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Review

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"*Not much room for mushrooms*" in the heart: knowns and unknowns of fungal infective endocarditis

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Abstract

Fungal infective endocarditis is a rare but highly lethal condition. Its diagnosis is often delayed due to nonspecific symptoms, inconclusive medical imaging, and negative blood cultures. Recent reviews of cases and series over the last 5 years indicate that the condition remains rare and lethal. If fungi are identified as the causative agents in more than 5% of patient cases with infective endocarditis, it is likely that risk factors such as immune suppression or cardiac implants are probably involved. A series derived from recent case reports indicates that *Candida* and *Aspergillus* are still the main causative infectious agents, with. *C parapsilosis* on the rise. From these cases, diagnostic clues (frequent embolisms, ophthalmic involvement, large, mobile and friable vegetation, non-valvular cardiac manifestations) are pointing towards fungal IE. These reports, however, are not standardized and a publication bias towards rare microorganisms or towards a favorable outcome might exist. Complications might be underreported, and important data such as diagnostic delay are absent or difficult to retrieve. Pharmacologic treatment is not fully standardized. Knowledge of resistant strains in this respect is important. Statistical analysis for the effect of complications and treatment modalities on outcome shows that any result should be treated cautiously. The current series is by no means a valid substitute for a well-designed series of fungal endocarditis. However, the better outcome with *Candida* and patients treated with surgery confirm earlier results. An international multicentric standardized registry of cases with fungal endocarditis in order to improve the outcome of this disease is highly needed. The effect of diagnostic delay on outcome remains elusive and should be resolved.

Keywords: Endocarditis, diagnosis, complication, management, mortality

INTRODUCTION

Infective endocarditis (IE) has a low incidence but a high mortality and complication rate[1]. The available series studying IE are usually small and randomized controlled trials are absent. IE is typically observed in patients with pre-existent valve disease, valve prostheses, and specific risk factors such as an immune compromised state or a colorectal neoplasm serving as port-of-entry[2]. Fungal IE is even more uncommon compared to bacterial IE. Often, blood cultures are negative[1,3], but echocardiographic changes might offer some clues in fungal IE[4]. Its incidence, however, is expected to rise because of the increase in cardiac implants and the prolonged use of intravenous catheters and antibiotics[3]. The two most common microorganisms in fungal IE are *Candida* and *Aspergillus*. *Candida* IE carries an early mortality rate of almost 50%. Long-term data are scarce[5]. Aspergillus accounts for about a quarter of fungal IE, is difficult to diagnose, has mostly a negative blood culture, and is therefore a risk for a delayed diagnosis. Cardiac surgery is a necessary part of the treatment. Mortality after the procedure is also high[3] and the diagnosis is often post-mortem[6]. Other fungal IE such as *Trichosporon*, *Histoplasma*, *Cryptococcus*[7-9], and other rare species should also be held into account in patients with risk factors. Since this is an evolving field, the research questions focus on the last 5 years. These are

- (1) What is the rate of fungal IE in published series?

- (2) What organisms have been identified in the cases published?

- (3) What are the short and long-term outcomes of fungal IE?

- (4) Are these cases sufficiently documented with respect to potential predictors for outcome, especially with respect to delayed diagnosis?

- (5) Are there recently developed management policies for fungal IE?

METHODS

This is a systematic review based on the Web of Science source. The search terms "endocarditis AND fung*" were used. Using simple search terms limits the risk of missing important manuscripts. A search of the last 5 years resulted in 1,741 hits, with 1,601 articles. Exclusion criteria were articles concerning pharmacologic and environmental issues. Reviews, editorials, and manuscripts describing entirely pediatric series were excluded. From the remaining 708 manuscripts, only full articles with explicit analysis of fungal endocarditis (n = 30) were included. Articles referring to "other microorganisms" and "negative culture" were too vague to consider and were also excluded. In a second round, 86 reports describing 91 cases were studied for known risk factors, estimated time between first symptoms and diagnosis being > 30 days, emboli and especially stroke, heart failure, cardiac abscesses, acute renal injury, type of fungus, antifungal treatment, surgical treatment, surgery indicated but deemed too risky, hospital mortality, long-term survival. The effect of risk factors on hospital mortality was analyzed with a chi-square analysis and significant factors were entered in a multivariate logistic regression, to identify independent predictors. One- and three-year survival rates were estimated by a Kaplan-Meier analysis.

