

Prosthetic valve endocarditis due to *Candida parapsilosis* – a rare case report

Shivang Sharma¹, Subhashree Samantaray¹, Deepak Kumar^{1,*}, Durga Shankar Meena¹, Rahul Chaudhary², Vidhi Jain³, Gopal Krishana Bohra¹ and Mahendra Kumar Garg¹

Abstract

Fungal endocarditis is a rare and fatal condition, most frequently caused by species of the genera *Candida* and *Aspergillus*. Fever and changing heart murmur are the most common clinical manifestations. The diagnosis of fungal endocarditis is challenging, with prosthetic valve endocarditis being extremely difficult to diagnose. The optimal management of the condition still remains debatable. We present a case of prosthetic valve endocarditis caused by *Candida parapsilosis*, managed empirically with liposomal amphotericin B, which was later shifted to combination therapy with high-dose echinocandin and fluconazole, but had a fatal outcome because the patient could not undergo timely surgical intervention. Treating *C. parapsilosis* endocarditis cases is difficult because of their biofilm production on native and prosthetic heart valves. A combined approach consisting of a high index of clinical suspicion, early diagnosis using serological markers followed by culture or PCR and prompt initiation of appropriate antifungals may aid in improving outcomes.

DATA SUMMARY

No new data were generated in the study.

INTRODUCTION

Infective endocarditis (IE) is challenging to diagnose, having many presentations, ranging from an indolent infection to septicemia with life-threatening systemic embolizations [1]. The incidence of fungal endocarditis (FE) has been increasing, accounting for 1.3–6% of all reported IE and ~3% of prosthetic valve endocarditis cases, with a mortality rate as high as 50% [2, 3]. The two most common fungi causing endocarditis are species of the genera *Candida* and *Aspergillus*, usually isolated from surgically removed emboli, resected valves or infected foreign bodies [4]. Even though *Candida albicans* is the most common *Candida* species causing FE, the non-albicans *Candida* (NAC) species have also contributed to significant in-hospital mortality and morbidity [5]. Among the NAC species, incidence of *C. parapsilosis* IE has increased in the past two decades [2, 6]. Such patients most commonly present with fever and changing or new onset cardiac murmurs [7]. The common risk factors associated with FE are underlying cardiac abnormalities, prosthetic heart valves, previous cardiac surgery, intravenous drug abuse and other immunocompromised conditions predisposing to invasive candidiasis [4]. The diagnosis of FE is often difficult because of its close resemblance to bacterial IE. Additionally, treating the condition after diagnosis is often difficult because of the ability of the *Candida* species to form biofilms on native and prosthetic valves, causing poor penetration of antifungal agents [8]. Hence a combination of source removal and prolonged antifungal therapy is recommended for the treatment of FE cases. We hereby report a case of prosthetic valve endocarditis caused by *C. parapsilosis* and managed with a combination of high-dose caspofungin and fluconazole that had a fatal outcome because of the inability of the patient to undergo timely source removal. This case illustrates

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Keywords: endocarditis; *Candida parapsilosis*; combined surgery and antifungal treatment.

Abbreviations: AFST, anti-fungal susceptibility testing; AHA, American Heart Association; AR, aortic regurgitation; BDG, 1,3- β -D-glucan; BYC, budding yeast cells; CE, *Candida* endocarditis; ECG, electrocardiogram; FE, Fungal endocarditis; IDSA, Infectious Diseases Society of America; IE, Infective endocarditis; LVEF, left ventricular ejection fraction; MALDI-TOF MS, matrix-assisted laser desorption/ionization time-of-flight mass spectrometry; NAC, Non-albicans *Candida*; PCR, polymerase chain reaction; PVE, prosthetic valve endocarditis; TTE, Transthoracic echo-cardiography.

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the importance of a multidisciplinary approach of both surgical intervention and antifungal antibiotics in treating a case of FE in order to obtain a good outcome.

CASE DETAILS

A 55-year-old male, with no known co-morbidities, having a history of rheumatic heart disease with severe mitral stenosis 10 years previously, presented at our tertiary care hospital with complaints of fever and weight loss over the past 5 months. He had been admitted to a local hospital 1 month previously with a similar complaint and received ceftriaxone by injection along with symptomatic management for 10 days. He had been operated on for mitral valve regurgitation with prosthetic valve insertion 5 years previously. Since then he had been taking oral anticoagulants such as aspirin 75 mg OD, warfarin 6 mg OD, digoxin 25 mg OD (5/7) and torsemide 10 mg OD. He also had a history of undergoing right inguinal hernia repair 7 years previously. On examination, he was extremely cachexic and had grade 3 clubbing. He was febrile with an axillary temperature of 102° F and a respiratory rate of 20 min⁻¹, and his blood pressure was 110/80 mm Hg in the right arm supine position. Upon examining the cardiovascular system, a precordial bulge was observed with a mid-sternal scar suggestive of previous sternotomy. On auscultation, a pansystolic murmur of grade 3/6 without ejection systolic click was heard. Per-abdominal examination revealed mild splenomegaly and left reducible indirect inguinal hernia along with a surgical scar over the same site. Other systemic examinations were normal. An urgent electrocardiogram (ECG) was ordered, which was suggestive of atrial fibrillation with a heart rate of 114 min⁻¹. The chest X-ray findings were within normal limits. The patient was admitted to our hospital for further evaluation.

