Exploration of Cardiology

Open Exploration

Open Access Review

Fungal endocarditis: microbial insights, diagnostic and therapeutic challenges in the modern era

Sudeep Edpuganti*

Department of Medicine, Faculty of Medicine, Tbilisi State Medical University, 0177 Tbilisi, Georgia

***Correspondence:** Sudeep Edpuganti, Department of Medicine, Faculty of Medicine, Tbilisi State Medical University, 33 Vazha Pshvela Avenue, 0177 Tbilisi, Georgia. edpugantisudeep@gmail.com
Academic Editor: Alexandre Abizaid, Institute Dante Pazzanese de Cardiologia, Brazil
Received: May 26, 2025 **Accepted:** July 8, 2025 **Published:** July 23, 2025

Cite this article: Edpuganti S. Fungal endocarditis: microbial insights, diagnostic and therapeutic challenges in the modern era. Explor Cardiol. 2025;3:101264. https://doi.org/10.37349/ec.2025.101264

Abstract

Fungal endocarditis (FE) is still an uncommon but devastating infection, especially when immunosuppression, prosthetic valve surgery, or prolonged health care is involved. Although being only responsible for 1–6% of infective endocarditis cases, the mortality rate is higher than 40–60% due to the time lag from diagnosis and therapeutic complexity. Etiology is led by *Candida* species, especially *Candida albicans*, followed by *Aspergillus*, and new pathogens like multidrug-resistant *Candida auris* are also seen. Non-*C. albicans* and the biofilm-forming species also add more complexity to the manageability. Diagnosis is challenging due to the high percentage of culture-negative cases, particularly for molds, requiring sophisticated investigations such as fungal biomarkers (β-*D*-glucan, galactomannan), molecular tests, and imaging studies such as ^{18}F-FDG PET/CT (fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography). Early transesophageal echocardiography is crucial in the diagnosis of vegetations, whereas histopathology of resected non-cardiac tissue offers a definitive diagnosis. Treatment requires aggressive antifungal therapy, echinocandins, amphotericin B, or azoles, in conjunction with urgent valve surgery to reduce embolic risk and enhance survival. However, drug resistance, biofilm resistance, and patient comorbidities counteract the efficacy. Novel treatments such as rezafungin and ibrexafungerp are promising but have limited clinical hands-on evidence. Risk factors of immunosuppression, indwelling devices, and IV drug use imply a need for increased clinical suspicion in high-risk groups. Although there have been minor improvements in FE survival, the grim situation of FE persists, highlighting the importance of a multidisciplinary approach, early diagnosis, and tailored antifungal therapy to control this deadly infection.

Keywords

Fungal endocarditis, *Candida auris*, biofilm-associated infections, antifungal resistance, prosthetic valve endocarditis

Introduction

Fungal endocarditis (FE) is a rare but aggressive form of infective endocarditis (IE), responsible for roughly 1–6% of all endocarditis cases [1, 2]. Over the past decade, due to the increase in immunocompromised and prosthetic valve patients, there has been a dramatic increase in the total number of endocarditis and other invasive fungal infections [1, 3]. *Candida albicans* causes most of FE and is implicated in over half of the cases worldwide, while *Aspergillus* and *Histoplasma* spp. are the next most common pathogens [1, 4]. A systematic review by Meena et al. [5] (2022) on FE reported that out of 250 patients, *Candida* accounted for nearly 50% of cases and *Aspergillus* for 30%. Non-*C. albicans* (such as *Candida parapsilosis* and *Candida glabrata*) have also risen in prominence and contribute significantly to morbidity [6, 7]. Because FE often mimics bacterial endocarditis, diagnosis is frequently delayed; blood cultures may be negative (especially for molds), and patients present with fever, embolic phenomena, or new murmurs [2, 8].

Several forces underscore the need for an updated review in this modern era of invasive fungal disease. First, the new high-risk populations, including patients with advanced immunosuppression (transplant recipients, malignancies, biologic therapy) and chronic healthcare exposures (central venous catheters, long-term antibiotics, total parenteral nutrition), have emerged [1, 9]. Second, diagnosing and treating novel and multiresistant fungi like *Candida auris* presents challenges not previously encountered [9]. Third, advances in diagnostics (molecular assays, fungal biomarkers, and advanced imaging) and therapeutics (new antifungal agents, interventional techniques) have not yet been comprehensively integrated into clinical practice. Finally, delayed or missed diagnosis of FE, often due to culture-negative disease or atypical presentation, is common, necessitating greater clinician awareness.

Although FE is rare, it affects vulnerable patients (transplant recipients, prosthetic valves, IV drug users) and has life-threatening complications (embolization, heart failure) [1, 3]. According to the CDC, there are over 25,000 cases of candidemia in the U.S. each year, according to recent data, which increases the risk pool for endocarditis [10, 11]. At the same time, high-profile "super fungi" like *C. auris* have emerged with multidrug resistance, underscoring an urgent need for awareness [9]. New diagnostic modalities [T2MR, fungal polymerase chain reaction (PCR), β-*D*-glucan, fluorodeoxyglucose (FDG)-PET] hold promise but are not yet standardized. This review addresses these contemporary issues and collates recent evidence to guide clinicians facing FE.

Methods

A structured literature search and selection following PRISMA guidelines was conducted. Major databases (e.g., PubMed, Scopus, Web of Science) were searched using combinations of keywords and subject headings relevant to our topic. The search was limited to English-language publications from 2015–2024 (a 10-year window), with older seminal studies included when particularly relevant to ensure completeness. A PRISMA flow diagram was used to summarize the literature selection process (Figure 1).

Search strategy

Databases and search terms: PubMed, Scopus, and Web of Science were searched using key terms (and their synonyms/MeSH equivalents) related to the review topic. Boolean operators (AND/OR) combined concepts as appropriate.

Timeframe and language: Searches were limited to 2015–2024, but important earlier publications were captured via references. Only English-language articles were considered.

Additional sources: Reference lists of relevant articles and recent reviews were hand-searched to identify any studies not captured in the database search.

Inclusion and exclusion criteria

Inclusion criteria: Peer-reviewed original studies, reviews, and meta-analyses that focused on the topic of interest (e.g., interventions or outcomes) were included. Studies had to report on at least one outcome relevant to our research question.

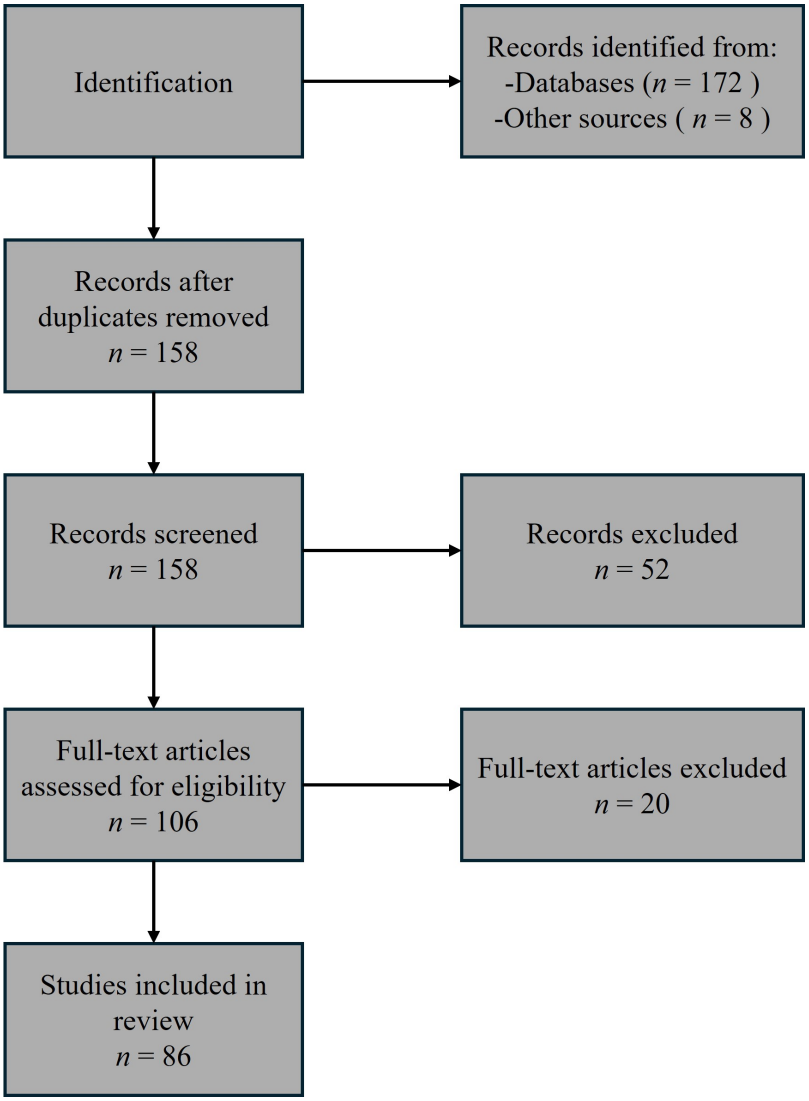

Figure 1. PRISMA flow diagram summarizing the literature selection process. The flow diagram maps the number of records identified, screened, and included at each stage of the review. Initially, the total number of records from database searches (and other sources) is shown at the top. After duplicates were removed, the remaining records were screened by title and abstract. The diagram then indicates how many full-text articles were assessed for eligibility and how many were excluded with reasons (e.g., not meeting inclusion criteria). The bottom of the diagram displays the final number of studies included in the review. This flowchart provides a clear, PRISMA-compliant visualization of the inclusion/exclusion criteria and screening steps

Exclusion criteria: Studies were excluded if they were non-English or outside the scope of our topic. For example, case reports, animal studies, or articles without sufficient data were not included.