RESULTS

Rate of fungal microorganisms in the included series of infective endocarditis

The prevalence of fungal IE in large series is summarized in Table 1. Thirty series could be identified. There is a large variation in the rates of fungal IE, which ranges from less than 1%[10-16], between 1% and 2%[17-29], between 2% and 5%[30-34], to over 5%[35-39]. The latter series included patients with an immune compromised

Table 1. The incidence (rate) of fungal infection in the included series of endocarditis

Refs.	n/N	% fungi	Time span	Comment
Acibuca *et al*. 2021[10]	1/139	0.7	2009-2019	Descriptive series
Berisha *et al*. 2022[17]	14/749	1.9	2008-2020	PVE series
Cahill *et al*. 2019[12]	6/706	0.8	2008-2016	Congenital heart disease
Vallejo Camazón *et al*. 2019[19]	5/271	1.9	2003-2018	Surgery *vs*. no surgery
Cao *et al*. 2020[39]	7/62	11.3	1997-2018	PVE, stroke
Chen *et al*. 2020[35]	16/678	2.4	2015-2019	NLR as predictor
Chuang *et al*. 2019[36]	1/70	1.4	2008-2014	Transplant
Elad *et al*. 2020[20]	1/92 6/128	1.1 4.6	2013-2016	Effect IE-team: pre : post
Fosbøl *et al*. 2019[18]	6/422 12/584	1.4 2.9	2008-2012	Vegetation size: small : large
Geirsson *et al*. 2020[30]	361/11,756 351/23,149	3.1 1.5	2011-2018	STS-IV drug pts STS-other patients
Gröning *et al*. 2019[37]	2/23	8.7	NS	RVOT repair
Guo *et al*. 2021[31]	4/124 15/414	3.2 3.6	1997-2017	Hemodialysis: yes : no
Gutierrez-Villanueva *et al*. 2021[22]	6/27 8/407 39/3,242	22.2 2.0 1.2	2008-2017	Mural IE Device IE Valve IE
Houhamdi *et al*. 2021[33]	3/16	18.8	2011-2015	BCNE
Jeronimo *et al*. 2022[11]	18/1,655	1.6	1998-2020	*Candida*
Jia *et al*. 2019[21]	3/161	1.9	2007-2016	Evaluate diagnostic criteria
Martinez *et al*. 2021[26]	82/4,696 7/4,696 3/18	1.7 0.1 16.7	2008-2019	*Candida* (all patients) Other fungi (all patients Other fungi tHTx patients)
Mir *et al*. 2022[27]	1122/255,838 250/16,670	0.5 1.7	NS	All IE nationwide Fatal IE nationwide
Okura *et al*. 2021[28]	0/59 3/179	0.0 1.7	1998-2008 2008-2019	Pre infect dept consult Post infect dept consult
Pasupula *et al*. 2019[29]	683/48,500	1.4	2010-2014	Fungal IE constant
Polewczyk *et al*. 2021[13]	8/1,241	0.6	2006-2017	CIED
Ponnambath *et al*. 2021[38]	13/47	27.7	2010-2020	PVE
Pyo *et al*. 2021[32]	3/56 4/213	5.4 1.9	2013-2019	PVE NVE
Ragnarsson *et al*. 2021[14]	5/864 5/806 2/516	0.6 0.6 0.4	2006-2017	< 65 year age class 65-79 year age class > 80 year age class
Ramanathan *et al*. 2021[34]	13/296 4/215	4.4 1.9	2013-2016	Not invasive at surgery Invasive at surgery
Rodger *et al*. 2019[15]	1/212 5/68	0.5 7.4	2007-2017	First IE in IV drug Recurrent IE in IV drug
Salsano *et al*. 2019[23]	3/191	1.6	2000-2019	Surgery, BCNE
Sousa *et al*. 2021[16]	10/7,574	0.1	2010-2018	Trends
Sunder *et al*. 2019[24]	46/4,003	1.3	2011-2011	BCNE excluded
Tahon *et al*. 2021[25]	3/270 1/10	1.1 10.0	2000-2007	First IE Early recurrent IE

BCNE: Blood culture negative endocarditis; CIED: cardiac implanted device IE; HTX: heart transplantation; IE: infective endocarditis; IV: intravenous; NLR: neutrophil-lymphocyte ratio; NS: not stated; NVE: native valve endocarditis; PVE: prosthetic valve endocarditis; STS: the society of thoracic surgeons database.

state such as after transplantation[36] or with prosthetic valves[38,39]. Most authors group all fungal IE in one category[13,15-20,29,30,32,34-36]; some only mention *Candida* ssp[10,15,22-24,28]. or specify the *Candida* subspecies[11,21,37,39], or group *Candida* together with *Aspergillus*[25] or focus on one specific agent such as *Malassezia*[33].

