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REVIEW

Fungal Endocarditis: Pathophysiology, Epidemiology, Clinical Presentation, Diagnosis, and Management

George R. Thompson III,[a,b] Jeffrey D. Jenks,[c,d] John W. Baddley,[e] James S. Lewis II,[f] Matthias Egger,[g] Ilan S. Schwartz,[d] Johannes Boyer,[g] Thomas F. Patterson,[h] Sharon C.-A. Chen,[i,j] Peter G. Pappas,[k] Martin Hoenigl[g,l]

[a]Department of Internal Medicine, Division of Infectious Diseases, University of California-Davis Medical Center, Sacramento, California, USA
[b]Department of Medical Microbiology and Immunology, University of California-Davis, Davis, California, USA
[c]Durham County Department of Public Health, Durham, North Carolina, USA
[d]Division of Infectious Diseases, Department of Medicine, Duke University, Durham, North Carolina, USA
[e]Department of Medicine, Division of Infectious Diseases, University of Maryland School of Medicine, Baltimore, Maryland, USA
[f]Department of Pharmacy, Oregon Health & Science University, Portland, Oregon, USA
[g]Division of Infectious Diseases, ECMM Excellence Center for Medical Mycology, Department of Medicine, Medical University of Graz, Graz, Austria
[h]Department of Medicine, Division of Infectious Diseases, The University of Texas Health Science Center, San Antonio, Texas, USA
[i]Centre for Infectious Diseases and Microbiology Laboratory Services, Institute of Clinical Pathology and Medical Research, New South Wales Health Pathology, Sydney, New South Wales, Australia
[j]Centre for Infectious Diseases and Microbiology, Westmead Hospital, The University of Sydney, Sydney, New South Wales, Australia
[k]Department of Medicine Division of Infectious Diseases, University of Alabama at Birmingham, Birmingham, Alabama, USA
[l]BioTechMed-Graz, Graz, Austria

Address correspondence to George R. Thompson III, grthompson@ucdavis.edu, or Martin Hoenigl, hoeniglmartin@gmail.com.

SUMMARY Fungal endocarditis accounts for 1% to 3% of all infective endocarditis cases, is associated with high morbidity and mortality (>70%), and presents numerous challenges during clinical care. *Candida* spp. are the most common causes of fungal endocarditis, implicated in over 50% of cases, followed by *Aspergillus* and *Histoplasma* spp. Important risk factors for fungal endocarditis include prosthetic valves, prior heart surgery, and injection drug use. The signs and symptoms of fungal endocarditis are nonspecific, and a high degree of clinical suspicion coupled with the judicious use of diagnostic tests is required for diagnosis. In addition to microbiological diagnostics (e.g., blood culture for *Candida* spp. or galactomannan testing and PCR for *Aspergillus* spp.), echocardiography remains critical for evaluation of potential infective endocarditis, although radionuclide imaging modalities such as ^{18}F-fluorodeoxyglucose positron emission tomography/computed tomography are increasingly being used. A multimodal treatment approach is necessary: surgery is usually required and should be accompanied by long-term systemic antifungal therapy, such as echinocandin therapy for *Candida* endocarditis or voriconazole therapy for *Aspergillus* endocarditis.

KEYWORDS cardiac, diagnosis, endocarditis, endocardium, fungal, mycologic, mycology, treatment

INTRODUCTION

Invasive fungal diseases (IFD) continue to increase with the growing immunocompromised patient population. Advances in the care of patients with underlying malignancy and rheumatologic diseases, and within the intensive care unit (ICU) setting, as well as pandemics of respiratory viral infections, have resulted in a net increase of patients at risk for IFD (1). In 2017, an estimated 15 million cases of pulmonary and other forms of IFD occurred worldwide (2). An uncommon but serious complication of fungal infection is endocarditis, which presents unique challenges in diagnosis and management.

Endocarditis can complicate a wide number of fungal infections. *Candida* spp. account for ~50% (3) of all fungal infective endocarditis across different geographic regions, while *Aspergillus* and *Histoplasma* spp. account for the majority of non-*Candida* fungal endocarditis (Fig. 1). However, a broad spectrum of molds (4), yeasts (5), and dimorphic fungal pathogens (6) have been reported to cause fungal endocarditis. While there are individual differences in epidemiology, diagnosis, and management according to each pathogen, there are some common general features. Fungal endocarditis accounts for 1% to 3% of all infective endocarditis cases, affects nearly 0.1% of all prosthetic cardiac valves (3, 7–9), is disproportionately associated with high morbidity and case fatality rates (>70%), especially for mold pathogens compared with bacterial endocarditis, and presents significant and often unique difficulties during clinical care. Furthermore, the diagnosis of fungal endocarditis is even more challenging in view of its overall low incidence (and thus low pre-test probability in the absence of other suggestive information), nonspecific clinical findings, and limitations in diagnostics.

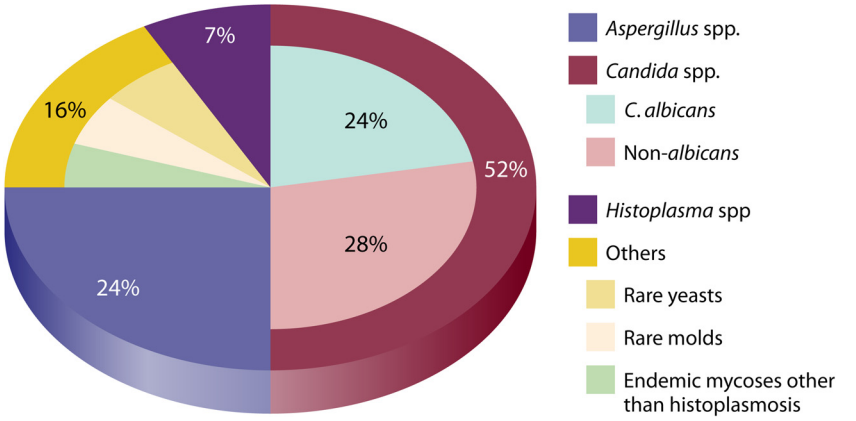

FIG 1 Causative pathogens of fungal endocarditis.

Typical clinical signs of endocarditis may be absent, with fever present in only 60% to 70% of cases (10), and classic peripheral stigmata of endocarditis are rarely observed. Subacute and nonspecific symptoms are common, with weight loss, diaphoresis, chills, malaise, and fatigue occurring more frequently in cases of fungal endocarditis than in cases of bacterial endocarditis (3). Important risk factors have been identified as predisposing to fungal endocarditis, including the presence of prosthetic valves, prior heart surgery, and injection drug use (3). Blood culture remains the gold standard for diagnosis of *Candida* and rare yeast fungemia, and persistently positive cultures may be suggestive of underlying endocarditis. However, blood culture results may take days to return positive, and autopsy studies have demonstrated a wide range of blood culture sensitivities for candidiasis alone (21% to 71%) (11). Fungal antigen tests from serum, such as 1,3-β-D-glucan (BDG) for *Candida* infections or the galactomannan test (GM) for *Aspergillus* infections, are associated with improved turnaround times compared to culture in some geographic locations (12). Negative BDG results may decrease the likelihood of *Candida* endocarditis (BDG), while positive BDG results may conversely increase clinical suspicion and trigger further radiologic examination; for example, with a positive GM result in suspected cases of *Aspergillus* or *Histoplasma* endocarditis (13, 14). Echocardiography remains the backbone imaging modality in evaluation of potential infective endocarditis, although radionuclide imaging modalities such as ^{18}F-fluorodeoxyglucose (FDG) positron emission tomography (PET)/computed tomography (CT) are increasingly being utilized for this purpose (15). Surgery, when feasible, is a cornerstone of management (16) and should be accompanied by long-term biofilm active systemic antifungal therapy, such as echinocandin therapy for *Candida* endocarditis or voriconazole therapy for *Aspergillus* endocarditis.

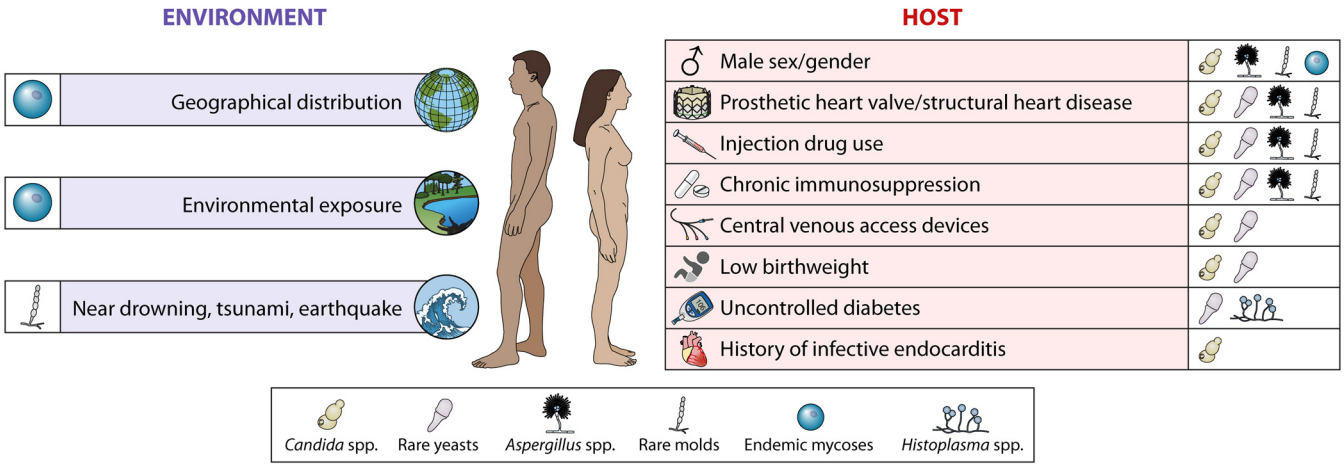

FIG 2 Environmental and host risk factors for fungal endocarditis and rare fungal infections.

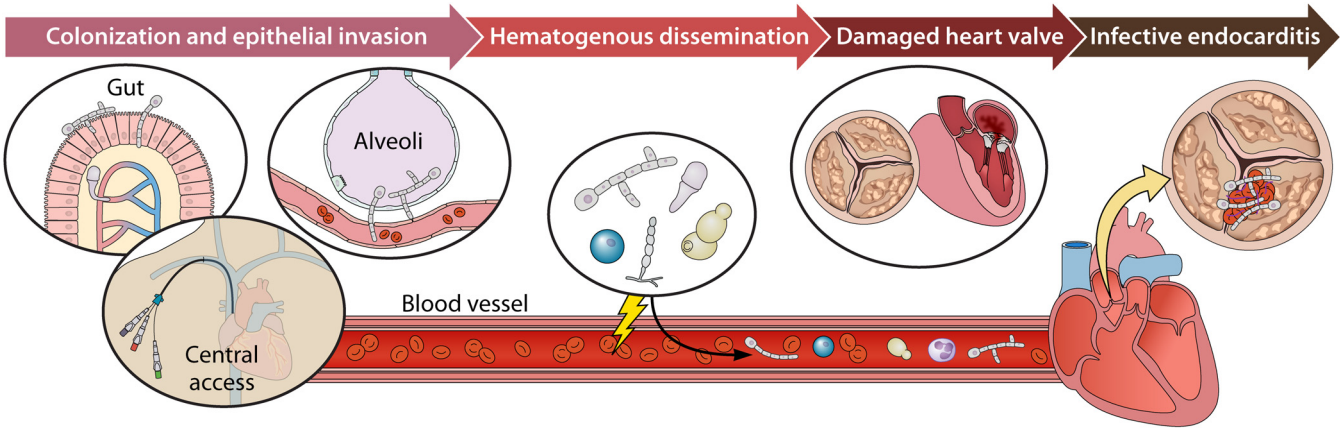

FIG 3 Pathogenesis of fungal endocarditis. Invasion of fungal pathogens through the gastrointestinal tract, through pulmonary alveoli, or via disruption of skin barrier. Following invasion, hematogenous dissemination occurs, allowing fungal endocarditis in the setting of a damaged endocardial surface.