Epidemiology and risk factors

Incidence and clinical course

FE is rare. Only 892 cases of *Candida* endocarditis (CE) out of 272,798 endocarditis admissions (0.33%) were found in a recent U.S. analysis [12], and about 23% of the 703 patients with CE in a multicenter U.S. cohort from 2015 to 2019 underwent heart surgery. The inpatient mortality rate was 16.2% [11]. However, worldwide reviews of all FE cases, including those with native and prosthetic valves, have found a higher mortality rate, between 40 and 60 percent [3, 5]. Meena et al. [5] (2022) found a 1-year mortality rate of ≈ 42%. While other studies noted that mortality is > 50–70%, especially without surgery [1, 3]. The disparity implies that although mortality is still too high, results are somewhat improved by more recent management.

Geography and setting

FE can occur on native or prosthetic valves. In reported FE cases, roughly one-third are prosthetic valve endocarditis (PVE) [4, 5]. Meena et al. [5] (2022), among the 250 cases, found 35% PVE and 16% involving intravenous drug use (IVDU). The majority of cases in high-income countries involve prosthetic valves or cardiac devices. In endemic regions (central U.S.), dimorphic fungi (*Histoplasma*, *Coccidioides*, *Blastomyces*) cause a minority of FE, often in specific geographic or travel contexts [13]. A recent Mayo Clinic series showed that endemic fungal IE is becoming more widely recognized in the U.S. *Coccidioides* accounts for about 18% of cases, and *Histoplasma capsulatum* for almost half [13]. These endemic fungal cases were often diagnosed late or postmortem, reflecting diagnostic challenges.

Host risk factors

Any condition predisposing to fungemia or abnormal heart valves is a significant risk factor for FE. Prosthetic heart valves, cardiac device implants (pacemakers, defibrillators), previous valve surgery, and congenital heart disease (particularly after repair) are known risk factors [14]. Immunosuppression, whether due to hematologic malignancy, transplant-related drugs, HIV or AIDS, or chronic corticosteroids, is another strong risk factor, particularly for FE [15]. In an extensive review, 64% of native-valve *Aspergillus* endocarditis cases had severe immunosuppression (cancer, transplant) [15]. Long-term use of invasive vascular lines or devices is critical: The risk of candidemia and subsequent endocarditis is higher in patients receiving total parenteral nutrition or with chronic central venous catheters [16, 17]. Another significant risk factor is IVDU. While IVDU is usually linked with a higher risk of staphylococcal infection, heroin and other drug use can also introduce mold and *Candida* [5, 18]. Additional factors related to healthcare include extended hospital stays, hemodialysis (central catheter and turbulent flow on calcified valves), and intensive broad-spectrum antibiotics (which disturb normal flora) [9, 19].

Several comorbidities elevate risk. Chronic kidney disease and hemodialysis are essential: one study found hemodialysis conferred ≈ a 2-fold higher mortality risk in CE patients (suggesting also increased occurrence) [11]. Another significant risk is acute or chronic liver disease; according to Huggins et al. [11], acute/subacute liver failure had the strongest mortality association (OR ≈ 9) in CE, suggesting that endocarditis could exacerbate critical illness. Multiple studies have reported this counterintuitive finding: patients who inject drugs (often opioids) sometimes have lower short-term mortality in endocarditis. For example, a large U.S. study of CE learned that a documented history of opioid abuse was independently associated with a significantly reduced risk of inpatient death (OR ≈ 0.4) [11]. Similarly, cohorts of general IE report comparable or even slightly better short-term survival in IVDU vs. non-IVDU patients [20]. In one Finnish registry, 1-year mortality was essentially identical (4.0% vs. 4.1%) in IE patients with vs. without a history of injecting drug use [20]. These findings suggest a "protective" association of IVDU against mortality, though the effect is almost certainly due to patient factors rather than any beneficial effect of drug use.

- Age and health status: IVDU patients are typically decades younger than other IE patients (median ≈ 35 vs. ≈ 62 years in one study). They also have far fewer chronic comorbid conditions (much lower Charlson comorbidity scores). Being younger and generally healthier makes them more resilient to a severe infection [20].
- Valve involvement: IVDU-related IE is predominantly right-sided (e.g., tricuspid valve) in one cohort, ≈ 70% of PWID cases vs. < 10%. Right-sided endocarditis generally causes fewer lethal complications than left-sided disease [20].
- Clinical management factors: People who inject drugs often have more acute, obvious infections (e.g., *Staphylococcus aureus*) that prompt aggressive care. They may also receive valve surgery more often or earlier, which improves survival in IE. In contrast, sicker non-IVDU patients often have multiple comorbidities that limit treatment options.

In short, the "**paradox**" arises because IVDU patients with endocarditis tend to be younger and have fewer other illnesses. These favorable baseline features (plus the tendency toward right-sided disease) offset the risks of drug use. Thus, the observed lower mortality in IVDU is likely a confounding effect of patient demographics and disease patterns, not a true protective effect of opioids themselves. Even so, clinicians should remember that IVDU remains a major risk factor for acquiring fungal or bacterial endocarditis; the lower mortality is only relative to other very ill patients, and long-term outcomes (especially if addiction is untreated) remain poor [20]. Finally, emerging reports suggest that even extracardiac risk factors (malignancies of the gastrointestinal tract or genitourinary tract, prolonged steroid therapy) are increasingly seen in FE patients [9].

In conclusion, patients with complicated cardiac histories, prosthetic devices, and substantial healthcare exposures are more likely to develop FE in contemporary practice. The risk is further increased by immunosuppression and the use of broad-spectrum antibiotics. Although fungal IE is rare, a greater portion of the cardiology community is at risk. Patients with persistent candidemia or unexplained IE risk factors should have ongoing FE monitoring [9, 11]. Key host, procedural, and comorbidity-related risk factors for FE are detailed in Table 1.

Table 1. Risk factors for FE

Category	Risk factor	Associated risk	Reference
Cardiac history	Prosthetic heart valves	35% of FE cases are prosthetic valve endocarditis	[4, 5, 14]
	Cardiac device implants (pacemakers, defibrillators)	Predisposes to biofilm formation; increases embolic risk	[14, 38]
	Previous valve surgery or congenital heart disease	Endocardial injury provides a nidus for fungal adhesion	[5, 6, 15, 23]
Immunesuppresion	Hematologic malignancy, transplant recipients, and biologic therapy	64% of *Aspergillus* endocarditis cases involve severe immunosuppression	[1, 9, 15]
	Chronic corticosteroids (> 1 month)	Increases the risk of mold infections (e.g., *Aspergillus*)	[9, 15]
	HIV/AIDS	Associated with disseminated fungal infections	[15]
Healthcare exposures	Indwelling central venous catheters	Risk of candidemia; biofilm colonization (especially *C. parapsilosis*)	[9, 16, 17]
	Total parenteral nutrition (TPN)	Linked to candidemia—secondary FE	[16, 17]
	Prolonged broad-spectrum antibiotics (> 7 days)	Disrupts normal flora; facilitates fungal overgrowth	[9, 19]
	Hemodialysis (via central catheter)	Turbulent flow on calcified valves; 2 times higher mortality in CE	[11, 19]
	Extended ICU/hospital stay	Correlates with invasive fungal exposure	[9]
Comorbidities	Chronic kidney disease (CKD)	Hemodialysis independently increases FE risk and mortality	[11, 19]
	Acute/Chronic liver disease	Strongest mortality predictor (OR ≈ 9) in CE	[11]
	Diabetes mellitus	Favors *C. glabrata*	[6]
	Gastrointestinal tract/Genitourinary tract malignancies	Emerging extracardiac risk factors	[9]
Behavioral	Intravenous drug abuse (IVDU)	Introduces *Candida*/molds; paradoxically, lower short-term mortality due to younger age and right-sided involvement	[9, 11, 20]

FE: fungal endocarditis; IVDU: intravenous drug use; CE: *Candida* endocarditis; *C. parapsilosis*: *Candida parapsilosis*; *C. glabrata*: *Candida glabrata*

Microbial landscape of FE

Candida species

Candida is the most common pathogen causing FE. Recent data show that *Candida* spp. causes roughly half of all FE cases [1, 5]. In one systematic review of FE, *Candida* accounted for 49.6% of cases; of these, *C. albicans* was the major species, followed by *C. glabrata* (around 20%), *C. parapsilosis* (15–20%), and *Candida tropicalis* (5–10%) [5]. *C. lusitaniae*, *C. krusei*, *C. dubliniensis*, and *C. guilliermondii* have been reported less commonly. Recent large-cohort studies demonstrate that *Candida* spp. are still the most

common cause, ≈ 50–60% of all FE, but non-*C. albicans* is increasing. *C. parapsilosis* is currently implicated in 15–41% of cases of CE, *C. tropicalis* in 10–13% and *C. glabrata* in 4–9%, dramatically changing the species distribution in the last decade. *Aspergillus* spp. are the second most frequent etiological agents (≈ 25% of fungal IE), mostly in culture-negative IE (CNIE) and the immunocompromised patient [1, 21].

The species distribution can vary by geography and patient population. For example, *C. parapsilosis* is often linked to catheter-related biofilm infection and may be overrepresented in intensive care or neonatal populations, while *C. Glabrata* is more common in older or diabetic hosts [6]. Recent case series note an emergent role for intrinsically drug-resistant species like *C. auris* (see below).

Clinically, CE tends to form large, friable vegetations, often leading to systemic emboli and metastatic infection. Patients with CE usually have a preceding or simultaneous candidemia, as *Candida* readily grows in blood culture (unlike many moulds). One review noted that CE was associated with persistent fungemia and relapsing infection [22, 23]. Despite being culture-positive, CE has a poor prognosis; even with antifungal therapy, mortality frequently exceeds 30–40%. Contemporary management emphasizes early combined surgical and medical treatment [24]. Current guidelines (IDSA, 2016) recommend valve surgery plus amphotericin B or echinocandin therapy for CE [25].

