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Fungal endocarditis. A retrospective analysis from a high-volume surgical centre and review of the literature

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Abstract

Purpose Fungal endocarditis (FE), a rare but severe subset of infective endocarditis (IE), accounts for 2–4% of cases, with significant morbidity and mortality despite combined clinical and surgical interventions. The incidence of FE has been rising due to an increase in patients with predisposing risk factors, such as prosthetic heart valves, indwelling central venous catheters, prolonged fungemia, and intravenous drug use, alongside advancements in diagnostic techniques. Diagnosing FE is challenging due to nonspecific symptoms and often negative or delayed blood culture results, necessitating repeated cultures and sometimes surgical specimen collection for confirmation. FE is associated with a higher incidence of extracardiac complications, such as systemic and central nervous system embolization, compared to bacterial endocarditis.

Methods This study retrospectively analyzed 687 patients with non-device-related IE admitted to a high-volume surgical center from January 2013 to December 2023, identifying 8 cases of FE (1.2%). The diagnostic work-up followed European Society of Cardiology guidelines, including blood cultures and echocardiography. Management involved a multidisciplinary team approach, combining antifungal therapy and early surgical intervention.

Results Despite advancements, the prognosis of FE remains poor, with a mortality rate exceeding 50%. Early diagnosis and timely intervention, including early surgery, are crucial for improving outcomes.

Conclusion This study and the review of the literature aim to enhance understanding of FE by reviewing clinical presentations, diagnostic challenges, and management strategies, emphasizing the importance of a high index of suspicion and comprehensive diagnostic evaluation in high-risk patients.

Keywords Fungal endocarditis, Cardiac surgery, Prognosis, Diagnostic workup

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Introduction

Fungal endocarditis (FE) accounts for only 2–4% of all infective endocarditis (IE) cases but is associated with substantial morbidity and mortality despite combined clinical and surgical treatment. In recent years, the incidence of FE has been rising, primarily due to the growing number of patients with predisposing risk factors (such as prosthetic heart valves, indwelling central venous catheters, prolonged fungemia, or intravenous drug use) and advancements in diagnostic approaches [1–3]. Diagnosing FE is challenging due to nonspecific symptoms and often negative or delayed blood culture results [2], requiring repeated cultures and sometimes surgical specimen collection for confirmation [1–3]. FE is associated with a higher incidence of extracardiac complications, such as systemic and central nervous system embolization, compared to bacterial endocarditis [3]. Considering the rarity of this condition, we described 8 cases of FE and reviewed the available literature to increase knowledge of this challenging valve infection.

Methods

Patient selection

We retrospectively analyzed 687 consecutive patients with non-device-related IE admitted to our high-volume surgical center between January 2013 and December 2023. The study was approved by the local ethics committee (Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana), with the approval date of March 13, 2018 (Registration number: 12113_oss). The local ethics committee, in accordance with statements by the Italian Regulatory Authorities for retrospective, observational studies, granted a waiver of informed consent from study participants. The study was approved in accordance with the revised Declaration of Helsinki. Additionally, all alive patients or their relatives confirmed the agreement to participate in the study when contacted for follow-up and signed informed consent for publication in the case series. Data were extracted from electronic hospital records, anonymized, and secured with password protection. All patients agreed to participate in the study when contacted for follow-up and signed informed consent for publication.

Diagnostic work-up

We followed current European Society of Cardiology (ESC) guidelines for diagnostic work-up and treatment strategies [4]. Accordingly, three sets of blood cultures were collected on admission, and transthoracic and transesophageal echocardiography (TTE and TOE) were performed in all patients for diagnosis confirmation. Systemic embolism was evaluated using clinical assessment and imaging, including brain, chest, and abdominal CT scans or ultrasound. All patients were treated with empirical and, whenever feasible, targeted antimicrobial therapy. FE was diagnosed through blood cultures, which were processed using standard microbiological techniques, clinical presentation, and echocardiographic findings, following the European Society of Cardiology guidelines [4].

Surgical indication and operative technique

A Heart Team, including a cardiac surgeon, a cardiologist, an anesthesiologist, and an internist, evaluated each patient. Surgical risk was estimated using EuroSCORE II, and surgery was advised according to current European Society of Cardiology guidelines [4].