Most series are descriptive; some compare subgroups of patients, such as the effect of the installation of an endocarditis team[20,28], size of vegetation over *vs*. under 10mm, and IV drug users *vs*. non-drug users[18,30]. Other authors studied the effect of hemodialysis[31], certain subtypes of IE (valvular *vs*. mural *vs*. electronic device IE), the effect of immune suppression in heart transplant patients, fatal *vs*. non-fatal cases[26,27], prosthetic *vs*. native valve endocarditis, age classes, invasiveness of IE at surgery[14,32,34], and first *vs*. recurrent IE[14].

Case reports

In 86 reports, 91 cases of definitive fungal IE were described. These reports involved fifteen cases with *Candida parapsilosis*[40-54], seven cases with *C. albicans*[55-61], three cases with *C. tropicalis*[62-64], eight other species with *Candida*[65-72], eight cases with *Candida* with a bacterium[73-80], ten cases with *Aspergillus fumigatus*[81-90], nine cases with other species of *Aspergillus*[91-99], four cases with *Cryptococcus*[100-103], four cases with *Histoplasma*[104-107], four cases of *Trichosporon*[108-111], two cases of *Fusarium*[112,113], one case of *Scediosporium*[114], *Chaetomium*[115], *Malassezia*[116], *Rhizomucor*[117], *Exopholia*[118], *Purpureocillium*[119], *Sarocladium*[120], *Paecilomyces*[121], *Cunninhamella*[122], *Geotrichum*[123], *Bipolaris*[124] and *Volvariella*[125]. In this case series, 74 patients were males. The mean age was 57+/-17.5 years. Thirty-six patients had a prior implanted valve prosthesis, 16 patients had other implants, of which 7 were pacemakers, 25 patients were immune compromised because of prior transplant, or steroid treatment for auto-immune disease, and 11 patients were IV drug users. Symptoms of fungal IE were usually insidious, non-specific, and heterogenous, including asthenia, feeling of weakness, anorexia, fever, headache and weight loss. In 30 cases, there were sudden embolic phenomena such as stroke or limb ischemia. Symptoms and signs suggestive of congestive heart failure were present in 14 cases, but distinguishing these from pulmonary infections was not always straightforward.

A blood culture was almost universally performed, but these were not always positive [Table 2]. Often, a culture or a histologic examination of a valve specimen (native or prosthetic) or thrombus after surgical treatment was necessary. This additional examination was performed for most patients as further identification of the involved infective microorganisms. In some cases, a culture was performed after bronchoalveolar lavage to detect *Aspergillus*[81,89,93], *Fusarium*[113], *Rhizomucor*[117], and *Cunninghamella*[122]. Cerebrospinal fluid was examined in two patients with a *Cryptococcus* infection[100,102] and in one with a *Volvariella* endocarditis[125]. A urine examination was performed on three patients infected with *Histoplasma*[104,106,107]. Skin lesions and skin appendages were examined in cases with Histoplasma[105], Trichosporon[111], and *Fusarium*[112]. Table 2 shows the most common fungal agents, mostly *Candida* ssp. and *Aspergillus* ssp., followed by *Cryptococcus*, *Histoplasma*, and *Trichosporon*. The table lists only the most common subspecies, the reference, the number identified in the case series, the number with positive blood culture, and the rate of delay of more than 30 days. The rate of positive blood cultures for *Candida* was 32/44 or almost 75%, while for *Aspergillus*, this rate was much lower (4/23). A delay in diagnosis of 30 or more days was documented in 33 cases; in 24 other patients, there was no report of delay. In spite of more negative blood cultures in *Aspergillus*, compared to *Candida*, the delay in diagnosis for *Aspergillus* IE was not higher. In patients with emboli, the delay to diagnosis was more often shorter, but this was not significant (1/7 *vs*. 21/48, $P = 0.223$).

In many cases with negative cultures or difficulties in identifying the infecting fungal microorganism, beta-D-glucan testing was performed. This was needed in a minority of *Candida* infections[51,54,55] but more often in *Aspergillus*[81,84,87,90,92,96] and certain other fungal species[101,106,107,118,120-124]. Detection for the presence of galactomannan was also performed in IE by *Aspergillus*[85,89,92,93] and other uncommon species[112-114,120,121,125]. Matrix-Assisted Laser Desorption Ionization Time-of-Flight Mass Spectrometry (MALDI-TOF MS) has been developed to sequence proteins, map biomolecules in tissues, identify microorganisms, and analyze