Emerging threat: *C. auris*

C. auris, a multidrug-resistant yeast that has been reported on every continent, is a new concern [9]. Despite being a rare cause of IE, *C. auris* is significant because it is inherently resistant to many azoles and can result in treatment failure if left undiagnosed. Hospitalized patients may develop endocarditis as a result of *C. auris* because it has been shown to colonize indwelling lines and induce persistent fungemia. If blood cultures reveal an uncommon yeast or a patient with a known *C. auris* colony exhibits symptoms of IE, clinicians should consider *C. auris.* (*C. auris* endocarditis prevalence is currently not quantified by any large series, but its emergence necessitates vigilance [26, 27]).

Aspergillus species

Aspergillus is the second most common cause of FE, especially in prosthetic valves and immunocompromised hosts [1, 15]. *Aspergillus* accounts for roughly 20–30% of FE cases in major case compilations [5]. Although *Aspergillus fumigatus* is the most common species, there are other species as well, such as *A. flavus*, *A. terreus*, *A. niger*, etc. Notably, *Aspergillus* rarely grows in blood culture, so *Aspergillus* endocarditis frequently occurs in patients without overt fungemia. It usually presents as bacterial IE or as culture-negative endocarditis. A recent case series identified 74 reported cases of native-valve *A. fumigatus* endocarditis; immunosuppression was present in 64% of cases [15]. *Aspergillus* also commonly affects cardiac grafts and prosthetic valves. The high mortality rate (> 80% in older reports) reflects the difficulty of diagnosis. Since blood cultures are nearly always negative, diagnosis frequently depends on tissue PCR or galactomannan (GM) antigen [15]. Large vegetations may be seen on echocardiogram, but FE may also invade the myocardium, leading to abscess formation. Optimal therapy requires voriconazole or liposomal amphotericin B (LAmB), usually combined with valve surgery [1, 15].

Rare and emerging fungi

In addition to *Candida* and *Aspergillus*, a range of rare fungi have been reported in cases of endocarditis, particularly in severely immunocompromised or geographically exposed hosts. Other dimorphic fungi, like *Histoplasma capsulatum*, *Coccidioides* spp., and *Blastomyces dermatitidis*, rarely cause IE in endemic areas but almost exclusively occur there (or in travelers) and most often in immunocompetent hosts with underlying valvular abnormalities [13]. These fungi usually require special culture or antigen tests (urine *Histoplasma* antigen), and are notable for frequent delays in diagnosis.

Other moulds (*Zygomycetes*) and yeasts have been reported in case reports. *Fusarium* species can cause PVE, especially in neutropenic or oncology patients, but these cases are exceedingly rare and usually fatal [15]. *Mucormycetes* (e.g., *Rhizopus*, *Mucor*) have been reported as causes of focal aggressive angioinvasive IE in selected diabetic or transplant patients. Rare yeasts such as *Trichosporon asahii*, *Cryptococcus*

neoformans, and *Malassezia* have all been reported to cause IE, typically in the context of severe immunodeficiency or indwelling devices. *Scedosporium*/*Pseudallescheria* and dematiaceous molds (e.g., *Exophiala* and *Lichtheimia*) are also anecdotal etiologies. Novel diagnostic methods add increasingly exotic organisms (e.g., *Sarocladium kiliense*, formerly *Gliomastix*). When encountering culture-negative endocarditis, clinicians must consider broad fungal possibilities based on patient history (e.g., travel, exposures, and immune status) [13, 15].

Biofilms and host interaction

Prosthetic device-associated biofilm is the cornerstone of FE pathogenesis. Both species of *Candida* and *Aspergillus* produce biofilm that adheres to mucosal surfaces and are refractory to immune clearance and antifungal penetration. *C. parapsilosis*, in particular, has a reputation for being device-related [9]. The pathogenesis typically includes a transient fungemia, which seeds the valve or device; e.g., candidemia from a central line that secondarily infects a valve. A nidus is afforded by endocardial injury due to prior IE or surgery. Importantly, fungal vegetations tend to be large and friable ("fungal balls"), predisposing to embolic strokes, septic emboli, or mycotic aneurysms [5, 23]. Host factors like neutrophil defects (neutropenia, steroids) and cell-mediated immunity deficits are especially relevant in mould infections [6, 15]. The spectrum of fungal pathogens implicated in endocarditis, along with their clinical features and biofilm associations, is presented in Table 2.

Table 2. Causative fungi in fungal endocarditis

Fungus	Frequency (%)	Key clinical features	Biofilm association	References
***Candida* spp.**	50–60%	Large friable vegetations; embolic events; culture-positive (blood); persistent/relapsing fungemia	Yes (especially *C. parapsilosis*)	[1, 5, 21, 22]
- *C. albicans*	> 50% of *Candida*	Most common: high mortality (30–40%)	Yes	[5, 24]
- *C. glabrata*	4–20%	Intrinsic azole resistance; common in diabetes/older adults	Yes	[5, 6, 77]
- *C. parapsilosis*	15–41%	Catheter-related neonatal/ICU settings	Yes (device linked)	[9, 21, 41]
- *C. tropicalis*	5–13%	Associated with malignancy	Moderate	[5, 21]
- *C. auris*	Emerging	Multidrug-resistant; colonizes lines; persistent fungemia	Yes	[9, 26, 79]
***Aspergillus* spp.**	20–30%	Culture-negative (blood); invades myocardium; abscesses; high mortality (> 80%)	Yes	[1, 5, 15, 29]
- *A. fumigatus*	Most common	Immunocompromised hosts (64%), diagnosed via PCR/galactomannan	Yes	[15]
Dimorphic fungi	< 5%	Endemic regions (e.g., U.S. Midwest), delayed diagnosis; *Histoplasma* (most common)	No	[13]
Rare fungi	< 5%	*Fusarium* (neutropenic hosts); *Mucormycetes* (diabetic/transplant); *Trichosporon* (echinocandin-resistant)	Variable	[15, 57, 59]

PCR: polymerase chain reaction; *C. auris*: *Candida auris*; *C. parapsilosis*: *Candida parapsilosis*; *C. glabrata*: *Candida glabrata*; *C. albicans*: *Candida albicans*; *C. tropicalis*: *Candida tropicalis*; *A. fumigatus*: *Aspergillus fumigatus*

Diagnostic challenges

FE frequently eludes routine diagnostic methods. Standard blood cultures yield low numbers, especially for filamentous fungi and dimorphic yeasts [28, 29]. *Candida* spp. can often be cultured with prolonged incubation, but hyaline molds (e.g., *Aspergillus*) and endemic mycoses (e.g., *Histoplasma*, *Coccidioides*) rarely grow in an automated system [28, 29]. Diagnosis is often delayed in *Aspergillus* endocarditis because of culture negativity; only large vegetations or tissue specimens reveal branching hyphae [29]. Prolonged incubation (up to several weeks) and multiple sets of cultures, including fungal media, are recommended when FE is suspected [21]. Even so, only cell-wall components (GM or β-*D*-glucan) circulate in blood, not viable organisms [21]. Consequently, histopathology and culture of excised valve tissue remain the gold standard when feasible [29].

Cultural negativity and delayed growth

Culture-negative endocarditis is common in fungal infections. One study mentions that *Candida* accounted for only ≈ 25–30% of FE, while most cases are due to molds or fastidious yeasts [28]. Blood cultures of CE often require multiple samples and can still be negative in up to 50% of cases. Non-*Candida* fungi (e.g., *Aspergillus*, *Fusarium*, *Histoplasma*, *Coccidioides*) virtually never grow in routine blood culture and can only be detected by tissue culture or serology [28, 29]. Automated systems consistently miss dimorphic fungi like *Histoplasma capsulatum* and *Coccidioides immitis*, which require specialized media or antigen tests [21, 28]. Delayed growth can occur: some *Candida* species exhibit prolonged lag phases. Clinicians should communicate with microbiology labs to hold cultures for extended periods (up to 4–6 weeks) when FE is suspected [21]. In practice, the combination of negative cultures and high clinical suspicion often triggers empiric therapy or alternative diagnostics.

Advanced biomarkers and imaging

Serologic and molecular markers: Fungal cell-wall assays can greatly aid diagnosis. For example, serum 1,3-β-*D*-glucan (BDG), a pan-fungal marker, has moderate accuracy—pooled sensitivity ≈ 78% and specificity ≈ 81% for invasive fungal infections [30]. The GM assay (for *Aspergillus*) has a sensitivity of ≈ 71% and a specificity of ≈ 89% [31]. These tests are often strongly positive in reported FE cases. Pan-fungal PCR (broad-range fungal DNA PCR) on blood or excised valve tissue can markedly improve detection in culture-negative cases (one review notes that PCR-based methods "expedite the diagnosis" when blood cultures fail) [23]. Metagenomic next-generation sequencing (mNGS) of blood or tissue is an emerging tool—in one surgical endocarditis series, valve mNGS had ≈ 82% sensitivity and 100% specificity vs. the adjudicated diagnosis [32]. Combining markers can boost yield (e.g., using both BDG and GM together may improve sensitivity for *Aspergillus* infections) [23]. Note: False negatives can occur, for example, neutrophil clearance may lower BDG levels, and cutoffs for endocarditis are not firmly established.

Imaging modalities: Echocardiography and advanced imaging are crucial. Transesophageal echocardiography (TEE) is far more sensitive than transthoracic echocardiography (TTE) in IE. In studies of *S. aureus* bacteremia, for example, TEE detected endocarditis in ≈ 93–100% of cases, vs. only ≈ 40–80% for TTE [33]. Both tests have very high specificity (often > 95%) when findings are positive [33]. Thus, a negative TTE does not rule out endocarditis; a TEE is recommended if suspicion remains. Cardiac computed tomography (CT) (especially modern ECG-gated 4D CT angiography) can identify vegetations or abscesses not seen on echo. For instance, one study found 4D-CT had ≈ 96% sensitivity and 97% specificity for prosthetic-valve vegetations [34]. ^{18}F-FDG PET/CT is also a valuable adjunct: meta-analysis shows PET/CT sensitivity ≈ 77% and specificity ≈ 78% for endocarditis overall [35], higher sensitivity, ≈ 81%, in prosthetic-valve cases. FDG PET/CT has been incorporated into diagnostic criteria [e.g., as a significant criterion in European Society of Cardiology (ESC) guidelines] and improves the detection of occult infection [36]. AI-enhanced image analysis is an active research area: machine learning algorithms applied to TEE and FDG-PET improve sensitivity and standardize interpretation [36]. In practice, a multimodal approach is used, e.g., serial TEE plus PET/CT (and CT angiography) to maximize detection of the infection.