Results

Clinical presentation and treatment of the 8 patients with FE

Table 1 summarizes the main clinical and microbiological characteristics of the 8 patients with FE out of 687 (1.2%), predominantly caused by *Candida* species. The patients, aged 31 to 77, faced significant diagnostic and treatment challenges, with a notable one-month mortality rate (4 cases). The majority had prosthetic valves and predisposing factors such as intravenous drug use and central venous catheters. Vegetations varied in size, with some cases involving abscesses. Embolism was a common complication, highlighting the fragility of fungal vegetations. Treatment regimens included Amphotericin B, Echinocandins, and Fluconazole, reflecting the complexity of managing these infections. In this section, we describe the 8 cases in detail.

Case 1

A 74-year-old woman was admitted to the emergency department (ED) for persistence of fever, present for at least 10 days not responding to antibiotic therapy. One year before, she had mitral valve replacement and tricuspid plastic surgery for primary insufficiency. After a few months, she was readmitted to the hospital for confusion and hyposthenia in the lower limbs. After endocarditis and infective embolic stroke were diagnosed, she underwent a redo of mitral valve replacement and definitive pacemaker implantation for post-operative advanced atrioventricular block. Two sets of blood cultures were taken prior to antibiotic therapy. An echocardiogram evidenced a voluminous mobile structure on the mitral prosthesis, suggestive of endocarditic vegetation (Fig. 1). Empirical antibiotic therapy (daptomycin + gentamicin + ceftriaxone) was started. While waiting for cardio surgery, she developed neurological symptoms (right hemiplegia and motor aphasia). A cranial CT demonstrated an ischemic stroke with probable cardioembolic aetiology. As blood cultures demonstrated the presence of mycetes (*Candida albicans*), amphotericin B (3 mg/

Table 1 Clinical and microbiological characteristics of 8 patients with fungal endocarditis

N	Sex	Age	One-month death	Germ 1	Germ 2	Maximum vegetation length (mm)	Infected valve	Prosthesis	Surgery	Predisposing factors	Embolism	Therapy
1	F	73	Y	Candida albicans	.	15	Mitral	Y	N	Prosthetic valve	Y	Amphotericin B
2	M	31	Y	Candida glabrata	Rothia mucillaginosa	- (abscess)	Aortic	Y	Y	Prosthetic valve Intravenous drug use	Y	Amphotericin B
3	M	59	N	Candida parapsilosis	.	27	Tricuspid	N	Y	Central venous catheter	N	Echinocandine
4	F	40	N	Candida albicans	Staphylococcus aureus, S anginosus	14	Tricuspid	N	Y	Intravenous drug use	N	Caspofungin
5	F	76	N	Candida albicans	.	18	Mitral	Y	Y	Prosthetic valve Central venous catheter	Y	Amphotericin B, fluconazole
6	F	77	N	Candida albicans	.	7 (abscess)	Mitral	Y	N	Prosthetic valve Central venous catheter	N	Caspofungin, fluconazole
7	F	71	Y	Candida albicans	.	8	Mitral	**Y**	N	Prosthetic valve Central venous catheter	N	Caspofungin
8	F	70	Y	Candida albicans	.	9	Mitral	Y	Y	Prosthetic valve	N	Echinocandine, fluconazole

Fig. 1 Transoesophageal image of two large, mobile structures (red arrows) on the mitral prosthesis, suggestive of endocarditic vegetation. Mid-oesophageal view, angle 113 degrees. case 1

kg every 24 h, infusion over 60 min, diluted in glucose solution) was added to the already prescribed antibiotic therapy. An ophthalmological evaluation ruled out the presence of endophthalmitis. As her clinical condition deteriorated, the patient died from respiratory arrest before surgery.

