Candida parapsilosis endocarditis. Report of cases and review of the literature

Petros Ioannou^{1,*}, Maria Volosyraki², Vasiliki Mavrikaki³, Ioanna Papakitsou⁴, Anna Mathioudaki⁵, George Samonis⁶, Diamantis P Kofteridis⁷

Abstract

Introduction Infective endocarditis (IE) due to *Candida* species is a rare disease representing about 1-2% of all IE cases and carries a high mortality rate. Given the rarity of the disease, there are no clear guidelines on the type and duration of antifungal therapy. Thus, long-term or even life-long antifungal treatment is commonly used.

Case report We report two patients with prosthetic valve *C. parapsilosis* IE and persistent candidemia that failed conservative treatment and ultimately developed heart failure. They underwent prosthetic valve replacement and prolonged antifungal treatment with favorable outcome.

Discussion *Candida* IE commonly occurs in the setting of underlying malignancy, chronic liver disease, previous endocarditis, previous antimicrobial exposure, previous abdominal surgery, intravenous drug use, presence of a central venous catheter, and previous cardiac surgery. Both present patients had undergone a cardiac surgery and had a prosthetic heart valve, while one patient had an underlying autoimmune disease that could be associated with higher risk of IE. In both patients transthoracic ultrasound failed to diagnose IE. In our patients, conservative treatment alone was not enough to control the infection, thus, both patients underwent valve replacement and were subsequently treated with antifungals for 6 weeks. Furthermore, both patients were put on long-term antifungal suppression treatment.

Conclusions Given the absence of controlled randomized trials, the treatment of *Candida* endocarditis mostly relies on experts' opinion, and, thus, future studies focusing on the type and duration of antifungal treatment are required.

Keywords *Candida*, endocarditis, fungi.

Introduction

Infective endocarditis (IE) by *Candida* species is an uncommon disease that accounts for about 1-2% of all cases of IE. This infection carries a mortality rate that can be as high as 43%.^{1,4} Both native valve (NVE) and prosthetic valve

endocarditis (PVE) due to *Candida* species are considered biofilm-related infections that follow after colonization of the heart valves by the fungus after an episode of candidemia, most likely originating in the gastrointestinal tract.⁵

Received: 27 April 2020; revised: 04 July 2020; accepted: 11 July 2020.

¹MD, MSc, PhD, Department of Internal Medicine, University Hospital of Heraklion, Stavrakia and Voutes crossroad, Heraklion, PC 71110, Crete, Greece; ²MD, Department of Internal Medicine, University Hospital of Heraklion, Stavrakia and Voutes crossroad, Heraklion, PC 71110, Crete, Greece; ³MD, Department of Internal Medicine, University Hospital of Heraklion, Stavrakia and Voutes crossroad, Heraklion, PC 71110, Crete, Greece; ⁴MD, Department of Internal Medicine, University Hospital of Heraklion, Stavrakia and Voutes crossroad, Heraklion, PC 71110, Crete, Greece; ⁵MD, Department of Internal Medicine, University Hospital of Heraklion, Stavrakia and Voutes crossroad, Heraklion, PC 71110, Crete, Greece;

⁶MD, PhD, Department of Internal Medicine, University Hospital of Heraklion, Stavrakia and Voutes crossroad, Heraklion, PC 71110, Crete, Greece; ⁷MD, PhD, Department of Internal Medicine, University Hospital of Heraklion, Stavrakia and Voutes crossroad, Heraklion, PC 71110, Crete, Greece.

*Corresponding author: Petros Ioannou, p.ioannou@med.uoc.gr

Article downloaded from www.germs.ro
Published September 2020
© GERMS 2020
ISSN 2248 - 2997
ISSN - L = 2248 - 2997

Given the rarity of this disease and the lack of definitive data on optimal treatment, management of *Candida* IE is debatable and mostly consists of chronic suppressive therapy with azoles.⁶ Herein, we describe two cases of PVE due to *Candida parapsilosis* successfully treated with prosthetic valve replacement and long-term antifungal therapy with fluconazole.

