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Emerging trends in fungal endocarditis: clinical complexity, diagnostic challenges, and therapeutic implications – a case series and literature review

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Abstract

Background: Fungal infective endocarditis (IE) is a rare, yet increasingly recognised condition associated with substantial mortality rates. *Candida* and *Histoplasma* are among the notable causative agents, presenting diverse clinical manifestations and complexities in diagnosis and management.

Objectives: This study was undertaken to examine the clinical profiles, diagnostic challenges, treatment modalities, and outcomes of four compelling cases involving *Candida* and *Histoplasma* endocarditis.

Methods & Design: This was a descriptive case series study conducted from July 2021 to July 2023. All patients with definite/possible endocarditis diagnosed based on modified Duke's criteria were reviewed in this study. Data on demographics, risk factors, clinical signs and symptoms, echocardiography findings, microbiological aetiology, complications, treatment, and outcomes were collected.

Results: Among 212 suspected IE cases reviewed, 54 met the modified Duke's criteria for possible or definite IE, with four instances identified as fungal endocarditis. *Candida* species accounted for three cases, while an uncommon instance of *Histoplasma* Endocarditis (HE) was also observed. Clinical presentations varied, with fever and dyspnoea being prominent symptoms. Risk factors included chronic kidney disease, prior surgeries, prosthetic valves, and immunocompromised states. Diagnosis posed challenges due to the resemblance to bacterial IE, low blood culture yields, and delayed suspicion. Various diagnostic approaches, including blood cultures, serological markers, and imaging, were employed. Therapeutic strategies involved antifungal agents and surgical intervention, where feasible. However, despite prompt treatment initiation, many patients faced rapid clinical deterioration, emphasising the severity and aggressive nature of fungal endocarditis. Mortality rates remained notably high across the cohort.

Conclusion: This study highlights the criticality of early suspicion, prompt diagnosis, and a multidisciplinary approach to managing fungal endocarditis. While recognising the limitations in current diagnostic tools and therapeutic options, the study underscores the urgent need for enhanced diagnostic modalities and novel treatment strategies to improve outcomes in these challenging cases.

Keywords: candida, echocardiography, endocarditis, fungal biomarker, histoplasma

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Introduction

Infective endocarditis (IE) due to fungal aetiology is rare but is associated with significant mortality.[1–3] In general, there has been an increase in cases of fungal IE, with *Candida* Endocarditis (CE) being the most common (49.6%) followed by *Aspergillus* (30%).[2–4] Among the species, *Candida albicans* is known to be the predominant, but increasing trend of non-albicans candida including *C. parapsilosis*.[1,2,5] *Histoplasma* Endocarditis (HE) is an extremely rare complication of disseminated infection.[2,6–8]

Diagnosing fungal endocarditis poses a challenge owing to its resemblance in presentation to bacterial IE, the delayed suspicion of its presence, and the limited yield of positive results from blood cultures.[1,2] Additionally, after diagnosis, treatment is difficult due to the side effects of the antifungals, the requirement for surgical management, the high cost, the ability of candida to form biofilms, etc.[1,2,9] A combination of surgery and antifungal therapy is associated with better outcomes.[2,9]

In this context, we present four compelling cases of fungal IE caused by Candida and Histoplasma. These cases underscore the diverse array of presentations, and the complexities in management, and emphasise the criticality of early diagnosis through a multidisciplinary team approach for the effective treatment of fungal IE, thereby striving for favourable patient outcomes.

Materials and methods

This study was a descriptive case series conducted from July 2021 to July 2023, following approval from the institutional ethics committee. Informed consent was obtained from all patients or their legal guardians as a part of Endocarditis registry at the time of inclusion. All patients with definite/possible endocarditis diagnosed based on modified Duke's criteria were reviewed in this study. All suspected IE patients had three sets of blood cultures drawn from three separate venepuncture sites, 1 h apart before the initiation of antibiotics. Data on demographics, risk factors, clinical signs and symptoms, echocardiography findings, microbiological aetiology, complications, treatment, and outcomes were collected.