Case 2

A 31-year-old young man was admitted to the ED complaining of fever and vomiting for the past 2 days. In his past medical history, he reported intravenous drug addiction and multiple valve replacements for endocarditis recurrences. During the last cardiac surgery, he underwent an aortic valve replacement with mechanical prosthesis as well as mitral and tricuspid plastic surgery. A few months earlier, he had been hospitalized for a recurrence of endocarditis on mechanical aortic valve prosthesis with positive blood cultures for *Candida glabrata* and *Streptococcus mitis*. A TOE showed the presence of a small mobile round mass on the aortic prosthesis suspicious for endocardial vegetation. Despite his critical clinical condition, he decided to voluntarily discharge from the hospital. A few months later, he was readmitted for fever and vomiting. The electrocardiogram demonstrated the presence of Q wave in V1-V4. Transthoracic echocardiography showed a new-onset depression in the left ventricular ejection fraction (LVEF 30%) with segmental kinetic asinergy associated. A TOE confirmed the presence of an endocarditic vegetation on the prosthesis aortic valve and a periprosthetic abscess that was not present during the first admission. After a few days, he developed abdominal pain. A CT scan was done which showed splenic and renal ischemia. New blood cultures were taken with positivity to *Candida glabrata*, *Rothia mucilaginosa*, and *Bacillus pumilus*. Antibiotic therapy was started with vancomycin, gentamicin, and liposomal amphotericin B. Due to the worsening of the abdominal

pain and the findings at the CT scan check-up, he underwent an exploratory laparoscopy, which excluded intestinal ischemia. A Bentall surgery was then performed. Due to multiple intra-operative and post-operative complications, the patient died after a few days from multi-organ failure.

Case 3

A 58-year-old man was admitted to the ED complaining of fever for the past month. He had a history of polycystic kidney disease, determining end-stage renal failure on dialysis treatment, and a hypokinetic dilated cardiomyopathy. During the years, the arteriovenous fistula occluded frequently, necessitating the use of a central venous catheter. On admission, a TOE showed the presence of an endocarditic vegetation, which seemed to originate from the dialysis catheter, in close proximity to the tricuspid ring and the tricuspid valve; tricuspid flap dynamics were normal with mild to moderate insufficiency. Blood cultures were positive for *Candida parapsilosis*. Echinocandin therapy was initiated. He underwent tricuspid valve surgery. Culture examination of the removed central venous catheter was positive for a Gram-positive coccus. Vancomycin was added to the therapy. During his hospitalization, blood cultures and inflammatory markers became negative. The antifungal therapy was continued for 15 days after the first negative blood culture for fungi.

Case 4

A 39-year-old female with a history of intravenous drug addiction was admitted to the ED for pain in the left hemithorax that had been present for a few days. On admission, she was febrile and presented a purulent collection in the groin (due to drug injection), which progressively resolved with antibiotic therapy. A TTE evidenced a conspicuous vegetative lesion on the tricuspid valve; blood cultures were positive for *S. aureus*, *S. anginosus*, and *Candida albicans*. Antibiotic treatment with caspofungin, oxacillin, ceftriaxone, and linezolid was started and prolonged for 4 weeks after surgery. A CT scan of the thorax revealed abscess-like thoracic lesions of probable cardio-embolic origin. She was treated with tricuspid plastic surgery with quadrangular resection and sliding of the tricuspid anterior leaflet.

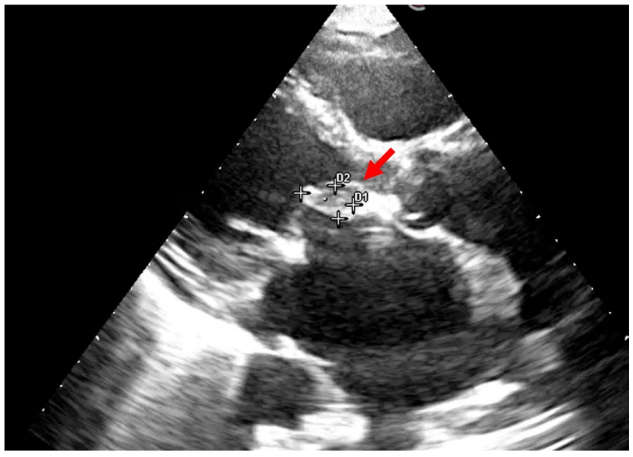

Fig. 2 Transthoracic image of a large vegetation (red arrows) on the anterior leaflet of the mitral prosthesis. D1 and D2 indicates the linear diameters, which were 12 and 8 mm, respectively. Parasternal, long axis view. case 5

Case 5

A 76-year-old woman with a history of mitral valve replacement was admitted to the Cardiac Intensive Care Unit for acute pulmonary edema. A TTE showed a large mobile endocarditic vegetation on the bioprosthesis (Fig. 2). She had a fever up to 39 °C. Urine culture was negative. Blood cultures were positive for *Candida albicans*, sensitive to fluconazole and amphotericin B, and therapy was initiated according to the antibiogram. A brain CT showed two focal lesions suggestive of embolization (anterior left bulb and left Rolandic fissure), with clinical signs consistent with transient ischemic attack (TIA), involving sensory and motor deficits. She underwent a redo of mitral valve replacement, which was uneventful. The patient was treated with fluconazole for 8 weeks.

