

***Candida Tropicalis* Endocarditis: A case report and literature review**

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Abstract

Fungi rarely cause infective endocarditis but when they do, they are often associated with poor outcomes. *Candida tropicalis* accounts for only 10% of *Candida* endocarditis cases. A case of a 30-year-old male with a history of intravenous drug abuse was reported to the emergency department in August, 2021 with right-sided leg pain and fever for 3 days. A trans-thoracic echocardiogram showed a vegetation on the aortic valve and a computed tomography angiogram showed complete non-opacification of the right-sided common iliac artery and the superficial femoral artery just distal to its branching of the right profunda femoris artery. An emergent right iliofemoral embolectomy was done. *Candida tropicalis* was isolated from tissue and blood cultures. The patient was successfully treated with aortic valve replacement and intravenous caspofungin. The other reported cases of *Candida tropicalis* were reviewed and findings were compared with those reported in patients with *Candida albicans* and *Candida parapsilosis* endocarditis.

Keywords: Endocarditis, *candida*, *candida tropicalis*, thromboembolism, antifungal agents.

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Introduction

Infective Endocarditis is a disease in which a native valve, prosthetic valve, endocardial surface or an indwelling cardiac device in the heart becomes infected.¹ Fungal organisms are rarely implicated but when present, *Candida* and *Aspergillus* species are most commonly isolated and are often associated with poor outcomes.²

Among patients with *Candida endocarditis*, *Candida albicans* and *Candida parapsilosis* are the most commonly isolated species while *Candida tropicalis* accounts for only 10% of the cases.³ Mortality due to *Candida* species may vary depending on the isolated organism, with the highest mortality observed in those infected with *Candida tropicalis*, and the lowest in those infected with *Candida parapsilosis*.⁴

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A case of a young male with *Candida tropicalis* endocarditis is presented who was successfully treated with intravenous caspofungin and surgical aortic valve replacement. The review of the literature identified 37 patients with *Candida tropicalis* endocarditis, including this case. Moreover, findings were also compared with those reported in patients with *Candida albicans* and *Candida parapsilosis* endocarditis.

Case Report

On the 21st of August, 2021, a 30-year-old male with a history of intravenous drug abuse presented to The Aga Khan University Hospital, Karachi, Pakistan with an episode of syncope one week before presentation, followed by right leg pain and fever for 3 days. After developing right leg pain and a fever for the past 3 days, he sought medical attention in the emergency room.

Upon arriving at the emergency department, he had a Glasgow Coma Score (GCS) of 15/15 and no focal neurological deficits. On cardiovascular examination, the first and second heart sounds were normal with no murmurs audible. Pulses in the right lower limb were not palpable, while they were intact in all other limbs. There were no stigmata of infective endocarditis on examination.

Blood cultures were sent, and the patient was empirically treated with intravenous ceftriaxone and vancomycin. Plain Computed Tomography (CT) scans of the brain demonstrated low attenuation in the left temporal lobe, primarily in the subcortical and sub-insular regions. However, he did not have any neurological deficits, hence, further evaluation with Magnetic Resonance Imaging (MRI) of the brain was not pursued. A CT angiogram of the abdominal aorta and bilateral lower limbs was performed. It revealed complete non-opacification of the right-sided common iliac artery and the superficial femoral artery just distal to its branching of the right profunda femoris artery throughout its length, as shown in (Figure 1-A). A transthoracic echocardiogram was done which demonstrated a large, mobile, echogenic density measuring 20 x 16 mm attached to the aortic valve with moderate eccentric aortic regurgitation and a probable bicuspid aortic valve, as shown in (Figure 1-B).

He was urgently taken to the operating room and underwent a successful right iliofemoral embolectomy. Septic embolus was sent for culture and sensitivity. It

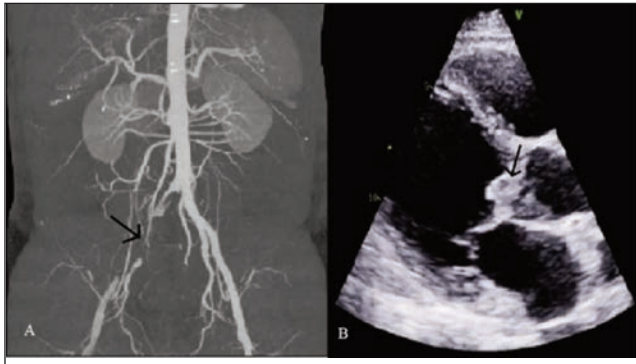


Figure: (A) Computed tomography angiogram showing complete non-opacification of the right-sided common iliac artery and complete non-opacification of the superficial femoral artery just distal to its branching of the right profunda femoris artery throughout its length (B) Transthoracic echocardiogram showing a mobile echogenic density attached to the aortic valve