Upon admission, detailed physical examination was performed and the above clinical findings were confirmed. Routine blood investigations were sent, the findings of which showed haemoglobin of 9.0 gm dl⁻¹, total leucocyte count of 4390 mm⁻³ with 69% neutrophil and 28% lymphocytes. The platelet count of 63000 mm⁻³ and urine routine examination showed one to two pus cells per high power field. The patient's ESR (78 mm/1st hour) and CRP (64.72 mg l⁻¹) were raised. His fasting blood sugar was 94 mg dl⁻¹ and HBA1c was 5.1%. Liver function test showed mild unconjugated hyperbilirubinemia (indirect bilirubin 1.44 mg dl⁻¹) with reversal of albumin (2.78 gm dl⁻¹) to globulin (4.42 g dl⁻¹) ratio. Kidney function tests were normal (urea 33 mg dl⁻¹, creatinine 0.88 mg dl⁻¹). D-dimer was 0.43 ug ml⁻¹ (0–0.5 ug ml⁻¹), rheumatoid factor was 13.0 U ml⁻¹ (<14 U ml⁻¹), PT/INR was 71.1/6.89 (11–13 s/2–3) and APTT was 67.8 (21–35 s). Serological tests for HIV, HCV and HBsAg were negative. Three sets of blood culture bottles (BACTEC, BD) and urine culture were sent and the patient was started empirically on ceftriaxone by injection (1 gm i.v. BD), vancomycin (500 mg i.v. BD) and gentamycin by injection (80 mg i.v. BD). Ultrasonography of the whole abdomen showed mild hepatomegaly (15.5 cm), splenomegaly (16 cm) with mild ascites and partially thrombosed aneurysm of ~2.8×1.9 cm of the superior mesenteric artery. CT angiography was also performed, showing normal common carotid arteries, internal carotid arteries, vertebral arteries and anterior, middle and posterior cerebral arteries of normal anatomy and calibre without any arterio-venous malformations. Fundoscopic examination was also normal. Transthoracic echo-cardiography (TTE) was performed, which showed restricted prosthetic mitral valve leaflet and vegetation over aorto-mitral continuity (dimensions: 35×9 mm) with mild aortic regurgitation (AR) and left ventricular ejection fraction (LVEF) of 55%. Urine culture was found to be sterile after 48 h. However, all three blood cultures sent had been flagged as positive, showing growth of budding yeast cells (BYCs) on Gram stain, following which injection of liposomal amphotericin B (200 mg i.v. infusion OD) was added to the treatment regimen awaiting the identification and anti-fungal susceptibility testing (AFST) report on the BYCs. On day 4, the organism was identified as *C. parapsilosis* by matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) (bioMérieux, France) and it was susceptible to fluconazole (MIC=0.5 µg ml⁻¹), voriconazole (MIC=0.125 µg ml⁻¹), itraconazole (MIC=1 µg ml⁻¹) and caspofungin (MIC=0.5 µg ml⁻¹), and was intermediate for amphotericin B (MIC=4 µg ml⁻¹) using the AFST E-strip method. Following this, the ongoing antimicrobial regimen was stopped and a combination of high-dose caspofungin (150 mg i.v. OD) and fluconazole (400 mg i.v. OD) was started for the patient. After 10 days of treatment, fever subsided and the patient started regaining appetite and weight. The isolate was later on reported to be susceptible to amphotericin B by broth microdilution (MIC=2 µg ml⁻¹), but the patient was continued on the caspofungin and fluconazole combination because of better clinical response.

On day 18 of hospitalization, the patient developed left lower limb pain and persistent headache, not relieved by analgesics. Abdominal and left lower limb arterial Doppler showed a thrombus occluding the superior mesenteric artery (2.5 cm in length) and left common femoral artery (2 cm in length extending into the superior femoral artery and dorsal femoral artery). CE-MRI brain showed acute embolic infarcts in the right fronto-parietal region, left frontal lobe and bilateral cerebellar hemispheres, along with chronic infarct in the right temporal lobe with cortical laminar necrosis in the right superior and inferior temporal gyrus and occlusion in the right middle cerebral artery in its M2 segment. Throughout the hospitalization, the patient had persistent thrombocytopenia, for which peripheral blood film examination was performed, which showed large platelets along with mild anisocytosis. Bone marrow biopsy was also performed, whose findings were otherwise normal except for some reactive changes. The bone marrow aspirate was also sent for culture in two BACTEC blood culture bottles, which again flagged positive for BYCs. However, repeat TTE performed around the same time revealed a reduced vegetation size (28×8 mm) (Fig. 1). The patient was treated with 28 days of high-dose caspofungin and fluconazole along with continuation of oral anti-coagulants. The patient was symptomatically better after at the end of 4 weeks and repeat paired blood cultures were sterile. He was discharged on fluconazole maintenance therapy (400 mg PO BD) along with oral aspirin 75 mg OD, acenocoumarol 1 mg OD, digoxin 0.25 mg (5/7) and