When to suspect FE?

Clinicians should maintain a **high index of suspicion** for FE in any patient with culture-negative endocarditis or persistent endocarditis symptoms and relevant risk factors. Important risk factors include: prior valve surgery or prosthetic valve, indwelling central venous catheters or grafts, prolonged broad-spectrum antibiotics or total parenteral nutrition, intravenous drug use, and immunosuppression (e.g., transplant, steroids, hematologic malignancy) [23]. Native valves in patients on immunosuppressants or with congenital heart disease are also at risk. FE often presents subacutely with **fever and new or changing murmurs**, and tends to produce large, friable vegetations (often causing emboli) even when blood cultures are repeatedly negative. Blood cultures are positive in **< 50%** of FE cases [23].

Key clinical scenarios that should prompt additional fungal testing include:

- Culture-negative endocarditis with risk factors. Any patient meeting Duke criteria for endocarditis (e.g., fever + murmur + embolic phenomena) who has *negative* blood cultures and one or more fungal risk factors should trigger work-up for FE.
- Persistent infection despite antibiotics. If a presumed bacterial endocarditis fails to improve, especially with bulky vegetations or systemic emboli, consider fungal etiology.
- Recurrent candidemia or fungal sepsis in a patient with a new murmur or valve lesion.

In these settings, additional tests are warranted. For example, serum BDG and GM assays should be obtained (a high BDG or positive GM suggests invasive candidiasis or aspergillosis, respectively) [30, 31]. Fungal PCR on blood and especially on excised valve tissue (if surgery is done) can detect pathogen DNA even when cultures are sterile [23]. Metagenomic NGS of blood or tissue can also be considered (one case series showed that valve mNGS gave definitive results in cases with negative cultures [32]). Repeat imaging is important, for example, if the initial TTE was negative, a TEE or PET/CT should be done to look for vegetations or abscesses. In summary, any culture-negative endocarditis with suggestive clinical features or risk factors should prompt fungal-specific tests (BDG/GM serology, fungal PCR/mNGS) and advanced imaging to avoid missing FE [23, 30].

Biofilm-associated false negatives

Fungal biofilms on valves and devices further hinder diagnosis. Mature biofilms may harbor organisms that intermittently seed the bloodstream, leading to transient or absent positive cultures [37]. Patients with prosthetic material (pacemakers, valves) often have negative blood cultures despite heavy fungal colonization [38]. Molecular tests (PCR, mNGS) on valve tissue are particularly valuable for biofilm-associated infections, as cultures from tissue can still be falsely negative [39]. For example, a 2023 study demonstrated that 16S/18S rRNA PCR/sequencing of valve tissue identified pathogens in 75% of blood culture-negative endocarditis cases, compared to 55% for blood cultures alone [40]. Clinicians should prioritize histopathological examination and molecular testing of surgically resected tissue, as biofilm-embedded fungi often evade conventional cultures [41, 42]. A case of *C. parapsilosis* PVE highlighted this necessity: blood cultures were negative, but valve tissue analysis confirmed the diagnosis, enabling targeted therapy [41].

In summary, sterile blood cultures do not exclude FE in biofilm-associated cases. A multimodal approach that combines surgery, molecular assays, and histopathology is crucial for accurate diagnosis.

The framework still has the modified Duke/ISCVID criteria, but no fungal-specific diagnostic score exists. In practice, a methodical approach is used, in which standard serologies (*Coxiella* and *Bartonella*) are obtained first, followed by several extended blood cultures [28, 43]. Clinicians frequently use PCR and fungal biomarkers (BDG, GM) in all culture-negative cases. Early imaging (TEE, TTE) is performed, and if suspicion is still high, PET/CT is added [43–45]. A surgical consultation for valve excision may be crucial if the results are still nondiagnostic [23, 45, 46]. The 2023 ESC Guidelines and external validation studies endorse combining microbiologic, imaging, and surgical criteria to improve diagnostic sensitivity, especially for fungal IE [45, 47]. Overall, high clinical suspicion and a low threshold for combining microbiological, serological, and imaging modalities are key to diagnosing FE.

Therapeutic approaches

Treatment for FE must be aggressive and multifaceted. The fundamental idea is source control, which states that infected material must be removed whenever possible [48]. Systemic antifungal therapy must be initiated promptly and continued for a prolonged duration.

First-line antifungal therapy

Echinocandins, triazoles, and amphotericin B all have different functions in treating FE. Because of its effectiveness and wide range of applications, LAmB is frequently suggested as an initial treatment. The usual dosage for LAmB is 3–5 mg/kg IV daily (deoxycholate amphotericin B 0.7–1 mg/kg), with flucytosine (25 mg/kg Q6h) added for synergy if tolerated. Echinocandins, such as caspofungin, micafungin, and anidulafungin, have activity against *Candida* spp. and are a desirable substitute, particularly in patients who are at high risk for amphotericin toxicity [49]. However, one study found better survival with liposomal amphotericin vs echinocandins alone (6-month survival) [50].

Azoles like fluconazole, voriconazole, posaconazole, and isavuconazole are generally used for consolidation and chronic suppression once the patient is stable. Following initial treatment with echinocandins or amphotericin B, fluconazole, 400–800 mg/day, is frequently used for step-down therapy. However, because azoles are known to cause QT interval prolongation and hepatotoxicity, their use necessitates close monitoring of liver function [51, 52]. Being a potent CYP3A4 inhibitor, fluconazole raises the risk of drug interactions. Blocking CYP2C9 and CYP3A4, for example, raises serum levels of warfarin and direct oral anticoagulants, requiring careful monitoring of bleeding risk [52, 53]. Furthermore, while studies indicate the absolute risk is still low (≈ 4.7% when combined with ciprofloxacin), co-administration of other QT-prolonging agents (such as amiodarone) may increase cardiac risks [54].

Alternatives to *Aspergillus* molds include voriconazole and posaconazole; however, therapeutic drug monitoring (TDM) is necessary for optimal effectiveness and to prevent toxicity [55]. Compared to voriconazole, isavuconazole is a more recent triazole with benefits like a lower risk of QT-prolongation and fewer CYP450 interactions, making it safer for patients with cardiac comorbidities [55, 56]. All azoles mandate liver function tests and ECG monitoring as needed.

However, certain rare fungi causing endocarditis require pathogen-specific, aggressive regimens. *Trichosporon* endocarditis is intrinsically resistant to echinocandins [57], and often refractory to amphotericin alone; published cases therefore report using LAmB induction followed by voriconazole [58]. Likewise, *Lomentospora prolificans* endocarditis is virtually untreatable with monotherapy, so salvage therapy is usually voriconazole plus terbinafine [59]. Similar combination approaches are described for other uncommon agents: a *Fusarium solani* PVE was cleared with LAmB plus voriconazole [60], and *Malassezia furfur* endocarditis has been successfully managed with LAmB and voriconazole [61]. Even *C. parapsilosis* PVE has been treated with combination regimens (e.g., amphotericin B with flucytosine) in case series [62]. In each scenario, early combination therapy (typically with surgery) is followed by prolonged azole suppressive therapy, as per standard practice. Notably, these tailored regimens have led to survival in infections otherwise usually lethal with standard therapy. Taken together, these cases underscore that FE often demands therapy customized to the pathogen with synergistic drug combinations, rather than standard monotherapy.

Routine laboratory monitoring is essential. Amphotericin B carries well-known nephrotoxicity; serum creatinine, electrolytes (Mg, K), and hydration must be closely tracked [48]. In summary, treatment regimens typically involve an initial induction phase (LAmB ± flucytosine) followed by step-down to an azole for prolonged (≥ 6–12 months) suppressive therapy.

Surgical intervention

Early surgical consultation is mandatory in FE. Valve replacement or device removal for infected hardware is considered source control and significantly improves outcomes [48, 63]. In cases of heart failure, abscess formation, large vegetations (> 10 mm or rapid growth), or persistent fungemia despite the best antifungal

treatment, surgery is recommended. Many experts suggest surgery as soon as the patient can handle it, ideally during the same admission, because fungal vegetations frequently result in structural damage (valve perforation, regurgitation). Crucially, compared to antifungal therapy alone, combined therapy (antifungal plus surgery) has been linked to noticeably lower mortality. For example, a systematic review found that patients managed medically without surgery had much worse survival [5, 63].

Surgery timing is unique to each patient. Some centers recommend an initial 1–2 weeks of antifungal induction to lower fungal burden and embolic risk before surgery [23, 64]. Others place a higher priority on hemodynamic compromise and urgent surgery. Unless emergency care is needed, patients are frequently operated on after stabilizing on antifungals [64, 65]. Lifetime suppressive therapy may be required in cases where surgery is not practical (for example, due to prohibitive operative risk or refusal); patients in these situations should be advised of the high risk of relapse [66, 67]. Notably, the mainstay of treatment continues to be removing all possible sources of infection, including pacemakers, indwelling catheters, and prosthetic materials [23, 65]. Recurrent emboli and drug interactions are among the complications that patients with retained devices or high surgical risk must deal with. Case studies show how combination treatments, such as amphotericin B + flucytosine, can be used to treat breakthrough infections in situations where source control is not possible [48, 68]. For a stepwise visualization of the diagnostic and treatment pathway in FE, refer to Figure 2.

