising incidence of fungal species with intrinsic or acquired resistance to fluconazole therapy poses a challenge to its utility [51]. Mutations and overexpression of *ERG11*, upregulation of sterol biosynthesis pathways, overexpression of efflux pumps and decreased azole influx are frequently encountered in resistant *Candida* isolates, mostly in non-*albicans Candida* species and in patients with prior azole exposure or advanced FE [39]. Since resistance to azoles is frequently encountered in isolates such as *C. glabrata* and *C. auris*, clinicians should be wary of the situation and adjust treatment appropriately in a timely manner [15]. Moreover, interactions between fluconazole and other medications metabolized in the cytochrome P450 pathway, particularly antiretrovirals and some immunosuppressants, further limit its use in select patient populations [52].

6.2 Echinocandins

Echinocandins, including caspofungin, anidulafungin and micafungin, exert fungicidal activity by inhibiting the synthesis of β-(1,3)-D-glucan and disrupting the structure of the fungal cell wall [53]. These agents are useful in azole-refractory infections and severe disease, while they also represent a favorable option for patients receiving multiple concomitant medications due to limited drug-drug interactions [54,55]. Their use should also be considered in cases with prior exposure to azole therapy, where infections by azole-resistant species, mainly *C. glabrata* and *C. krusei*, are more common [56].

Resistance to echinocandins is uncommon. From a molecular perspective, mutations in *FKS* genes, most frequently encountered following prolonged or repeated exposure to echinocandins, reduce drug binding to β-(1,3)-D-glucan synthase and limit their antifungal effect. In addition to genetic resistance, biofilm formation and fungal adaptation to increased cellular oxidative stress further contribute to reduced susceptibility to echinocandins [57].

6.3 Polyenes

Amphotericin B is a polyene antifungal agent with broad-spectrum activity that has been used in the treatment of fungal infections for decades. It exerts its antifungal activity by binding directly to ergosterol and forming pores in the cell membrane, leading to depolarization and cellular disruption [58]. Newer lipid formulations are preferred due to reduced nephrotoxicity [59,60]. Resistance to amphotericin B is rarely encountered due to difficulties in producing viable ergosterol alterations that do not compromise the viability of the fungal membrane. Furthermore, its concomitant use with other antifungals such as micafungin has emerged as a new treatment strategy against resistant species such as *C. auris* [61]. Therefore, it should be considered in severely ill patients and those with refractory or resistant FE caused by *Candida* or other fungal species, with careful monitoring recommended to limit the incidence of potential side effects [6].

7. Emerging Antifungal Agents

The increasing incidence of antifungal resistance and limitations of currently available treatments have highlighted the importance of the development of novel antifungal agents with different molecular targets. The efficacy of emerging agents, including rezafungin, ibrexafungerp, and manogepix, in the treatment of FE is still hypothetical, as they have not been specifically evaluated in clinical trials for esophageal candidiasis. Although these agents have shown promise in the treatment of invasive candidiasis, their potential role in the treatment of high-risk or resistant FE cases is not yet established, and should only be considered as potential future options for these patients.

7.1 Rezafungin

Rezafungin is a novel echinocandin derived from anidulafungin. It is characterized by early efficacy when administered in high initial loading doses and a long half-