Here, we comprehensively review fungal endocarditis, focusing on the most common causative fungal pathogens, pathogenesis, epidemiology, risk factors, clinical presentation, diagnosis, treatment, complications, and outcomes (Fig. 2).

CANDIDA SPP.

Pathogenesis and Pathophysiology of *Candida* Endocarditis

Most data concerning the pathogenesis of *Candida* spp. are derived from studies involving *Candida albicans*, and the major pathogenic mechanisms of invasive candidiasis have been reviewed previously (17). *C. albicans* possesses several virulence factors that contribute to its ability to adhere to and persist in the human gastrointestinal tract, invade host tissues, evade immune responses, and adhere to cardiac valves.

The development of *Candida* endocarditis requires entry of *Candida* into the bloodstream, which results from opportunistic translocation across a damaged gastrointestinal epithelium (e.g., from cytotoxic chemotherapy or surgical transection) or across skin and soft tissue via endovascular catheters or contaminated injections (Fig. 3). Necessary steps include colonization and adherence to epithelial surfaces, epithelial invasion, immune evasion, and hematogenous dissemination, followed by adherence to cardiac valves.

The intestinal microbiota appears to be an important determinant of *Candida* colonization and risk of disease. The presence of anaerobic bacteria attenuates *Candida* colonization (18). Dysbiosis can occur following antibiotic exposure, in critical illness (19), and following stem cell transplantation (20), resulting in a loss of bacterial biodiversity and an increase in *Candida* within the gastrointestinal tract. In mice, the loss of bacterial microbiota following antibiotic exposure led to a higher fungal burden, diminished Th17 cells, and an inability to contain experimental candidemia (21). Similarly, in allogeneic stem cell transplant recipients, loss of bacterial biodiversity and clonal expansion of intestinal *Candida* spp. precedes *Candida* bloodstream infections (22).

Morphological switching from yeast-like blastospores to pseudohyphae and true hyphae is a critical virulence factor in many *Candida* spp., including *C. albicans* (23). Genetically engineered *C. albicans* strains incapable of hyphal transformation are rendered avirulent (24, 25), although *Nakaseomyces glabrata* (formerly *C. glabrata*) can cause disease despite its intrinsic inability to form hyphae. Intestinal colonization can occur with yeasts or hyphae. Transformation to hyphae is regulated by an array of internal and external factors (26). In the yeast phase, *C. albicans* expresses surface adhesin proteins to facilitate adhesion and commensal growth. Hyphal adhesin proteins, including agglutinin-like sequence 3 (Als3p) (27) and hyphal wall protein 1 (Hwp1p), promote adhesion to epithelial cells (28). Hyphal invasion occurs by active penetration into and between gastrointestinal epithelial cells, and additionally by induced endocytosis in oral epithelial cells (28). The hyphae of *C. albicans* and other species exhibiting true hyphae (*C. dubliniensis* and *C. tropicalis*) cause epithelial damage, trigger a

MAPK (mitogen-activated protein kinase) danger response, and induce host inflammation through secretion of cytolytic peptide toxins known as candidalysins (29, 30).

An important *Candida* virulence factor is the production of extracellular biofilms that enable persistence on abiotic materials such as endovascular catheters, intracardiac devices, and prosthetic heart valves (31). Controlled by a complex signaling mechanism (32), biofilms may be produced by yeasts, hyphae (in those species capable of morphological transformation) or a combination of these, and involve an extracellular matrix comprised of proteins, polysaccharides, lipids, and nucleic acids (31). Biofilms sequester organisms beyond the reach of immune cells and trap antifungals.

An experimental animal model of *C. albicans* endocarditis has been described (33–35). In experimental studies, damage to the host endocardium appears to be a necessary precursor for experimental endocarditis with *C. albicans*, as intravenous injection of *C. albicans* causes endocarditis only when preceded by trauma to the valve (35, 36). Transvalvular trauma with a catheter leads to non-bacterial thrombotic endocarditis comprised mostly of a fibrin-platelet matrix; transvalvular inoculation of blastospores results in early (<48 h) incorporation of yeast cells into the surface of these vegetations, mostly within macrophages, and after 7 days, only pseudohyphae were observed (33). In autopsy cases following natural infection, a mix of yeasts and hyphae is seen (37). Virulence factors that facilitate adherence causing endocarditis are poorly understood, but there are intra- and interspecies differences among *Candida* in non-bacterial thrombotic endocarditis adherence and propensity to cause endocarditis (38, 39).

Epidemiology

Candida spp. are the most common cause of fungal endocarditis, causing <5% of all infective endocarditis cases (40) but over half of all fungal endocarditis cases (11). The morbidity and mortality rates of *Candida* endocarditis are high, with an in-hospital mortality rate of 36% and a 1-year mortality rate of 59% in one multinational study (41), and endocarditis is one of the most serious sequelae of invasive candidiasis. In cases of *Candida* endocarditis, *C. albicans* is the most commonly isolated species (35% to 60% of cases), followed by *C. parapsilosis* (15 to 41%), *C. tropicalis* (10 to 13%), *N. glabrata* (4 to 9%), *Meyerozyma guilliermondii* (formerly *C. guilliermondii* [4%]), and *Pichia kudriavzevii* (formerly *C. krusei*) (1%) (41–43). Other species, including *Candida auris*, are very uncommon causes. The distribution of *Candida* species as the etiology of endocarditis differs from the distribution of candidemia alone. The reduced frequency of *N. glabrata* infective endocarditis may be due to the lack of several pathogenic attributes in *N. glabrata* strains (44, 45).

Risk Factors

Prosthetic heart valves or other structural heart disease. Compared to individuals diagnosed with bacterial endocarditis, those diagnosed with *Candida* endocarditis are more likely to have a prosthetic heart valve (41, 46, 47) and/or to have had a prior coronary artery bypass graft (46). In one study of 70 cases of *Candida* endocarditis, 46% of individuals had a prosthetic heart valve (41). The propensity for *Candida* spp. to cause prosthetic valve endocarditis is likely due to its ability to adhere to surfaces and form biofilms, particularly on prosthetic devices.

Cardiac implantable electronic device. *Candida* spp. are uncommon causes of cardiac implantable electronic device-related endocarditis (CIED-IE), accounting for only 2% of these infections in one series of patients (48). Risk factors for device-related endocarditis include a newly implanted device, device revision, or generator change. Devices that have been in place for longer periods (>1 year) are less likely to become infected (49).

Injection drug use. Injection drug use is a known and increasing risk factor for candidemia and *Candida* endocarditis (50), particularly in persons who inject brown heroin, which has poor solubility in water and is usually dissolved in lemon juice or other acidic substances prior to injection. Because *C. albicans* grows readily in the lemon juice used to cut this particular type of heroin, those who inject brown heroin cut with lemon juice are at particular risk of *Candida* endocarditis (51). In one 7-year review of 83 cases of disseminated candidiasis among persons who injected drugs, all had recently used brown heroin diluted in fresh

lemon juice (52). Another series of 20 patients found that the tricuspid valve was the primary valve involved in those who injected drugs, with *C. albicans* being the most frequently isolated organism (53). More recent series have observed an increase in *C. parapsilosis* associated with injection drug use in those injecting heroin, methamphetamines, cocaine, buprenorphine/naloxone, benzodiazepines, and oxycodone (54). The increased use of black-tar heroin has been linked to *Clostridium* infections and botulism, but no association with *Candida* infections has thus far been reported.

Indwelling central catheters. The presence of a chronic indwelling catheter is a risk factor for both candidemia and *Candida* endocarditis (46, 55–57). As previously noted, this is likely due to the ability of *Candida* spp. to adhere to prosthetic devices and form biofilms. As the biofilm matures, an extracellular matrix accumulates which can lead to persistent organisms and high treatment failure rates unless the prosthetic devices are removed. *C. albicans* has been reported to form larger and more complex biofilms than other *Candida* species (58).

Immunosuppression. Chronic immunosuppression, such as that from chemotherapy or following solid organ transplantation, impairs the immune system's ability to fend off fungal pathogens that often colonize the skin and other mucosal surfaces, including the gastrointestinal and respiratory tracts; thus, it is a risk factor for IFD, including *Candida* endocarditis (46, 59). In addition, the use of antibacterial agents following transplantation increase the risk of developing *Candida* infections due to changes in the intestinal flora after the use of agents which favor the overgrowth of *Candida* spp. (60).

History of infective endocarditis. A history of prior infective endocarditis is a risk factor for *Candida* endocarditis. Previous damage to valvular structures serves as a persistent nidus for adhesion by other bloodstream pathogens, including *Candida* spp. In one multinational prospective study of individuals diagnosed with infective endocarditis, of those with a history of previous infective endocarditis, 21.2% had *Candida* endocarditis compared to 7.8% with non-*Candida* endocarditis (46). In another retrospective study in Spain and France of individuals with prosthetic valve endocarditis, 48% had a history of prior infective endocarditis (43).

Low birthweight. Low birthweight in premature infants is a risk factor for candidemia and *Candida* endocarditis (17–19), largely due to the presence of an indwelling venous catheter for parenteral nutrition and an immature immune response, although candidemia may also occur via skin contamination or by swallowing or aspiration of vaginal secretions containing *Candida* spp. during delivery (61). In a study of 86 neonates with candidemia hospitalized over a 10-year period, 15% had thrombi or vegetations revealed on an echocardiogram, illustrating the frequency of this complication in a high-risk patient group (62).

Male sex. Similar to the higher observed risk of all fungal diseases in men (63), infective endocarditis is twice as likely to occur in males compared to females, although mitral valve endocarditis is more likely to occur in women and aortic valve endocarditis is more likely in men (64). In most studies, invasive candidiasis occurs more commonly in males than females (63). In one case review over a 20-year period, fungal endocarditis occurred at a 2.2:1 male-to-female ratio, with *Candida* endocarditis occurring in 24% of these individuals (3). Other studies showed a preponderance of *Candida* endocarditis in males compared to females, ranging from 52% to 78% (41–43, 46). In contrast to male sex, race and ethnicity may not play major roles as risk factors for *Candida* endocarditis, with the higher prevalence of *Candida* infections among African-Americans primarily explained by factors related to socioeconomic status, underlying medical conditions, and health care access (65).

Clinical Presentation

Candida endocarditis has a variety of clinical manifestations which are dependent on the extent of infection, the valve involved, and accompanying host/risk factors. It may initially present as a subacute illness with nonspecific symptoms, including weight loss, diaphoresis, chills, malaise, and fatigue, over weeks to months, and be indistinguishable from symptoms secondary to bacterial endocarditis (3, 66, 67). Conversely, some cases present with acute life-threatening disease with septic shock. The most frequent presenting symptom in endocarditis is fever (68), and while a fever of $>$38°C is present in over 90% of bacterial

endocarditis cases, a recent systematic review of fungal endocarditis revealed a lower rate of 60% to 70% (10, 69).

Accompanying symptoms of dyspnea, orthopnea, and/or chest pain are also nonspecific for endocarditis, but the presence of fever and other systemic symptoms may point the clinician to diseases of the cardiopulmonary system. Clinical findings such as the development of a new heart murmur or change in the quality of a pre-existing murmur and signs of heart failure such as swollen legs, distended neck veins, or pulmonary rales (crackles) may be present upon physical examination. These symptoms are present primarily with worsening valvular disease, although an intracardiac fistula following perforation or valve obstruction may lead to acute heart failure as well (68).