initially showed rare pus cells and a few budding yeasts. The patient was initially started on intravenous amphotericin B. However, due to a severe drug reaction after the first dose, he was switched to intravenous caspofungin. *Candida tropicalis* was isolated from tissue and blood cultures on day 4 of hospitalization with sensitivity to caspofungin, voriconazole, and fluconazole. *Candida* was isolated on Sabroud dextrose agar media followed by additional media including urea agar, corn meal tween agar, bismuth sulfite glucose glycine yeast agar, and chrome agar.

During the operation, a severely damaged aortic valve causing near-severe aortic stenosis was noted. The vegetation and valve were excised and aortic valve repair with a 23 mm mechanical aortic valve was performed. Post-operatively, multiple blood cultures were sent which were negative.

Appendix # 1

Table: List of 37 reported cases of *Candida Tropicalis* endocarditis identified in the peer reviewed literature from 1974-2021 with individual patient details.

Study Reference	Age(years)	Gender	Risk Factor	Valve/Device Involved	Outcome
Roupie, et al. ¹⁷	64	Male	Abdominal surgery	Aortic	Expired after 11 months from other causes
Gerritson, et al. ¹⁸	73	Male	Genitourinary surgery	Aortic	Expired in hospital
Montague, et al. ¹⁹	49	Male	Abdominal surgery	Aortic	Survived (one year follow up)
Gottlieb, et al. ²⁰	22	Male	IVDU	Aortic	Survived and discharged on 15 POD
Rubinstein, et al. ²¹	34	Female	None	Tricuspid, Aortic, Mitral	Expired
Pasternak, et al. ²²	63	Male	Abdominal Surgery	Mitral	Expired POD 20
Malouf, et al. ²³	52	Male	IHSS	Mitral	Expired after 2 months of treatment
Guzman, et al. ²⁴	30	Male	Abdominal surgery, CVC	Aortic	Survived than relapse on POD 63 then survived on readmission
Mansur, et al. ²⁵	50	Male	Bioprosthetic mitral valve, RHD	Mitral	Survived initially than after 44 months relapse and expired
Zedtwitz-Liebenstein, et al. ²⁶	46	Male	Prosthetic Aortic Valve	Aortic	Survived, 4 years follow up
Mishra, et al. ²⁷	79	Male	Bioprosthetic mitral and aortic valves, PPM	Aortic and mitral	Expired in hospital
Bauer, et al. ²⁸	64	Male	PPM, history of candida tropicalis bacteremia	Eustachian valve	Survived, Follow up 14 months
Shmueli, et al. ²⁹	75	Male	PPM	Pacing leads	Expired in hospital 3rd week of admission
Kurup, et al. ³⁰	77	Male	PPM	Tricuspid	Expired on POD 5
Bazarrica, et al. ³¹	68	Female	PPM	Pacing leads	Survived, 28 months follow up
Bandyopadhyay, et al. ³²	86	Male	PPM	Pacemaker electrode	Survived, 2 months follow up
Lefort, et al. ³³	-	-	-	Aortic	Survived, 6 months follow up
Lefort, et al. ³³	-	-	Bioprosthetic valves	Mitral, Aortic and pulmonary	Expired, 10 days of hospitalization
Lefort, et al. ³³	-	-	IVDU	Aortic	Expired after 10 days
Davoodi, et al. ³⁴	66	Male	Prosthetic valve	Mitral	Expired in hospital day 4
Prabhudas-Strycker, et al. ³⁵	41	Male	Hemodialysis catheter	SVC mass attached to the right atrium, possible aortic root abscess	Survived, one year follow up
Hitzenbichler, et al. ³⁶	83	Female	CVC	LAA occluder	Expired during hospital stay
Dhakal, et al. ³⁷	35	Female	RHD	Mitral valve	Survived for 2 years than episode of C.Parapsillosis after 2 years than survived for further 16 years
Falcone, et al. ³⁸	60	Male	PPM, CVC	Tricuspid valve	Expired on follow up after 8 months from other causes
Pipa, et al. ³⁹	49	Male	IVDU	Mitral and aortic valves	Survived, Follow up 8 weeks
Shin, et al. ⁴⁰	43	Male	ESRD	Tricuspid valve	Expired after 3 days
Kozłowska, et al. ⁴¹	36	Male	Pancreatitis, Total hip replacement	Tricuspid valve	Survived, 6 weeks exact follow up not mentioned
Abgueuen, et al. ⁴²	-	-	Abdominal surgery, CVC	Mitral valve	Expired during hospital stay
del Castillo, et al. ⁴³	66	Male	CVC	Aortic	Expired during the hospital stay
Baddley, et al. ⁴⁴	-	-	-	-	Expired in hospital
Baddley, et al. ⁴⁴	-	-	-	-	Survived to hospital discharge
Baddley, et al. ⁴⁴	-	-	-	-	Expired in hospital
Morelli, et al. ⁴⁵	55	Male	IVDU, CVC	Tricuspid	Survived, follow up 12 months
Morelli, et al. ⁴⁵	51	Female	IVDU	Aortic	Survived, follow up 12 months
Morelli, et al. ⁴⁵	42	Male	IVDU, CVC	Aortic	Survived to discharge
Morelli, et al. ⁴⁵	31	Female	IVDU	Tricuspid	Survived to discharge
Present case Jibril et al.	30	Male	IVDU	Aortic	Survived to clinic follow up in 3 months