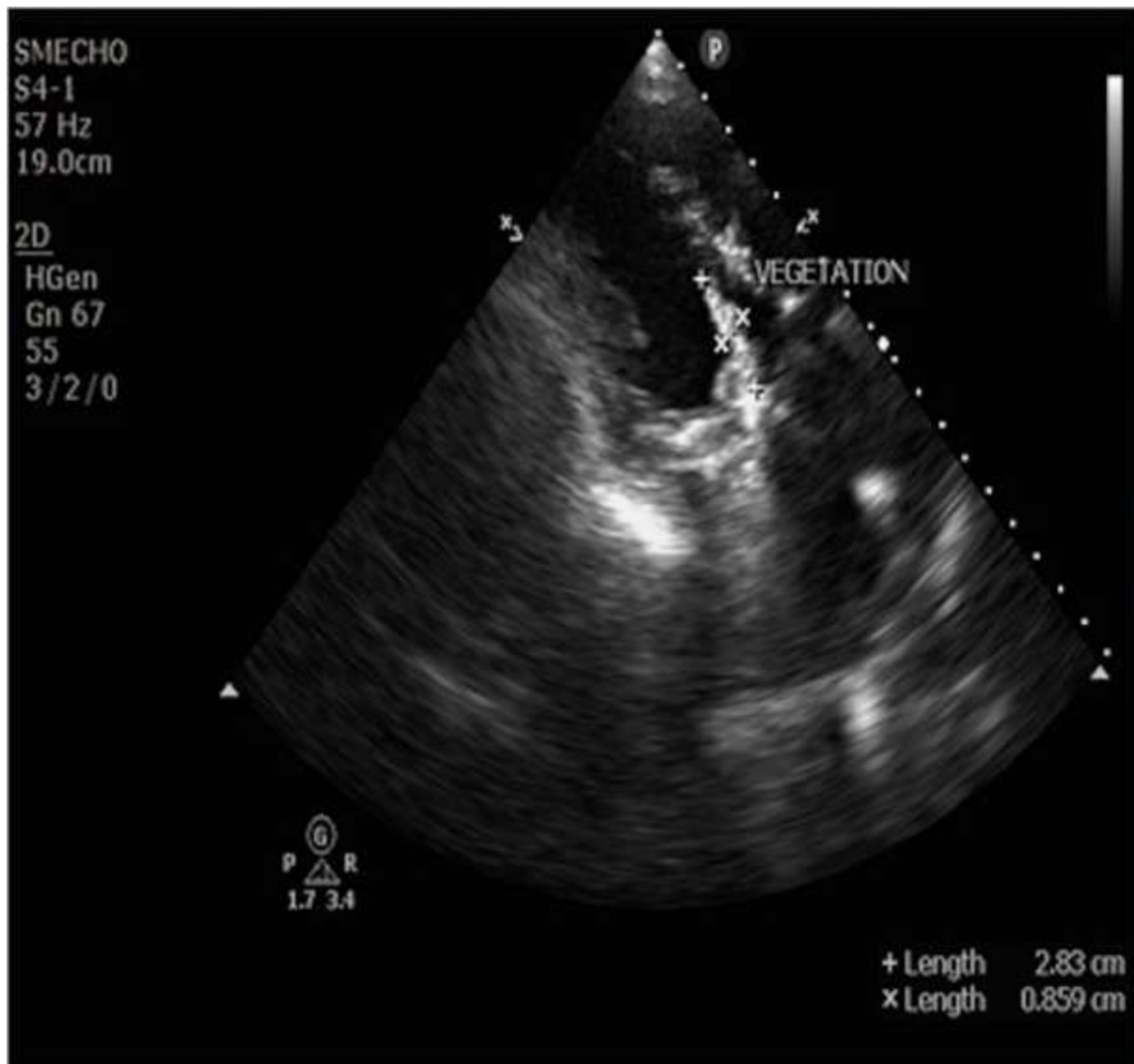


Fig. 1. Restricted prosthetic mitral valve leaflet and vegetation over aorto-mitral continuity (28×8 mm).

torsemide 10 mg OD. He was advised to come back for fortnightly follow-up in order to make a prompt decision on undergoing surgical intervention. The post-discharge follow-up period was uneventful for the next two visits. After a week, the patient presented at the emergency room with respiratory distress. Cardiology reference was sought. Echocardiography was suggestive of acute heart failure and the patient succumbed to the illness.

DISCUSSION

Candida endocarditis (CE) is a rare disease that can occur following *Candida* bloodstream infections or secondary to translocation from gut flora or due to antibiotic pressure in critically ill patients [9]. A recently performed systematic review showed that *C. albicans* and *C. parapsilosis* are the most common species causing FE [10]. Other non-*albicans* *Candida* species such as *C. krusei*, *C. dubliniensis*, *C. lusitanae* and multidrug-resistant *C. auris* have also been associated with a substantial rise in in-hospital morbidity and mortality among the FE cases [5, 11].

CE commonly occurs in the setting of underlying malignancy, chronic liver disease, previous endocarditis, antimicrobial exposure, abdominal surgery or intravenous drug abuse, in the presence of a central venous catheter and also previous cardiac surgery [9]. In our case, the patient had undergone cardiac surgery and prosthetic valve replacement 5 years previously. *Candida* prosthetic valve endocarditis (PVE) is more commonly left-sided, occurs mostly at the aortic valve and is often

missed by TTE because of its anatomical location [12]. Our patient had a mitral prosthetic valve vegetation and was easily caught on TTE because of its larger size [13]. It was a case of late PVE, occurring beyond 12 months of cardiac surgery [14]. Even though most of the late PVE cases are community acquired and are caused by streptococci and *Staphylococcus aureus*, followed by coagulase-negative staphylococci and enterococci [14], in our case it was due to *C. parapsilosis*. Cases of later presentation with PVE, causing candidaemia following heart valve replacement, have been reported to occur within 1 year of surgery. However, our patient had no previous history of symptoms necessitating hospitalization and possible isolation of *Candida* [12]. Hence the source of infection in the patient could not be established. Thus, it could be that an episode of candidaemia did occur but was not clinically evident before the patients presented with PVE.