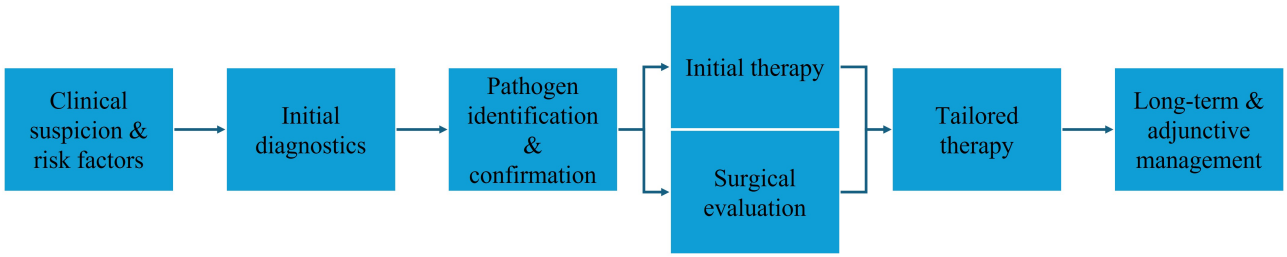

Figure 2. Diagnostic and treatment pathway in fungal endocarditis

Novel & adjunctive therapies

Emerging antifungals and adjunctive strategies may improve FE outcomes. Among new agents, rezafungin is a second-generation echinocandin approved in 2023 for candidemia and invasive candidiasis [69, 70]. Its once-weekly dosage and ability to fight *Candida,* including some resistant species, may make long-term treatment in FE more convenient [69]. Oral triterpenoid glucan synthase inhibitor ibrexafungerp penetrates biofilms and exhibits broad activity against *Aspergillus* and *Candida*, including azole-resistant strains. Ibrexafungerp demonstrated efficacy against multidrug-resistant *C. auris* biofilms in animal models. Ibrexafungerp is safe and effective, according to clinical studies (non-endocarditis), but its function in IE is still being studied [71].

Immunotherapy is still in the experimental stage. Animal models have demonstrated the effectiveness of monoclonal antibodies or vaccines that target fungal cell-surface antigens, such as *Candida* Als3p. For instance, mice were protected from deadly *C. auris* endocarditis by the NDV-3A (Als3p) vaccine, which improved antifungal treatment [72].

For FE, isolated case reports have investigated passive immunotherapies like intravenous immune globulin (IVIG) and cytokine adjuncts like interferon-gamma (IFN-γ). In immunocompromised patients, these treatments strengthen the host immune response. Nevertheless, the search results show no concrete clinical proof of their effectiveness in FE. For example, although IFN-γ is known to increase neutrophil and macrophage activity against fungal pathogens such as *Candida* and *Aspergillus*, its use in FE is still anecdotal [63, 73]. Likewise, IVIG has been used to neutralize toxins or control inflammation in cases of severe fungal infections; however, there is a dearth of reliable data from FE-specific research [63].

The limited adoption of these treatments results from clinical trial gaps and the variability of FE cases, where immunosuppression and comorbidities make results more difficult to interpret. Although translation to human FE has not been confirmed, preclinical models indicate possible advantages [73].

To break down biofilms and get rid of infections, antimicrobial lock therapy (ALT) involves injecting high-concentration antifungal solutions into infected catheters. Although it has been extensively researched concerning bacterial infections caused by catheters (*Staphylococcus*), its use in FE is less well-established [74].

Fungal infections, such as *Candida*, were not included in a 2025 study on ALT for catheter-related bacteremia because of insufficient data, but bacterial cases showed an 88.9% success rate. Because biofilm persistence increases the chance of relapse, guidelines advise against using ALT for *Candida* unless catheter removal is not feasible [75]. Compared to bacterial cases, fungal biofilms have intrinsic resistance mechanisms (such as efflux pumps and extracellular matrix barriers), which lower ALT efficacy.

Hyperbaric oxygen therapy (HBOT) increases tissue oxygenation, potentially enhancing antifungal activity and immune responses. When conducting the literature search and data extraction for this article, I obtained conflicting evidence.

- Preclinical support: HBOT enhanced survival in murine models of invasive pulmonary aspergillosis and decreased *A. fumigatus* biofilm proliferation by 50% in vitro [64]. Additionally, it reduces tissue hypoxia, a characteristic of fungal vegetations, which may enhance antibiotic penetration and neutrophil function [73, 76].
- Clinical data: Although no clinical trials specifically for FE, a 2022 review suggested HBOT as a treatment for IE because of its anti-biofilm and immunomodulatory properties [73]. HBOT has limited standalone utility, as evidenced by a 2018 study that found no synergy between HBOT and subtherapeutic antifungals (such as voriconazole) [76].
- Limitations: HBOT's adoption in FE management is restricted by its temporary fungistatic effect and practical issues (such as access to hyperbaric chambers) [73, 76].

Antifungal resistance & stewardship

FE management is made more difficult by antifungal resistance, especially in emerging species such as multidrug-resistant *C. glabrata* and *C. auris*, which often show azole and/or echinocandin resistance as a result of chromosomal aneuploidy, efflux pump upregulation, or mutations in ERG11 [77–79]. Biofilm-related tolerance on prosthetic valves or devices further mimics resistance by shielding fungi from antifungals, as seen in *C. glabrata* and *C. auris* biofilms [79–81]. Stewardship strategies, such as de-escalating from amphotericin B to fluconazole in susceptible cases, reduce toxicity and pressure, aligning with IDSA guidelines. Table 3 summarizes the major antifungal regimens, surgical indications, and emerging therapies utilized in the management of FE.

Table 3. Treatment approaches for FE

Approach	Agent/Intervention	Regimen/Indications	Key considerations	References
First-line antifungals	Liposomal amphotericin B (LAmB)	3–5 mg/kg/day IV; ± flucytosine (25 mg/kg Q6h) for synergy	Nephrotoxic; monitor creatinine/electrolytes	[48, 49]
	Echinocandins (caspofungin, micafungin)	Preferred for *Candida*; alternative to LAmB in renal impairment	Less effective against *C. parapsilosis*; biofilm penetration is limited	[49, 79]
	Azoles (voriconazole, posaconazole)	Consolidation: voriconazole (*Aspergillus*); fluconazole (*Candida*, susceptible strains)	TDM required; hepatotoxic/QT prolongation; drug interactions (CYP450)	[51, 55]
Surgical intervention	Valve replacement/device removal	Indications: heart failure, abscess, vegetations > 10 mm, persistent fungemia, embolic risk	Reduces mortality by 80% vs. medical therapy alone; perform early (within 1–2 weeks)	[5, 23, 63, 64]

Table 3. Treatment approaches for FE (*continued*)

Approach	Agent/Intervention	Regimen/Indications	Key considerations	References
Pathogen-specific	*C. auris*	Rezafungin (once-weekly echinocandin); combination therapy (LAmB + echinocandin)	Intrinsic multidrug resistance	[69, 77]
	Aspergillus	Voriconazole (primary); LAmB if contraindicated	Galactomannan/PCR guides diagnosis	[15, 55]
	Trichosporon/Lomentospora	LAmB + voriconazole (echinocandin-resistant)	Salvage therapy	[57, 59]
Novel therapies	Rezafungin	Long-acting echinocandin; weekly IV dosing	Limited FE data; active against resistant *Candida*	[69, 70]
	Ibrexafungerp	Oral triterpenoid; biofilm penetration; broad activity	Pending IE trials	[71]
	NDV-3A vaccine (Als3p target)	Preclinical; enhances host immunity against *C. auris*	Not yet human-tested	[72]

FE: fungal endocarditis; IE: infective endocarditis; PCR: polymerase chain reaction; TDM: therapeutic drug monitoring; *C. auris*: *Candida auris*; *C. parapsilosis*: *Candida parapsilosis*

Outcomes and prognosis

FE carries high morbidity and mortality. Overall mortality rates in reported series exceed 40–50% [5, 82], reflecting delayed diagnoses and the fragile patient populations affected. *Aspergillus* endocarditis performs worse: As per Meena et al. [5] (2022), *Aspergillus* etiology independently predicted mortality almost four times higher than *Candida*'s (HR ≈ 3.7). Early in-hospital mortality remains ≈ 40–50%, with 1-year mortality approaching 60% according to some cohort studies [21].

Mortality and morbidity trends

Recent studies reveal a slight increase in survival over several decades, mainly due to combined treatment. Meena et al. [5] found an overall mortality rate of about 40% in 220 cases, which is lower than previous reports and probably reflects more frequent surgeries. Similarly, retrospective data indicate that patients managed surgically have significantly lower mortality than those treated medically [5]. CE tends to have better outcomes than non-*Candida*: in one cohort, mortality was lower in *Candida* (15%) vs. others (47%) [21]. Thompson et al. [1] reported in a multinational cohort that CE carries an in-hospital mortality of 36% and a 1-year mortality of 59%. Nevertheless, FE survivors frequently suffer complications such as embolic infarcts, extended hospital stays, and heart failure due to valve destruction.

Evidence from recent series indicates substantially higher mortality when FE is managed with antifungals alone. For example, Arnold et al. [83] reported in-hospital mortality of 34% with medical therapy vs. 38% with adjunctive surgery in a multicenter cohort of CE patients (1-year mortality ≈ 62% vs. 66%). By contrast, Siciliano et al. [84] found overall in-hospital mortality of 54% among 78 FE cases (85% *Candida*) and identified exclusive medical management as a strong independent risk factor (OR ≈ 11.1) for death. In that series, ≈ 68% of patients treated without surgery died vs. roughly 46% of those having surgery (≈ 22% absolute risk reduction). Taken together, these data suggest that combining valve surgery with antifungals lowers mortality compared to medical therapy alone, roughly translating to ≈ 30–40% survival with surgery vs. ≈ 10–30% without (i.e., ≈ 20–30% absolute difference) in recent series [5, 83].