Case 6

A 76-year-old woman with a history of mitral valve redo for mitral prosthesis degeneration and tricuspid valve repair for severe regurgitation developed fever after the surgical procedure. Urine culture and the central venous catheter cultures were positive for *Candida albicans*. The central venous catheter was removed, and the catheter tip culture confirmed *Candida albicans*. An infectious disease consultation recommended therapy with caspofungin. Following the results of the antibiogram, the treatment was switched to fluconazole. An ophthalmologic consultation excluded the presence of inflammatory foci at the ocular level. A follow-up echocardiogram revealed a suspected periprosthetic abscess of the mitral bioprosthetic valve. The CT scan confirmed the suspicion of a cardiac abscess (Fig. 3). The patient was offered a new cardiac surgery procedure, which she refused. A new infectious disease consultation recommended therapy with Ambisome. The patient was then dismissed from the hospital and lost from follow-up.

Case 7

A 78-year-old female was admitted to the ED for inferior ST-elevation myocardial infarction (STEMI) complicated by third-degree atrioventricular block (AVB) and ventricular septal defect. She underwent percutaneous angioplasty of the right coronary artery and subsequent

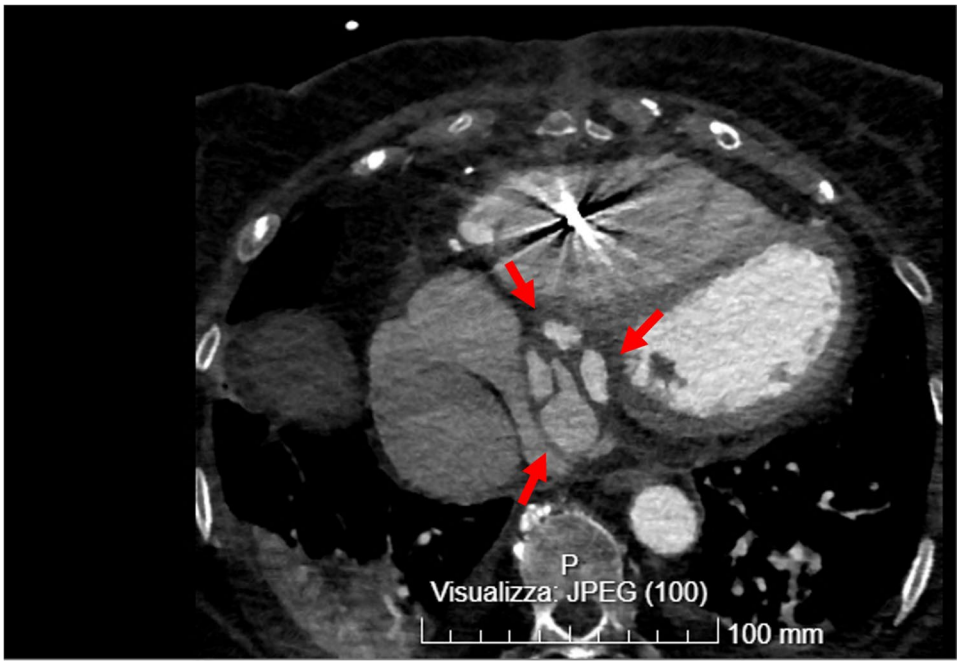

Fig. 3 Computed Tomography image of a pluriconcamerated abscess (red arrows), pressing against the inferior vena cava. case 6