Embolic complications may also occur in *Candida* endocarditis (70). Cerebral embolism is most common within the distribution of the middle cerebral artery and its branches, leading to hemiplegia, unilateral hypoesthesia, unilateral facial drop, unilateral hemianopsia, or aphasia (71, 72). Pulmonary embolism may present with pleuritic chest pain, dry cough, dyspnea, or hemoptysis (70, 73, 74). Other common embolism sites include the lower extremities, with signs and symptoms of acute ischemia (75), peripheral gangrene of the extremities or involved site, or endophthalmitis with decreased vision or ocular pain (68, 76). While these may be the most common manifestations, *Candida* endocarditis can lead to infarction of any organ, causing localizing symptoms at the involved site. Due to their embolic origin, these symptoms are usually of acute onset. In contrast to subacute bacterial endocarditis, classical features such as Osler's nodes, Janeway lesions, and Roth spots are rarely observed in *Candida* endocarditis (46, 69).

Diagnosis

The diagnosis of infective endocarditis can be challenging given the variability of presenting symptoms (68), and it is based on the modified Duke criteria, which include clinical findings, microbiological evidence in blood cultures, and imaging features suggestive of infective endocarditis (77). The low incidence of *Candida* endocarditis, even in patients with other forms of invasive candidiasis, exemplifies the need for a high degree of clinical suspicion to initiate a proper diagnostic course (78). Current data suggest that most cases occur in patients with known risk factors for infective endocarditis (3). Accurate diagnosis thus requires an understanding of the factors which place patients at heightened risk and a detailed medical history and examination.

Due to the various clinical presentations of infective endocarditis, blood cultures are the cornerstone for diagnosis and should be obtained whenever a diagnosis of endocarditis is considered (68). In cases where blood cultures are positive for multiple bacterial species in addition to *Candida*, the etiology of valvular lesions can be difficult to determine. Most *Candida* endocarditis cases exhibit positive blood cultures, with a sensitivity of ~90% in reported cases (13, 78). However, endocarditis may be seen even in those with negative blood cultures. While large autopsy controlled studies on invasive candidiasis show a less-than-perfect sensitivity of blood cultures, ranging between 21% and 71% (11), sensitivity may be slightly higher in *Candida* endocarditis, where autopsy series have shown positive blood cultures in 50% to 100% of proven cases (79–82). Nevertheless, blood culture may be falsely negative in cases with *Candida* endocarditis, and the diagnosis should therefore be considered a possible cause of culture-negative endocarditis (83). Increased sensitivity may be achieved by obtaining serial cultures and/or larger blood culture volumes (84).

One shortcoming of blood cultures is the prolonged time to positivity for *Candida* spp. compared to bacterial cultures, which may delay the initiation of appropriate treatment (84, 85). When positive, blood cultures allow pathogen identification to the species level and susceptibility testing to be performed. Positive cultures may also be the initial prompt for additional diagnostic evaluation prior to identification of *Candida* endocarditis (84). While European guidelines recommend routine screening for endocarditis by echocardiography and frequent physical examination in patients with candidemia, this is not recommended in current Infectious Diseases Society of America (IDSA) guidelines due to the relatively low prevalence (1.9% to 5.9%) of *Candida* endocarditis in patients with candidemia (42, 86–89). However, in a recent European multicenter study involving 64 centers, 10.7% of patients

with candidemia in whom echocardiography was performed showed signs of cardiac involvement (90). While more research is needed to identify the best approach, the diagnostic challenge of the disease, devastating mortality rates, and need for timely appropriate treatment may justify broader utilization of echocardiography until further evidence emerges (42, 86–89).

Echocardiography is the mainstay imaging technique when infective endocarditis is suspected (68). Although transthoracic echocardiography (TTE) is widely available and relatively rapid, its sensitivity to adequately evaluate all valves is often limited, especially in the presence of prosthetic valves or intracardiac devices and in obese patients (15, 68, 91, 92). In these cases, transesophageal echocardiography (TEE) is the first-line imaging technique (68). The reported sensitivity of TTE for infective endocarditis (IE) is 70% for native valves and 50% for prosthetic valve endocarditis, while the sensitivity of TEE is 96% for native valves and 92% for prosthetic valves (10, 46, 68). While echocardiography does not allow *Candida* endocarditis to be distinguished from endocarditis due to other pathogens, fungal endocarditis lesions are often large and highly mobile (3). Data from the MYCENDO study showed vegetations of $>$13 mm in half of the 30 cases, with vegetation size ranging from 4 to 30 mm, while another report of 15 cases also showed large vegetations in *C. albicans* endocarditis with a mean size of 19.4 mm (range: 8.8 to 29.9 mm) (13, 93). Hyperechoic lesions are also suggestive of vegetations caused by *Candida* spp. (94, 95).

Other imaging modalities to evaluate IE include cardiac computed tomography (CCT), FDG-PET/CT, and indium-111 leukocyte-scintigraphy (15, 96). CCT has shown promise for diagnosing and detecting complications of IE from other pathogens but has not been evaluated in *Candida* endocarditis (97). Moreover, CCT might provide additional information of anatomical circumstances, which may be useful in surgical planning (15). Successful diagnosis using CCT in a case of *Candida* endocarditis has been reported (98).

Radionuclide imaging techniques are increasingly being used in diagnostic work-up for infective endocarditis. While the sensitivity of FDG-PET is low for native valve endocarditis, with a pooled sensitivity of 31%, its diagnostic accuracy improves in cases of prosthetic valves and intracardiac devices, where imaging via ultrasound has limitations (99, 100). Furthermore, FDG-PET might visualize signs of infection early when initial echocardiography is negative and may also identify septic embolization (15, 101), leading to earlier diagnosis. The utility of FDG-PET has been highlighted in case reports of *Candida* endocarditis (102, 103). Indium-111 leukocyte-scintigraphy may also show high specificity in prosthetic valve *Candida* endocarditis and can also detect extracardiac foci (15, 91). Because leukocyte-scintigraphy has high specificity but low sensitivity and several limitations regarding its execution (e.g., labor-intensive, long imaging duration, higher radiation), a stepwise approach of nuclear imaging techniques is proposed, with leukocyte-scintigraphy following FDG-PET when findings are inconclusive (91).

If surgery is performed, histopathological examination with adjunctive microbiological and molecular-based testing (pan-fungal or *Candida*-specific PCR) can help confirm the pathogenic microorganism or identify it if blood cultures remain negative (67). Tissue samples should not be placed in formalin until the appropriate portions have been sent to the microbiology laboratory.

Biomarkers and molecular-based techniques may provide adjunctive diagnostic and prognostic information during the care of patients with *Candida* infections (104). Antigen tests (detecting mannan antigen and anti-mannan antibody or BDG) and PCR-based tests are available, although data are limited on their role in endocarditis diagnosis and management (13, 84).

BDG is a component of the cell wall of most pathogenic fungi and is detectable in patient serum samples (105). In cases of invasive candidiasis, BDG has a sensitivity ranging between 76.7% and 100% and a specificity of 40.0% to 91.8%, with a high negative predictive value (84). In a recent systematic review, BDG was positive in 24 out of 27 cases of fungal endocarditis (88.9%) (69). However, BDG detection should be interpreted with caution because positive results may also occur in patients with conditions that are associated with fungal translocation (106, 107), including recent abdominal surgery, hemodialysis or sepsis (108, 109),

receipt of blood products, and certain immunoglobulin preparations (84, 105). Notably, the sensitivity of BDG varies by the *Candida* spp. present. In infection with *C. parapsilosis*, which is the most common non-*albicans Candida* spp. causing endocarditis and is associated with increasing resistance rates against fluconazole (110), BDG has a lower sensitivity due to the lower amounts of BDG produced by this species (111).

Mannan and anti-mannan detection is useful for diagnosing invasive candidiasis, with a reported combined sensitivity of 83% and a specificity of 86%, although no data regarding its use in endocarditis diagnosis have yet been presented (112). Its primary utility is its high negative predictive value (113).

The T2Candida panel (T2 Biosystems, Lexington, MA) detects the 5 most common *Candida* spp. (*C. albicans*, *N. glabrata*), *C. parapsilosis*, *C. tropicalis*, and *P. kudriavzevii* in whole blood samples, with a mean time of *Candida* detection and species identification of 4.4 h (114, 115). In previous studies, this test has shown excellent sensitivity and specificity of 89% to 91.1% and 99.4%, respectively (114, 115); and in two *Candida* endocarditis cases, the T2Candida panel was utilized to assess the suppression of disease in prosthetic valve endocarditis with medical treatment only (116). More recent studies have indicated that sensitivity might be as low as 65% in candidemia, however, and its primary strength may therefore be its specificity (117, 118) with the ability to only detect species targeted by the assay. Other PCR-based assays, such as Fungiplex Candida (Bruker Daltonics GmbH & Co., Bremen, Germany), and LightCycler SeptiFast (Roche Diagnostics, Mannheim, Germany), have similar performance characteristics and are also commercially available (104).

PCR-based diagnostic tests for diagnosing invasive candidiasis are usually obtained by investigation of blood samples and cover the most common *Candida* spp. mentioned above (119). In a meta-analysis, blood-based PCR showed pooled sensitivity and specificity of 92% and 95%, respectively, for candidemia in patients with suspected invasive candidiasis (120). The results of PCR testing may be helpful and aid in the initial diagnosis. However, quantitative PCR (qPCR) testing for *Candida* is not yet commercially available and, despite its potential utility for monitoring patients for recurrence or determining responses to therapy, its role in the diagnosis of *Candida* endocarditis is currently unclear (13, 119).

Treatment and Prognosis of *Candida* Endocarditis

Because *Candida* endocarditis remains an uncommon condition, it is not amenable to prospective randomized trials. As such, recommendations for the treatment of this disorder are based almost entirely on anecdotal reports, retrospective reviews, and expert opinion.

The treatment of *Candida* endocarditis typically involves a combined approach of antifungal therapy and surgical intervention (valve replacement/repair or vegetectomy) for native valve and prosthetic valves (3, 43, 46, 47, 93, 121–125). Pre-operative evaluation for subclinical embolic phenomenon is performed at some centers; however, there is little evidence this significantly alters surgical decision-making in the absence of intracranial hemorrhage (126). Controlled, comparative studies for treatment of *Candida* endocarditis are lacking due to the relative rarity of the infection, but combination medical and surgical therapy may be associated with better outcomes compared to medical therapy alone (3, 13, 41, 43, 69, 121). However, data are conflicting, and most reports describe relatively small cohorts of patients with outcomes confounded by indication or comorbidities. In an early review, Ellis et al. evaluated 270 patients with fungal endocarditis from 1965 to 1985 (3). For all patients, those receiving combined treatment with antifungal therapy and surgery trended toward better outcomes (55% 1-year survival) compared to those who had antifungal therapy alone (36% 1-year survival). Similarly, for 103 patients with *Candida* endocarditis, survival was significantly better with combined therapy (58%) than with antifungal therapy alone (41%; $P = 0.024$) (3).

Steinbach et al. reviewed 879 cases of *Candida* endocarditis published from 1996 to 2002 to evaluate management (121). Of the 163 patients who met the inclusion criteria, patients who had received adjunctive surgery had lower odds of death (prevalence odd ratio, 0.56; 95% confidence interval [95% CI], 0.16 to 1.99) compared to those who did not have surgery, and higher mortality was seen in patients who were treated with antifungal monotherapy, although neither finding reached statistical significance.