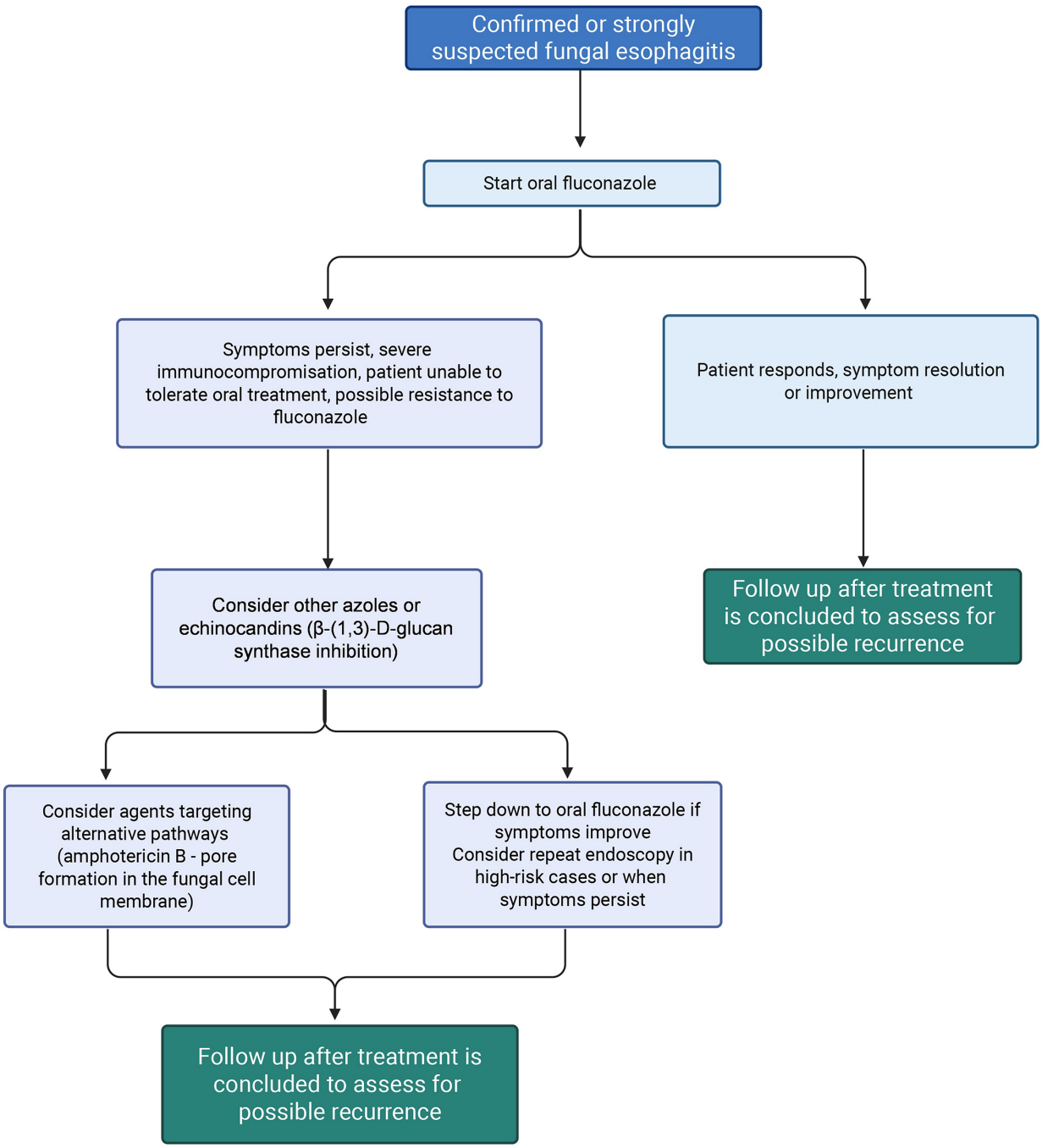

Fig. 2. Proposed practical algorithm for the treatment of fungal esophagitis based on current literature. Created in BioRender. Tsounis, E. (2026) https://BioRender.com/btcryoj.

life, which allows for once-weekly intravenous administration. Like other echinocandins, it inhibits β-(1,3)-D-glucan synthase and disrupts the synthesis of the fungal cell wall [62]. Studies have demonstrated potent activity against both *Candida* and non-*Candida* species, such as *Aspergillus*, even in strains resistant to azoles. Moreover, rezafungin retains activity against strains that exhibit high MICs of other echinocandins such as anidulafungin, and studies have shown positive results in patients with resistant candidiasis while also retaining a comparable safety profile to other echinocandins. However, resistance to rezafungin due to *FKS* hotspot mutations has also been reported [62,63].