Predictors of poor outcome

Aspergillus etiology, absence of surgery, postponed therapy, and host factors all predict unfavorable results. According to Meena et al. [5], immunocompromise (HR 2.8) and *Aspergillus* infection (HR 3.7) were independent risk factors for death. Patients who have intracardiac devices or prosthetic valves have worse outcomes than those who have native valves [5]. The risk is significantly increased when infected material is not removed surgically; multivariate analysis revealed that antifungals plus surgery decreased mortality by about 80% [5]. Despite treatment, perivalvular abscess, ample vegetation (> 10 mm), and ongoing fungemia are further indicators of a poor prognosis. Mortality is further increased by renal failure brought on by treatment and end-organ damage from septic emboli (such as stroke). According to these findings, the best chance of lowering FE mortality is early diagnosis and vigorous intervention [5, 21].

Quality of life and follow-up

There is a lack of research on the long-term impacts of FE survivors. The information that is currently available indicates that quality of life (QoL) is considerably impacted, even among survivors. Disabilities from embolic strokes, pacemaker dependence, or chronic heart failure due to valve damage may endure. Patients frequently need long-term antifungal treatment (months to lifelong suppression), which calls for regular checkups and observation. Anecdotal evidence suggests that the severity of the illness causes anxiety and post-traumatic stress disorder. If necessary, follow-up care should involve neurologic evaluation and cardiac rehabilitation. Serial imaging and serological monitoring are recommended due to the high relapse rates (recurrence ≈ 10% in one systematic review [5]). Although there aren't many formal studies on QoL, FE survivors ultimately require multidisciplinary follow-up to manage medication side effects, optimize cardiac function, and screen for reinfection.

Future directions and research gaps

Coordinated research and innovation are desperately needed to improve FE outcomes. A systematic review of recent case series (2018–2023) highlighted that fungal IE still comprises 1–5% of all endocarditis, rising above 5% in prosthetic-valve or immunocompromised cohorts. *Candida* and *Aspergillus* remain predominant, but complications such as large friable vegetations (predisposing to embolism in > 50% of cases) and diagnostic delays (> 30 days in ≈ 40% of reports) persist. Publication bias and lack of standardized data hamper true incidence estimates, underlining the urgent need for an international, multicenter registry with uniform reporting criteria [21].

An additional frontier is point-of-care diagnostics. In environments with limited resources, fungal diagnostics has been transformed by rapid lateral-flow assays (for GM or BDG) [71]. Similarly, on-site pathogen identification from blood or tissue may be possible with bedside PCR platforms or nanopore sequencing. In order to address global injustices, the recent SSS (speed, simplicity, sensitivity) movement strongly emphasizes creating quick, inexpensive tests for common fungal pathogens and endemic mycoses [85]. Such tools would be game-changing for FE.

Research on immunologic treatments is ongoing. Clinical trials are now being conducted for vaccines that target *Candida* adhesins, such as NDV-3A against Als3p, which have demonstrated promise in preventing systemic candidiasis [72]. For invasive fungal infections, host-directed therapies (cytokines, checkpoint modulators) and passive immunotherapy using monoclonal antibodies (anti-β-glucan, anti-mannan, etc.) are still in the early stages of development. Immunocompromised patients, who are at the highest risk, are complex to vaccinate [72]. Recent reviews have called fungal pathogens a global health priority, underscoring the urgent need for investment in fungal vaccines and immunotherapies [72, 86].

FE care will increasingly benefit from artificial intelligence and machine learning (AI/ML). Algorithms for PET/CT and AI-enhanced echocardiography can better detect embolic lesions or subtle vegetations. Risk calculators and other machine learning models could help stratify patients for early surgery. Neural-net metagenomic classifiers and ML-based MALDI-TOF (matrix-assisted laser desorption ionization-time-of-flight) interpretation in microbiology promise quicker pathogen identification and resistance prediction. One recent review, for instance, focuses on AI models that diagnose IE by integrating various data (labs, imaging) and performing better than traditional risk scores. Although there are still logistical and ethical issues, with cooperation, AI tools may be incorporated into endocarditis teams in the upcoming ten years [36].

Lastly, global equity is critical in FE care. Patients with FE are more likely to live in low-resource environments with limited access to antifungals and diagnostics. International guidelines need to consider cost-effective tactics and ensure that treatments and diagnostics are easily accessible. As observed with HIV/AIDS and tuberculosis, fungal diseases require more funding and policy attention [86]. Regional reference centers and telemedicine may facilitate an extension of expertise. In conclusion, improving surveillance (registries), accelerating diagnostics, developing new treatments (immunotherapies/vaccines), precise AI, and providing universal access to care are all necessary to address FE's high mortality rate.

Conclusions

FE is still a daunting problem for 21st-century cardiologists, with high morbidity and mortality rates, even in the age of new diagnostic methods and therapeutic agents. This review confirms that although *Candida* and *Aspergillus* species cause most cases, there is an increasing spectrum of rare molds and yeasts, highlighting the importance of improved clinical vigilance and laboratory identification capabilities. By combining molecular tests, imaging, and traditional cultures, initial detection may decrease the time needed to diagnose and thus lead to the timely initiation of fungal therapy.

Surgical resection in combination with an appropriate antifungal regimen has led to more favorable outcomes than in the past; however, overall outcomes continue to be limited by drug toxicities, drug resistance, and patient co-morbidities. New agents (e.g., echinocandins with better tissue penetration) and additional strategies (e.g., immunomodulatory agents) offer hope but need to be tested in controlled trials.

The current literature's limitations include the prevalence of case reports and small retrospective cohorts, variability in diagnostic criteria, and heterogeneity in reported outcomes.

Abbreviations

^{18}F-FDG PET/CT: fluorine-18 fluorodeoxyglucose positron emission tomography/computed tomography

AI/ML: artificial intelligence and machine learning

ALT: antimicrobial lock therapy

BDG: 1,3-β-*D*-glucan

C. albicans: *Candida albicans*

C. auris: *Candida auris*

C. glabrata: *Candida glabrata*

C. parapsilosis: *Candida parapsilosis*

C. tropicalis: *Candida tropicalis*

CE: *Candida* endocarditis

CT: computed tomography

ESC: European Society of Cardiology

FDG: fluorodeoxyglucose

FE: fungal endocarditis

GM: galactomannan

HBOT: hyperbaric oxygen therapy

IE: infective endocarditis

IFN-γ: interferon-gamma

IVDU: intravenous drug use

IVIG: intravenous immune globulin

LAmB: liposomal amphotericin B

MALDI-TOF: matrix-assisted laser desorption ionization-time-of-flight

mNGS: metagenomic next-generation sequencing

PCR: polymerase chain reaction

PVE: prosthetic valve endocarditis

QoL: quality of life

SSS: speed, simplicity, sensitivity

TDM: therapeutic drug monitoring

TEE: transesophageal echocardiography

TTE: transthoracic echocardiography

Declarations

Acknowledgments

I would like to acknowledge Krupa Sara Thomas for her valuable assistance in reviewing and going through the manuscript.

Author contributions

SE: Conceptualization, Investigation, Writing—original draft, Writing—review & editing. The author has read and approved the submitted version.

Conflicts of interest

The author declares that there are no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

Publisher's note

Open Exploration maintains a neutral stance on jurisdictional claims in published institutional affiliations and maps. All opinions expressed in this article are the personal views of the author(s) and do not represent the stance of the editorial team or the publisher.

References

1. Thompson GR 3rd, Jenks JD, Baddley JW, Lewis JS 2nd, Egger M, Schwartz IS, et al. Fungal Endocarditis: Pathophysiology, Epidemiology, Clinical Presentation, Diagnosis, and Management. Clin Microbiol Rev. 2023;36:e0001923. [DOI] [PubMed] [PMC]
2. Sharma S, Samantaray S, Kumar D, Meena DS, Chaudhary R, Jain V, et al. Prosthetic valve endocarditis due to *Candida parapsilosis* - a rare case report. Access Microbiol. 2023;5:acmi000462.v4. [DOI] [PubMed] [PMC]