A more recent review from Arnold et al. evaluated 70 cases of *Candida* endocarditis from the International Collaboration on Endocarditis (ICE) Prospective Cohort Study (41). In comparing patients who had received adjunctive surgical therapy ($n = 32$) to those who had received medical therapy alone ($n = 38$), there was no difference in within-hospital mortality (38% versus 34%; $P = 0.77$) or 1-year mortality (66% versus 62%; $P = 0.76$). Patient characteristics were similar between the two groups except that the patients receiving surgery were significantly younger and more likely to have an intracardiac abscess (41). Another recent comparative study evaluated the long-term prognosis of *Candida* prosthetic valve endocarditis cases collected in France and Spain from 2001 to 2015 (43). Of 46 cases followed for a median of 9 months, patients who received adjunctive surgery did not have improved survival rates at 6 months.

In contrast to these studies, Meena et al. recently described a systematic review of 250 patients with fungal endocarditis, of which 124 (49.6%) had *Candida* endocarditis (69). Treatment with surgery in addition to antifungal therapy was associated with decreased mortality compared to antifungal therapy alone (hazard ratio, 0.20, 95% CI, 0.09 to 0.42; $P < 0.001$).

For native valve or prosthetic valve *Candida* endocarditis, the recommended initial treatment regimens are lipid amphotericin B 3 to 5 mg/kg per day, with or without 25 mg/kg flucytosine four times daily, or a high-dose echinocandin (150 mg/d micafungin, 200 mg/d anidulafungin, or 150 mg/d caspofungin) (Table 1) (124, 125). Clinical trials of antifungal therapy for endocarditis are limited and much of the efficacy data are derived from treatment of candidemia and candidiasis (124, 125, 127–130).

Most reported cases of *Candida* endocarditis have historically been treated with an amphotericin B preparation (3, 9, 41, 46, 47, 61, 121, 131, 132). Lipid preparations of amphotericin B are now more commonly used to reduce nephrotoxicity and infusion-related reactions. Flucytosine is often added for potential synergistic activity; when it is used, it is important to monitor for dose-related bone marrow toxicity (124). Data supporting combination therapy are scarce: a meta-analysis of reported cases of *Candida* endocarditis suggested that combination therapy, primarily with amphotericin B deoxycholate plus flucytosine, is associated with improved outcomes compared to monotherapy, although the difference was not statistically significant (121). Dosing differences between amphotericin B deoxycholate and lipid amphotericin B formulations and the enhanced biofilm activity of lipid formulations has caused these to be preferred in recent years (133).

Recent studies highlight the role of echinocandins in the treatment of *Candida* endocarditis (13, 41, 43, 46, 129). The use of echinocandins, either as monotherapy or in combination with fluconazole, flucytosine, or amphotericin B, is becoming more common for the treatment of *Candida* endocarditis. Recent case series have described echinocandin use in up to 75% of patients with *Candida* endocarditis (13, 41, 43, 134). The increase in echinocandin use reflects its overall improved safety profile (decreased renal toxicity) and similar efficacy compared to amphotericin B preparations for the treatment of candidemia and candidiasis (124, 130, 135–137). Data are limited regarding the efficacy of higher-dose echinocandins for *Candida* infections, but they appear to be safe (129, 137, 138). Compared to amphotericin B deoxycholate and fluconazole, echinocandins have increased activity against *Candida* biofilms *in vitro*, although lipid amphotericin B formulations appear comparable to echinocandins (133, 139).

Data comparing amphotericin B preparations and echinocandins for the treatment of *Candida* endocarditis are limited and may be subject to confounding (41, 43). In a recent observational study of prosthetic valve *Candida* endocarditis, patients who had received liposomal amphotericin B alone had improved survival at 6 months compared to those who had received an echinocandin alone (43). In contrast, a small subgroup analysis of 33 patients by Arnold et al. showed that mortalities (at 42 days or 1 year) with these regimens were not significantly different (41). Of note, the sample size was small and 46% of people who received an echinocandin also received another antifungal in combination.

Fluconazole in combination with one or more other antifungal therapies has been effective in some cases of *Candida* endocarditis; however, fluconazole alone as an initial

TABLE 1 Antifungal agents used during the treatment or suppression of endocarditis[a]

Medication	Dosing regimen[b]	TDM and target trough concentrations	Adverse events
Triazoles			
Fluconazole	400 mg (or 6 mg/kg) once daily	Rarely needed	QTc prolongation, headache, alopecia, xerosis, cheilitis, LFT abnormality
Isavuconazole	372 mg (isavuconazole 200 mg) every 8 hours for 6 doses; maintenance: 372 mg (isavuconazole 200 mg) once daily	>1 μg/mL[c]	Edema, hypokalemia, abdominal pain, LFT abnormality, infusion reactions with intravenous formulation
Itraconazole	Solution (preferred) or capsule: itraconazole 200 mg twice daily; may give a loading dose of 200 mg 3 times daily for the 3 days of therapy	Itraconazole: >1 μg/mL; hydroxyitraconazole + itraconazole (>2 μg/mL)	QTc prolongation, edema, hypertension, hypokalemia; negative inotrope, LFT abnormality
Posaconazole	300 mg twice daily for 2 doses, then 300 mg once daily	>1 μg/mL[d]	Gastrointestinal, edema, hypertension, hypokalemia
Voriconazole	6 mg/kg twice daily for 2 doses, then 4 mg/kg twice daily	1−5.5 μg/mL	QTc prolongation, photopsia, hallucinations, photosensitivity, periostitis, alopecia/nail changes, LFT abnormality
Echinocandins			
Caspofungin	70 mg on day 1, then 50 mg once daily	Not indicated	Hepatotoxicity, infusion reactions, gastrointestinal effects
Micafungin	100 mg once daily		
Anidulafungin	200 mg on day 1, then 100 mg once daily		
Rezafungin	400 mg once on day 1, then 200 mg once weekly beginning on day 8		Hypokalemia, diarrhea, infusion reactions
Glucan synthase inhibitors			
Ibrexafungerp	750 mg twice daily for 4 doses, then 750 mg daily[e]	Not indicated	Abdominal pain, diarrhea, nausea, headache
Polyenes			
Liposomal amphotericin B	3 to 5 mg/kg per day	Not indicated	Infusion-reactions, nephrotoxicity (higher rate with Amb-d than lipid formulations), electrolyte abnormalities (hypokalemia, hypomagnesemia, and hyperchloremic acidosis)
Amphotericin B lipid complex	5 mg/kg per day		
Amphotericin B deoxycholate	0.5 to 0.7 mg/kg/day; dose may be increased to as high as 1 mg/kg/day		
Antimetabolites			
Flucytosine	Only to be used in combination with other agents: 25 mg/kg/dose 4 times daily	<100 μg/mL	Hematologic (leukopenia and thrombocytopenia), hepatic, and gastrointestinal
DHODH			
Olorofim	Available under compassionate use program	Not indicated	Hepatoxicity

[a]LFT, liver function tests; TDM, therapeutic drug monitoring.
[b]Doses used for suppression are often similar to those used for treatment and reflect the opinions of the authors, clinical data for suppression dosing is lacking. None of the listed agents are FDA approved for the treatment of fungal endocarditis (349).
[c]Isavuconazole troughs of <4.6 μg/mL have been advocated in some reports.
[d]Posaconazole toxicity seen primarily with levels of >4 μg/mL.
[e]Listed ibrexafungerp dosing is based on ongoing clinical trials and may need to be optimized pending additional data.

therapy for *Candida* endocarditis has been associated with poor outcomes (132). Smego et al. performed a meta-analysis of fluconazole use in endocarditis (132). Among patients who received monotherapy with fluconazole, only 58% were cured or improved. In contrast, among patients who received fluconazole in addition to another antifungal, 84% were cured or improved (132).

Duration of Therapy

The recommended duration of antifungal therapy for *Candida* endocarditis is at least 6 weeks (124, 125). Step-down therapy to an azole such as fluconazole or voriconazole in infections caused by azole-susceptible isolates can be considered provided that the patient is clinically stable and has cleared *Candida* from the bloodstream (124, 125).

Following completion of initial therapy for *Candida* endocarditis, long-term suppressive antifungal therapy is indicated in selected groups of patients. Because of the convenience

of oral suppressive therapy, most clinical experience has been with azole antifungals, particularly fluconazole. Among patients with native valve *Candida* endocarditis, there are few data that support the use of chronic suppressive antifungal therapy following a combined approach of valve removal with replacement or vegetectomy, together with concomitant antifungal therapy with either amphotericin B, with or without flucytosine, or an echinocandin or for several weeks post-valve replacement (124). Stepdown therapy to an azole such as fluconazole following an initial course of amphotericin B or an echinocandin is a relatively common practice, although the rationale for these decisions is rarely discernible in published reports (41, 46, 54, 121, 125, 132, 140). The driving force behind this practice is based on a concern for relapsing disease in patients with a newly placed prosthetic device. As such, these decisions are determined on a case-by-case basis and preclude evidence-based recommendations.

There is more agreement for the role of chronic suppressive antifungal therapy with an azole in the setting of prosthetic valve endocarditis (41, 93, 141–143) or if surgery is not performed (41, 132). There are also limited data to suggest that right-sided *Candida* endocarditis has a much lower associated mortality than left-sided disease and could be managed with azole therapy alone in selected cases (144). For those with *Candida* prosthetic valve endocarditis, fluconazole or voriconazole chronic suppression is associated with better outcomes (134), ideally following a 6-week course of primary therapy with an echinocandin or amphotericin B formulation. Data for posaconazole and isavuconazole is limited and these agents should thus be used with caution, but either of them may be useful for chronic suppression. Drug-drug interactions are common with the use of triazoles (e.g., methadone, cyclosporine, tacrolimus) and it is essential to review concurrent medications during therapy. This practice is based on an observed high risk of relapsing disease and death associated with *Candida* prosthetic valve endocarditis (41, 43, 69, 134).

Among patients for whom valvular surgery is either contraindicated or not an option, chronic (lifelong) suppressive antifungal therapy with frequent clinical follow-up is prudent (124, 132). For patients with fluconazole-susceptible pathogens, fluconazole has proven to be both safe and effective and has been administered for years with favorable tolerability (43, 141, 142, 145). Voriconazole, posaconazole, or isavuconazole are options for those in whom fluconazole is not an acceptable therapy (43). Lifelong suppressive antifungal therapy is rarely possible for patients for whom no oral option is available, and sometimes investigational drugs/drugs in clinical development are used in this setting. There are anecdotal reports of successful suppression with ibrexafungerp therapy for more drug-resistant *Candida* spp. (e.g., *N. glabrata* and *C. auris*) (personal communication, G.R.T.).

Complications

Complications in *Candida* endocarditis include both cardiac-related issues and extracardiac manifestations due to septic emboli (Fig. 4). Heart failure from significant valvular regurgitation via valve destruction may occur in 20% to 35% cases, a lower rate than observed in bacterial endocarditis (10, 13, 41, 43, 46, 68, 146). Other complications include abscess formation (17% to 26% of cases) (46, 68), aneurysm, heart block, and myocardial infarction (95, 147–150).

Septic embolism in *Candida* endocarditis occurs in 30% to 80% of cases, with the highest percentage reported in a cohort consisting predominantly of people who injected drugs (10, 13, 43, 46, 53). *Candida* endocarditis affects primarily the mitral and aortic valves. Embolic complications are most frequently observed in the brain, spleen, and peripheral extremities, although virtually any organ may be involved (13, 151, 152). The reported embolic risk tends to be greater than in bacterial endocarditis (20% to 50%), probably due to the overall larger vegetations which are a well-known risk factor for septic embolization (10, 68, 153).