Case reports

A 66 year old man with medical history of coronary artery disease and aortic valve replacement 16 months ago, arterial hypertension, dyslipidemia, and urothelial papillomas treated with BCG infusions 4 years ago, presented complaining of weakness and unintentional weight loss during the previous 3 months, as well as dyspnea during the last few days. The clinical examination was unremarkable. The laboratory examination revealed pancytopenia; hence, he was admitted to the Internal Medicine Department. During the first days of hospitalization he developed fever and 2 sets of blood cultures yielded *Candida parapsilosis*, while transthoracic ultrasound (TTE) of the heart revealed malfunction of the prosthetic valve. Additionally, an abdominal ultrasound revealed splenomegaly. A subsequent transesophageal ultrasound of the heart revealed vegetations and severe malfunction of the prosthetic valve due to paravalvular leak, as well as presence of pseudoaneurysm of the aortic valve along with aortic valve dehiscence. The patient did not have any other signs of IE, such as Janeway lesions, Roth spots or splinter hemorrhages. At that point in time, new blood cultures came back positive for *C. parapsilosis*. Immediately, treatment with intravenous liposomal amphotericin B at a dose of 5 mg/kg/d and intravenous micafungin at a dose of 150 mg/d was initiated. Blood cultures drawn on the 9th day of hospitalization were sterile, but the same day he developed acute pulmonary edema managed with nitrates, oxygen therapy and intravenous diuretics, and was transferred to a Cardiac Surgery Unit. Replacement of the prosthetic aortic valve was performed, and consequently, he was treated with a 6-week course of intravenous liposomal

amphotericin B at the dose of 5 mg/kg/d. He was discharged on fluconazole at a dose of 400 mg once daily orally for the following 3 years and was followed up for the same duration, having an uneventful course.

A 59-year old man with medical history of systemic lupus erythematosus, cholecystectomy, choledocholithiasis treated with a stent at the common bile duct, epileptic seizures and a bioprosthetic aortic valve due to aortic stenosis that was replaced four years before presentation, was admitted to the Rheumatology Department because of fever due to consideration of systemic lupus erythematosus exacerbation. However, serial blood cultures grew *Candida parapsilosis* sensitive to all antifungals tested. Hence, the patient was transferred to the Internal Medicine Department. Clinical examination revealed the presence of a 3/6 systolic murmur, but was otherwise unremarkable. Laboratory examination was notable for hypochromic microcytic anemia and elevated erythrocyte sedimentation rate (ESR). A TTE revealed the presence of mild mitral stenosis and blood regurgitation, as well as aortic stenosis, with aortic valve area of 1.1 cm², and mild dilation of the ascending aorta. A transesophageal heart ultrasound revealed malfunction of the bioprosthetic aortic valve and, next to it, presence of an abscess of the aorta (Figure 1). The patient did not have any other signs of IE, such as Janeway lesions, Roth spots or splinter hemorrhages. He was treated with intravenous liposomal amphotericin B at a dose of 5 mg/kg/d once daily and flucytosine at a dose of 100 mg/kg/d divided in four doses orally, but due to persistent fungemia was transferred to Cardiac Surgery Unit. He had surgical replacement of the aortic valve one week later, and, consequently, was treated for 6 weeks with liposomal amphotericin B at a dose of 5 mg/kg/d in combination with micafungin 150 mg/day. The blood cultures drawn two days after surgery were sterile. He was discharged on oral fluconazole at a dose of 400 mg once daily for the next 2 years, and then at a dose of 200 mg once daily for the next 3 years, followed by a dose of 150 mg once weekly. Ever after surgery, he had an uneventful course for 6 years of follow-up.