surgery for ventricular septal repair with bovine pericardium patch and mitral valve replacement with biological prosthesis for papillary rupture. The subsequent clinical course was characterized by hemodynamic instability, requiring further cardiac surgery revision for cardiac tamponade. After a long complicated course, she was discharged. At discharge, she had a reduced ejection fraction (LVEF 30%) with no signs of shunt. The rehabilitation course was complicated by septic shock, for which the patient was readmitted to the ICU. Blood cultures were positive for *Pantoea agglomerans* and *Candida albicans*; therapy with piperacillin/tazobactam and caspofungin was started. An echocardiography showed an interventricular defect with left-right shunt and clinical signs of heart failure. A cardiac angiography confirmed the patch detachment, which was treated with percutaneous patch closure with mild residual shunt. The patient was discharged, but after 1 month, she was readmitted to the emergency department for acute pulmonary edema. A transesophageal echocardiography detected a 7 × 7 mm vegetation on the anterior leaflet of the mitral prosthesis, causing moderate-severe mitral stenosis associated with severe biventricular dysfunction (LVEF 15%, TAPSE 14 mm). Blood cultures were positive for *Candida albicans*. Moreover, she developed left common iliac embolic obstruction. In a few hours, the patient rapidly progressed to cardiogenic shock and died from multi-organ failure.

Case 8

This 70-year-old patient had a complex medical history, including atrial fibrillation under oral anticoagulant therapy, previous pacemaker (PM) implantation, post-radioiodine hypothyroidism, chronic obstructive pulmonary disease, and haemolytic anaemia under steroid therapy. Additionally, she underwent multiple cardiac surgeries for infectious endocarditis (mitral and aortic valve prostheses, tricuspid valve repair). Noteworthy, she reported recurrent episodes of sepsis from candidemia, requiring prolonged antifungal therapy. In December 2015, she experienced a febrile relapse. Blood cultures confirmed candidemia. A TOE revealed a new endocarditis on the mitral bioprosthesis. The patient underwent a redo procedure with aortic and mitral valve replacement (CE Magna prostheses), removal of the PM, and subsequent implantation of a leadless device (Micra VVI, 80 bpm). The postoperative course was stable and free of complications. She died one year later from an unknown cause.

Discussion

Epidemiology and risk factors

Fungal endocarditis (FE) is a rare form of infective endocarditis (IE), but its incidence has increased in recent decades due to a rise in patients with predisposing risk factors and advancements in diagnostic methods [4–6]. FE is primarily linked to host-predisposing conditions such as immunocompromised states (e.g., HIV, neutropenia, organ transplants, and long-term steroid use), intravenous drug use (as for cases 2 and 4), prolonged broad-spectrum antibiotic use, parenteral

nutrition, valve-related factors (e.g., prior valvular surgery or endocarditis, as for cases 1, 2, 5, 6, 7, 8), cardiovascular devices (e.g., pacemakers, and ventricular assist devices), and indwelling foreign bodies [7, 8]. Additional risk factors include diabetes mellitus, with multiple risk factors increasing susceptibility and fungal-bacterial co-infections worsening outcomes [9]. *Candida species* are responsible for 53%–68% of fungal endocarditis cases, with *Candida albicans* being the most common. The most commonly detected pathogen in blood cultures in our series was *Candida albicans*. *Non-albicans Candida* species associated with endocarditis include *Candida parapsilosis*, *Candida glabrata*, and *Candida tropicalis*. *Aspergillus species* account for 20%–25% of fungal endocarditis, occurring primarily in prosthetic heart valves. Other less common fungal pathogens include *Coccidioides*, *Cryptococcus neoformans* (responsible for about 5–10% of cases), *Histoplasma*, and *Blastomyces* [9–11].

Clinical presentation

FE typically manifests as subacute endocarditis, characterized by prolonged fevers lasting two weeks or more. The most frequent symptom in our series, presenting in all 8 cases, was fever. The clinical presentation of FE is similar to bacterial endocarditis, with some peculiarities [12]– [13]. FE is often associated with ophthalmological complications and typical findings on fundoscopy (more typical of FE associated with *Candida albicans*) [14]. Cutaneous manifestations, such as macronodules or maculopapules, are also linked to FE cases (more typical of Aspergillus-related FE) [4]. A hallmark of FE is the presence of large, "bulky" vegetations, which significantly increase the risk of embolic events and valvular destruction [15–17]. Severe embolic complications, often the first or only sign of FE [1–3], occur more frequently than in bacterial endocarditis [18]. Neurological complications are relatively common in endocarditis, affecting approximately 20%–40% of patients with central nervous system involvement, particularly in FE and *Staphylococcus aureus* IE [12]. Three out of 8 cases in our series had neurological complications such as stroke or transient ischemic attacks (TIAs): cases 1, 5, 7. Hemorrhagic complications are more common in FE than in bacterial endocarditis. These often result from septic emboli causing ischemic strokes that transform into hemorrhagic strokes, typically due to mycotic aneurysm rupture or vessel fragility from immune complex arteritis [15]. In FE, myocardial ischemia is often caused by the compression of coronary arteries due to peri-annular abscesses or pseudoaneurysm formation. Although embolic infarcts can also lead to ischemia, only a small percentage of coronary embolisms are attributed to endocarditis [4].