Trans-thoracic echocardiography (TTE) was conducted when there was suspicion of IE, while transesophageal echocardiography was carried out as deemed necessary.

Positive blood culture bottles were subjected to culture on blood agar, chocolate agar and MacConkey agar and identification was done based on gram stain, colony morphology, VITEK 2 system (BioMerieux) and MALDI-TOF MS (BioMerieux). Serodiagnosis was done in culture-negative endocarditis, based on the epidemiological risk factors including endemic infections like brucella, fungal biomarkers – beta-D-glucan (BDG), galactomannan and histoplasma urinary antigen.

The Fungitell assay was employed to identify serum levels of (1,3)-β-D-glucans. The interpretation of (1,3)-β-D-glucan values is as follows: less than 60 pg/mL is considered negative, 60–79 pg/mL is categorised as indeterminate, and levels exceeding 80 pg/mL are regarded as positive.

The Aspergillus Galactomannan Antigen detection method (IMMY lateral flow assay) was employed. In this study, a threshold of 1 was utilised for diagnosing Aspergillus endocarditis. This criterion was based on the recent EORTC MSGERC. To classify a patient as positive for the Aspergillus Galactomannan Antigen, the test had to yield positive results in two consecutive tests conducted within a week.

The histoplasma urinary antigen detection (OIDx Histoplasma Lateral Flow Assay) was employed. It is a rapid test, and a positive test was interpreted when there was a well-defined band in the test region, with the control line satisfactory.

Definitions

The Table 1 describes the criteria used in our study for diagnosing CE and HE.

Results

Between July 2021 and July 2023, our study involved the enrollment of 212 patients suspected of having IE, from which 54 cases met the criteria for possible or definite IE according to the modified Duke's criteria.[10] Among these cases, four instances were classified as fungal endocarditis, comprising three cases of CE and an uncommon case of HE. Fever and dyspnoea were the most

Table 1. Criteria used in our study for diagnosing CE and HE.

Candida Endocarditis (CE)	• Definite CE – culture and/or histology of cardiac material or embolic tissue demonstrated Candida species, or if there was the combination of persistently positive blood cultures for *Candida* species or beta-D-glucan and evidence of endocardial involvement on echocardiogram • Possible CE – —positive blood cultures for *Candida* species and a predisposing heart condition, but no evidence of endocardial involvement on the echocardiogram
Histoplasma Endocarditis (HE)	Positive HE, if: Evidence of valve involvement by *H. capsulatum* either by • Histopathology and/or microbiologic culture of the valve and/or embolic tissue following surgery or autopsy (or) • Clinical evidence of valve involvement (i.e. vegetation(s) seen by trans-thoracic or transesophageal echocardiogram) in conjunction with positive microbiology culture, serum/urine antigen, and/or serology (complement fixation and/or immunodiffusion)

Source: adapted from Boyanton et al.[6] and Lefort et al.[13]
HE, *Histoplasma* Endocarditis.

prevalent presenting complaints observed in all patients. Within our cohort, we identified several risk factors associated with fungal endocarditis, notably chronic kidney disease requiring haemodialysis, previous intestinal perforation with multiple abdominal surgeries, the presence of a prosthetic valve, and HIV/AIDS.

Cultures revealed positivity in two cases, while in others, the diagnosis was established through fungal serological markers. Most patients initially received Inj. Caspofungin, later adjusted based on susceptibility. Combination antifungal therapy was administered to two out of the four patients. Surgical intervention was planned for several cases; however, unfortunately, many patients succumbed to complications before this intervention was feasible. The overall mortality rate was notably high, with all patients ultimately succumbing to the disease.

The clinical characteristics of these cases are outlined in Table 2. Below, we provide a brief overview of the four cases.