Mycotic aneurysms (dilatation of the arterial wall secondary to infection) may also occur (154). This complication is fortunately rare (95), although it may involve any vascular structure of any size. The presence of a mycotic aneurysm carries a poor prognosis, with reported mortality rates of 60% in those with an intracranial mycotic aneurysm and 80% when a rupture occurs (155, 156).

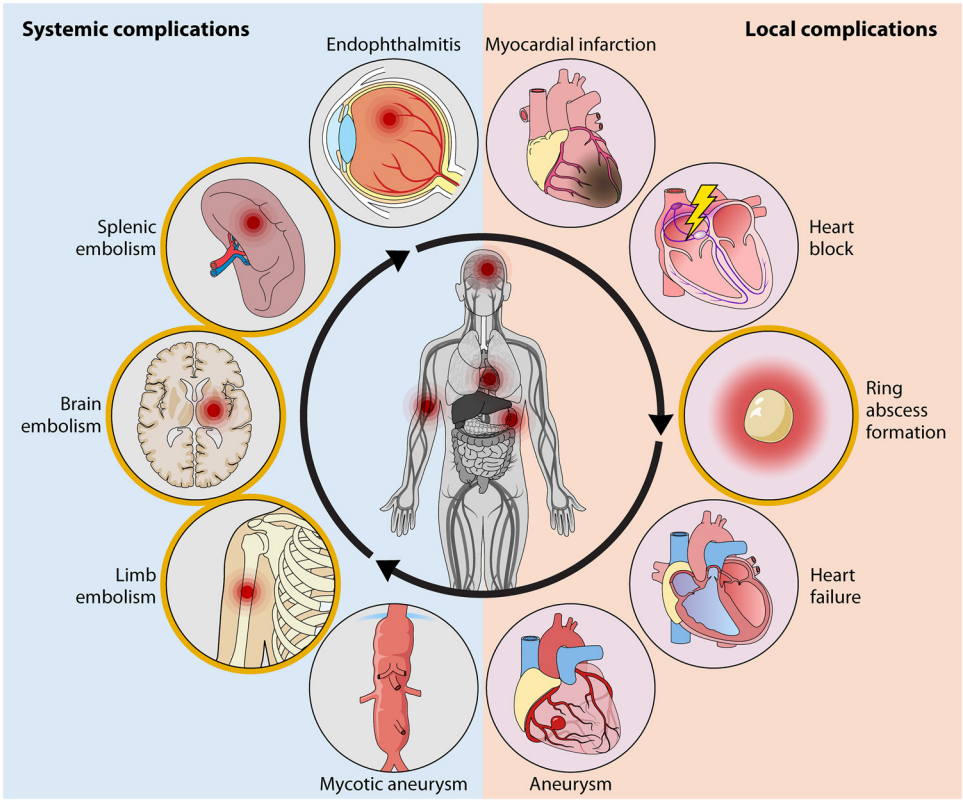

FIG 4 Systemic and local complications of fungal endocarditis. Yellow rim indicates greater risk compared to bacterial endocarditis.

Ophthalmological screening is recommended in candidemia for infectious involvement of the eye based on a randomized clinical trial showing eye involvement in 16% of cases, although this was lower, 11%, in a more recent study (87, 124, 157–159). It should be noted that for *Candida* endocarditis, the incidence of eye involvement varies substantially (5% to 25%) (53, 140).

CRYPTOCOCCUS SPP.

Cryptococcus is a rare cause of infective endocarditis, with fewer than 20 cases reported to date. Prior valvular surgery (repair or replacement) and immunosuppression are the most common predisposing factors, with the mitral valve being most frequently involved (160–166). Surgical treatment has been associated with survival, although a survival bias is likely. Serum cryptococcal antigen (CRAG) testing is highly sensitive for the diagnosis of invasive cryptococcosis, but it is not specific for the site of disease. The majority of cases have been diagnosed in the setting of positive blood or thrombus cultures in conjunction with echocardiography findings (160–166). Guidance regarding treatment is based on therapy for disseminated cryptococcal infection. A lumbar puncture to evaluate for evidence of central nervous system involvement is indicated in all cases of disseminated cryptococcal infection. Surgical consultation in conjunction with combined liposomal amphotericin B and flucytosine for a minimum of 2 weeks followed by long-term fluconazole is recommended. Attempts to improve any host immunologic deficits should also be undertaken.

NON-*CANDIDA*, NON-*CRYPTOCOCCUS* YEASTS

Non-*Candida* yeasts have emerged as significant pathogens in the last decade (167–170). Endocarditis caused by the ascomycetous yeasts *Geotrichum*, *Kodamaea*, *Saccharomyces*, and *Saprochaete/Magnusiomyces* and the basidiomycetous yeasts *Trichosporon*, *Malassezia*, *Rhodotorula*, and *Sporobolomyces* have been reported (5). These yeasts are commensals of the human skin, mucosa, and gastrointestinal tract and are prevalent worldwide and

common in the environment (171, 172). They may be dismissed as contaminants and, unsurprisingly, are often misidentified. Serious disease is most commonly observed in immunocompromised settings, but infections also occur in immunocompetent patients, both with high mortality (173, 174). Fungemia is a common clinical manifestation for uncommon yeast pathogens and is associated with *in situ* central venous access devices (CVADs). Organ involvement is well-described, including dissemination to the liver, spleen, brain, and heart. Endocarditis has been reported and hinges on the timely recognition of disease syndromes. Given the rarity of such infections, the burden of disease is uncertain.

Geotrichum spp.

Many species previously classed as *Geotrichum* spp. have been reassigned to the genera *Saprochaete* and *Magnusiomyces*. *Geotrichum candidum* is the predominant remaining pathogenic species in this genus and is ubiquitous in soil, decaying matter, and food (175). At-risk host groups include those with hematologic diseases, malignancy, and uncontrolled diabetes mellitus (173). Endocarditis is rare, with a single case reported in a child with pulmonary atresia (176).

Kodamaea spp.

Of the *Kodamaea* fungi, *K. ohmeri* is the most well established, yet it is a rare pathogen. Case reports of endocarditis have been described with or without fungemia, which is the most common manifestation of *Kodamaea* infection. Endocarditis has occurred in a neonate with necrotizing enterocolitis (NEC) in the ICU, as well as in adults with underlying heart disease, cardiac prostheses, intravenous drug use, and infectious hepatitis. Embolic phenomena, including splenic infarcts and vascular emboli, have been elucidated by the appropriate imaging techniques (177–179). Vegetations on an echocardiogram are relatively large (11 to 30 mm).

Malassezia spp.

The two species most commonly reported to cause IFD are *Malassezia furfur* and *Malassezia pachydermatis* (180, 181). *Malassezia* are lipid-dependent (except for *M. pachydermatis*) fungi which are stable, dominant components of the human skin microbiome. They form biofilms and can colonize devices such as CVADs. Hence, if the skin is breached, they may enter into the bloodstream in vulnerable populations such as premature babies or patients receiving lipid supplements or parenteral nutrition (5). Fungemia is frequent but endocarditis has been rarely reported, with only one case each in a neonate with NEC and an adult with injection drug use and melanoma (182, 183). However, the frequency is likely underestimated because *M. furfur* does not grow in routine blood culture systems. Of interest, in a study of culture-negative endocarditis, Hammou et al. found *Malassezia restricta* DNA in 3/16 cases, with histopathology showing the presence of fungi consistent with *Malassezia* forms (184).

Saccharomyces spp.

Few cases of *Saccharomyces* endocarditis have been reported (9, 185–190). None of the patients affected were immunocompromised. Five cases occurred in persons with prosthetic valves, as early as 2 weeks post-operatively (9, 187–190), with two of the five cases occurring in persons who had injected drugs (187, 188). In one case, the authors discovered that cocaine injected 2 weeks previously had been adulterated with a flour mix containing dried yeast (188). The diagnosis was usually made from blood culture in the context of a vegetation on the prosthetic valve. Two patients with negative cultures of blood and valve or para-aortic root abscess tissue had the diagnosis confirmed by 18S rRNA sequencing of affected tissue (186, 188). Amphotericin B formulations and/or azoles were typically used. Four patients were also managed surgically, and three who were managed conservatively without surgery recovered with antifungals. Of note, in a review of 20 cases of *S. cerevisiae* var. *boulardii* infection where fungemia was common, endocarditis was not described (191), suggesting the rarity of this manifestation.

Saprochaete/*Magnusiomyces* spp.

Members of the genus *Saprochaete* were previously placed under the genera *Geotrichum* or *Blastoschizomyces*; hence, previous clinical data may be found under the names of these genera. These yeasts likewise commonly cause fungemia and disseminated disease in hematology/oncology patients, including those receiving echinocandin agents, but may also cause disease in immunocompetent hosts. Four cases of endocarditis caused by *Magnusiomyces capitatus* have been reported (under prior nomenclature as *Trichosporon capitatum*) (192, 193): 3 patients had intracardiac prosthetic valves, with 1 having undergone hematopoietic stem cell transplantation, and 1 patient had asthma and was receiving corticosteroid therapy (192).

Rhodotorula spp.

Rhodotorula spp. are found in dairy products and in fomites such as shower curtains (194), as well as in the natural environment. The main pathogenic species are *Rhodotorula mucilaginosa*, *R. glutinis*, and *R. minuta* (195). Fungemia is observed in patients with indwelling CVADs, but endocarditis and other end organ infections have been described (196, 197). The first case was reported in 1960 (198) in a 47-year-old woman with rheumatic heart disease. Since then, at least 10 cases of *Rhodotorula* endocarditis have been reported (197, 199–203). Infection in those with prosthetic cardiac valves (197, 200), in the setting of prior kidney transplantation (197, 203), and in cases of cardiac transplantation have been observed (201, 202). All patients were treated with antifungals (mainly with amphotericin B formulations) and four had cardiac surgery; all patients survived.

Trichosoporon spp. and *Cutaneotrichosporon* spp.

In light of recent taxonomic revisions, a number of clinically relevant species previously classified as *Trichosporon* species, such as *T. cutaneum* (synonym: *T. beigelii*) and *T. dermatis*, were transferred to a new genus, *Cutaneotrichosporon* (204). However, because these changes have not yet been widely adopted by clinicians or microbiology laboratories, and to maintain continuity with the literature, we have chosen to use the old name for *Cutaneotrichosporon cutaneum* (*T. cutaneum*). *Trichosporon asahii* is the most common pathogenic species implicated in human disease, followed by *T. inkin*, *T. faecale*, *T. asteroides*, and *T. coremiiforme* (5, 205). However, among cases of endocarditis, *T. cutaneum* (now: *C. cutaneum*, synonym: *T. beigelii*) predominates (5).

We identified 23 patients reported in the literature with endocarditis caused by *Trichosporon* spp. (206–228). The most common species causative of endocarditis in these genera is *T. cutaneum*, comprising 14 reported cases (209–222), followed distantly *by T. asahii* (3 cases [206–208]), *T. mucoides* (2 cases [225, 226]), and *T. inkin* (2 cases [223, 224]); in 2 cases (227, 228) the species was not specified. All but 1 case (212) occurred in patients with intracardiac prosthetic material. Of these cases, 18 occurred in the setting of prosthetic valves, one patient had infection of an artificial heart (ventricular assist device) (222), 1 had infection of a patch inserted for a ventricular septal defect (207), 1 had a peritoneovenous shunt with the tip extending into the right ventricle to the tricuspid valve (216), and 1 had a cardiac transplantation with vegetations at the aortic anastomotic suture line (228). There were two patients reported to inject drugs, including the only patient who had no history of intracardiac prosthetic material (212, 215). Clinical presentations with embolic phenomena were common and mortality rates were high. Sixteen patients were managed with surgery, and 18 received antifungals. Recalcitrant and relapsing infection has been particularly challenging in some cases, sometimes requiring repeated surgical revision even after many months of therapy (214, 215, 218).

