

# Clinical and Demographic Properties of *Candida* Endocarditis in a Tertiary Heart Center

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*Candida* spp.

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## SOUHRN

**Kontext:** Kvasinka rodu *Candida* je vzácnou, ale významnou příčinou infekční endokarditidy. Cílem studie bylo zjistit klinické údaje pacientů s kandidovou endokarditidou léčených na kardiologickém a kardiokirurgickém oddělení jedné nemocnice v letech 2012 až 2023.

**Metody:** Dokumentace pacientů s diagnózou infekční endokarditidy byla prohlédnuta retrospektivně. Sledovaly se demografické údaje, anamnéza, klinické údaje a informace o výsledném stavu a léčbě.

**Výsledky:** Čtyři (29 %) ze 14 pacientů byly ženy, v 10 (71 %) případech se jednalo o muže. Průměrný věk byl 49,7 ( $\pm 8,82$ ) roku. Průměrná délka hospitalizace byla 39 dní (33–130 dní). Postiženo bylo 5 (38 %) aortálních chlopní, 2 (15 %) aortální + mitrální chlopně, 3 (23 %) mitrální chlopně, ve 2 (16 %) případech byla příčinou vegetace na elektrodě a v 1 (7 %) případě vegetace na plicní chlopní. Ze základních onemocnění trpělo 5 (35 %) pacientů diabetes mellitus, 5 (35 %) bylo na hemodialýze a 4 (30 %) měli kardiostimulátor. Jeden (7 %) pacient prodělal transplantaci srdce, další transplantaci jater. Sedmi (50 %) pacientům byla implantována umělá chlopeň a 7 (50 %) biologická chlopeň. Mikrobiologické vyšetření prokázalo v 8 (57 %) případech přítomnost *C. parapsilosis*, v 5 (35 %) *C. albicans* a v 1 (7 %) případě *C. tropicalis*. V 7 (50 %) případech byla provedena výměna chlopně. Ve vzorku odebraném z chlopně jednoho pacienta prokázala kultivace přítomnost *C. albicans*. Fluconazol byl podáván 6 (43 %) pacientům a echinokandiny v 8 (57 %) případech. V průběhu jednoletého sledování zemřelo 6 (43 %) pacientů. Vyšetření magnetickou rezonancí prokázalo embolii v centrálním nervovém systému u 6 (43 %) pacientů.

**Závěry:** Kandidová endokarditida je spojena s vysokou mortalitou, přitom nejvhodnější způsob léčby lze vzhledem k jejímu vzácnému výskytu velmi obtížně formulovat.

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## ABSTRACT

**Background:** *Candida* is a rare but important cause of infective endocarditis. The study aimed to describe clinical data on patients with *Candida* endocarditis treated in cardiology and cardiovascular surgery hospital between 2012–2023.

**Methods:** Patients diagnosed with infective endocarditis were reviewed retrospectively. Demographic information, medical histories, clinical data, and information on outcome and treatment were presented.

**Results:** Four (29%) of 14 patients were female, and 10 (71%) were male. The mean age was 49.7 ( $\pm 8.82$ ) years. The mean hospital stay was 39 days (33–130 days). The valves involved were 5 (38%) aortic valves, 2 (15%) aortic + mitral valves, 3 (23%) mitral valves, 2 (16%) vegetation on the lead, and 1 (7%) in the pulmonary valve. In the underlying diseases, 5 (35%) had diabetes mellitus, 5 (35%) had hemodialysis, and 4 (30%) had pacemakers. One (7%) of the patients had a heart transplant, and 1 had a liver transplant. Seven (50%) had a prosthetic valve, and 7 (50%) had a natural valve. The detected microbiological factors are: 8 (57%) had *Candida parapsilosis* (*C. parapsilosis*), 5 (35%) *Candida albicans* (*C. albicans*) and 1 (7%) *Candida tropicalis* (*C. tropicalis*). There was a valve change in 7 (50%) of them. *C. albicans* grew in the valve culture of one patient. Fluconazole was used in 6 patients (43%), and echinocandins were used in 8 (57%) patients. Six patients (43%) died during 1-year follow-up. Embolism in the central nervous system was detected in 6 patients (43%) on magnetic resonance imaging (MRI).