Case 1

A 59-year-old male, known for chronic kidney disease (CKD) and undergoing regular haemodialysis for the past 5 years, presented to the emergency department complaining of progressively worsening shortness of breath over 2 weeks and a fever persisting for 20 days. Upon examination, the patient appeared conscious, and oriented, but notably emaciated. Physical examination revealed significant grade 3 clubbing, fever with a temperature of 101°F, low blood pressure at 90/60 mmHg, and a pulse rate of 100 beats per minute. Bilateral diffuse crepitations were noted during the respiratory examination, while the rest of the systemic assessment appeared unremarkable.

Suspecting sepsis, immediate management involved intravenous fluids and administering Inj. Ceftriaxone 2 g after blood cultures were obtained. Despite aggressive resuscitation efforts, the patient's condition did not improve, necessitating intubation and the use of adrenaline and vasopressin infusions to maintain blood pressure. Laboratory investigations revealed neutrophilic leucocytosis (21,000 with 87% neutrophils), a low platelet count (1.04 lakh/dL), and elevated inflammatory markers (Erythrocyte sedimentation rate (ESR) – 52 mm/1-h, high sensitivity complement reactive protein (hs-CRP) – 103.7 mg/L, procalcitonin – 0.24 ng/mL]. Paired blood cultures were sent, which were sterile.

Routine TTE disclosed a 17 × 11 mm vegetation on the mitral valve and an ejection fraction of 40%. Three sets of blood cultures were repeated as per IE protocol, which unfortunately yielded no organism. Fundus examination showed no abnormalities, A CT scan of the chest confirmed multiple septic emboli in the lungs. To identify the cause of blood culture-negative IE, the

Table 2. Summary of cases of fungal IE.

Patient profile	Case 1	Case 2	Case 3	Case 4
Age	59 y	40 y	58 y	53 y
Sex	Male	Male	Male	Male
Underlying condition	CKD	DM/Intestinal perforation, major abdominal surgery	RHD/MS/Post MVR 2 years back	HIV/AIDS
Symptoms	Fever, shortness of breath	Fever, shortness of breath	Low-grade fever, palpitations, shortness of breath	Low-grade fever, shortness of breath, bilateral pedal oedema
2D Echocardiography				
Vegetation size	17*11 mm	25*12	28*8	18*14 mm
Vegetation site	Mitral valve	Mitral valve	Mitral valve	Aortic valve
Organism	Candida (Beta-D-Glucan positive)	*Candida parapsilosis*	*Candida tropicalis*	Histoplasma (Urinary histoplasma antigen positive)
Treatment regimen	Inj Liposomal Amphotericin B with Caspofungin	Inj Caspofungin (high dose)	Inj Amphotericin B with Caspofungin	Inj Liposomal Amphotericin B Itraconazole Isavuconazole
Outcome	Expired (day 5)	Expired (day 7)	Expired (8 weeks)	Expired (day 30)

CKD, chronic kidney disease; DM, diabetes mellitus; HIV/AIDS, human immunodeficiency virus/acquired immunodeficiency syndrome; IE, infective endocarditis; RHD, rheumatic heart disease; MS, Mitral Stenosis; MVR, Mitral valve replacement.

Brucella standard agglutination test (SAT) was done, which was negative. Whole genome sequencing from the serum sample done, yielded negative results. Fungal serological tests were conducted, the beta-D glucan test initially returned positive, and galactomannan was negative. To validate the results, the test was repeated, confirming positivity on both occasions (280 and 250 pg/mL). A final diagnosis of possible CE was made, and treatment was initiated with intravenous liposomal Amphotericin B at 5 mg/kg along with Caspofungin once daily. Despite receiving adequate treatment, the size of the vegetation observed during his treatment course was the same on repeat TTE. Unfortunately, the patient's condition continued to deteriorate despite treatment. On the fifth day of combination treatment, the patient succumbed to acute heart failure secondary to CE.

Case 2

A 40-year-old man arrived at our emergency department complaining of fever and difficulty breathing. His recent medical history included surgery performed 20 days earlier for intestinal perforation accompanied by peritonitis at a different hospital. During his hospital stay, he underwent a second exploration and received total parenteral nutrition along with Inj Piperacillin Tazobactam. After discharge, he seemed well for a few days until a fever and dyspnoea emerged.