Diagnosis of Rare Yeast Endocarditis

Both laboratory-based and imaging techniques are often required for diagnosis. Blood cultures are essential, as is culture of cardiac tissue obtained at surgery. Of note, blood culture and other media require supplementation with lipids (e.g., olive oil) when *Malassezia* infections are suspected. Gram-stains of blood cultures and heart/vascular tissue provide important clues to rapid presumptive diagnosis where ovoid budding yeast cells with or

without hyphal forms are seen. Monopolar, broad-base budding yeast-like cells are highly suggestive of *Malassezia* spp. Identification of the yeast cultured is enabled through morphology with examination for distinctive arthroconidia or blastoconidia, phenotypic identification systems, MALDI-TOF MS (matrix-assisted laser desorption ionization–time of flight mass spectrometry), and, most definitively, by internal transcribed spacer (ITS) sequencing or *in situ* genome sequencing (IGS) in the case of *Trichosporon* species.

Histopathology using standard fungal stains is also essential for diagnosis and is strongly recommended for cardiac valves. Importantly, although these organisms are 'yeasts', they can exhibit yeast as well as hyphal or pseudohyphal forms *in vivo* and can be visualized as long slender hyphae. Direct detection in tissue by pan-fungal PCR targeting the ITS/IGS region followed by DNA sequencing can also provide rapid diagnosis; the sensitivity is highest when the specimen is freshly obtained and where fungal forms are visualized (229, 230). Susceptibility testing may guide therapy even though neither clinical breakpoints nor epidemiological cutoff values are defined for rare yeasts.

Regarding *Candida* endocarditis, TEE is superior to the transthoracic approach. Echocardiogram is essential for certainty of (pre-surgical) diagnosis and to delineate the extent of the disease. In one case of *Rhodotorula* endocarditis (197), indium-111 labeled leukocyte SPECT scanning showed a high likelihood of infection at the aortic root. More experience is required to establish the diagnostic utility of this and other newer imaging techniques. These diagnostic approaches and their application in clinical practice are summarized in recent guidelines for the management of rare yeast infections (5).

Treatment of Rare Yeast Endocarditis

The principles of management are similar for rare yeasts and consist of antifungal susceptibility testing of the isolate, antifungal therapy, and surgery. Early engagement with surgical colleagues for consideration of vegetectomy or valve replacement is essential. In general, a longer period of induction treatment (at least 6 to 8 weeks for native valve and up to 1 year for prosthetic valve infection) is required (5) followed by long-term (1 to 2 years) suppressive therapy, especially when surgery is not performed. Treatment duration should be guided by clinical responses and other factors such as unresected lesions, retained intra- or extracardiac prosthetic material, and immunosuppression.

In contrast to *Candida* spp., the non-*Candida* rare yeasts generally exhibit elevated MICs to the echinocandins, and this class is not recommended. In general, amphotericin B formulations are the preferred agents, with the notable exception of *Trichosporon* infections, for which an azole is preferred (231, 232). Table 2 shows the first-line or preferred treatment, alternative options, and which agents not to employ for these yeast infections. CVADs should be removed where possible (5).

Aspergillus

Epidemiology and risk factors. *Aspergillus* endocarditis accounts for approximately one-fourth of all fungal endocarditis cases. More recent estimates suggest that the incidence has declined, potentially from the use of antifungal prophylaxis in highly immunocompromised patients (233). *Aspergillus* endocarditis occurs primarily in males and in those with underlying cardiac abnormalities, those with prosthetic valves, the highly immunosuppressed, those who inject drugs, and those with implantable cardiac devices (233–236). Environmental exposures have been associated with hospital outbreaks, with contamination during surgical procedures or in the postoperative setting (233, 237, 238). Cardiac surgery seems to play a particular role as an independent risk factor for *Aspergillus* endocarditis. Among 124 cases of postoperative *Aspergillus* endocarditis reported in 2006, none of the patients were immunosuppressed or had evidence of bronchopulmonary aspergillosis (239). In another study, 74% of patients with *Aspergillus* endocarditis had a history of recent surgery (68% with prior cardiac surgery) (240). In children, congenital heart disease is the most common risk factor (241). The majority of cases are caused by *A. fumigatus*, followed by *A. terreus*, *A. niger*, and *A. flavus* (242), although cryptic species have been described (233, 243).

TABLE 2 Antifungal drug treatment in patients with fungal endocarditis caused by *Candida*, *Aspergillus*, rare molds, rare yeasts, and endemic fungi, by causative pathogen[a]

Pathogen(s)	First line (preferred) agent	Alternative agent	Agents to avoid
Candida spp.	L-AmB ± 5-FC or echinocandins (high dose)	L-AmB + 5-FC/echinocandins or echinocandins + 5-FC/FLU	FLU (for initial therapy)
Aspergillus spp.	VRC or L-AmB	POS or ISA	AmB-d
Rare Molds			
Mucorales	L-AmB ± echinocandin	POS or ISA	AmB-d
Fusarium spp.	VRC ± L-AmB	L-AmB	AmB-d
Lomentospora spp.	VRC + TRB	VRC	L-AmB
Scedosporium spp.	VRC	VRC+ L-AmB/echinocandin/TRB	L-AmB
Phaeohyphomycoses	POS or VRC ± echinocandins/TRB	L-AmB ± echinocandins	AmB-d
Scopulariopsis	ISA or VRC ± L-AmB	L-AmB	
Paecilomyces spp.	L-AmB ± POS	POS	
Rare yeasts			
Cryptococcus spp.	L-AMB + 5FC	FLU	Echinocandins
Kodamaea ohmeri	L-AmB or D-AmB	Echinocandins	-
Malassezia spp.	L-AmB	D-AmB	-
Pseudozyma (*Moesziomyces/ Dirkmeia)* spp.	L-AmB	VRC	FLU, echinocandins
Rhodotorula spp.	L-AmB ± 5-FC	D-AmB ± 5-FC	Triazoles, echinocandins
Saccharomyces spp.	L-AmB or D-AmB	FLU or echinocandin	-
Saprochaete/Magnusiomyces spp.	L-AmB ± 5-FC	VRC	Echinocandins
Sporobolomyces spp.	L-AmB	VRC	FLU
Trichosporon spp.	VRC or POS	FLU or POS	Echinocandins
Endemic mycoses			
Blastomyces spp.	L-AmB followed by ITR		
Coccidioides spp.	L-AmB followed by azole		
Histoplasma spp.	L-AmB followed by ITR		
Sporothrix spp.	L-AmB ± ITR		

[a]5-FC, 5-flucytosine; ABLC, amphotericin B lipid complex; AmB, amphotericin B; AmB-d, amphotericin B deoxycholate; FLU, fluconazole; ISA, isavuconazole; ITR, itraconazole; L-AmB, liposomal amphotericin B; POS, posaconazole; TRB, terbinafine; VRC, voriconazole. Adapted from previous treatment recommendations (4–6, 81, 126, 304, 305). Antifungals are adjunctive to surgical evaluation.

Diagnosis, Clinical Presentation, Complications, and Prognosis

Diagnosis is often difficult to make and almost always delayed, with diagnosis made postmortem in up to one-third of cases (240). Fever, the presence of a new murmur, heart failure or dyspnea, and stigmata of peripheral emboli, such as new neurologic deficits, are the most commonly encountered clinical features, and extracardiac manifestations are common (Fig. 5) (233, 244). However, fever is less common in *Aspergillus* endocarditis than in endocarditis from other causes (233, 244).

Blood cultures are generally negative in *Aspergillus* endocarditis. When blood cultures are positive, *Aspergillus* are more likely to be a contaminant than to represent true fungemia (245). Histopathology and culture of resected valvular tissue or emboli is the most common method used to confirm a diagnosis. The use of noninvasive diagnostics such as serum GM

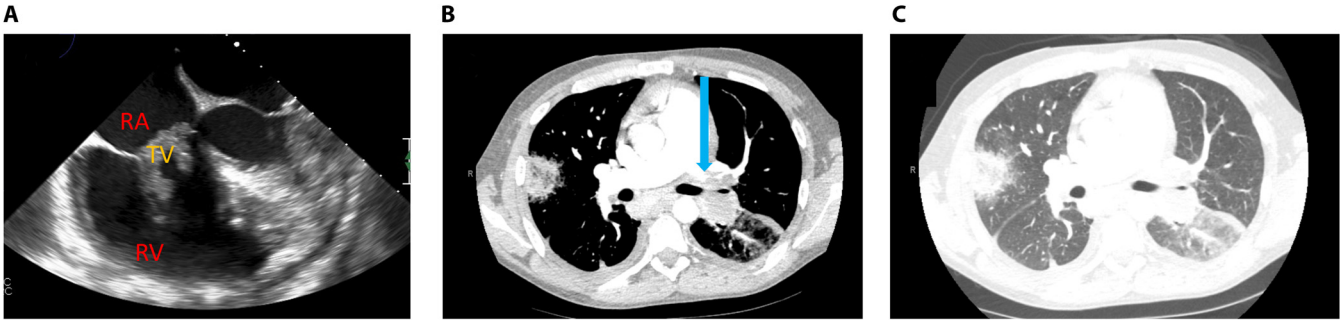

FIG 5 Tricuspid valve endocarditis caused by *A. fumigatus*. (A) Off-axis, 4-chamber view of large tricuspid valve (TV) vegetation on transesophageal echocardiogram (right atrium, RA; right ventricle, RV). (B) Left pulmonary artery embolus (blue arrow). (C) Peripheral consolidative opacity from emboli.

or BDG may be positive, but these are not specific for the site of disease (246), and additional diagnostic testing should be performed in an attempt to ensure that the correct diagnosis is made because GM and BDG assays may cross-react with other fungi (247). If GM testing is positive, this test may be useful to monitor the response to therapy (248). Molecular testing for *Aspergillus* spp. remains limited in the United States, but is commercially available in Europe, Australasia, and parts of Asia-Pacific (12, 249, 250) and has been used to confirm the diagnosis on resected tissue (233). The performance characteristics of PCR vary and are dependent upon the different technologies, cycle thresholds for positivity, microbial targets, and study populations (104, 251). Similar to GM and BDG testing, a positive *Aspergillus* PCR result may suggest active infection, but is not specific to any site. Serial PCR testing may be useful to monitor the response to therapy although no data in this regard are available yet. The aortic and mitral valves are most frequently infected (233). Multi-valve involvement is not uncommon (234). Prior valvular abnormalities and/or prior valvular surgery or prosthetic material particularly predisposes to vegetations by *Aspergillus* spp., either on prosthetic valves or the wire of pacemakers (235); however, affected native valves have also been reported, mostly in persons who inject drugs (240, 244). Echocardiographic features of *Aspergillus* endocarditis include large and/or pedunculated vegetations, which are associated with a high likelihood of large or catastrophic embolic complications in the absence of positive blood cultures.

Aspergillus vegetations, often the first sign of infection, may cause life-threatening emboli due to their size, and occur more frequently in *Aspergillus* endocarditis compared to bacterial endocarditis (16). Aortotomy site vegetations and aortic abscess/pseudoaneurysm are also commonly seen in *Aspergillus* endocarditis (244). Patients with *Aspergillus* endocarditis may also progress to *Aspergillus* pericarditis, or undergo rupture of chordae tendineae, leading to acute valvular decompensation (16, 252). Various additional complications, including pulmonary hypertension as a result of septic embolism to the lung, have been described (253). Radiographic imaging of any symptomatic site and of the brain are indicated to fully delineate the extent of disease because these findings may significantly impact surgical management. Mortality rates are high (50% to 95%) (69, 240) and the mean survival period in one study was only 11 days from the time to diagnosis (3).