Diagnosis

Diagnosing FE is challenging due to the absence of specific diagnostic criteria and the insidious presentation. While the Modified Duke Criteria are widely used for bacterial endocarditis, they may be less reliable for diagnosing FE because they were developed based on databases of bacterial endocarditis. Specific diagnostic criteria for FE have not yet been established. For these reasons, a comprehensive evaluation that includes clinical judgment, physical examination findings, blood culture results, echocardiography, and other diagnostic tests is essential [12]. The ESC guidelines recommend a diagnostic approach for FE based on clinical presentation, blood cultures, and echocardiography [19]. Diagnosing fungal endocarditis (FE) begins with clinical suspicion, followed by transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE), which typically reveal large, bulky vegetations [20]. Echocardiography is essential for diagnosing infective endocarditis (IE), with TTE recommended as the first-line modality, although its sensitivity is limited in prosthetic valve endocarditis (PVE). TEE is preferred for prosthetic valves or inconclusive TTE results. TTE has a sensitivity of 70% for native valves and 50% for prosthetic valves, while TEE offers 96% and 92% sensitivity, respectively, with both modalities having around 90% specificity. Large vegetations are typical of fungal endocarditis, though false negatives are not uncommon. Echocardiography is also crucial for detecting post-surgical complications of the ascending aorta. Multislice CT has comparable accuracy to TEE in identifying vegetations, abscesses, and pseudoaneurysms, with potential advantages in assessing perivalvular extensions. It is also valuable in evaluating aortic valve anatomy and pathology, aiding surgical planning in aortic IE. The 2023 European Society of Cardiology guidelines [4] highlight CT's crucial role in managing endocarditis, with a class I recommendation for detecting valvular lesions in possible cases. CT is also recommended for identifying paravalvular and periprosthetic complications when echocardiography is inconclusive or when extracardiac complications are suspected. Cardiac CT was crucial in confirming the diagnosis of mitral periprosthetic abscess in case 6. In prosthetic valve endocarditis, CT is particularly valuable due to echocardiography's limited diagnostic accuracy and its ability to assess potential complications. Routine TTE or TOE is advised for all patients with candidemia to detect potential endocarditis, even in the absence of risk factors [21–23]. Early diagnosis of FE is crucial for initiating appropriate antifungal therapy and identifying patients who may benefit from early surgery. However, blood cultures may be negative in more than 50% of FE cases because of the slow growth of fungi, which prolongs the time needed for isolation from blood cultures. Histopathologic examination