The diagnosis of CE is often difficult, as most of the patients do not present with typical clinical features of IE, such as fever, splenomegaly and clubbing, and typical immunological features, such as Roth spots and Osler nodes. However, such patients are at higher risk of embolic events compared to bacterial endocarditis because of the larger and more friable vegetations [10]. Our patient was extremely cachexic and presented with fever, mild splenomegaly, grade 3 clubbing and changing murmur. Later he also developed left lower limb emboli and multiple cerebral infarcts. From the blood culture as well as the bone marrow culture of the patient, *C. parapsilosis* was isolated, which confirmed the diagnosis of CE. Usually, the diagnosis of CE is done by isolating the pathogen from blood or tissue or vegetation by culture followed by confirmation with molecular methods such as polymerase chain reaction (PCR) [10, 12]. However, culture-negative CE cases are also common, in which case serological tests such as 1,3- β -D-glucan (BDG) is a good marker of invasive candidiasis, showing 90–100% sensitivity [15]. BDG can be used as an early diagnostic marker of CE and for prompt initiation of antifungal antibiotics after ruling out other potential causes [16].

In terms of treatment, the patient was first started on injectable liposomal amphotericin B empirically and was later shifted to a combination of high-dose caspofungin and fluconazole based on the AFST report. However, he could not be taken up for surgery immediately because he was extremely cachexic. The most recent Infectious Diseases Society of America (IDSA, 2016) [17] and American Heart Association (AHA, 2015) [18] guidelines suggest the treatment of *Candida* PVE with liposomal amphotericin B (3–5 mg/kg/day) in combination with or without flucytosine (25 mg/kg four times daily) or high-dose caspofungin (150 mg daily) as an alternative, along with valve replacement. This has to be followed by chronic suppressive therapy with fluconazole (6–12 mg/kg/day) to prevent recurrences. Echinocandins exert their fungicidal activity by inhibiting BDG synthesis and disrupting the fungal cell wall and are considered to be the drug of choice against most *Candida* species [19]. With medical therapy, the size of the vegetations was shown to reduce and the patient was afebrile. He was discharged on fluconazole maintenance therapy and it was planned for him to have surgery later. Even though lifelong fluconazole therapy has shown survival benefits in patients with *Candida* PVE who are unfit for surgery [10], the patient passed away due to cardiac failure before he could undergo valve replacement. Large vegetations (>2 cm) have been identified as an independent predictor of mortality in cases with fungal aetiology, which could have contributed to the fatality in our patient [20]. Despite the use of medical and surgical combination therapy, the mortality rate for *C. parapsilosis* endocarditis remains as high as 40% [21]. A combined approach from the ID team and the cardiology team is recommended for timely diagnosis and proper management of FE cases in order to reduce fatality.

CONCLUSION

We describe a case of *C. parapsilosis* prosthetic valve endocarditis in a patient with a history of undergoing cardiac surgery but without any other co-morbidities. The changing epidemiology of candidiasis cases indicates that invasive diseases due to this species may be much more frequent. Although the use of echinocandins and lipid formulations of amphotericin B have been promising in the management of such cases, fatality has been reported without surgical intervention. However, despite the use of a combined medical and surgical approach, the mortality due to *Candida* endocarditis still remains high. This emphasizes the need for a combined approach of a high index of clinical suspicion, early diagnosis by serological markers such as BDG followed by culture or PCR and prompt initiation of appropriate antifungals to improve the outcome.

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Author contributions

S.S.: conceptualization, data curation, investigation, methodology, writing – original draft, writing – review and editing. S.S.: conceptualization, data curation, investigation, methodology, writing – original draft, writing – review and editing. D.K.: conceptualization, data curation, investigation, methodology, visualization, writing – review and editing. D.S.M.: conceptualization, data curation, investigation, methodology, visualization, writing – review and editing. R.C.: conceptualization, data curation, investigation, methodology, visualization, writing – review and editing. V.J.: conceptualization, data curation, investigation, methodology, visualization, writing – review and editing. G.K.B.: conceptualization, data curation, investigation, methodology, visualization, writing – review and editing. M.K.G.: conceptualization, data curation, investigation, methodology, visualization, writing – review and editing.

Ethical statement

Was taken from the Institutional Ethics Committee (IEC).

Consent to publish

Written informed consent was obtained from the patient's relative (son). A copy of the consent form is available for review by the editor of this journal.

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Peer review history

VERSION 3

Editor recommendation and comments

<https://doi.org/10.1099/acmi.0.000462.v3.3>

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Nihal Bandara; University of Bristol, Bristol Dental School, Lower Maudlin Street, UNITED KINGDOM, Bristol

Date report received: 06 December 2022

Recommendation: Accept

Comments: This is a study that would be of interest to the field and community.

SciScore report

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iThenticate report

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Author response to reviewers to Version 2

Date-11.11.2022

Dear Editor,

The following table enlists the point-to-point changes as mentioned by the reviewers.