Treatment

A combined medical and surgical approach (valve replacement) is paramount in attempts to improve patient outcomes because neither alone has a significant influence on patient outcomes (16, 254, 255). Surgery aims to remove endocardial vegetations, as they are responsible for the catastrophic complications and contribute to the high mortality rates in *Aspergillus* endocarditis, to replace infected valves, and to aid diagnosis (16). Furthermore, in cases with embolic complications, surgical resection of the embolic mass may be indicated to restore blood circulation. In the case of *Aspergillus* vegetations on pacemaker wire, surgical removal via either intravascular retraction methods or thoracotomy (particularly if vegetations are larger than 1 cm, where the risk of fatal embolic events during retraction is high) is performed (236, 256). Host factors, comorbid conditions, and the presence of complications/emboli at the time of diagnosis may significantly impact the decision for surgical intervention. Treatment with antifungal agents alone is rarely successful; only 4% (2/53) of cases were treated successfully with antifungal therapy alone, while 17 of 53 reported cases (32%) who received combined surgery and antifungal treatment survived the acute episode of *Aspergillus* endocarditis (234). In another study, only 1/17 cases survived with antifungal treatment alone (240). Current guidelines recommend voriconazole or liposomal amphotericin B (3 to 5 mg/kg per day) as first-line agents (257). Prospective data are not available and are unlikely to be presented. Recommendations are therefore based on case reports (256), case series (240), and animal models of infection (258). Combination antifungal therapy, such as with an azole and an echinocandin, may also be used (259). Alternative treatment options may include isavuconazole or posaconazole; in the future, monotherapy with olorofim and fosmanogepix or combination therapy with liposomal amphotericin B and fosmanogepix or ibrexafungerp, for example, may be options (260–262).

The high mortality rate limits guidance on recurrence rates and recommendations for long-term therapy or follow-up. Recurrence may occur late, in some cases years after the

initial diagnosis. Long durations of therapy are recommended, and consideration for lifelong therapy should be discussed with the patient to prevent recurrence (240).

NON-*ASPERGILLUS* MOLDS

Data on endocarditis caused by rare molds are nearly exclusively available from case reports and small case series (4). It is evident that endocarditis occurs more frequently in certain rare mold infections (e.g., 10% of invasive *Paecilomyces* infections [263], 4% of phaeohyphomycoses [264], and relatively often in patients with scopulariopsis [265] or lomentosporosis [266]), while it is extremely rare in cases of mucormycosis or fusariosis. These differences may be due to the affinity of some of these organisms, particularly *Paecilomyces* and *Scopularia* spp., to cause foreign body infection, resulting in an accumulation of prosthetic valve endocarditis cases caused by these pathogens.

Mucormycosis

Endocarditis remains a very rare manifestation of mucormycosis despite the increasing incidence of these infections (267). When endocarditis does occur, it is predominantly caused by *Cunninghamella* spp. (268–271) (although small numbers of cases caused by other Mucorales, such as *Rhizomucor miehei* [272], have been reported) and occurs almost exclusively in immunocompromised patients (268–273). Very rarely, Mucorales endocarditis may occur in immunocompetent hosts (274), such as persons who inject drugs and/or those with prosthetic valves (275). Native valve endocarditis has been described in most case reports to date (268–273), but prosthetic valve endocarditis in people with and without injection drug use has also been observed (275, 276). Diagnosis in those cases was achieved by detection of Mucorales from valves or valve tissue post-surgery or at autopsy. Galactomannan and BDG testing are negative in patients with mucormycosis (277), and while a number of biomarkers have been described and are in various stages of clinical development (278), no other biomarker is currently available for clinical use. PCR testing is commercially available (MucorGenius, PathoNostics, Maastricht, Netherlands; MycoGenie, Ademtech, Pessac, France; and Fungiplex, Bruker, Bremen, Germany) (279), although we are unaware of any reports using PCR directly from blood for the diagnosis or follow-up of Mucorales endocarditis, while there are reports in which PCR analysis was used to identify vegetations (270). Despite aggressive and prompt treatment with high-dose liposomal amphotericin B and surgery, the outcome is nearly always fatal (280). Future treatment options include combination therapy with liposomal amphotericin B and synergistic new compounds (281, 282).

Fusariosis

Despite the relative frequency of fungemia in cases of fusariosis (4), surprisingly few cases of *Fusarium* endocarditis have been reported to date, although disseminated disease including the heart is seen in progressive uncontrolled infection. *Fusarium solani* species complex (283–286) and *Fusarium keratoplasticum* (287) have caused primarily native valve endocarditis (283, 284, 288), occurring in the immunocompromised (283–288), with three cases reported in children (283, 286, 289). Blood cultures or direct detection of *Fusarium* spp. from tissue or valves may confirm the diagnosis, with voriconazole or liposomal amphotericin B (or the combination of both) being the recommended first-line treatment together with surgery (4).

Scedosporosis

To date, few cases of endocarditis caused by *Scedosporium* have been reported. *Scedosporium apiospermum* infection of a native valve is responsible for approximately half of all cases (290–292), and is the cause of pacemaker and prosthetic valve endocarditis in the other half (293–295). Risk factors for native valve endocarditis included penetrating trauma (292), prolonged hospitalization (291), and immunosuppression after heart transplantation (290). Diagnosis is made by blood culture or culture and/or panfungal PCR from infected tissue or valves, and the antifungal treatment of choice, in combination with surgery, is voriconazole (4).

Lomentosporosis

Fungemia is a frequent clinical manifestation of lomentosporosis, with blood cultures yielding *Lomentospora prolificans* growth in about half of cases (296). The risk of dissemination in hematopoietic stem cell transplant and solid organ transplant patients depends on the type of transplantation and immunosuppressive regimen (297). However, few cases of *L. prolificans* endocarditis have been reported, and predisposing conditions include the presence of prosthetic valves or intracavitary devices (266, 298–300). Systemic, cerebral and/or pulmonary emboli, and other metastatic complications have been described in all reported cases, including septic arthritis, endophthalmitis, and meningitis (266, 298). Cases of endocarditis are more frequent in lomentosporosis than in other mold infections, and current guidelines recommend echocardiography (preferably TEE) when clinical suspicion arises (4, 298). Disease is uncommon in non-immunocompromised patients but has been reported (266, 298, 301, 302). In most immunocompromised hosts, *Lomentospora* endocarditis occurs as a breakthrough infection in patients receiving mold active antifungal prophylaxis (298, 303). Susceptibility testing commonly shows *in vitro* resistance to all currently available antifungals (299). Reported cases have received combination antifungal therapy with a mold-active triazole in conjunction with liposomal amphotericin B (298, 299), with the combination of voriconazole and terbinafine being the recommended first-line treatment for *Lomentospora* infections in general (4). Future treatment options may include olorofim or fosmanogepix, novel antifungals that are currently in late-stage clinical development (262). Surgical intervention is undertaken in ~50% of cases (299), yet mortality rates are ~80% overall and close to 100% in immunocompromised cases (266, 298, 299). Patients with right-sided endocarditis associated with a removable intracardiac device have a more favorable prognosis than other groups (266).

Phaeohyphomycoses

Melanized molds may cause endocarditis after valve replacement (304–306) or affect native valves (264, 307). While cases of prosthetic valve endocarditis have occurred in immunocompetent patients (304–306), 3 out of 4 patients with native valve endocarditis were solid organ transplant recipients, while the other patient was not immunosuppressed (264, 307). In one large study, 3/79 (4%) of cases with phaeohyphomycosis had endocarditis, indicating that endocarditis may be a relevant manifestation of disseminated phaeohyphomycosis (264). Blood cultures were positive in most reported cases, and all reported patients had large (>1-cm) vegetations noted on echocardiography (264, 304–307). A variety of fungal species were found as causative pathogens, including *Exophiala dermatidis*, *Thermomyces lanuginosus*, *Verruconis gallopava* (formerly *Ochroconis gallopava*), *Fonsecaea pedrosoi*, and *Curvularia lunata* (264, 304–307). Combination therapy with voriconazole/posaconazole plus an echinocandin or terbinafine has been used in most survivors (264, 305–307), while azole monotherapy was associated with failure in 3 out of 4 patients (264, 304, 305).

Scopulariopsis

There are several reports of prosthetic valve endocarditis caused by *Scopulariopsis* spp., highlighting the affinity of this rare mold to cause foreign body infections (9, 265, 308–315). Of note, all cases reported to date have been caused by *Scopulariopsis brevicaulis* (311). *Scopulariopsis* spp. can be difficult to distinguish from *Aspergillus*, *Fusarium*, or *Scedosporium* spp. by morphology alone, and therefore species-level identification with molecular techniques should be performed (316). *S. brevicaulis* is known to show resistance to broad-spectrum antifungal agents such as amphotericin B, flucytosine, itraconazole, voriconazole, and terbinafine (311, 317); therefore, antifungal susceptibility testing, even in the absence of defined clinical breakpoints, may be important for the selection of an optimal antifungal regimen (4, 309, 311). Given the high relapse rates, long-term suppressive therapy with antifungals after medical and surgical treatment of endocarditis has been recommended (9, 309, 311, 318, 319). Successful management has been reported with surgery and long-term combination antifungal therapy often containing voriconazole

or isavuconazole in conjunction with liposomal amphotericin B, followed by chronic suppression (309, 311).

Paecilomyces spp.

Among 59 cases of *Paecilomyces variotii* infection reported in a recent study, 6 (10%) had endocarditis affecting prosthetic heart valves while others had infections of other indwelling devices (29/59; 49%), and infection can be seen in immunocompetent and immunocompromised patient populations (263, 320). The mortality of prosthetic valve endocarditis is high, 67% (263, 320), although previous cases (prior to 2009) had mortality rates approaching 100% (321–325). Diagnosis is made either via blood cultures or by detection of the mold in infected tissue or explanted heart valves. Treatment is usually liposomal amphotericin B (4), often in combination with a mold-active azole and aggressive surgery (263, 320).

Other Rare Molds

Disseminated infections caused by *Penicillium* spp. have been rarely reported (4), including 3 case reports of endocarditis, all occurring in patients with prosthetic valves (326–328). Two case reports have described endocarditis caused by *Purpureocillium lilacinum*, in both cases complicated by subaortic aneurysm (329, 330). A single case of endocarditis caused by *Coprinus* spp. has also been reported (331).

ENDEMIC MYCOSES

The diagnosis of endemic mycoses has been recently reviewed in detail (104, 332, 333). Endocarditis with these organisms is infrequent and requires a high index of suspicion.

Blastomyces

There have been few cases of endocarditis due to *Blastomyces* spp. These have presented in late stages of disease, with a large intracardiac mass and respiratory failure (334), coronary artery dissection with disseminated disease (335), and left-sided endocarditis with renal, meningeal, and visceral emboli (336). The diagnoses in these cases were based on detection of the fungus in bronchial washings, arthrocentesis cultures, and autopsy findings, respectively. Treatment should consist of lipid amphotericin followed by itraconazole therapy (see Table 2).

Coccidioides

Coccidioidal endocarditis is also rare, even in patients with *Coccidioides* detected in blood cultures (337, 338). All patients reported to date have had multifocal coccidioidomycosis and involvement primarily of the mitral or aortic valves. Serologic testing was positive in all patients, although complement fixation titers varied widely (1:1 to 1:2,048) (339). Histopathology of the resected valve was positive for coccidiodal forms in all but one case. A mortality rate of 67% has been reported based on a review of previously identified cases. A combined surgical approach with a lipid amphotericin B formulation followed by a triazole is indicated.