of the explanted valve or peripheral emboli can be helpful [13]. When surgery is necessary, tissue or prosthetic material samples should undergo culture analysis, histological examination, and gene sequencing (16–18 S rRNA) to confirm microbial presence. For fungal infections, blood cultures and 18 S rRNA sequencing of tissue are essential diagnostic methods [19]. The modified Duke criteria have limitations, especially in cases of prosthetic valve endocarditis (PVE) and device-related endocarditis. To enhance diagnostic accuracy, the ESC guidelines have introduced additional major criteria, including the use of 18 F-Fluorodeoxyglucose (FDG) Positron Emission Tomography (PET)/CT, radiolabeled leukocyte single-photon emission computed tomography (SPECT)/CT, and cardiac CT for identifying endocardial involvement [24, 25]. FDG PET-CT is also useful for detecting peripheral embolic events and infection sites, both inside and outside the heart, though its sensitivity in candidal endocarditis is under 60% [26]. Cardiac CT, moderately sensitive and specific for PVE, is costlier, exposes patients to radiation, and may produce artifacts with prosthetic valves [24]. The diagnostic approach for FE includes evaluating specific biomarkers. Mannan, a key component of the Candida spp. cell wall, is measured through mannan antigen and anti-mannan antibody levels, which have a high negative predictive value. However, exposure to antifungal agents may reduce the levels of these antibodies [21]. The measurement of (1,3)-β-D-glucan, a polysaccharide found in the cell wall of fungi, can be used to diagnose invasive fungal disease [2, 4]. Studies have reported higher serum levels of (1,3)-β-D-glucan in infections caused by *Candida parapsilosis*, *Candida tropicalis*, and *Candida guilliermondii* compared to *Candida albicans* infections [3]. Galactomannan, an important component of the Aspergillus cell wall, is released during its proliferation and can be detected alongside (1,3)-β-D-glucan in Aspergillus endocarditis, facilitating diagnosis. A galactomannan index of 0.5 indicates *Aspergillus* infection. In high-risk patients for *Aspergillus* endocarditis (e.g., those with prolonged neutropenia or post-transplantation), its sensitivity and specificity are 100% and 97.5%, respectively [24]. However, several factors can affect the accuracy of galactomannan antigen, including infections with other fungi that cross-react with galactomannan, blood contamination with cotton, enteral feeding with certain proteins, and recent antibiotic therapy with piperacillin/tazobactam. Additionally, antifungal treatment reduces the sensitivity of galactomannan antigen. Given the difficulty in diagnosing Aspergillus, the benefits of using this test may outweigh the risks of false-positive results when applied in appropriate clinical settings [25]. Molecular methods, such as specific polymerase chain reaction (PCR), can improve diagnostic sensitivity by quickly identifying organisms through the detection of fungal nuclear material in blood or cardiac explanted material, especially in culture-negative IE [3, 4]. In cases of suspected embolic complications, various imaging modalities can aid in diagnosis and assessment. FDG PET-CT can identify potential embolic sites, while head CT or MRI/MRA is recommended for suspected brain emboli, with MRI/MRA preferred due to its higher sensitivity. If other modalities are inconclusive, cerebral angiography is the gold standard for diagnosing cerebral mycotic aneurysms. Abdominal CT is used to detect or rule out visceral infarction or mycotic aneurysm, and fundoscopy should be performed to assess ophthalmic thrombus complications when indicated [17].

Management

Managing FE requires a multidisciplinary team of cardiologists, cardiothoracic surgeons, infectious disease specialists, and microbiologists [2]. Treatment is particularly challenging due to the biofilm-forming ability of *Candida* spp., especially on prosthetic heart valves [3]. Recommendations suggest a combination of antifungal agents and early surgery due to the potential complications and high mortality associated with medical therapy alone [4–6]. Antifungal therapy should begin promptly, with a recommended duration of 6–8 weeks. In cases of persistent positive blood cultures or complications like peripheral abscess formation or embolic events, extended treatment may be required [2]. Long-term suppressive antifungal therapy is recommended following medical and surgical treatment of FE due to its high relapse rate and delayed response. This approach is also suitable for patients who are poor surgical candidates, following an initial induction phase with fungicidal agents [27, 28]. The ESC guidelines and related literature recommend treating *Candida* endocarditis (CE) with liposomal amphotericin B (AmB) with or without flucytosine, or high-dose echinocandins, combined with surgical intervention [5–7, 26]. In our series, Amphotericin B was administered for cases 1, 2, 5, and 8, while Echinocandins (Caspofungin, Micafungin) were used for cases 3, 4, 6, and 7. AmB-based therapy has traditionally been the standard treatment for CE [29, 30]. Liposomal AmB is preferred over conventional AmB due to its improved safety, better tolerability, and enhanced fungicidal activity against biofilms [31]. However, its penetration into fibrin clots and vegetations may be limited. Consequently, combination therapy with flucytosine is recommended, particularly when surgery is not an option, as it offers advantages over monotherapy [32]. Echinocandins are increasingly favored as first-line therapy for *Candida* infections because of their low toxicity, minimal drug interactions, rapid fungicidal action, and excellent penetration into *Candida* biofilms [26]. Azoles, primarily fungistatic agents, have limited standalone use in CE [29, 30]. However, they demonstrate