Sl No	Correction suggested	Correction done & highlighted in the main manuscript
Reviewer 2		
1	L57: complains of fever and weight loss over past five months. With similar complaints, he was to be corrected as : complaints of fever & weight loss over past five months. With similar complaints, he was	L57: corrected as : complaints of fever & weight loss over past five months. With similar complaints, he was

2	L185-L186: the patient passed away before he could undergo valve replacement due to cardiac failure. The sentence should be rephrased as , "the patient passed away due to cardiac failure before he could undergo valve replacement. "	L185-186: The sentence has been rephrased as 'the patient passed away due to cardiac failure before he could undergo valve replacement'.
Reviewer 3:		
3	69 Rest of the systemic examinations were 70 normal. Should read "Other systemic examinations were normal.	L69-70: The sentence has been rephrased as 'Other systemic examinations were normal'.
4	75 showed Haemoglobin of 9.0 gm/dL, total leucocyte count of 4390/mm3 with 69% neutrophil, Comment: Should read haemoglobin (small "h")	L75: 'Haemoglobin' changed to 'haemoglobin'.
5	188 Despite of the use of a combination of medical and 189 surgical therapy, the mortality rate of <i>C. parapsilosis</i> endocarditis remains as high as 40%. Should read "Despite the use of medical and surgical combination therapy, the mortality rate of <i>C. parapsilosis</i> endocarditis remains as high as 40%."	L 188-190: The sentence has been rephrased as "Despite the use of medical and surgical combination therapy, the mortality rate of <i>C. parapsilosis</i> endocarditis remains as high as 40%."

6	However despite of the combined medical and surgical 199 approach, the mortality due to Candida endocarditis still remains high, which emphasizes the 200 need of combined approach of high index of clinical suspicion, early diagnosis by serological 201 markers like BDG followed by culture or PCR and prompt initiation of appropriate 202 antifungals to improve the outcome. This sentence is too complex and will need to be broken into 2 different sentences. For example, "However, despite the use of combined medical and surgical approach, the mortality due to Candida endocarditis still remains high. This emphasizes the need for combined approach using high index of clinical suspicion, early diagnosis by serological markers like BDG, followed by culture or PCR and prompt initiation of appropriate antifungals to improve the outcome."	L199- 203: the sentences have been modified as 'However, despite the use of combined medical and surgical approach, the mortality due to <i>Candida</i> endocarditis still remains high. This emphasizes the need of combined approach of high index of clinical suspicion, early diagnosis by serological markers like BDG followed by culture or PCR and prompt initiation of appropriate antifungals to improve the outcome.'
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VERSION 2

Editor recommendation and comments

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Nihal Bandara; University of Bristol, Bristol Dental School, Lower Maudlin Street, UNITED KINGDOM, Bristol

Date report received: 18 October 2022

Recommendation: Minor Amendment

Comments: The reviewers have highlighted major concerns with the work presented. Please ensure that you address their comments.

Reviewer 3 recommendation and comments

<https://doi.org/10.1099/acmi.0.000462.v2.1>

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Date report received: 27 September 2022
 Recommendation: Minor Amendment

Comments: 1. Description of the case(s) 69 Rest of the systemic examinations were 70 normal. Comment: Should read "Other systemic examinations were normal." 75 showed Haemoglobin of 9.0 gm/dL, total leucocyte count of 4390/mm³ with 69% neutrophil, Comment: Should read haemoglobin (small "h") 2. Presentation of results None 3. How the style and organization of the paper communicates and represents key findings None 4. Literature analysis or discussion 188 Despite of the use of a combination of medical and 189 surgical therapy, the mortality rate of *C. parapsilosis* endocarditis remains as high as 40%. Comment: Should read "Despite the use of medical and surgical combination therapy, the mortality rate of *C. parapsilosis* endocarditis remains as high as 40%." However despite of the combined medical and surgical 199 approach, the mortality due to *Candida* endocarditis still remains high, which emphasizes the 200 need of combined approach of high index of clinical suspicion, early diagnosis by serological 201 markers like BDG followed by culture or PCR and prompt initiation of appropriate 202 antifungals to improve the outcome. Comment: This sentence is too complex and will need to be broken into 2 different sentences. For example, "However, despite the use of combined medical and surgical approach, the mortality due to *Candida* endocarditis still remains high. This emphasizes the need for combined approach using high index of clinical suspicion, early diagnosis by serological markers like BDG, followed by culture or PCR and prompt initiation of appropriate antifungals to improve the outcome." 5. Any other relevant comments None

Please rate the quality of the presentation and structure of the manuscript
 Very good

To what extent are the conclusions supported by the data?
 Strongly support

Do you have any concerns of possible image manipulation, plagiarism or any other unethical practices?
 No

Is there a potential financial or other conflict of interest between yourself and the author(s)?
 No

If this manuscript involves human and/or animal work, have the subjects been treated in an ethical manner and the authors complied with the appropriate guidelines?
 Yes

Reviewer 2 recommendation and comments

<https://doi.org/10.1099/acmi.0.000462.v2.2>

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Date report received: 29 September 2022
 Recommendation: Minor Amendment

Comments: 1. Description of the case(s): the description gives a clear picture of the case and its progress. in L57: complains of fever and weight loss over past five months. With similar complains, he was to be corrected as : complaints of fever & weight loss over past five months. With similar complaints, he was 2. Presentation of results : The results are presented well. 3. How the style and organization of the paper communicates and represents key findings, the style & organization of paper communicates about the key findings, 4. Literature analysis or discussion: literature has been analysed well. L185-L186: the patient passed away before he could undergo valve L 186 replacement due to cardiac failure. The sentence should be rephrased as , "the patient passed away due to cardiac failure before he could undergo valve replacement. " 5. Any other relevant comments: nil

Please rate the quality of the presentation and structure of the manuscript
 Very good

To what extent are the conclusions supported by the data?

Strongly support

Do you have any concerns of possible image manipulation, plagiarism or any other unethical practices?

No

Is there a potential financial or other conflict of interest between yourself and the author(s)?

No

If this manuscript involves human and/or animal work, have the subjects been treated in an ethical manner and the authors complied with the appropriate guidelines?