**Conclusions:** *Candida* endocarditis has a high mortality, and it is not easy to define the most appropriate treatment because of its rarity.

### Keywords:

*Candida* spp.

Endocarditis

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## Introduction

Infective endocarditis (IE) is the inflammation of the endocardium, the innermost surface of the heart. Fungal endocarditis remains the most severe form of IE, with a 50% mortality rate. The disease may present as native valvular endocarditis, prosthetic valvular endocarditis, endocardial surface inflammation, or cardiac device-associated IE.<sup>1</sup>

The *Candida* and *Aspergillus* species are the two most common etiologic fungi found responsible for fungal endocarditis.<sup>2</sup>

The most common cause of fungal endocarditis is *C. albicans* among the *Candida* species. *Candida* species are commensal microorganisms found in the gastrointestinal tract, lower genital tract, and oral cavity. Because of their low innate virulence, they are of less medical importance in an immunocompetent individual. If the host is immunocompromised for various reasons, the risk of candidiasis increases significantly.<sup>3</sup>

Fungal endocarditis is rarely seen in healthy individuals and is associated with immunocompromised conditions, intravenous drug use, long-term antibiotic use, and long-term parenteral nutrition. People with a prosthetic heart valve or a history of reconstructive heart surgery are also at a higher risk of fungal endocarditis.<sup>4</sup>

In our study, we aimed to evaluate *Candida* endocarditis's clinical and demographic properties in our tertiary heart centre.

## Material and methods

The patients with IE diagnoses between 2012 and 2023 were retrospectively analyzed, and 14 patients were included. The inclusion criteria were: patients >18 years, diagnosed with IE according to the modified Duke criteria, and microbiological confirmation of candidemia. *Candida* identification and susceptibility, VITEK 2 micro-identification system.

Numerical variables were expressed as mean and standard deviation (SD). Discrete data were shown as percentages and absolute numbers.

## Results

In our study, 4 (29%) of 14 patients were female, and 10 (71%) were male. The mean age was 49.7 ( $\pm 8.82$ ) years. The mean hospital stay was 39 days (range 33–130 days). The diagnosis of 5 (36%) was made by transthoracic echocardiography (TTE) and 9 (64%) by transesophageal echocardiography (TEE). The valves involved were 5 (38%) aortic valves, 2 (15%) aortic+mitral valves, 3 (23%) mitral valves, 2 (16%) vegetation on the lead, and 1 (7%) in the pulmonary valve. Five (35%) of the patients had diabetes mellitus (DM), 5 (35%) had hemodialysis, and 4 (30%) had a history of pacemakers. One (7%) patient had a heart transplant, and 1 had a liver transplant. Seven (50%) had a prosthetic valve, and 7 (50%) had a natural valve. The detected microbiological factors are: 8 (57%) had *C. parapsilosis*, 5 (35%) *C. albicans* and 1 (7%) *C. tropicalis*. Valve replacement occurred in 7 (50%) pa-

tients. *C. albicans* obtained in one valve culture. Flucanazole was used in 6 patients (43%), and echinocandins were used in 8 (57%). Six patients (43%) died within one year. Central nervous system embolism was detected in 6 patients (43%) on MRI.

## Discussion

Both native and prosthetic valve endocarditis due to *Candida* species are considered to be biofilm-associated infections that occur after fungal colonization of the heart valves, most likely after an episode of candidemia originating from the gastrointestinal tract.<sup>4</sup>

*Candida* endocarditis is an acute disease and a growing health problem, especially in the elderly population and immunosuppressed.

In a study involving 398 patients with endocarditis in Egypt, the male gender predominated in 61%.<sup>5</sup> Infective endocarditis series such as Saudi Arabia, the United Kingdom, and Japan have reported that the male gender is at the forefront. There are theories that this is because estrogen is potentially protective against endothelial damage and that women are less likely to develop sepsis. However, the exact mechanism still needs to be fully understood.<sup>6–8</sup> In our study, by others male gender was predominant (70%).