Initial investigations revealed neutrophilic leukocytosis, a platelet count of 124 [10^3/μL], an ESR of 81 mm/1 h, a hs-CRP level of 64.72 mg/L, and procalcitonin levels of 0.259 ng/mL. Blood cultures indicated the presence of budding yeast cells on the gram stain, identified as *C. tropicalis*. The patient was promptly started on Inj. Caspofungin with a loading dose of 70 mg followed by 50 mg daily while awaiting antifungal susceptibility results. As part of the protocol for candida bloodstream infection, a TTE was done which revealed a 25*12 mm vegetation on the mitral valve, leading to a diagnosis of CE. Consequently, the dosage of Inj. Caspofungin was increased to 150 mg IV OD in accordance with guidelines.

Repeat blood cultures confirmed the presence of *C. tropicalis*, susceptible to Fluconazole, voriconazole, Caspofungin, and Amphotericin B. The patient continued on high-dose Caspofungin and was scheduled for surgery. Despite the treatment, the repeat TTE indicated an increase in vegetation size, ultimately leading to sudden cardiac arrest in patients on day 7 of treatment.

Case 3

A 58-year-old male, who underwent mitral valve replacement 2 years ago due to rheumatic heart disease-associated mitral valve stenosis, presented at the Infectious Diseases clinic with a persistent low-grade fever over the last 2 months, accompanied by palpitations and severe dyspnoea for the past 20 days. Upon examination, the patient exhibited a moderate build, was febrile (101°F), displayed grade 3 clubbing, and had a blood pressure of 110/70 mmHg, a respiratory rate of 24/min, and a pulse rate of 100/min. A cardiovascular examination revealed a mid-sternal scar indicative of previous surgery. Auscultation revealed a grade 3/6 pan systolic murmur predominantly over the mitral area, radiating to the axilla. Systemic examinations were otherwise unremarkable. Initial investigations showed leukocytosis (14,000, 80% neutrophils), a platelet count of $45 \times 10^3/\mu L$, an ESR of 112 mm/1-h, hs-CRP of 124.32 mg/L, and procalcitonin of 0.59 ng/mL.

Due to suspicion of IE, three sets of blood cultures were drawn. After 27 h, the blood culture returned positive, revealing budding yeast cells on the gram stain. The patient was promptly initiated on high-dose Caspofungin (150 mg once daily) while awaiting antifungal susceptibility test results. TTE disclosed a 28×8 mm vegetation on the prosthetic mitral valve, with a left ventricular ejection fraction of 55%. The fundoscopy was normal. *Candida parapsilosis* was identified by MALDI-TOF MS (Biomerieux), and susceptibility results were documented in Table 3.

Cultures repeated on the fifth day of therapy indicated persistent growth of *C. parapsilosis*. During the first week of treatment, the patient developed weakness in the left lower limb and a headache. A CT brain scan revealed multiple embolic infarcts in the bilateral cerebellar region and left frontal lobe. Subsequently, the patient was transitioned to a combination therapy of Inj Amphotericin B (5 mg/kg) once daily along with Caspofungin.

Table 3. Susceptibility of Candida species isolated in CE.

Yeast	Case 2	Case 3
Species	*C. parapsilosis*	*C. tropicalis*
TTP	26 h	24 h
Caspofungin	S	S
Fluconazole	I	S
Itraconazole	I	S
Voriconazole	S	S
Amphotericin B	S	S
Flucytosine	S	S

CE, Candida Endocarditis; I, Intermediate; R, Resistant; S, Susceptible.

The patient responded well to the current therapy, with sterile cultures on week 2 of therapy. Follow-up TTE revealed that the size of the vegetation remains unchanged, with no additional findings. Surgical intervention was recommended, but the patient declined. After 6 weeks of treatment, the patient was discharged with chronic prophylaxis of oral Fluconazole 400 mg and scheduled for regular follow-ups. Unfortunately, 2 weeks later, the patient presented to the emergency department in severe respiratory distress and palpitations, succumbing to biventricular failure.