Yes

Reviewer 1 recommendation and comments

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Date report received: 12 October 2022

Recommendation: Accept

Comments: Thank you for adapting the manuscript in line with the previous review comments. I am happy with the manuscript to recommend for publication

Please rate the quality of the presentation and structure of the manuscript

Very good

To what extent are the conclusions supported by the data?

Strongly support

Do you have any concerns of possible image manipulation, plagiarism or any other unethical practices?

No

Is there a potential financial or other conflict of interest between yourself and the author(s)?

No

If this manuscript involves human and/or animal work, have the subjects been treated in an ethical manner and the authors complied with the appropriate guidelines?

Yes

Author response to reviewers to Version 1

Date-01.09.2022

Dear Editor,

The following table enlists the point to point changes as mentioned by the reviewers.

Sl No	Correction suggested	Correction done & highlighted in the main manuscript
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Editor

1	Please upload figures as separate, high resolution, editable files. Acceptable file types are PDF, GIF, TIFF, EPS, JPEG, PNG, SVG, and PPT. Please ensure the figures and legends are also in the main manuscript as this will be preprinted again	Uploaded in JPEG format.
Reviewer 1	L103/104: Patient expiration information would be useful here - is it due to the fungal infection or other factors? Particularly as patient was discharged. I see this now in line 158 - please add into the above section.	L129-132: The post-discharge follow-up period was uneventful for the next two visits After a week, the patient presented to emergency room with respiratory distress. Cardiology reference was sought. Echocardiography was suggestive of acute heart failure and the patient succumbed to the illness.
Minor comments	L35: rephrase to 'species of the genera <i>Candida</i> and <i>Aspergillus</i> '	L35: The two most common fungi causing endocarditis are species under genera <i>Candida</i> and <i>Aspergillus</i>
	L39: English language review of this sentence	L37-40: Even though <i>Candida albicans</i> is the most common <i>Candida</i> species causing FE, the non-albicans <i>Candida</i> (NAC) species have also contributed to significant in-hospital mortality and morbidity. ⁵ Among the NAC species, incidence of <i>C. parapsilosis</i> infective endocarditis has increased in the past two decades. ^{2,6}
	L54: Not sure of the significance of 'businessman' in this sentence. Specify gender.	L55: A 55-year-old male, with no known co-morbidities, having history of rheumatic heart disease with severe mitral stenosis ten years prior
	L54/55: 'severe mitral stenosis ten years prior'	L56: A 55-year-old male, with no known co-morbidities, having history of rheumatic heart disease with severe mitral stenosis ten years prior.
Reviewer 2		

Fungal endocarditis cases are prone for thromboembolic episodes as per the literature and discussion. However as per the description of the case, there is no mention of prevention or management of VTE events, other investigations, doppler studies of other areas including chest. Post discharge Follow up details not mentioned. Review after fortnight is a long gap for follow up esp. when the mortality in such cases is high and early surgical procedure was to be planned.

L 88-91: CT angiography was also performed showing normal common carotid arteries, internal carotid arteries, vertebral arteries and anterior, middle and posterior cerebral arteries of normal anatomy and calibre without any arteriovenous malformations.

L110-112: Abdominal and left lower limb arterial doppler showed a thrombus occluding the superior mesenteric artery (2.5 cm in length) and left common femoral artery (2 cm in length extending into superior femoral artery and dorsal femoral artery)

L113-116: CE-MRI brain showed acute embolic infarcts in right fronto-parietal region, left frontal lobe and bilateral cerebellar hemispheres along with chronic infarct in right temporal lobe with cortical laminar necrosis in right superior and inferior temporal gyrus and occlusion in right middle cerebral artery in its M2 segment.

L125-127: He was discharged on fluconazole maintenance therapy (400 mg P.O. BD) along with oral aspirin 75 mg OD, acenocoumarol 1mg OD, digoxin 0.25mg (5/7) and torsemide 10mg OD.

Description of the case(s) - History of severe Mitral stenosis (line 54-55), operated for mitral valve regurgitation (line 56), No mention of history or status of diabetes, cancer or any other condition, causing immunocompromised state- HIV, Cancer etc. History and examination findings to rule out any respiratory disease is not mentioned. Investigations mentioned does not comment on other investigations viz. Blood sugar, Hba1c, DLC, chest xray, and other tests for work up of case of fever with weight loss over 5 months., and their findings. Treatment history over last 5 months is also not mentioned to establish/rule out Antibiotic pressure. Follow up investigations done during the hospital stay are not mentioned in the description to establish persistent thrombocytopenia, Liver enzymes. Indication for Brain angiography not mentioned. Doppler study of other areas abdomen, chest is not mentioned after VTE event Management of VTE viz Anticoagulant given for prevention of thromboembolic events after diagnosis of Fungal endocarditis is not mentioned.	Details added in text as mentioned above.
Presentation of results : Other Relevant history, examination, investigations and their results are not mentioned as described above.	Details added in text as mentioned above.
Presentation of results : Other Relevant history, examination, investigations and their results are not mentioned as described above.	Details added in text as mentioned above.
How the style and organization of the paper communicates and represents key findings description of the case: the paper communicates about the key findings, however other relevant information to be included as mentioned before.	Details added in text as mentioned above.

Literature analysis or discussion: literature has been analysed well. Discussion to include other relevant information of this case with respect to the literature.

Details added in text as mentioned above.

Line 197- 199: Although the use of echinocandins and lipid formulations of amphotericin B have been promising in management of such cases, fatality has been reported without surgical intervention.

Any other relevant comments: conclusion does not mention/comment about surgical management.