Histoplasma

Histoplasmosis is the most common cause of endocarditis among the endemic mycoses, yet fewer than 100 cases have been reported. In areas where *Histoplasma* spp. are endemic, they may cause around 14% of fungal endocarditis cases; 3/21 fungal endocarditis cases observed at the Mayo clinic between 1970 and 2008 were caused by *Histoplasma capsulatum* (82). *Histoplasma* endocarditis is most common in men (~80%) with pre-existing diabetes mellitus, chronic pulmonary disease, or known cardiac valvular disease (340). Prosthetic valves are most often affected, and in one case series of 14 cases within a decade across medical centers in the US, 10/14 had an infected prosthetic aortic valve (341). The diagnosis is commonly made based on urine or serum *Histoplasma* antigen positivity, which appears to have a higher sensitivity in those with prosthetic valve involvement. *Histoplasma* serology is positive in over 90% of cases (340, 341). Histopathologic evaluation of the resected valves is positive in almost all cases. Dissemination is common with the diagnosis confirmed on

cultures from distant sites (bone marrow, blood culture) (340). Combination surgery and antifungal treatment with a lipid amphotericin B formulation is recommended, followed by itraconazole. In many cases, lifelong suppression with itraconazole or another triazole is administered (340–342).

Sporothrix

Sporothrix spp. are not considered highly virulent in immunocompetent persons and typically cause localized infection in cutaneous and subcutaneous tissues. Infection can result in dissemination in immunocompromised persons, such as those with HIV infection (343, 344) or chronic immunosuppressive therapy such as tumor necrosis factor alpha (TNF-α) antagonists (345). There has been only a single case to date reported in a patient with HIV and disseminated sporotrichosis. Valve replacement in conjunction with amphotericin B and itraconazole for 12 months was successful (346).

FUTURE DIRECTIONS AND CONCLUSION

While fungal pathogens remain a relatively rare cause of endocarditis, fungal endocarditis remains a major challenge for microbiologists and clinicians alike. In light of mortality rates of over 70%, early diagnosis and appropriate treatment initiation remain essential to reduce embolism and other life-threatening complications. Microbiological diagnosis often relies on blood culture results, which are particularly insensitive for *Aspergillus*, other molds, and endemic fungi but also show imperfect sensitivities for *Candida* and rare yeasts. Molecular testing including next-generation sequencing presents a hypothesis-free unbiased approach that may detect a broad range of pathogens, including novel and rare pathogens, and may overcome some of those limitations in the future. Echocardiography in conjunction with microbiological evidence remains the gold standard for clinical diagnosis of fungal endocarditis, but given its frequent atypical presentation as a subacute disease without classic endocarditis signs and symptoms, there is a need for further research on the optimal pathways that trigger echocardiography. Future studies will need to identify risk factors that trigger echocardiography in patients with candidemia, as well as other fungal diseases, for guidelines to find common ground in their recommendations. More data are also needed on the performances of radionuclide imaging modalities such as immune PET-MR/CT, which may be increasingly utilized in patients with fungal diseases and may improve diagnosis of fungal endocarditis (347). While surgery and valve replacement will remain a mainstay of treatment, changes are on the horizon for systemic antifungal therapy, where, after 2 decades of stagnation, new agents and antifungal classes are now in late-stage clinical development. These new antifungal agents include broad-spectrum agents with biofilm activity that can be given orally, such as ibrexafungerp, fosmanogepix or—for some molds and endemic fungi—olorofim. In addition, rezafungin, an echinocandin with extended half-life allowing for once-weekly administration (348), may present another promising option facilitating the treatment of fungal endocarditis, including long-term/lifelong treatment in patients where surgery is not an option.

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George R. Thompson III, M.D., is a professor of Medicine at the University of California-Davis School of Medicine with a joint appointment in the Department of Medical Microbiology and Immunology and the Department of Internal Medicine, Division of Infectious Diseases. Dr. Thompson specializes in the care of patients with invasive fungal infections and has research interests are in fungal diagnostics, clinical trials, novel antifungal agents, and host immunogenetics. Dr. Thompson has served on the IDSA Journal Club is a member of the Coccidioidomycosis Study Group Planning Committee, and as chair of the Mycoses Study Group Education Committee. He has been active in the field of mycology for over 15 years and has published over 200 manuscripts to date.

Jeffrey D. Jenks, M.D., M.P.H., is the Medical and Laboratory Director at the Durham County Department of Public Health (Durham, North Carolina, United States) and an Adjunct Associate in the Division of Infectious Diseases, Department of Medicine, at Duke University. He received his M.D. and M.P.H degrees from the Wright State University Boonshoft School of Medicine (Fairborn, Ohio, United States), completed his internal medicine internship and residency at Boston Medical Center (Boston, Massachusetts, United States), and completed his infectious diseases fellowship at the University of California San Diego (La Jolla, California, United States). He has published over 50 peer-reviewed scientific manuscripts. His research interests include clinical mycology, the epidemiology of fungal diseases, sexually transmitted infections, and the intersection between social determinants of health and infectious diseases.

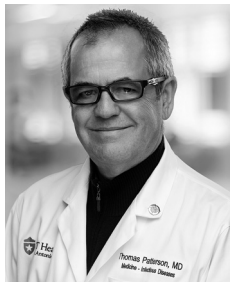
John W. Baddley, M.D., is a Professor of Medicine in the Division of Infectious Diseases at the University of Maryland School of Medicine. He was previously a Professor of Medicine in the Division of Infectious Diseases at the University of Alabama at Birmingham. After receiving an undergraduate degree from the University of North Carolina at Chapel Hill, Dr. Baddley earned his medical degree from Louisiana State University (LSU) School of Medicine, New Orleans. He completed an internship and residency at LSU Medical Center and fellowship in infectious diseases at University of Alabama at Birmingham. His clinical work focuses on management of infections in the immunocompromised host, and he has been a clinical mycologist for over twenty years.

James S. Lewis II, PharmD, is the co-director of the Oregon Health Sciences University (OSHU) antibiotic stewardship program and serves as the infectious diseases clinical pharmacist for OHSU. He is the co-chair of the antibiotic subcommittee of the Clinical Knowledge and Therapeutics Executive Committee (formerly Pharmacy and Therapeutics Committee) and also serves as the PGY-1 and 2 ID rotation preceptor. Dr. Lewis' professional interests are antibiotic susceptibility testing, antibiotic/antifungal utilization, and the optimal integration of rapid microbiology diagnostics in antibiotic stewardship. Dr. Lewis also currently serves as the co-chair of the breakpoint working group of the Clinical and Laboratory Standards Institute (CLSI) and is a member of the editorial board for Antimicrobial Agents and Chemotherapy.

Matthias Egger, M.D., is a research assistant at the Division of Infectious Diseases in Graz, Austria. He received his tertiary education at the Medical University of Graz and currently works on his doctoral thesis focusing on the lung mycobiome and fungal translocation in patients with liver cirrhosis. He is part of the Translational Medical Mycology Research Unit, ECMM (European Confederation of Medical Mycology) Excellence Center for Medical Mycology, Medical University of Graz, Austria with its PI Hoenigl. His primary research interests include diagnostics of invasive fungal infections, novel antifungal agents, and the composition of the gut and lung mycobiome in health and disease. He is a member of the ECMM, ISHAM, and ESCMID, especially its young associations.

Ilan S. Schwartz, M.D., PhD., is an associate professor of infectious diseases and clinical researcher whose primary interests include invasive fungal disease, immunocompromised hosts, and global health. After clinical and research training in Canada, South Africa, Belgium, and the United States, he joined the University of Alberta before joining Duke University School of Medicine in 2022. There, he is an Associate Professor of Medicine and Medical Director of the Division of Infectious Diseases Clinical Research Unit. He is a board member of the Mycoses Study Group Education & Research Consortium and is a Fellow of the European Confederation of Medical Mycology and the Infectious Diseases Society of America.

Johannes Boyer, M.D., is a resident of the Division of Infectious Diseases at the university hospital of the Medical University of Graz, Austria, where he also earned his MD in 2020. He is a dedicated researcher with a passion in the field of invasive fungal infections. His interests lie in diagnostic strategies and new therapeutic approaches for the management of invasive fungal infections.



Thomas F. Patterson, M.D., is a professor and division chief of infectious diseases at the University of Texas Health Science Center in San Antonio. His clinical and research interests focus on the diagnosis and treatment of fungal diseases. He has been involved in developing new antifungal drugs and in clinical trials of new antifungal compounds, and is funded by the NIH and industry for grants and contracts on drug and diagnostic development. He has conducted pre-clinical studies and clinical trials for invasive mycoses and received the UTHSA Presidential Distinguished Research Scholar award. He has been a co-chair or member of the IDSA *Aspergillus* Guideline committees. Dr. Patterson has published and lectured extensively with over 350 peer reviewed publications, chapters, books and reviews. He has served as a member of the American Board of Internal Medicine, Subspecialty Committee for Infectious Diseases, and is a Fellow of the American College of Physicians and the Infectious Diseases Society of America, Past-President of the Texas Infectious Disease Society, and past-President of the International Immunocompromised Host Society.

Sharon C.-A. Chen, M.D., is an Infectious Diseases physician/Clinical Microbiologist at Westmead Hospital, Institute of Clinical Pathology and Medical Research, Sydney, Australia. She received her tertiary education at The University of Sydney. Her PhD focused on *Cryptococcus* epidemiology and phospholipase enzymes. She is the Director of the Centre of Infectious Diseases and Microbiology Laboratory Services, which incorporates reference functions for diagnostic mycology, including governance and service provision for regional NSW laboratories. At Westmead Hospital, she undertook primary clinical liaison for the stem cell and solid organ transplant services until 2022 and continues to perform laboratory liaison. Dr. Chen's long-standing interests include fungal disease epidemiology, translation of new diagnostic tests into practice, antifungal drug resistance, and novel agents. She is a primary investigator of national antifungal drug trials and has coordinated national/international fungal management guidelines. A founding member of the Australia and New Zealand Mycoses Interest Group, she has links with the ECMM and the MSC-ERC.

Peter G. Pappas, M.D., is a Professor of Medicine and has been an active University of Alabama- Birmingham site investigator and chair of the Mycoses Study Group over the last fifteen years. He has also served as Protocol Chair or Co-Chair for multiple MSG studies. Dr. Pappas' specific interests include the epidemiology of invasive fungal infections and investigation of newer antifungal agents for the treatment and prevention of invasive fungal infections. He has published clinical data concerning a wide variety of invasive mycoses, including cryptococcosis, blastomycosis, sporotrichosis, invasive candidiasis, and invasive aspergillosis.

Martin Hoenigl, M.D., is an Associate Professor for Translational Mycology at the Division of Infectious Diseases, Medical University of Graz, Austria. After his graduation and clinical education at the Medical University of Graz, he became an Associate Professor of Medicine at the Division of Infectious Diseases and Global Public Health at the University of California San Diego, before returning to Graz for his new appointment. Hoenigl has a particular interest in conducting research on clinical mycology, including fungal diagnostics, host-fungal pathogen interactions, and pharmacology of antifungal drugs; he has been in the field for over 15 years, and has published over 300 scientific papers. Hoenigl is the current president of the ECMM. He serves as an Associate Editor at Open Forum Infectious Diseases (OFID) and a Deputy Editor at Mycopathologia. More information on Hoenigl is available on his Clinical Mycology YouTube channel and on Twitter under @martinhoenigl.