Table 2. Fungi in case reports

Microbial agent	Reference	Number	Positive culture	Delay > 30 days
Candida (all)	[40-80]	44	32	13/30 (43.3%)
- *C. parapsilosis*		19	16	
- *C. albicans*		10	6	
- *C. tropicalis*		4	3	
Aspergillus (all)	[81-99]	23	4	6/19 (31.6%)
- *A. fumigatus*		14	4	
Cryptococcus	[100-103]	4	4	1/3 (33.3%)
Histoplasma	[104-107]	4	1	3/4 (75.0%)
Trichosporon	[104-107]	4	2	2/4 (50.0%)

several biochemical assays in a short time. It was used in five patients with *Candida* infection[52,63,66,68,72], and in 5 patients with other species[109,111,113-116], but not with *Aspergillus*. Quantitative polymerase chain reaction (qPCR) with genetic sequencing was performed in only one patient with *Candida* infection[71], three with *Aspergillus* infection[81,92,95], and for several other microorganisms[112,117,122,124,125]. To document and, if necessary, treat ocular involvement, an ophthalmic examination was performed in ten patients with *Candida* infection[45,49,52,56,57,59,62,63,76,78], five patients with *Aspergillus*[81,87,88,93,97], and three patients with other species[113,114,124].

Transthoracic (TTE) and transesophageal (TEE) echocardiography were almost universally performed in the included case reports since this imaging modality is a cornerstone in the diagnosis of native and prosthetic infective endocarditis. Most of the cases underwent computer tomographic (CT) imaging and MRI of the brain, thorax, abdomen, and pelvis, as well as CT-angiography, encompassing almost all infective species involved. A positron emission tomography or PET/CT scan was performed in order to confirm or exclude other septic foci for various fungal species such as *Candida*[50,60,69,80], *Aspergillus*[96,97], and other infective agents[104,119].

IE was left-sided in 71, right-sided in 14 and on both sides in 6 cases. Reporting of the pharmacologic treatment for fungal IE was not standardized. Amphotericin was used in 63 cases, Azoles in 55 cases, Echinocandins in 41 cases, and Flucytosine in 15 cases. Monotherapy was used in 25 cases, mostly with amphotericin. There was a switch in treatment in 25 patients because of lack of effect. Valve surgery and removal of fungal balls were performed in 55 cases. In 10 patients, an electronic cardiac device was removed. Surgery was indicated in another 11 cases, but was not performed because of the poor condition of the patients. The need for emergent surgery (< 24 h) is almost nowhere described. Complications are not described in a uniform way and are therefore probably incomplete. Most frequently, thromboembolism affects the brain, liver, spleen, kidneys, and limbs. A cardiac abscess was documented in 14 cases, but heart failure was rarely reported. The renal condition was mentioned in only 35 reports: it remained unaffected in 8 cases, while in 27 cases, there was impaired renal function. Twenty-nine patients (31.9%) died within the hospital. Long-term survival was recorded in 56 patients, but only 27 of them had a follow-up duration of 12 months or more. A chi-square analysis showed that hospital mortality was significantly lower with *Candida vs.* non-*Candida* (6/42 *vs.* 23/49, $P < 0.001$), while *Aspergillus vs.* non-*Aspergillus* showed significantly higher mortality (11/23 *vs.* 18/70 with $P = 0.047$). Left-sided IE was also unfavorable (26/73 *vs.* 2/18, $P = 0.044$). Valve surgery was protective against mortality (11/55 *vs.* 15/34, $P = 0.015$). However, patients deemed too sick to undergo cardiac surgery fared not significantly worse (5/12 *vs.* 3/4, $P = 0.248$), but numbers were low and might be incomplete. Other factors such as gender, antifungal drug type, IV drug use, other cardiac implants or central venous lines, immune suppression, emboli, cardiac abscesses, a negative blood culture, and delay of diagnosis of > 30 days showed no significant effect. This window was chosen somewhat

arbitrarily[76]. Remarkably, patients with prior cardiac surgery did better (7/36 *vs*. 23/55, $P = 0.036$), although they had no less delay of diagnosis, nor did they undergo more cardiac surgery for the current episode of IE. Multivariate logistic regression analysis showed a protective effect of cardiac surgery (odds ratio 0.15, $P = 0.001$), and patients with *Candida* IE (odds ratio 0.15, $P = 0.004$) also fared better. The effect of prior cardiac surgery lost its significance for mortality. Data on long-term survival are notably incomplete due to the limited data available in the case reports. Observed one-year survival was 83.0+/-5.6% (26 patients reported) and 3-year survival was 73.7+/-10.0% (8 patients reported). A delay in diagnosis of > 30 days showed a trend for lower 1-year survival: 74.2+/-10.1% *vs*. 95.0+/-4.9% ($P = 0.079$). None of the other factors had an effect on long-term survival.