Serological marker 1, 3 beta d glucan is discussed based on literature but whether done in this case is not mentioned.

Reply to the reviewer (not added in text)- In our case, at first fungal IE was not suspected and patient was managed in line of bacterial IE as earlier blood cultures were negative but Duke's criteria was met for possible IE. However, the blood culture flagged positive for *Candida parapsilosis* after which antifungals were started. The literature states that, in culture negative IE, 1,3-BDG can be done in patients to screen for fungal cause, which can aid in early initiation of antifungals, which is a point we wanted to highlight but could not do for our patient.

Reviewer 3:

84 After this, ceftriaxone, vancomycin and amphotericin B were stopped and high dose caspofungin
85 (150 mg i.v. OD) and fluconazole (400 mg i.v. OD) were added to the treatment regimen.

Correction/input: Having stopped the ongoing antimicrobial regimen, the statement should state that the new regime was started or commenced but not added since we're not informed of other non-antimicrobial treatment.

L103- 105: Following this, the ongoing antimicrobial regimen was stopped and a combination of high dose caspofungin (150 mg i.v. OD) and fluconazole (400 mg i.v. OD) was started for the patient.

CECT brain angiography was also performed which showed multiple right frontal, occipital-temporal gyrus and right cerebellar sub-acute embolic 95 infarcts.

Correction/input: Is there any effect of the multiple infarcts found in the brain, since the lower limb pain can be justifiably attributed to the embolic found by Doppler scan of the lower limb.

104 But unfortunately, the patient expired before the prosthetic valve replacement and vegetation removal could be performed.

Correction/input: I suppose that the word "expired" meant that the patient had died. I do not know if this is an acceptable formal way to describe the situation.

117 *Candida* PVE (prosthetic valve endocarditis) is more commonly left-sided and occurs most of the times at the aortic valve and is often missed by TTE (Trans-thoracic ECHO).

Correction/input: Is there any reason why TTE (Trans-thoracic ECHO) is unable to regularly visualize left-sided vegetation? Reasons such as anatomical locations and relation.

125 reported to occur within one year of surgery. However, our patient gave a negative history of

126 any previous episodes of candidemia. Correction/input: Should read, there were no previous history of symptoms necessitating hospitalization and possible isolation of candida.

L110- The patient had persistent headache, which is why CE-MRI Brain was done.

L 184- 187: Even though lifelong fluconazole therapy has shown survival benefits in the patients with *Candida* PVE who are unfit for surgery¹⁰, the patient passed away before he could undergo valve replacement due to cardiac failure.

L145- 147: *Candida* PVE (prosthetic valve endocarditis) is more commonly left-sided and occurs most of the times at the aortic valve and is often missed by TTE (Trans-thoracic ECHO) because of its anatomical location.

L154-155: However, our patient had no previous history of symptoms necessitating hospitalization and possible isolation of *Candida*.¹²

156 Even though lifelong fluconazole therapy has shown survival benefits in the patients with *Candida* PVE who are unfit for surgery
 157 , our patient expired before he could undergo valve replacement
 158 due to pulmonary embolism.
 Correction/input: I do not think using the word "expired" to describe the passing of away of a patient is respectful and empathic.

L184- 187: Even though lifelong fluconazole therapy has shown survival benefits in the patients with *Candida* PVE who are unfit for surgery¹⁰, our patient passed away before he could undergo valve replacement due to cardiac failure.

VERSION 1

Editor recommendation and comments

<https://doi.org/10.1099/acmi.0.000462.v1.6>

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Nihal Bandara; University of Bristol, Bristol Dental School, Lower Maudlin Street, UNITED KINGDOM, Bristol

Date report received: 02 August 2022

Recommendation: Major Revision

Comments: The reviewers have highlighted major concerns with the work presented. Please ensure that you address their comments.

Reviewer 3 recommendation and comments

<https://doi.org/10.1099/acmi.0.000462.v1.3>

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Emeka Walter Alobu; Jos University Teaching Hospital, Medical Microbiology, Medical Microbiology Dept. Jos University Teaching Hosp, #1 Alex Kazen Close Lamungo Jos North Plateau State, Jos, NIGERIA

<https://orcid.org/0000-0003-2694-7596>

Date report received: 01 August 2022

Recommendation: Minor Amendment

Comments: 1. Description of the case(s) The article is well written and of an appropriate length, however I have noted the following corrections and input. 84 After this, ceftriaxone, vancomycin and amphotericin B were stopped and high dose caspofungin 85 (150 mg i.v. OD) and fluconazole (400 mg i.v. OD) were added to the treatment regimen. Correction/input: Having stopped the ongoing antimicrobial regimen, the statement should state that the new regime was started or commenced but not added since we're not informed of other non-antimicrobial treatment. 94 CECT brain angiography was also performed which showed multiple right frontal, occipital-temporal gyrus and right cerebellar sub-acute embolic 95 infarcts. Correction/input: Is there any effect of the multiple infarcts found in the brain, since the lower limb pain can be justifiably attributed to the embolic found by Doppler scan of the lower limb. 104 But unfortunately, the patient expired before the prosthetic valve replacement and vegetation removal could be performed. Correction/input: I suppose that the word "expired" meant that the patient had died. I do not know if this is an acceptable formal way to describe the situation. 117 *Candida* PVE (prosthetic valve endocarditis) is more commonly left-sided and occurs most of the times at the aortic valve and is often missed by TTE (Trans-thoracic ECHO). Correction/input: Is there any reason why TTE (Trans-thoracic ECHO) is unable to regularly visualize left-sided vegetation? Reasons such as anatomical