IVDU: Intravenous Drug Use. CVA: Cerebrovascular Accident. POD: Postoperative Day. IHSS: Idiopathic Hypertrophic Sub-aortic Stenosis. RHD: Rheumatic Heart Disease. CVC: Central Venous Catheter. PPM: Permanent Pacemaker. ESRD: End Stage Renal Disease. LAA: Left Atrial Appendage.

Table: Findings from a review and analyses of 37 reported cases of *Candida tropicalis* endocarditis in the peer reviewed literature from 1974 to 2021.

Variable	Total Cases (n=37) n (%)	In-Hospital Mortality: Yes (n=17) n (%)	In-Hospital Mortality: No (n = 20) n (%)	p value
Valve Involved				
Aortic	12 (32.4)	3 (17.6)	9 (45.0)	0.094
Mitral	6 (16.2)	5 (29.4)	1 (5.0)	0.075
Tricuspid	6 (16.2)	2 (11.8)	4 (20.0)	0.667
Multiple valves involved	4 (10.8)	3 (17.6)	1 (5.0)	0.315
Risk Factors				
History of prosthetic valve placement	5 (13.5)	4 (23.5)	1 (5.0)	0.159
History of pacemaker insertion	7 (18.9)	3 (17.6)	4 (20.0)	1.00
History of intravenous drug abuse	8 (21.6)	1 (5.9)	7 (35.0)	0.048
Presence of central line	8 (21.6)	3 (17.6)	5 (25.0)	0.701
History of abdominal surgery	6 (16.2)	3 (17.6)	3 (15.0)	1.00
Embolitic Complications	12 (35.1)	3 (17.6)	9 (45.0%)	0.077
Surgical Intervention	17 (45.9)	7 (41.2)	10 (50.0%)	0.591

His condition remained stable and he was discharged on intravenous caspofungin. The patient was followed up in the clinic and intravenous caspofungin was continued. After the completion of 6 weeks of therapy, intravenous caspofungin was stopped. The patient continued the follow up visits in cardiothoracic surgery and infectious disease clinic for 3 months after discharge and remains in good health to date. The patient was continued on warfarin for anticoagulation for mechanical aortic valve and counselled regarding cessation of intravenous drugs.

Discussion

The case of a 30-year-old male is reported with a history of intravenous drug abuse presenting with embolic complications of endocarditis caused by *Candida tropicalis*. Early treatment with embolectomy, intravenous caspofungin, and surgical valve replacement resulted in the survival of the patient. Multidisciplinary approach with involvement of specialists from vascular surgery, cardiothoracic surgery and infectious diseases is essential in such complicated cases.

The PubMed database was searched and several articles were identified of adult patients with *Candida tropicalis* endocarditis. Articles reporting cases of patients less than 18 years of age, or with polymicrobial infections on blood culture reports were excluded. Even, those cases which were based on autopsy or surgical histopathology results after the patient's death were not included. This led us to identify 36 patients from 29 articles in the peer-reviewed literature from 1974 to 2021 with *Candida tropicalis* endocarditis apart from this case. Presence of a history of prosthetic valve placement, intravenous drug abuse, permanent pacemaker insertion, or abdominal surgery was noted. Data including valve involvement, presence of

central line, embolic complications, and outcome was also collected. The only data available for three of these patients was treatment and outcome. Individual patient details are provided in (appendix 1). As the duration of follow-up reported was variable, therefore, in-hospital mortality was used as the primary outcome to maintain conformity. Data was analysed using IBM Statistical Package for Social Sciences (SPSS) version 23. The frequency and percentage of qualitative variables were determined. Chi-square test and Fisher's exact test were used to determine the relationship between categorical variables with $p < 0.05$ taken as significant at a 95% confidence interval. The analyses of these 37 cases of *Candida tropicalis* endocarditis revealed an in-hospital mortality of 45.9%. Further findings of the review are presented in (Table) along with, a comparison of patients who expired during the hospital stay versus those who survived.