DISCUSSION

The designs and the patient sample sizes of the included series [Table 1] varied considerably. Fungal IE is mostly between 1 and 4%, while the most common infectious agents are *Staphylococci*, *Streptococci*, and *Enterococci*. Only in series with known risk factors such as valve prosthesis implant, immune compromised states such after transplantation, IV drug use, or special manifestations such as mural IE, the rate of fungal IE exceeds 5%. These sample sizes, however, are much smaller, indicating that it is difficult to collect large series with fungal IE. Furthermore, the majority of the included series group all fungal infective agents in one category as "fungal" or as "*Candida*" without further specification. *Aspergillus* is mentioned only once. Nevertheless, from prior reports[1] and current cases, it can be derived that *Candida* and *Aspergillus* are dominant. However, the currently included case reports are by no means a substitute for a properly designed patient series since there is no uniformity with respect to patient inclusion, diagnostic work-up, or treatment. As a result, many complications may be underreported and there might be a publication bias concerning the uniqueness of a case or an unexpected outcome. This could be the reason for the surprisingly low mortality rate of the current case series, particularly those with prosthetic valve endocarditis (PVE)[1,53,58,80,89,103,107]. However, in line with prior observations, *Candida* species, with a reported 40%-60% rate[44,52,57,60,69,62,94,96,123,126], is the most frequently reported infectious agent in the current case series. *Candida parapsilosis* is the most frequent non-albicans fungus causing IE[] and exhibits an escalating trend[11,53]. Corresponding with prior reports, the outcomes associated with *Candida*-related IE in the current case series are more favorable and cardiac surgery protects against early death. Following *Candida*, *Aspergillus* emerges as the second most significant fungus, which accounts for about 25% of fungal IE cases[81,88,89,95].

Signs and symptoms of fungal IE

Although signs and symptoms can vary significantly and are non-specific, fungal IE has some peculiarities. First, emboli are more frequent in fungal IE compared to bacterial IE, and their occurrence might offer a clue. These emboli can be related to large fungal vegetations, which are friable and highly mobile[43,52,56,57,76,78,90,93,95,98,99]. Stroke was documented in 29 of the included cases, while splenic, renal, pulmonary, or peripheral embolism were documented in 20 cases. Endophthalmitis and ophthalmic emboli should be reasons for an ophthalmologic examination[49,50,57,71,78,87,88,97,114]. Second, prior valve implantation and electronic cardiac implants or indwelling central catheters should also raise suspicion. An infection of ascending aortic graft is also a cause for concern[96,121,123]. Prior valve replacement might lead to sooner detection of fungal IE[106]. Third, immune compromised conditions[71,83,107,120], such as post-splenectomy[82] organ transplantation or malignancy[45,85,100,112-114,117,122,125], or need for steroids for other reasons[16,46,81,93], also offer an indication. However, some immunocompetent patients could suffer from fungal IE[121] and risk factors may either be absent[99,101] or restricted to an indwelling urinary catheter[59,67]. Fourth, other clues can be IV drug use[40,55,57,61,66,73,74,92], hemodialysis[16,94], an earlier IE[56,61], or extended treatment by antibiotics for other reasons[54,70,86,101]. Last, a high index of suspicion for fungal IE should be maintained in patients with sepsis, negative blood culture before any antibiotic treatment, and known risk factors who do not respond

well to broad-spectrum antibiotics. In the absence of proof of fungal IE, antifungals are not considered till late in the course of disease progression. Rapid diagnosis and treatment for fungal IE are essential for good outcomes[48,83,87,97,98]. Some fungi with low virulence can become widespread before causing symptoms[121].

Blood cultures are a first pillar in the diagnosis of IE. At least three sets of blood cultures from separate venous puncture sites should be obtained[127]. A negative culture can occur in over 50% of the cases[43,48,58,74,80,126]. A negative culture can delay the diagnosis of IE with all its consequences. Reasons for this are prior antibiotic treatment, inadequate microbial techniques, fastidious organisms, and non-bacterial pathogens such as fungi. Culturing fungi requires mediums rich in carbohydrates, nitrogen, and a pH of 5-[128], but there is no "one size fits all" scenario. After discussion with clinical laboratory experts, serial blood testing or incubation for several weeks can be considered necessary since these organisms are fastidious[41,55,64,90,102,107,118]. So-called negative results should not be discarded[86,96,102,104]. *Candida* is likely to be recovered as a causative agent in blood cultures, but a timely diagnosis of *Aspergillus* endocarditis remains elusive. When viable *Aspergillus* hyphae enter the bloodstream, they might be sequestered through endocytosis by endothelial cells, which could lead to endothelial cell injury and thrombosis. The only fungal elements that circulate in the bloodstream are non-viable, which explains the negative culture in many cases[54,82-84,86]. *Aspergillus* endocarditis was diagnosed postmortem in approximately one‐third of cases and was diagnosed preoperatively in less than half of patients[97]. For *Histoplasma*, serologic examination can be performed[106], which is useful in areas where this organism is endemic[104,106,107]. Another difficulty arises when bacteria and fungi are identified simultaneously[73,77,78,103] or cultures are positive for bacteria without demonstration of fungi, while the latter can be found in the excised valve, indicating a mixed infection. The presence of bacteriemia should not reduce the suspicion of fungal IE, if other indicators such as large vegetation and emboli are present[74]. Valve specimens, infected grafts[96], abscesses[88], and vegetations or emboli can be cultured and examined by histology and immunohistochemistry. Sometimes, identification can only be obtained postmortem[48,120]. Cultures and histology of cutaneous nodules[112,114], systemic ulcers, or abscesses[55] can also give an early identification of the agent.