synergistic effects when combined with echinocandins or AmB. Fluconazole is often employed as long-term suppressive therapy to prevent relapse, particularly in non-surgical candidates or patients with irremovable cardiac devices [33, 34]. Flucytosine, with broad antifungal activity against most *Candida* species, is often combined with lipid-formulated AmB or echinocandins for a synergistic effect in initial treatment. However, it may cause bone marrow suppression [2, 3, 7, 8, 11]. Surgical timing for FE should be carefully considered, with patient-specific factors playing a crucial role. While medical therapy, especially with new antifungal agents, can be effective, most experts still consider FE a primary indication for valvular surgery [13]. Surgery should ideally be performed within 1 week for native valve CE and within a few days for *Candida* prosthetic valve endocarditis. Surgical indication is mandatory for heart failure, heart block, annular abscesses, destructive lesions, or large vegetations, which are typical of fungal infection. Common procedures include valve explantation, debridement, prosthetic valve reimplantation, and aortic root replacement for aortic valve infections with perivalvular abscesses [35].

Prognosis

Despite advancements in diagnostic and therapeutic approaches, the prognosis of FE remains poor. Its mortality rate exceeds 50%, which is higher compared to bacterial causes of endocarditis [17]. In our cohort, 4 out of 8 (50%) patients died due to complications such as multi-organ failure (case 2), cardiogenic shock (case 7), and respiratory arrest (case 1). Heart failure, persistent candidemia, nosocomial acquisition of infection, older age, and the presence of intracardiac abscess have been identified as predictors of mortality in FE. Increased mortality risk has been associated with acute and subacute liver failure, female sex, medical treatment alone, transfer from an outside medical facility, aortic valve pathology, hemodialysis, cerebrovascular disease, neutropenia, and alcohol abuse. Isolated right-sided endocarditis has been linked to a lower risk of mortality [36]. Hemorrhagic complications occur in 3–7% of IE cases, often resulting from hemorrhagic conversion of septic emboli-induced ischemic strokes. In such cases, mortality rates can be as high as 80% [3].

Conclusion

Fungal endocarditis (FE) is a rare but serious form of endocarditis with a severe prognosis and high mortality. Its nonspecific and inconsistent presentation poses significant diagnostic challenges, requiring a high index of suspicion for early detection and timely intervention. Embolic events may serve as key indicators, and accurate diagnosis often relies on serial imaging [37], repeated blood cultures, and molecular methods, which provide the highest sensitivity for pathogen identification. In high-risk patients with prolonged fever, empiric antifungal therapy at sufficient doses and duration is critical. The management of FE typically involves a combination of medical and surgical interventions. Combined antifungal therapy and surgical debridement yield superior outcomes, though medical therapy alone may be considered for patients who are not surgical candidates. Our study highlights the need for increased awareness, early diagnosis, and multidisciplinary management to improve the outcomes of patients with FE.

Abbreviations

FE	Fungal endocarditis
IE	Infective endocarditis
ESC	European Society of Cardiology
TTE	Trans thoracic echocardiography
TOE	Trans oesophageal echocardiography
CT	Computed tomography
ED	Emergency department
LVEF	Left ventricular ejection fraction
TIA	Transient ischemic attack
STEMI	ST-elevation myocardial infarction
AVB	Atrioventricular block
TAPSE	Tricuspid anular plane systolic excursion
PM	Pacemaker
PVE	Prosthetic valve endocarditis
18F	Fluorodeoxyglucose (FDG)
(PET)/CT	Positron Emission Tomography
(SPECT)/CT	Single-photon emission computed tomography
PCR	Polymerase chain reaction

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NA.

Authors' contributions

AF wrote the manuscript. VS managed the database. PLS performed the vast majority of surgical interventions. MP revised the paper.

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None to declare.

Data availability

The dataset will be available on reasonable request.

Declarations

Ethics approval and consent to participate

The study was approved by the local ethics committee (Comitato Etico Regionale per la Sperimentazione Clinica della Regione Toscana), which, in accordance with statements by the Italian Regulatory Authorities for retrospective, observational studies, granted a waiver of informed consent from study participants. Registration number: 12113_oss. Registration date 13/3/2018. The study was approved in accordance with the revised Declaration of Helsinki. Data were extracted from electronic hospital records, anonymized, and secured with password protection.

Consent for publication

All authors give consent to publication upon acceptance. All patients (8 patients with FE) agreed to participate in the study when contacted for follow-up and signed informed consent for publication.

Competing interests

The authors declare no competing interests.

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