locations and relation. 125 reported to occur within one year of surgery. However, our patient gave a negative history of 126 any previous episodes of candidemia. Correction/input: Should read, there were no previous history of symptoms necessitating hospitalization and possible isolation of candida. 156 Even though lifelong fluconazole therapy has shown survival benefits in the patients with Candida PVE who are unfit for surgery 157, our patient expired before he could undergo valve replacement 158 due to pulmonary embolism. Correction/input: I do not think using the word "expired" to describe the passing of away of a patient is respectful and empathic. 2. Presentation of results The findings are significant and represent an advance in knowledge and understanding? The results and conclusions are adequate and well discussed in relation to published literature. 3. How the style and organization of the paper communicates and represents key findings The article is well written and of an appropriate length, however I have noted the above corrections and input. 4. Literature analysis or discussion This is adequate. 5. Any other relevant comments None

Please rate the quality of the presentation and structure of the manuscript

Very good

To what extent are the conclusions supported by the data?

Strongly support

Do you have any concerns of possible image manipulation, plagiarism or any other unethical practices?

No

Is there a potential financial or other conflict of interest between yourself and the author(s)?

No

If this manuscript involves human and/or animal work, have the subjects been treated in an ethical manner and the authors complied with the appropriate guidelines?

Yes

Reviewer 2 recommendation and comments

<https://doi.org/10.1099/acmi.0.000462.v1.4>

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MEENAKSHI AGARWAL; Northern Railway Central Hospital New Delhi, Department of Microbiology, Basant Lane, New Delhi, New Delhi, INDIA

<https://orcid.org/0000-0003-3782-0865>

Date report received: 28 July 2022

Recommendation: Major Revision

Comments: 1. Description of the case(s) - History of severe Mitral stenosis (line 54-55), operated for mitral valve regurgitation (line 56), No mention of history or status of diabetes, cancer or any other condition, causing immunocompromised state- HIV, Cancer etc. History and examination findings to rule out any respiratory disease is not mentioned. Investigations mentioned does not comment on other investigations viz. Blood sugar, HbA1c, DLC, chest xray, and other tests for work up of case of fever with weight loss over 5 months., and their findings. Treatment history over last 5 months is also not mentioned to establish/ rule out Antibiotic pressure. Follow up investigations done during the hospital stay are not mentioned in the description to establish persistent thrombocytopenia, Liver enzymes. Indication for Brain angiography not mentioned. Doppler study of other areas abdomen, chest is not mentioned after VTE event Management of VTE viz Anticoagulant given for prevention of thromboembolic events after diagnosis of Fungal endocarditis is not mentioned. 2. Presentation of results : Other Relevant history, examination, investigations and their results are not mentioned as described above. 3. How the style and organization of the paper communicates and represents key findings description of the case: the paper communicates about the key findings, however other relevant information to be included as mentioned before. 4. Literature analysis or discussion: literature has been analysed well. Discussion to include other relevant information of this case with respect to the literature. Death due to pulmonary embolism is mentioned in discussion but no mention in the description of the case. 5. Any other relevant comments: conclusion does not mention/comment about surgical management Serological marker 1, 3 beta d glucan is discussed based on literature but whether done in this case is not mentioned.

Please rate the quality of the presentation and structure of the manuscript

Good

To what extent are the conclusions supported by the data?

Strongly support

Do you have any concerns of possible image manipulation, plagiarism or any other unethical practices?

No

Is there a potential financial or other conflict of interest between yourself and the author(s)?

No

If this manuscript involves human and/or animal work, have the subjects been treated in an ethical manner and the authors complied with the appropriate guidelines?

No: Fungal endocarditis cases are prone for thromboembolic episodes as per the literature and discussion. However as per the description of the case, there is no mention of prevention or management of VTE events, other investigations, doppler studies of other areas including chest. Post discharge Follow up details not mentioned. Review after fortnight is a long gap for follow up esp. when the mortality in such cases is high and early surgical procedure was to be planned.

Reviewer 1 recommendation and comments

<https://doi.org/10.1099/acmi.0.000462.v1.5>

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Date report received: 27 July 2022

Recommendation: Minor Amendment

Comments: 1. Description of the case(s) Clear and detailed 2. Presentation of results Use of normal ranges would be beneficial for non-clinical reading audience. 3. How the style and organization of the paper communicates and represents key findings Key findings are relatively clear, 4. Literature analysis or discussion Discussion links well with previous research and cases, and highlights the importance of invasive fungal infections, particularly re: cardiac infection 5. Any other relevant comments L103/104: Patient expiration information would be useful here - is it due to the fungal infection or other factors? Particularly as patient was discharged. I see this now in line 158 - please add into the above section. Minor comments L35: rephrase to 'species of the genera *Candida* and *Aspergillus*' L39: English language review of this sentence L54: Not sure of the significance of 'businessman' in this sentence. Specify gender. L54/55: 'severe mitral stenosis ten years prior'

Please rate the quality of the presentation and structure of the manuscript

Good

To what extent are the conclusions supported by the data?

Strongly support

Do you have any concerns of possible image manipulation, plagiarism or any other unethical practices?

No

Is there a potential financial or other conflict of interest between yourself and the author(s)?

No

If this manuscript involves human and/or animal work, have the subjects been treated in an ethical manner and the authors complied with the appropriate guidelines?

Yes

SciScore report

<https://doi.org/10.1099/acmi.0.000462.v1.1>

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iThenticate report

<https://doi.org/10.1099/acmi.0.000462.v1.2>

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