3. Soriano A, Honore PM, Puerta-Alcalde P, Garcia-Vidal C, Pagotto A, Gonçalves-Bradley DC, et al. Invasive candidiasis: current clinical challenges and unmet needs in adult populations. J Antimicrob Chemother. 2023;78:1569–85. [DOI] [PubMed] [PMC]
4. Baracioli LM, Eulálio Filho WMN, Siciliano RF, Franci A, Marinaro G, Saretta R, et al. Fungal endocarditis after transcatheter aortic valve implantation complicated with pseudoaneurysm of the ascending aorta. J Cardiothorac Surg. 2024;19:623. [DOI] [PubMed] [PMC]
5. Meena DS, Kumar D, Agarwal M, Bohra GK, Choudhary R, Samantaray S, et al. Clinical features, diagnosis and treatment outcome of fungal endocarditis: A systematic review of reported cases. Mycoses. 2022;65:294–302. [DOI] [PubMed]
6. Mamtani S, Aljanabi NM, Gupta Rauniyar RP, Acharya A, Malik BH. Candida Endocarditis: A Review of the Pathogenesis, Morphology, Risk Factors, and Management of an Emerging and Serious Condition. Cureus. 2020;12:e6695. [DOI] [PubMed] [PMC]
7. Mori G, Gottardi M, Guffanti M, Castagna A, Lanzafame M. Treatment of *Candida glabrata* native valve endocarditis with rezafungin: a case report. JAC Antimicrob Resist. 2024;6:dlae042. [DOI] [PubMed] [PMC]
8. Wu W, Xu J, Ruan J, Tian B, Xuan N. Metagenomic next-generation sequencing identifies native valve Aspergillus fumigatus endocarditis with cerebral involvement: a case report. Front Cardiovasc Med. 2025;12:1487543. [DOI] [PubMed] [PMC]
9. Jamil Y, Akinleye A, Mirzaei M, Lempel M, Farhat K, Pan S. Candida endocarditis: Update on management considerations. World J Cardiol. 2023;15:469–78. [DOI] [PubMed] [PMC]
10. Data and Statistics on Candidemia [Internet]. CDC; 2024 [cited 2025 May 10]. Available from: https://www.cdc.gov/candidiasis/data-research/facts-stats/index.html
11. Huggins JP, Hohmann S, David MZ. *Candida* Infective Endocarditis: A Retrospective Study of Patient Characteristics and Risk Factors for Death in 703 United States Cases, 2015-2019. Open Forum Infect Dis. 2020;8:ofaa628. [DOI] [PubMed] [PMC]
12. Meyahnwi D, Ahmed A, Zinyandu T, Opoku I. A rising threat: epidemiologic trends in incidence, mortality, and cost of *Candida* endocarditis in the United States [Internet]. [Cited 2025 May 13]. Available from: https://scholar.bridgeporthospital.org/poster_presentations/64
13. Kasule SN, Grant LM, Apolinario MA, Speiser LJ, Saling CF, Blair JE, et al. Endemic Fungal Infective Endocarditis Caused by Coccidioides, Blastomyces and Histoplasma Species in the United States. Cureus. 2024;16:e60285. [DOI] [PubMed] [PMC]
14. Andreas M, Burri H, Praz F, Soliman O, Badano L, Barreiro M, et al. Tricuspid valve disease and cardiac implantable electronic devices. Eur Heart J. 2024;45:346–65. [DOI] [PubMed] [PMC]
15. Caroselli C, Suardi LR, Besola L, Fiocco A, Colli A, Falcone M. Native-Valve *Aspergillus* Endocarditis: Case Report and Literature Review. Antibiotics (Basel). 2023;12:1190. [DOI] [PubMed] [PMC]
16. Foong KS, Sung A, Burnham JP, Kronen R, Lian Q, Salazar Zetina A, et al. Risk factors predicting Candida infective endocarditis in patients with candidemia. Med Mycol. 2020;58:593–9. [DOI] [PubMed] [PMC]
17. Labchuk A, Hamwi M, Han A, Khan M, Stone A. Fungal Endocarditis With Severe Vegetations of the Aortic Valve and Septic Emboli Secondary to Total Parenteral Nutrition. Cureus. 2022;14:e32357. [DOI] [PubMed] [PMC]
18. Poowanawittayakom N, Dutta A, Stock S, Touray S, Ellison RT 3rd, Levitz SM. Reemergence of Intravenous Drug Use as Risk Factor for Candidemia, Massachusetts, USA. Emerg Infect Dis. 2018;24:631–7. [DOI] [PubMed] [PMC]
19. Almuhammadi GA, Alzughaibi RA, Amer LA, Alzahrani TS. Challenges in Diagnosing and Treating Fungal Endocarditis: A Case Report of Recurrent Candida Endocarditis in a Hemodialysis Patient. J Saudi Heart Assoc. 2025;37:4. [DOI] [PubMed] [PMC]

20. Halavaara M, Anttila VJ, Järvinen A. Infective Endocarditis in People Who Inject Drugs-A 5-Year Follow-up: "I've Seen the Needle and the Damage Done". Open Forum Infect Dis. 2025;12:ofaf057. [DOI] [PubMed] [PMC]
21. Mistiaen W. "Not much room for mushrooms" in the heart: knowns and unknowns of fungal infective endocarditis. Vessel Plus. 2024;8:1. [DOI]
22. Taib R, Penny DJ. CHAPTER 55 - Infective Endocarditis. In: Anderson RH, Baker EJ, Penny DJ, Redington AN, Rigby ML, Wernovsky G, et al., editors. Paediatric Cardiology (Third Edition). Philadelphia: Churchill Livingstone; 2010. pp. 1135–46. [DOI]
23. Ojha N, Dhamoon AS. Fungal endocarditis. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025. [PubMed]
24. Yuan SM. Fungal Endocarditis. Braz J Cardiovasc Surg. 2016;31:252–5. [DOI] [PubMed] [PMC]
25. Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62:e1–50. [DOI] [PubMed] [PMC]
26. Sears D, Schwartz BS. Candida auris: An emerging multidrug-resistant pathogen. Int J Infect Dis. 2017; 63:95–8. [DOI] [PubMed]
27. Chowdhary A, Sharma C, Meis JF. Candida auris: A rapidly emerging cause of hospital-acquired multidrug-resistant fungal infections globally. PLoS Pathog. 2017;13:e1006290. [DOI] [PubMed] [PMC]
28. McHugh J, Saleh OA. Updates in Culture-Negative Endocarditis. Pathogens. 2023;12:1027. [DOI] [PubMed] [PMC]
29. Gopal K, Bhaskaran PN, Moni M, Shashindran N. Aspergillus endocarditis. Indian Heart J. 2024;76: 240–6. [DOI] [PubMed] [PMC]
30. He S, Hang JP, Zhang L, Wang F, Zhang DC, Gong FH. A systematic review and meta-analysis of diagnostic accuracy of serum 1,3-β-D-glucan for invasive fungal infection: Focus on cutoff levels. J Microbiol Immunol Infect. 2015;48:351–61. [DOI] [PubMed]
31. Pfeiffer CD, Fine JP, Safdar N. Diagnosis of invasive aspergillosis using a galactomannan assay: a meta-analysis. Clin Infect Dis. 2006;42:1417–27. [DOI] [PubMed]
32. Lazarevic V, Gaïa N, Pham TT, de Lorenzi-Tognon M, Girard M, Mauffrey F, et al. Identification of causative agents of infective endocarditis by metagenomic next-generation sequencing of resected valves. Front Cell Infect Microbiol. 2025;15:1532257. [DOI] [PubMed] [PMC]
33. Sekar P, Johnson JR, Thurn JR, Drekonja DM, Morrison VA, Chandrashekhar Y, et al. Comparative Sensitivity of Transthoracic and Transesophageal Echocardiography in Diagnosis of Infective Endocarditis Among Veterans With *Staphylococcus aureus* Bacteremia. Open Forum Infect Dis. 2017;4: ofx035. [DOI] [PubMed] [PMC]
34. Saeedan MB, Wang TKM, Cremer P, Wahadat AR, Budde RPJ, Unai S, et al. Role of Cardiac CT in Infective Endocarditis: Current Evidence, Opportunities, and Challenges. Radiol Cardiothorac Imaging. 2021;3:e200378. [DOI] [PubMed] [PMC]
35. Mahmood M, Kendi AT, Ajmal S, Farid S, O'Horo JC, Chareonthaitawee P, et al. Meta-analysis of 18F-FDG PET/CT in the diagnosis of infective endocarditis. J Nucl Cardiol. 2019;26:922–35. [DOI] [PubMed]
36. McHugh JW, Challener DW, Tabaja H. Change of Heart: Can Artificial Intelligence Transform Infective Endocarditis Management? Pathogens. 2025;14:371. [DOI] [PubMed] [PMC]
37. Iñigo M, Del Pozo JL. Fungal biofilms: From bench to bedside. Rev Esp Quimioter. 2018;31 Suppl 1: 35–8. [PubMed] [PMC]
38. Oberbach A, Schlichting N, Hagl C, Lehmann S, Kullnick Y, Friedrich M, et al. Four decades of experience of prosthetic valve endocarditis reflect a high variety of diverse pathogens. Cardiovasc Res. 2023;119:410–28. [DOI] [PubMed]

39. Burban A, Słupik D, Reda A, Szczerba E, Grabowski M, Kołodzińska A. Novel Diagnostic Methods for Infective Endocarditis. Int J Mol Sci. 2024;25:1245. [DOI] [PubMed] [PMC]
40. Hong HL, Flurin L, Greenwood-Quaintance KE, Wolf MJ, Pritt BS, Norgan AP, et al. 16S rRNA Gene PCR/Sequencing of Heart Valves for Diagnosis of Infective Endocarditis in Routine Clinical Practice. J Clin Microbiol. 2023;61:e0034123. [DOI] [PubMed] [PMC]
41. Collins F, Wenlock RD, Curtis S, Hyde J, James PR. Fungal endocarditis after type A dissection, a positive outcome from *Candida parapsilosis* prosthetic aortic valve endocarditis and aortic graft infection: a testament to multidisciplinary practice. Clin Infect Pract. 2021;12:100106. [DOI]
42. Fungal Biofilm-Related Diseases: Diagnosis, Treatment, and Emerging Challenges [Internet]. MJH Life Sciences® - Infectious Disease News & Expert Insights; c2025 [cited 2025 May 17]. Available from: https://www.contagionlive.com/view/fungal-biofilm-related-diseases-diagnosis-treatment-and-emerging-challenges
43. Clinical Criteria for Infective Endocarditis According to the 2023 Duke-International Society for Cardiovascular Infectious Disease [Internet]. Merck & Co., Inc.; c2025 [cited 2025 May 18]. Available from: https://www.merckmanuals.com/professional/multimedia/table/clinical-criteria-for-infective-endocarditis-according-to-the-2023-duke-international-society-for-cardiovascular-infectious-disease
44. Fowler VG, Durack DT, Selton-Suty C, Athan E, Bayer AS, Chamis AL, et al. The 2023 Duke-International Society for Cardiovascular Infectious Diseases Criteria for Infective Endocarditis: Updating the Modified Duke Criteria. Clin Infect Dis. 2023;77:518–26. [DOI] [PubMed] [PMC]
45. Delgado V, Ajmone Marsan N, de Waha S, Bonaros N, Brida M, Burri H, et al.; ESC Scientific Document Group. 2023 ESC Guidelines for the management of endocarditis. Eur Heart J. 2023;44:3948–4042. [DOI] [PubMed]
46. Kumar R, Kirtana J, Kodan P, Y Ray, P Kumar, A Biswas. Culture-negative fungal endocarditis. Heart Mind. 2019;3:27–30. [DOI]
47. van der Vaart TW, Bossuyt PMM, Durack DT, Baddour LM, Bayer AS, Durante-Mangoni E, et al. External Validation of the 2023 Duke-International Society for Cardiovascular Infectious Diseases Diagnostic Criteria for Infective Endocarditis. Clin Infect Dis. 2024;78:922–9. [DOI] [PubMed] [PMC]
48. Sahra S, Javed A, Jahangir A, Thind SK. Pharmacological options for Candida albicans Endocarditis at the roadblock with irrecoverable prosthetics and drug interactions: a case report and review of literature. BMC Infect Dis. 2023;23:304. [DOI] [PubMed] [PMC]
49. Sankar NP, Thakarar K, Rokas KE. *Candida* Infective Endocarditis During the Infectious Diseases and Substance Use Disorder Syndemic: A Six-Year Case Series. Open Forum Infect Dis. 2020;7:ofaa142. [DOI] [PubMed] [PMC]
50. Rivoisy C, Vena A, Schaeffer L, Charlier C, Fontanet A, Delahaye F, et al.; French Mycoses Study Group and Grupo de Apoyo al Manejo de las Endocarditis en España (GAMES). Prosthetic Valve Candida spp. Endocarditis: New Insights Into Long-term Prognosis-The ESCAPE Study. Clin Infect Dis. 2018;66:825–32. [DOI] [PubMed]
51. Govindarajan A, Bistas KG, Ingold CJ, Patel P, Aboeed A. Fluconazole. In: StatPearls. Treasure Island (FL): StatPearls Publishing; 2025.
52. Fluconazole (Rx) [Internet]. [Cited 2025 May 19]. Available from: https://reference.medscape.com/drug/diflucan-fluconazole-342587
53. Sahadevan NV. Drug interactions of azole antifungals. J Skin Sex Transm Dis. 2021;5:50–4. [DOI]
54. Berger FA, Monadian N, de Groot NMS, Santbergen B, van der Sijs H, Becker ML, et al. QTc prolongation during ciprofloxacin and fluconazole combination therapy: prevalence and associated risk factors. Br J Clin Pharmacol. 2018;84:369–78. [DOI] [PubMed] [PMC]
55. Sienkiewicz BM, Łapiński Ł, Wiela-Hojeńska A. Comparison of clinical pharmacology of voriconazole and posaconazole. Contemp Oncol (Pozn). 2016;20:365–73. [DOI] [PubMed] [PMC]