7.2 Ibrexafungerp

Ibrexafungerp (IBX) is the first agent of a novel class of antifungals known as triterpenoids. It is a synthetic derivative of enfumafungin and acts by inhibiting β-(1,3)-D-glucan synthase through binding to sites that are distinct from those targeted by echinocandins. These ac-

tions disrupt the integrity of the fungal cell wall and increase its permeability, ultimately causing cell lysis [64]. The availability of oral formulation makes IBX an attractive option for step-down therapy and outpatient management. Importantly, IBX remains effective against resistant strains harboring *FKS* mutations due to its effects on alternative molecules involved in glucan synthesis. Furthermore, IBX exhibits significant antibiofilm activity compared with echinocandins [65,66]. These attributes make it a very appealing treatment choice for non-*albicans* resistant strains, including *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, and *C. krusei* [67,68]. Although clinical data regarding its efficacy in FE treatment are currently lacking, its oral availability and distinct molecular interactions could make its use in the treatment of refractory or resistant FE reasonable.

7.3 Manogepix

Manogepix is a novel agent that acts by inhibiting Gwt1, an enzyme essential for proper glycosylphosphatidylinositol (GPI) biosynthesis. Its action prevents fungal adhesion to mucosal surfaces and limits fungal virulence. Manogepix is available both in oral and intravenous forms as fosmanogepix, a prodrug which is rapidly converted to manogepix by systemic phosphatases following administration [69]. Importantly, manogepix demonstrates high efficacy in resistant systemic fungal infections and reduces the possibility of cross-resistance, likely due to its unique molecular target [70]. Its distinct mechanism of action makes manogepix a promising candidate for patients with multidrug-resistant FE.

8. Possible Adjunctive Strategies

8.1 Immunomodulation

Given the central role of host immune dysfunction in the development of FE, immunomodulatory approaches are gaining increasing attention. As mentioned above, impairment of the Th17/IL-17/IL-22 axis increases susceptibility to fungal infections [28]. Both IL-17 and IL-22 are pivotal for host protection, with actions such as upregulation of proinflammatory cytokine expression and production of antimicrobial peptides [71]. Therefore, it is reasonable to assume that restoration of this axis could enhance antimicrobial peptide production and support the integrity of the mucosal barrier. Administration of recombinant IL-17 in preclinical trials has shown beneficial effects on host antifungal defense [72]. However, its role in FE treatment has not yet been investigated, and its use is currently limited by the lack of clinical trials and concerns regarding inflammatory toxicity.

8.2 Vaccination Against Fungal Species

Vaccination against common fungal pathogens could be important in the prevention of severe infection, especially in immunocompromised populations. Such an approach would represent an important strategy to reduce disease burden and limit healthcare costs [73]. Several candidate vaccines have been developed that target adhesins and other fungal cell wall components with the aim of preventing adhesion and biofilm formation. NDV-3A, a vaccine that contains a recombinant adhesin of *C. albicans*, has shown clinical efficacy in reducing the frequency of symptomatic episodes of recurrent vulvovaginal candidiasis in women [74]. Despite these advances, development of antifungal vaccines for FE prevention remains challenging. Most patients who develop FE are severely immunocompromised and cannot easily enter clinical trials for evaluation of live attenuated vaccines. Moreover, heterogeneity among fungal isolates might limit the effectiveness of type-specific vaccines [73]. Further evaluation of panfungal vaccines can help to determine their potential role in providing broad-spectrum antifungal protection.

8.3 Probiotics and Microbiome Alterations

The disruption of the gastrointestinal microbiome, whether due to antibiotic exposure, severe illness, or immunosuppression, promotes fungal colonization throughout the digestive tract, including the esophagus. Probiotics have previously demonstrated significant protective effects against fungal infections in experimental models, with inhibition of hyphal production, prevention of fungal adhesion to host cells, and reduction of biofilm formation suggested as possible protective mechanisms [75]. These observations have prompted clinical evaluation of probiotics as adjunctive therapy in the treatment of fungal infections, although the variability of host microbiota makes appropriate probiotic selection and choice of treatment duration difficult. Evidence remains preclinical and is derived mostly from non-FE models [76]. Therefore, further randomized trials are required before probiotic use can be recommended as routine therapy for the treatment of fungal infections, including FE.