In the 10-year study of Arnold et al., the mortality rate of *Candida* endocarditis was high in people with congestive heart failure, candidemia, and heart failure.<sup>9</sup> It was shown that the left ventricular assist device (LVAD) used before heart transplantation may be contaminated with *Candida*.<sup>10,11</sup> It is one of the rare heart transplant centres in our country. There was vegetation on the pacemaker in four (30%) patients.

Prosthetic valve endocarditis is a severe complication after valve replacement surgery and is a prominent clinical entity compared to native valve endocarditis. The global annual incidence of prosthetic valve endocarditis ranges from 1.4% to 3.1%.<sup>12,13</sup>

Baddley et al. found that prosthetic valve endocarditis was 50% more common in patients with candidemia. The same study also concluded that patients with a previous history of Endocarditis and cardiac surgery are more susceptible to this infection.<sup>14</sup> Consistent with the literature, half of the patients in our study had prosthetic valves, and half had natural valves.

In the study of Rivoisy and Siciliano, it was shown that TEE has large vegetations in patients with *Candida* endocarditis and that transthoracic echocardiography (TTE) is less reliable in detecting vegetations.<sup>15,16</sup>

Since we are a cardiology and cardiovascular surgery centre, TEE is performed more frequently in patients with candidemia, which may lead to more diagnosed candida endocarditis. In our study, five patients (36%) were diagnosed with TTE and 9 (64%) with TEE.

The most common cause of *Candida* endocarditis is *C. albicans*, followed by *C. parapsilosis*, *C. glabrata* and *C. tropicalis*.<sup>17,18</sup>

Fungal invasive infections caused by *C. parapsilosis* often occur in patients receiving central venous lines and hyperalimentation solutions (parenteral nutrition). In ad-

Table 1 – Demographic and clinical characteristics of patients

| Patient No | Age/Gender | Comorbidity              | CNS Embolism | Valve type | EF (%) | Valve involvement | Vegetation size (mm) | Operation time (day) | Candida species        | Treatment                    | Mortality  |
|------------|------------|--------------------------|--------------|------------|--------|-------------------|----------------------|----------------------|------------------------|------------------------------|------------|
| 1.         | 52/F       | Valve replacement        | +            | Prosthetic | 25     | Mitral            | 15                   | No                   | <i>C. parapsilosis</i> | Fluconazole                  | Exitus     |
| 2.         | 64/M       | HCV                      | -            | Native     | 65     | Aortic            | 15                   | 14                   | <i>C. albicans</i>     | Anidulafungin                | Exitus     |
| 3.         | 55/M       | Heart tx, pacemaker      | +            | Prosthetic | 15     | Aortic + mitral   | 9                    | No                   | <i>C. parapsilosis</i> | Anidulafungin                | Exitus     |
| 4.         | 43/M       | Valve replacement        | -            | Prosthetic | 50     | Aortic abscesses  | 0                    | 7                    | <i>C. parapsilosis</i> | Fluconazole                  | Discharged |
| 5.         | 61/F       | CRF, ARF                 | -            | Native     | 35     | Mitral            | 21                   | 55                   | <i>C. albicans</i>     | Fluconazole                  | Exitus     |
| 6.         | 59/F       | Valve replacement        | +            | Prosthetic | 40     | Aortic            | 17                   | No                   | <i>C. albicans</i>     | Anidulafungin                | Exitus     |
| 7.         | 30/M       | Mitral regurgitation DVT | -            | Native     | 55     | Mitral            | 10                   | 27                   | <i>C. tropicalis</i>   | Fluconazole                  | Discharged |
| 8.         | 45/M       | Wilson disease           | -            | Prosthetic | 35     | Aortic            | 9                    | No                   | <i>C. albicans</i>     | Fluconazole + anidulofungin  | Discharged |
| 9.         | 61/M       | Pacemaker                | -            | Native     | 55     | Lead              | 5                    | No                   | <i>C. parapsilosis</i> | Anidulafungin                | Discharged |
| 10.        | 60/M       | Pacemaker                | +            | Native     | 15     | Lead              | 3                    | No                   | <i>C. parapsilosis</i> | Fluconazole                  | Discharged |
| 11.        | 23/M       | Liver tx                 | -            | Native     | 65     | Aortic + mitral   | 10                   | 13                   | <i>C. parapsilosis</i> | Fluconazole                  | Discharged |
| 12.        | 31/M       | Previous endocarditis    | -            | Prosthetic | 25     | Pulmonary         | 17                   | 21                   | <i>C. parapsilosis</i> | Anidulafungin                | Discharged |
| 13.        | 71/F       | Pacemaker                | -            | Native     | 45     | Aortic            | 5                    | No                   | <i>C. albicans</i>     | Anidulafungin                | Discharged |
| 14.        | 37/M       | Burn history             | +            | Prosthetic | 30     | Aortic            | 12                   | 5                    | <i>C. parapsilosis</i> | Fluconazole + amphotericin B | Exitus     |