Case 4

A 50-year-old male patient with a known case of HIV/AIDS on Anti retroviral therapy (ART) (tenofovir, lamivudine, dolutegravir) for 5 years, with good compliance to medication, presented to the infectious diseases clinic with complaints of fever for 4 months, new onset shortness of breath and bilateral pedal oedema. Fever was low grade, with evening rise, subsided on medication to reappear. He also gave a history of orthopnoea and paroxysmal nocturnal dyspnoea for the last 2 months. On examination patient showed diffuse hyperpigmentation with pigmentation of the crease lines, tachypnoeic with pallor and bilateral pitting pedal oedema of grade 3. Respiratory examination revealed bilateral basal crepitation in the infrascapular area with decreased left-sided air entry. A cardiovascular examination revealed a systolic murmur of grade 3/6 in the mitral area with radiation to the back. A provisional

diagnosis for new onset mitral regurgitation (MR) was made possibly IE was considered. Blood cultures were sent according to IE protocol. Chest X-rays revealed left-sided pleural effusion. A routine blood investigation showed deranged renal function and pancytopenia. The 24-h urinary protein sent showed an elevated albumin/creatinine ratio secondary to HIV-associated nephropathy. Ultrasonography (USG) of abdomen done showed normal kidney size with no echotexture abnormality. Ultrasound-guided pleural tap done for effusion showed a transudative picture. Microbiological workup is negative. Repeat blood cultures and fungal cultures did not show any growth. The patient continued to have fever spikes. TTE was done which showed friable vegetation of size 18×14 mm over the aortic valve with severe MR, moderate tricuspid regurgitation with moderate pulmonary arterial hypertension and ejection fraction of 60%.

To identify the cause of blood culture-negative IE, the Brucella SAT was done, which was negative. Fungal serological tests were conducted, serum galactomannan test was positive (Optical density – OD 2.5). In view of hyperpigmentation and pancytopenia, suspecting histoplasma, a urinary histoplasma antigen was done, which was strongly positive. To validate the results, the test was repeated, confirming positivity on both occasions. Blood cultures were repeated to arrive at an etiological diagnosis, which unfortunately was sterile after prolonged incubation and a diagnosis of possible HE was made.

Treatment commenced with intravenous liposomal Amphotericin B at 5 mg/kg/day. To address renal issues, the ART regimen was adjusted to an abacavir-based one following HLA B*5701 testing. After 2 weeks of therapy, the patient was planned for surgery but declined. Upon discharge, the patient was prescribed oral Itraconazole (200 mg twice daily) with stable vitals and no signs of deterioration. However, after 3 weeks, the patient returned to the emergency department with signs of heart failure, revealing non-compliance with prescribed medications.

Liposomal Amphotericin B therapy was resumed, but on the fifth day, renal function deteriorated further, prompting a change to intravenous isavuconazole (372 mg loading dose followed by 372 mg once daily). The patient required non-invasive mechanical ventilation on day five, progressing to invasive mechanical ventilation due to cardiac failure and necessitating haemodialysis. Despite undergoing treatment, follow-up TTE showed a marginal reduction in vegetation size along with a further decline in the patient's ejection fraction and an increase in the requirement for ionotropic support. Despite appropriate care, the patient succumbed to the illness on the fourteenth day.