Microbiologic diagnosis of fungal IE

Other advanced diagnostic techniques include the detection of 1,3-β-D-glucan and mannan for *Candida*[41,43,48,51,83,92,106] or for *Aspergillus*[84,85,89,95,96,102] and other fungi[52,107,118,121,123], but these methods are time-consuming[107] and are not always easily available[48]. Clearance of these antigens by neutrophil WBC can explain false negative results[89,95]. This method could shorten the time to start an adequate antifungal treatment[74,89]. For 1,3βDglucan, sensitivity is lower, but specificity remains high. For *Aspergillus*, the detection of galactomannan can be helpful. Molecular methods such as polymerase chain reaction (PCR) for the detection of fungal DNA can be used on blood or valve tissue in cases of negative blood cultures. The method is culture-independent and could give clarification in case of a contaminant. The results are rapidly obtained and large sequences are available in public databases. The method makes no distinction between viable and dead microorganisms, and false positive results can be obtained. Treatment success cannot be assessed with PCR[127]. Pan-fungal PCR of blood, with real-time PCR targets for 18S-rRNA and 28S-rDNA[41,43,71,83,92,112,121,125,126], has been used for *Aspergillus*[81,94,95], *Mucormycosis*[117], and *Sarocladium*[120]. Metagenomic next-generation sequencing is culture-independent[83,94,124,127,126] and allows the detection of fungi as causative agents of IE. It remains longer positive after the commencement of treatment. It is an efficient, rapid, and high-output technique that uses parallel and simultaneous sequencing of a multitude of gene fragments to determine the sequence of nucleic acid content from a sample. It can also identify fungi and antimicrobial resistance genes and responses to antimicrobial treatment. It allows the earlier institution of directed antifungal treatment with improved outcomes. The availability of this expensive and complex technique is limited, and if a specimen has to be sent out to a reference laboratory, results can be delayed. The method makes no distinction between viable and dead microorganisms. There is a contamination risk

with skin residing *Candida* and the method is not standardized[127,128]. The matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) system is a complementary technique, which can analyze large proteins. The sample of fungi is crystallized within a matrix. By using a laser, the sample is ionized without being decomposed, and analyzed in a mass spectrometer. The data are analyzed by a specially designed software program and compared with a high number of pre-existent profiles. This method is cheap and quick and could become necessary in identifying unusual *Candida* species with different behavior[52,66,68] or in cases for the distinction between a contaminant and rare pathogens[111,113,115].

Echocardiographic evaluation of fungal IE

Medical imaging is a second pillar in the diagnosis of fungal IE. Transthoracic and transesophageal echography (TTE/TEE) are the first-line imaging modalities in the diagnosis of IE, the assessment of severity of disease, presence of paravalvular involvement, cavitary lesions, mural lesions, risk of embolism by sizing vegetation, and follow-up of treatment. If TTE is inconclusive and a degree of suspicion remains, TEE is indicated. Transesophageal echocardiography is more sensitive and specific compared to TTE, but serial examination is often required[41], especially with a graft of the ascending aorta[96], in cases with ICD[103] or valve prosthesis[110]. Repetition of these imaging modalities after 5 to 7 days has been[1] recommended. Transesophageal echocardiography is also recommended when the patient is stable before switching from intravenous to oral antibiotic treatment (class IB), according to the latest ESC guidelines[1].