ARF – acute rheumatic fever; CRF – chronic renal failure; DVT – deep vein thrombosis; HCV – hepatitis C virus; tx – transplantation.

dition, a recent Spanish study showed that long-term vascular catheterization and previous surgery were the most critical risk factors.<sup>19,20</sup>

In a retrospective study of 8 patients treated for candida endocarditis and with a history of intravenous drug use, *C. parapsilosis* was found to be the causative agent in 7 patients, and *C. glabrata* was found in 1 patient.<sup>21</sup>

*C. parapsilosis* is most common in patients undergoing transcatheter aortic valve replacement, transplant recipients, and patients receiving parenteral nutrition. In our study, *C. parapsilosis* (67%) was our primary cause and differed from other studies. Other agents were 35% *C. albicans* and 7% *C. tropicalis*, respectively.

The American Society of Infectious Diseases (IDSA) recommends using maintenance therapy with fluconazole for non-surgical patients with candida endocarditis, and guidelines updated in 2016 recommend surgery to prevent relapse alongside medical therapy.<sup>22</sup> The latest European Society of Cardiology for the treatment of infective endocarditis (ESC) guidelines also recommend the use of echinocandins in higher doses for treatment.<sup>23</sup>

In the Pappas et al. study, eight patients received high doses of caspofungin and had no relevant side effects. Again, in this study, six patients were given fluconazole and a response was obtained with long-term antifungal therapy after surgery.<sup>22</sup> In our study, fluconazole was used in 6 patients (43%), and echinocandins were used in 8 patients (57%). In half of the patients, surgical treatment was performed in combination with medical therapy.

Infective endocarditis is a significant healthcare burden due to its high mortality and complications. In the International Collaboration on Endocarditis (ICE)-Prospective Cohort Study, in-hospital mortality was 36%, and one-year mortality was 59%.<sup>18</sup>

Despite the widespread availability of modern diagnostic and therapeutic methods, candidal endocarditis is a rising trend worldwide in developing and developed countries.<sup>24</sup> In-hospital mortality and readmission rates are on a dangerously increasing trend.<sup>25,26</sup> In our study, six patients (43%) died within one year, and although mortality rates have decreased in the recent past, the mortality rate was high in the past. Much of our knowledge of *Candida* endocarditis's clinical manifestations, treatment, and mortality comes from case series or small observational studies.<sup>27</sup> The mortality of the disease can be up to 43%, often associated with an underlying disease, immunocompro-

mised state, delayed diagnosis, and failure of antifungal therapy, especially in nonsurgical conditions.<sup>28</sup>

*Candida* endocarditis is an emerging disease and a growing health concern globally, particularly among the elderly population and immunocompromised individuals. In our study, the mean age was 49.7 years. This situation is due to the referral of patients to our hospital from many centres, the increase in awareness and the fact that it is a tertiary referral hospital.

Limitations of our study include the small sample size and the retrospective design.

## Conclusion

In patients with native or prosthetic valve *Candida* endocarditis, we recommend a combined approach using antifungal agents and valve replacement rather than antifungal therapy alone.

## Conflict of interest

None declared.

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