Discussion

Fungal endocarditis constitutes less than 2% of overall IE but is associated with high mortality (40%).[1,4,9] In general, there has been an increase in cases of fungal IE, with CE being the most common (49.6%) followed by *Aspergillus* (30%).[3,4,9,11] Fever (62.1%) was the predominant presenting symptom followed by shortness of breath with or without chest pain (37.1%). Most present with complications such as peripheral embolisation, stroke, and congestive heart failure due to larger and more friable vegetation when compared to bacterial endocarditis. The most common risk factors for fungal IE were cardiac implants (45.2%) (prosthetic valves, intracardiac devices), structural heart diseases (35.8%), intravenous drug abuse (16%), corticosteroid use, immunosuppressants.[1,4,9,12]

Diagnosis of fungal IE relies on a high degree of clinical suspicion, echocardiography, Blood cultures and histopathological examination. The aortic valve (43.2%) was the most involved followed by mitral (32%), and tricuspid (15%).[2–5,9,13]

As the sensitivity of blood cultures is low for fungal, especially for non-candida fungal endocarditis, biomarkers, and molecular diagnosis such as pan-fungal Polymerase chain reaction (PCR) can be considered.[13–15] Blood cultures were negative in 33.9%, the majority being *Aspergillus* species. Tissue culture yielded higher positivity (91.1%) but was difficult to obtain.[9] The use of beta-D-glucan was done in fewer studies with positivity noted in 88.9% of cases.[4,9,13] PCR showed excellent sensitivity and specificity (92% and up to 100%) for diagnosis of fungal IE on the tissue samples (vegetation, emboli or valve), hence every attempt must be made to obtain a tissue diagnosis.[2,3,9]

Combined therapy of antifungal and surgery is recommended due to better outcomes. Use of antifungal alone was associated with higher

mortality.[9,13,16,17] Amphotericin B (53%) was the most common drug used followed by azoles (33%) and echinocandins (15%).[2,4] In a systematic review, the mortality rate was significantly higher in patients with fever, history of endocarditis, immunocompromised state, prosthetic valve disease and Aspergillus endocarditis. CE was associated with poorer outcomes than other non-candida fungal IE.[9]

Candida endocarditis

Candida remains the predominant culprit behind fungal IE, characterised by significant morbidity and mortality rates. *Candida albicans* constitutes the most prevalent species, accounting for approximately 60% of cases, followed by *C. parapsilosis* (15%–40%) and *C. tropicalis* (10%).[1,2,9] Notably, there's a growing incidence of non-albicans Candida species observed.

Common risk factors include prosthetic devices such as valves, cardiac implantable electronic devices, indwelling catheters, and immunosuppression.[1,2,9] Case 1 lacked significant risk factors apart from undergoing haemodialysis for CKD. Case 2 exhibited a typical risk profile with intestinal perforation necessitating multiple abdominal surgeries, while Case 3 had a prosthetic valve.

Clinical manifestations of CE vary based on the extent of infection, associated risk factors, and the affected valve. Symptoms are typically subacute and non-specific, such as fever, chills, fatigue, dyspnoea, and orthopnea, often overlapping with those of bacterial IE, necessitating a high level of suspicion.[1–3,9] Some cases may present as sepsis or septic shock. In our cohort, Case 1 presented with sepsis, Case 2 displayed a more subacute form, and Case 3 showed typical IE symptoms like fever and dyspnoea. Additionally, patients might exhibit complications such as embolisation to the brain or lungs, leading to hemiplegia, pleuritic chest pain, or dry cough.

Blood cultures serve as a fundamental diagnostic tool for IE and should be considered in all suspected cases. However, their sensitivity is relatively low (20%–70%).[2,9] In our cases, two out of three showed positive blood cultures, with *C. parapsilosis* and *C. tropicalis* identified. Enhancing sensitivity involves sending high-volume samples, utilising multiple bottles, and conducting serial cultures.

T2Candida, an FDA-approved test used in the United States can overcome the low sensitivity of blood cultures by direct detection of candidemia from blood samples. It works by amplifying Candida nucleic acid and identifying amplicons using magnetic resonance. This test can detect five major Candida species, including *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. krusei* and *C. parapsilosis*, within a rapid turnaround time of 5 h.[18] A meta-analysis primarily based on clinical trial data reported a pooled sensitivity of 91% and specificity of 94% for T2Candida.[19] However, real-world clinical settings have shown slightly lower sensitivity ranging from 65% to 73%, while maintaining comparable specificity at 96% for candidemia.[18,20] T2Candida, despite its advantages, also has some limitations. The cost of implementing T2Candida testing in healthcare settings may be a barrier to its widespread adoption. Furthermore, the need for specialised equipment and expertise to perform the test may limit its availability in certain healthcare facilities. Due to these factors not all healthcare facilities may have access to this technology.[20]