8.4 Nanotechnology

Advances in nanotechnology may provide novel opportunities for the treatment of severe infections, including those caused by fungal pathogens resistant to conventional treatment. Nanoparticle-based drug delivery systems can improve treatment efficacy by enhancing drug solubility, providing targeted delivery to infected areas, and prolonging tissue exposure to therapeutic agents. Moreover, the use of certain antifungal agents with limited oral bioavailability and frequent adverse events caused by systemic toxicity, such as amphotericin B, may be safer with the use of nanotechnology and precise delivery of medications to intended targets [77]. Beyond drug delivery, certain nanomaterials exert antifungal activity through other mechanisms, such as the formation of reactive oxygen species (ROS), damage to the fungal membrane, and disruption of metabolic fungal pathways [78]. Various nanomaterials,

such as those based on copper, zinc, silver, selenium, and silica, have been examined in preclinical studies for their antifungal properties, with results showing considerable efficacy against a variety of fungal species [79]. Further *in vivo* examination of these technologies and continued improvements in drug-delivery systems may establish their use in the treatment of localized fungal infections, including FE.

9. Study Limitations

Some limitations of this review should be acknowledged. While a broad range of relevant studies was considered, the available literature is heterogeneous, with a notable lack of prospective trials that specifically focus on the treatment of FE. Sample sizes in existing studies are frequently limited, reducing statistical power and generalizability. As a result, certain data discussed in this review are derived from related mucosal candidiasis models and invasive fungal infections. Future research should prioritize prospective studies and multicenter cohorts to enable the formation of standardized diagnostic and therapeutic approaches. Moreover, the identification of reliable biomarkers that can be used to estimate disease severity and possible treatment response is needed to guide individualized patient management. Nevertheless, this synthesis integrates current molecular, immunological, and clinical insights to provide a comprehensive framework for understanding FE and to highlight key biological gaps that warrant further investigation.

10. Conclusions

FE remains a significant clinical entity whose management has become increasingly complex due to the expanding use of immunosuppressive therapies and the growing number of immunocompromised individuals. The increasing incidence of FE attributed to non-*albicans Candida* and other fungal species, along with the emergence of antifungal resistance, underscores the urgent need for a deeper understanding of FE pathophysiology and the development of individualized treatment strategies. Advances in molecular biology and immunology have improved our understanding of factors that promote fungal virulence and impair the integrity of the host immune system and ultimately enable FE development. Azole treatment, especially fluconazole, remains the cornerstone of FE management; however, alternative agents such as echinocandins and polyenes play an important role in cases of resistance, treatment failure, or clinically relevant drug-drug interactions. Several novel antifungal agents show promise for refractory or resistant disease, although clinical data regarding FE treatment remain limited. Besides antifungal agents, emerging adjunctive strategies that aim to improve host immune responses, prevent fungal colonization and adhesion, and achieve better drug delivery to specific sites represent promising avenues for future therapy. Further experimental and translational studies integrating molecular fungal virulence traits, host immune responses, endoscopic findings and resistance mechanisms are required to enable the development of mechanism-driven and precision-targeted therapeutic strategies for FE.

Abbreviations

FE, Fungal Esophagitis; HIV, Human Immunodeficiency Virus; AIDS, Acquired Immunodeficiency Syndrome; GERD, Gastroesophageal Reflux Disease; EoE, Eosinophilic Esophagitis; CE, *Candida* Esophagitis; ICIs, Immune Checkpoint Inhibitors; PPIs, Proton Pump Inhibitors; Hwp1, Hyphal Wall Protein 1; QS, Quorum-Sensing; SAPs, Aspartyl Proteinases; IL, Interleukin; PRRs, Pattern Recognition Receptors; TLRs, Toll-like Receptors; CARD9, Caspase Recruitment Domain-containing Protein 9; irAEs, immune-related Adverse Events; CDR, *Candida* Drug Resistance Transporters; MDR, Multidrug Resistance Transporters; MIC, Minimum Inhibitory Concentration; IBX, Ibrexafungerp; GPI, Glycosylphosphatidylinositol; ROS, Reactive Oxygen Species.

Author Contributions

IA and CT, conception and design; KP and PP acquisition of data; KP and PP, analysis and interpretation of data; KP and PP, drafting of the manuscript; IA and CT, critical reviewing of manuscript for important intellectual content. All authors have approved the final version of the manuscript for publication. All authors have agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All authors contributed to editorial changes in the manuscript.

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