56. Lewis JS 2nd, Wiederhold NP, Hakki M, Thompson GR 3rd. New Perspectives on Antimicrobial Agents: Isavuconazole. Antimicrob Agents Chemother. 2022;66:e0017722. [DOI] [PubMed] [PMC]
57. de Almeida Júnior JN, Hennequin C. Invasive Trichosporon Infection: a Systematic Review on a Re-emerging Fungal Pathogen. Front Microbiol. 2016;7:1629. [DOI] [PubMed] [PMC]
58. Oh TH, Shin SU, Kim SS, Kim SE, Kim UJ, Kang SJ, et al. Prosthetic valve endocarditis by Trichosporon mucoides: A case report and review of literature. Medicine (Baltimore). 2020;99:e22584. [DOI] [PubMed] [PMC]
59. Kelly M, Stevens R, Konecny P. Lomentospora prolificans endocarditis--case report and literature review. BMC Infect Dis. 2016;16:36. [DOI] [PubMed] [PMC]
60. Guzman-Cottrill JA, Zheng X, Chadwick EG. Fusarium solani endocarditis successfully treated with liposomal amphotericin B and voriconazole. Pediatr Infect Dis J. 2004;23:1059–61. [DOI] [PubMed]
61. Granok AB. Successful Treatment of *Malassezia furfur* Endocarditis. Open Forum Infect Dis. 2020;7: ofaa029. [DOI] [PubMed] [PMC]
62. Guo P, He Y, Fan R, Wu Z, Chen Y, Huang Y, et al. A case series of medically managed Candida parapsilosis complex prosthetic valve endocarditis. Ann Clin Microbiol Antimicrob. 2021;20:1. [DOI] [PubMed] [PMC]
63. Naguthevar S, Ravindra A, Kumar D, Meena DS, Bohra GK, Jain V, et al. Emerging trends in fungal endocarditis: clinical complexity, diagnostic challenges, and therapeutic implications - a case series and literature review. Ther Adv Infect Dis. 2024;11:20499361241293655. [DOI] [PubMed] [PMC]
64. Kang DH. Timing of surgery in infective endocarditis. Heart. 2015;101:1786–91. [DOI] [PubMed]
65. Pettersson GB, Hussain ST. Current AATS guidelines on surgical treatment of infective endocarditis. Ann Cardiothorac Surg. 2019;8:630–44. [DOI] [PubMed] [PMC]
66. Beaumont AL, Mestre F, Decaux S, Bertin C, Duval X, Iung B, et al. Long-term Oral Suppressive Antimicrobial Therapy in Infective Endocarditis (SATIE Study): An Observational Study. Open Forum Infect Dis. 2024;11:ofae194. [DOI] [PubMed] [PMC]
67. Lemmet T, Bourne-Watrin M, Gerber V, Danion F, Ursenbach A, Hoellinger B, et al. Suppressive antibiotic therapy for infectious endocarditis. Infect Dis Now. 2024;54:104867. [DOI] [PubMed]
68. Prasad Gourav KK, Mandal B, Mishra AK, Narayanan Nayanar VK. Successful medical management of fungal infective endocarditis post VSD closure. Ann Card Anaesth. 2021;24:95–8. [DOI] [PubMed] [PMC]
69. Cornely OA, Dupont H, Mikulska M, Rautemaa-Richardson R, Garcia-Vidal C, Thompson GR 3rd, et al. Rezafungin in special populations with candidaemia and/or invasive candidiasis. J Infect. 2025;90: 106435. [DOI] [PubMed]
70. Smith HL, Bensman TJ, Mishra S, Li X, Dixon CA, Sheikh J, et al. Regulatory Considerations in the Approval of Rezafungin (Rezzayo) for the Treatment of Candidemia and Invasive Candidiasis in Adults. J Infect Dis. 2024;230:505–13. [DOI] [PubMed]
71. El Ayoubi LW, Allaw F, Moussa E, Kanj SS. Ibrexafungerp: A narrative overview. Curr Res Microb Sci. 2024;6:100245. [DOI] [PubMed] [PMC]
72. Singh S, Uppuluri P, Mamouei Z, Alqarihi A, Elhassan H, French S, et al. The NDV-3A vaccine protects mice from multidrug resistant Candida auris infection. PLoS Pathog. 2019;15:e1007460. [DOI] [PubMed] [PMC]
73. Lerche CJ, Schwartz F, Pries-Heje MM, Fosbøl EL, Iversen K, Jensen PØ, et al. Potential Advances of Adjunctive Hyperbaric Oxygen Therapy in Infective Endocarditis. Front Cell Infect Microbiol. 2022;12: 805964. [DOI] [PubMed] [PMC]
74. Justo JA, Bookstaver PB. Antibiotic lock therapy: review of technique and logistical challenges. Infect Drug Resist. 2014;7:343–63. [DOI] [PubMed] [PMC]
75. Aksoy F, Karakoc Parlayan HN, Oncu Kurutas G, Yilmaz G. Antimicrobial Lock Therapy: A Strategy for Managing Catheter-Related Bacteremia. Antibiotics (Basel). 2025;14:461. [DOI] [PubMed] [PMC]

76. Dhingra S, Buckey JC, Cramer RA. Hyperbaric Oxygen Reduces Aspergillus fumigatus Proliferation *In Vitro* and Influences *In Vivo* Disease Outcomes. Antimicrob Agents Chemother. 2018;62:e01953–17. [DOI] [PubMed] [PMC]
77. Li J, Brandalise D, Coste AT, Sanglard D, Lamoth F. Exploration of novel mechanisms of azole resistance in *Candida auris*. Antimicrob Agents Chemother. 2024;68:e0126524. [DOI] [PubMed] [PMC]
78. Hassan Y, Chew SY, Than LTL. *Candida glabrata*: Pathogenicity and Resistance Mechanisms for Adaptation and Survival. J Fungi (Basel). 2021;7:667. [DOI] [PubMed] [PMC]
79. Amann V, Kissmann AK, Firacative C, Rosenau F. Biofilm-Associated Candidiasis: Pathogenesis, Prevalence, Challenges and Therapeutic Options. Pharmaceuticals (Basel). 2025;18:460. [DOI] [PubMed] [PMC]
80. Chedraoui C, Fattouh N, El Hachem S, Younes M, Khalaf RA. Induction of Antifungal Tolerance Reveals Genetic and Phenotypic Changes in *Candida glabrata*. J Fungi (Basel). 2025;11:284. [DOI] [PubMed] [PMC]
81. Pasha AK, Lee JZ, Low SW, Desai H, Lee KS, Al Mohajer M. Fungal Endocarditis: Update on Diagnosis and Management. Am J Med. 2016;129:1037–43. [DOI] [PubMed]
82. Koohsari P, Nakhaee A, Rahmanian M, Salahshour F, Parkhideh R, Larti F. Devastating fungal endocarditis involving ascending aorta in a patient with a history of aortic valve replacement: a case report. J Cardiothorac Surg. 2024;19:191. [DOI] [PubMed] [PMC]
83. Arnold CJ, Johnson M, Bayer AS, Bradley S, Giannitsioti E, Miró JM, et al. Candida infective endocarditis: an observational cohort study with a focus on therapy. Antimicrob Agents Chemother. 2015;59:2365–73. [DOI] [PubMed] [PMC]
84. Siciliano RF, Gualandro DM, Sejas ONE, Ignoto BG, Caramelli B, Mansur AJ, et al. Outcomes in patients with fungal endocarditis: A multicenter observational cohort study. Int J Infect Dis. 2018;77:48–52. [DOI] [PubMed]
85. Baker J, Denning DW. The SSS revolution in fungal diagnostics: speed, simplicity and sensitivity. Br Med Bull. 2023;147:62–78. [DOI] [PubMed] [PMC]
86. Oliveira LVN, Wang R, Specht CA, Levitz SM. Vaccines for human fungal diseases: close but still a long way to go. NPJ Vaccines. 2021;6:33. [DOI] [PubMed] [PMC]