Utilising fungal biomarkers like BDG can offer supplementary diagnostic value, often indicating positivity before blood cultures and aiding in culture-negative instances. The sensitivity of these biomarkers typically ranges between 76.7% and 100%, with a specificity of 40% to 90% and a notably high negative predictive value.[4,9]) Lefort et al. highlighted the 100% sensitivity of BDG in diagnosing CE.[13] Meanwhile, Dixit et al. demonstrated in their research that BDG could facilitate early identification of fungal IE, which is crucial in initiating appropriate antifungal therapy.[21]

The management of CE typically involves a blend of antifungal and surgical interventions, although the benefits lack confirmation from prospective randomised trials.[2,4] A recent review conducted by Meena et al. identified 124 cases (49.6%) of CE, indicating a lower mortality rate when a combination therapy approach was utilised as opposed to the use of antifungal therapy alone (with a hazard ratio of 0.20; p - 0.001).[9]

The recommended antifungal regimen for CE includes Amphotericin B with or without Flucytosine or a high dose of Caspofungin.[22,23] Alternatively, a combination of Amphotericin B with echinocandin or Flucytosine with Fluconazole can be given.[22] Amphotericin B

formulations were predominantly employed in most cases, while there remains limited data on the combined use of antifungal medications for CE. In our cases, initial therapy involved Caspofungin, later transitioning to a combination therapy of Amphotericin B with Caspofungin due to the unavailability of Flucytosine. Cases 1 and 3 commenced treatment with Amphotericin B along with Caspofungin due to the absence of species identification, while Case 2 was managed with a high dose of Caspofungin but unfortunately passed away before a shift could be made.

Comparative studies between Amphotericin B and echinocandins for CE have not been formally conducted, compounded by numerous confounding factors. An observational study by Rivoisy et al. suggested that Amphotericin B-based therapy resulted in better outcomes, whereas a study by Arnold et al. showed no disparity in mortality between the two groups.[24,25] While Fluconazole may be considered, using it as initial therapy was linked to poorer outcomes, whereas cases where it was employed in combination with other antifungals demonstrated improved outcomes (58% vs 84%).[2,26,27] The recommended duration of therapy for CE typically spans 6 weeks.[22,23] In cases where susceptibility is confirmed and cultures are sterile, a transition to Fluconazole or voriconazole might be contemplated. For patients ineligible for surgery, continuous suppressive therapy using azoles could be administered. In our experience, Case 3, a prosthetic CE case, initially received high-dose Caspofungin and later switched to Amphotericin B due to developing embolic complications during therapy. Given the refusal of surgery, the patient was placed on chronic suppressive therapy with Fluconazole following the initial 6 weeks of treatment. Unfortunately, despite appropriate therapy, all our patients succumbed to CE, resulting in high-mortality rates.