However, even repeated TEE can remain negative for some time[61]. Some echocardiographic features point to fungal IE, such as large vegetations[48,57,64,68,78,84,99], obstruction of a valve prosthesis[42,51,73,105,123], presence of fungal balls[76,91], and mural, intracardiac and other non-valvular manifestations[79,81,82,85,99,112,113,114,120,122]. TEE increases the diagnosis in TTE-negative patients, but this invasive procedure carries the risk of embolization[38]. In cases with inconclusive imaging but a remaining degree of suspicion, PET/CT techniques can lead to improved detection of paravalvular lesions, especially in PVE. The radiolabeled glucose analog accumulates in activated inflammatory cells. Qualitative and quantitative analysis of the high-resolution images is possible, but proper patient preparation is needed with a high-fat but low-carbohydrate diet for at least 2 meals. PET/CT is of less value in patients with native valve IE because of low sensitivity[38,129]. A PET/CT scan can be needed to detect fungal dissemination[16,69,114,119] or local extension of the infection[80,96].

Other imaging modalities in fungal IE

A cardiac CT can be needed to demonstrate the vegetation or filling defect[123] or cardiac abscesses[85]. Cardiac MRI can sometimes be necessary for the distinction between invasive aspergilloma and a tumor of the heart[69,98,99]. CT/MRI of other regions is part of the work-up, especially in cases of stroke or infarctions and abscesses of other solid organs.

For *Candida* IE, Amphotericin with surgery should be the mainstay[1,124], except for *C. lusitaniae*, which has a rapid mutation rate[66,67]. Liposomal Amphotericin formula is less nephrotoxic[40,45,47,77,82,106,121]. A combination of antifungal therapy with flucytosine or an echinocandin appears to offer a survival benefit over single-agent treatment[1,86]. Antifungal treatment reduces the risk of embolism within 2 weeks[63]. *C. parapsilosis* poses specific problems: it is a nosocomial microorganism on the rise, with often a delayed identification in blood culture[11], and a different type of biofilm compared to *C. albicans*. Biofilms are responsible for certain types of resistance[109,110], but Amphotericin can still act on it[49,52,82,92]. Antifungal susceptibility testing with minimal inhibitory concentrations with appropriate cut-off values is needed, especially when resistance is suspected[65,72,92]. Echinocandins are also recommended against *Candida*[16,49,56,76] because of their activity against fungal biofilms[65,109]. Afterwards, a step down towards oral fluconazole is possible if the microbial agent is susceptible[46,53]. However, fluconazole is fungistatic[43,63] and is not a first

choice in *Candida* IE, also because of the increasing resistance of *C. parapsilosis*[46,49,70].

Medical treatment of fungal IE in the acute phase

A liposomal amphotericin B preparation has been designed to reduce the nephrotoxicity, but it retains the antifungal activity. It has become a major component in the treatment of opportunistic fungal infections for over 20 years. The long half-life allows for intermittent administration. It was administered in patients with *C. parapsilosis*[45,46,49-52] and other *Candida* species[63,65,70] or a combination of *Candida* with a bacterial IE[74,75,77], but not in patients with *C. albicans* infection. It has also been applied in several species of *Aspergillus*[81,82,84-87,89,90,92,95-98], one patient with *Cryptococcus*[100], all patients with *Histoplasma*[104-107] and *Trichosporon*[109-112], as well as in some other fungal species[112,113,116,117,121-124]. Nevertheless, it was reduced in dosage in one of the cases[124] and had to be discontinued in two other cases with renal failure[116,121]. Voriconazole, fluconazole, caspofungin, micafungin were other often administered preparations. The regimen changed in some cases according to therapeutic failure and patterns of resistance. For *Aspergillus* IE, voriconazole seemed a first-choice drug[81,82,85,87,89,95]. An echinocandin or Amphotericin could be associated[1]. Amphotericin, however, could antagonize voriconazole[81], and resistance of *Aspergillus* against voriconazole is rising[87,94]. Voriconazole might be synergistic with caspofungin in some cases of Aspergillus, but this can be strain-dependent[92]. Echinocandins, in combination with azoles, can be considered as salvage against *Aspergillus*[81], but their value in association with Amphotericin is doubtful[92]. Terbinafine has also been used against *Aspergillus*[111]. For other types of fungal IE, such as *Cryptococcus, Mucormycosis, Histoplasma, Paecilomyces,* or *Trichosporon*, Amphotericin and some azoles have also been used[101-103,107,109,117,121,122]. There are possible pharmacologic interactions in antifungal treatment. Fluconazole might interact with warfarin, which is sometimes given to treat emboli[54]. In case of mixed bacterial/fungal infection or in patients needing immune suppression, interactions with antibiotics should also be anticipated[45,84,117]. There could also be an antagonism between Amphotericin and azoles, but this complex issue is not established and is dose-dependent[86].