In a comparison of 72 patients with *Candida parapsilosis* endocarditis and 52 patients with *Candida albicans* endocarditis, Garzoni et al. observed mortality rates of 33.0% and 41.7% respectively.⁵ However, they did not specify the duration of follow up. Lefort et al. in the prospective MYCENDO study observed that only one out of the eleven (9.1%) patients with *Candida albicans* endocarditis died due to ongoing infection on follow up while five out of nine (55.6%) patients with *Candida parapsilosis* expired.⁶ The highest mortality observed was for *Candida tropicalis* endocarditis as two out of the three (66.7%) patients expired due to ongoing infection.⁶ Jeronimo et al. in a more recent comparison among eight patients each with *Candida parapsilosis* and *Candida albicans* endocarditis, observed in-hospital mortality rates of 25.0% and 37.5% respectively.⁷

In this review, the aortic valve was most commonly involved in *Candida tropicalis* endocarditis as was the case in patients with *Candida Parapsilosis* and *Candida albicans* endocarditis.^{5,7} A history of prosthetic valve placement was present in 13.5% of patients with infection due to *Candida tropicalis* in this review. In the comparison by Garzoni et al., a history of prosthetic valve placement was present in 57.0% and 55.8% patients with *Candida* endocarditis due to *Candida parapsilosis* and *Candida albicans* respectively.⁵ In contrast, a history of prosthetic valve placement was present in 87.5% and 37.5% of patients with *Candida parapsilosis* and *Candida albicans* endocarditis respectively in the review by Jeronimo et al.⁷

We observed that a history of intravenous drug abuse was present in 21.6% of patients with *Candida tropicalis* endocarditis. In the review by Garzoni et al., a history of drug abuse was found in 16.6% and 7.7% of patients with *Candida parapsilosis* and *Candida albicans* endocarditis

respectively.⁵ In contrast, Jeronimo et al. observed that a history of intravenous drug abuse was present in 25.0% of patients with *Candida albicans* endocarditis while none of the eight patients with *Candida parapsilosis* had a history of intravenous drug abuse. Patients with the history of intravenous drug abuse tend to be younger and are more likely to have polymicrobial blood cultures⁸ compared to established risk factors for candidemia such as prolonged admission to the intensive care unit, total parenteral nutrition, and haemodialysis.⁹

Pathogenicity of *Candida* species involves adherence to host and/or medical device surfaces via *Candida* cell surface proteins, termed as, adhesins which is followed by cell division, proliferation, and subsequent biofilm formation.¹⁰ Biofilm formation has been associated with resistance to anti-fungal agents through multi-factorial mechanisms¹¹ and shown to be influenced by species, strain, and environmental conditions.¹² In a review of 39 patients with candidemia, all patients with *Candida tropicalis* isolates expressed biofilm formation while, a high biofilm mass was associated with mortality.¹³ *Candida tropicalis* has been shown to have the highest biofilm formation ability among all other *Candida* species which may explain why it is associated with the highest mortality among the *Candida* species.¹⁴

American Heart Association guidelines recommend surgical replacement of the infected valve along with amphotericin B as the initial drug of choice for fungal endocarditis.¹⁵ The European Society of Cardiology recommends a high dose of echinocandin or liposomal amphotericin B with or without flucytosine in addition to surgical valve replacement.¹⁶ Neither guideline addresses species-specific therapy.

Conclusion

In patients with *Candida tropicalis* endocarditis, a history of intravenous drug abuse and abdominal surgery is more commonly present than in *Candida albicans* and *Candida parapsilosis*. Furthermore, mortality rates in patients with *Candida* endocarditis are variable between species, being highest for *Candida tropicalis* and lowest for *Candida albicans*. Considering the variable mortality rates observed, further research should focus on species-specific therapy.

Consent: A written informed consent for the reporting of this case with an approval from the institutional ethical review committee (ERC) (ERC-Reference number: 2022-7353-21662) was obtained.

Disclaimer: An abstract of this case report has been published in the abstract book of the 13th Health Sciences Research Assembly held in December, 2021 at The Aga Khan University, Karachi, Pakistan.

Conflicts of Interest: None.

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Author Contribution:

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