Histoplasma endocarditis

Histoplasma is a dimorphic fungus capable of causing infections in immunocompromised individuals such as HIV/AIDS or transplant recipients.[7,28] This disease is prevalent in North and Central America, as well as certain areas in South America, Africa, Australia, and Asia.[7,28] Histoplasmosis manifests in various forms, ranging from mild, localised cases to widespread, disseminated infections.[1,2,7] The first case of HE was reported in Thailand in 2021 as per the case report by Amnuay et al.[29] IE due to endemic fungi are extremely rare, *Histoplasma capsulatum* being the commonest causative agent.[2] Overall around 61 cases have been reported in the literature. HE is commonly seen in men, uncontrolled diabetes, prosthetic valves or known cardiac valvular dysfunction etc.[2,6,7] Our patient in Case 4 had no classical risk factors, except for being HIV & recently diagnosed CKD. Our patient presented with prolonged fever, with dyspnoea, weight loss and bilateral pedal oedema and hence cardiac involvement was suspected, and auscultation confirmed the presence of a murmur. Patient had hyperpigmentation involving the mucosa, but there were no skin lesions nor were there peripheral signs of IE. Echocardiography confirmed the presence of vegetation but despite a high index of suspicion and clinical manifestations pointing towards endocarditis, conventional blood cultures failed to yield the causative pathogen. HIV patients are known to be at low risk for fungal IE due to a lack of neutrophilic dysfunction, making our case one of the unique presentations of HE.[2] Diagnosis of HE is challenging as commonly used automated blood cultures do not support the growth of *Histoplasma*, also the grade of fungaemia is not high.[6] Most of the cases reported in the literature were diagnosed based on morphology obtained on histopathology of the resected vegetation and by culture of the tissue.[6,29,30] Histoplasma antigen in urine and serum has been used in a few studies and has demonstrated good sensitivity & specificity for diagnosis in patients with a high degree of suspicion.[29,31] Antibody tests have been employed in endemic regions. In our patient, surgical excision was planned, but was not possible, and hence, the use of histoplasma antigen testing proved crucial in establishing the aetiology. Most of the cases in the literature had urine or serum histoplasma antigen positive (90%), while all the cases were positive for histoplasma on histopathology. A combination of surgery and antifungal therapy with Amphotericin B formulation, then Itraconazole is recommended.[28,32] Most of the cases may require lifetime suppression with Itraconazole or another triazole.[28,32] Our patient was initiated on Liposomal Amphotericin B for 2 weeks followed by *T. Itraconazole*. The management of this patient posed significant challenges. The patient's non-compliance with medications led to a relapse of symptoms and subsequent rapid deterioration, underscoring the crucial role of patient adherence in the success of treatment outcomes.

Conclusion

Fungal IE, although rare, presents significant challenges in diagnosis, management, and treatment, leading to substantial mortality rates. This study highlights the challenges in diagnosing and managing fungal IE, especially in patients with non-specific symptoms and negative blood cultures, necessitating the use of biomarkers such as BDG, galactomannan, and histoplasma antigen testing, demonstrating promising sensitivity and specificity. It also highlights the importance of timely initiation of appropriate antifungal therapy. Despite the appropriate therapeutic approach, mortality remains high in CE cases, emphasising the need for novel diagnostic modalities and treatment strategies to improve outcomes. Therapeutically, the combination of antifungal agents and surgical intervention, when feasible, is recommended for better outcomes. However, aggressive disease progression often leads to rapid clinical deterioration and high-mortality rates, emphasising the aggressive nature of fungal endocarditis. Additionally, patient adherence to prescribed medications plays a pivotal role in treatment success, accentuating the importance of patient education and support in achieving favourable treatment outcomes in fungal IE cases.

Declarations

Ethics approval and consent to participate

The study was approved by the Institutional Ethics Committee of AIIMS Jodhpur (ethical approval number AIIMS/IEC/2023/4287). Written informed consent to participate was obtained from participants. For this retrospective study, informed consent for inclusion in the endocarditis registry and the use of anonymised data for research purposes was obtained at the time of hospital admission.

Consent for publication

Written informed consent for publication was obtained from the legally authorised representatives or next of kin of all deceased patients included in this study. In situations where the patient had provided consent prior to their death, documented evidence of this consent was maintained.

Author contributions

Santhanam Naguthevar: Conceptualisation; Data curation; Investigation; Methodology; Validation; Writing – original draft.

Akshatha Ravindra: Conceptualisation; Data curation; Formal analysis; Investigation; Methodology; Writing – original draft; Writing – review & editing.

Deepak Kumar: Conceptualisation; Data curation; Formal analysis; Supervision; Validation; Visualisation; Writing – review & editing.

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Competing interests

The authors declare that there is no conflict of interest.

Availability of data and materials

All the available data is available with the corresponding author and will be made available on request.

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