Surgical approach for fungal IE

Surgery is needed in most cases of fungal IE, especially in cases where antifungal medication penetrates biofilms poorly[67], for abscesses debridement[65] or to prevent embolism[57]. Determining the optimal timing of surgery following cerebral events with hemorrhagic transformation poses challenges[41,84,87,93,110]. Early surgical intervention should be considered, particularly for patients with bulky and friable vegetation and biofilms on implanted materials[38,41,43,46,47,49,51,52,70,116], fungal PVE, and risk of recurrence, especially in the case of Aspergillus[82,85,86,87,88]. Without surgery and proper antifungal treatment, the prognosis of Aspergillus[85,88,104] or histoplasmosis and other fungal IE is dismal[43,106]. In the case of fungal IE, all central catheters, pacemakers, and internal defibrillators should be removed as early as possible[58,72,78,89,103].

The initial management for fugal IE should be followed by long-term treatment. Regimens recommended for PVE by *Candida* have an induction phase of 6 weeks with amphotericin or caspofungin, followed by lifelong suppressive maintenance therapy with high-dose fluconazole. Fluconazole for *Candida* and voriconazole for *Aspergillus* are recommended to prevent relapse[46,64,66,85]. Sometimes, this is for life, after fungal PVE[47,58,70,73,119], or when surgery is indicated but cannot be performed[43,76,47,70,111]. However, this issue is still debated[41,43,74,88,92,89,110,116].

Outcome of fungal IE: mortality

In spite of aggressive treatment, fungal IE had an early mortality of 40% to 50%[11,41,44,46,49,57,64,69,76,78] and 1-year mortality was up to 59%[57]. Prosthetic valve endocarditis by *C. parapsilosis* has a much higher complication (including emboli) and mortality rate compared to bacterial PVE[38]. Need for admission to the ICU, organ failure, and the presence of a central venous catheter were risk factors. Removal of these catheters had a

positive effect on outcomes at any time, while the inability to remove the catheter increased mortality[130]. Other factors for worse outcomes were large vegetation with a risk for embolization or an immune compromised state[52,126]. In the latter patients, it seemed reasonable to start an empirical antifungal treatment when fever persists and antibiotics are ineffective[126]. An older meta-analysis[131] showed that antifungal monotherapy without surgery had a poor prognosis. Brain abscesses have an estimated mortality of 85%-100%[41]. Consultation with an infection specialist from the Endocarditis Team is recommended[1,45,46,65,124] to optimize management and prevent resistance. Times to evaluation could become shorter and more adequate. A survey revealed that the endocarditis team improved communication between specialties by preventing fragmentation of information, influencing diagnostic evaluation, reducing management errors, and increasing access to surgery, thereby decreasing in-hospital mortality[132]

LIMITATIONS

This analysis has the limitations of any retrospective analysis of heterogeneous, observational studies and case reports. Patient series rarely elaborate on the fungus species. The presentation of the cases is not standardized. The only common factor is the diagnosis of definitive fungal IE. A distinction between right-sided and left-sided IE has not been made in this analysis. The uncontrolled variables are patient characteristics and medical and surgical management. There is a risk of underreporting complications. Above all, the delay in treatment has hardly been investigated. This makes it impossible to draw firm recommendations from the included cases. There is also potential for publication bias towards cases with rare fungi, or a favorable outcome, or a certain treatment modality. There is little mention in the individual reports of long-term suppressive antifungal therapy, so it is impossible to analyze how that may have impacted treatment outcomes. A long-term follow-up remains significantly incomplete.

CONCLUSION AND FUTURE DIRECTION

Fungal endocarditis remains a rare but highly lethal condition. *Candida* and *Aspergillus* are still the dominant microorganisms. Risk factors are prior implanted cardiac devices and valves, IV drug use, and immune suppression. Clinical symptoms and signs are unspecific, but imaging data such as large vegetation and non-valvular manifestation are suggestive of fungal IE. Additional imaging for locale extension and embolic complications is indispensable. Early diagnosis and prompt surgical intervention coupled with optimal antifungal therapy under the guidance of a specialized endocarditis team are the only options to reduce the extremely high mortality and morbidity. Due to the low incidence of fungal IE, most information available comes from case reports or small series, as currently included. Therefore, one can expect a lack of uniformity in the approach to this condition. Questions still unresolved are (1) what is the effect of a delay of diagnosis on outcome; (2) how can this delay be reduced effectively; (3) what is the most effective long-term strategy to reduce relapse; and (4) is the individual outcome more determined by the virulence of the fungi or by the pre-existing condition of the patient? To address these questions, a dedicated IE team has been recommended in the most recent ESC guidelines[1] for the treatment of fungal IE. Moreover, a multicenter international registry with a standardized diagnostic and therapeutic approach and recording of the treatment outcome is still lacking. The establishment of such a registry could be helpful in improving the results. The factors which need to be included are listed as a Supplementary Material.

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