Figure 1. Transthoracic cardiac ultrasound of the second patient, showing the aortic stenosis caused by the paravalvular abscess

Discussion

Candida IE is a rare disease that may occur after an initial episode of candidemia, most possibly via translocation from the gastrointestinal tract, that may pass clinically unnoticed.⁴ The disease's mortality can be as high as 43%, most times in association with an underlying disease, immunocompromised state, delayed diagnosis and failure of antifungal therapy, especially in cases where a surgery is not performed.^{4,7}

Even though *C. albicans* is the most common encountered species, non-*albicans* species have emerged as important causes of invasive fungal disease.^{8,9} Among them, *C. parapsilosis* is of particular importance, since it is able to easily form biofilms on medical devices, such as on central venous catheters,¹⁰ while, on the other hand, it tends to grow rapidly in parenteral nutrition, thus placing patients to whom parenteral nutrition is administered, at increased risk for invasive candidiasis.^{9,11,12} Even though infections by *C. parapsilosis* are generally

associated with lower morbidity and mortality compared to infections by *C. albicans*, the particular antimicrobial susceptibility to antifungals of several clinical isolates of *C. parapsilosis*, with increased resistance to echinocandins and in some geographic regions, to azoles as well, may make treatment of these infections problematic.^{10,13-15} Furthermore, horizontal transmission of *C. parapsilosis* has been described, in contrast to the colonization-dependent vertical transmission of *C. albicans*,¹⁶ making *C. parapsilosis* one of the most frequently isolated *Candida* species in critical care units.¹⁰ The characteristics of *Candida* endocarditis (CE) have been recently reviewed.⁴ The most common cause was *C. albicans* followed by *C. parapsilosis*, *C. glabrata* and *C. tropicalis*. CE commonly occurs in the setting of underlying malignancy, chronic liver disease, previous endocarditis, previous antimicrobial exposure, previous abdominal surgery, intravenous drug use, presence of a central venous catheter, and previous cardiac

Table 1. Antifungal susceptibilities of isolated strains of *C. parapsilosis*

MICs (µg/mL)	Patient 1	Patient 2
Fluconazole	2	≤1
Voriconazole	≤0.12	≤1
Caspofungin	1	NP
Micafungin	0.5	NP
Amphotericin B	0.5	1
Flucytosine	≤1	≤1

MICs – minimum inhibitory concentrations; NP – not performed.

surgery.⁴ Both present patients had undergone cardiac surgery in the past, and had a prosthetic heart valve. One patient had an underlying autoimmune disease that could be associated with higher risk of IE. Both patients had aortic valve PVE. Indeed, *Candida* PVE is more commonly left-sided and occurs most times at the aortic valve.⁴ In both patients TTE failed to diagnose IE, being in line with the literature indicating that TTE could not diagnose CE, even in patients without prosthetic valve.⁴ Interestingly, in a previous study comparing the characteristics of IE by *C. parapsilosis* with those by *C. albicans*, no significant differences were noted, with the exception of a slightly higher mortality in the group of patients with *C. parapsilosis* IE.¹⁷

The source of candidemia could not be established in these two cases. Even though there are descriptions of cases of candidemia after heart valve replacement surgery associated with a later presentation with PVE, occurring even one year after surgery, the history of our patients was negative for a previous episode of candidemia.^{18,19} Thus, it could be that an episode of candidemia did occur but was not clinically evident before the patients presented with PVE.

In terms of treatment, the first patient was treated with liposomal amphotericin B and flucytosine, while the second with a combination of high dose echinocandin and liposomal amphotericin B. As shown in a recent review, amphotericin B is commonly used either alone (20.4%) or in combination with another antifungal agent for CE treatment (27.7%). However, no differences in terms of survival were noted, independently of the antifungal used.⁴ Use of amphotericin B in patients with *Candida*

PVE has been shown in a recent study to be associated with increased survival,²⁰ which was also the case with the patients presented herein. On the other hand, combination of antifungals was found to be superior to monotherapy in a model of simulated *C. albicans* endocardial vegetations, and more specifically, combinations including amphotericin B and micafungin.²¹ In our patients, both treatments included amphotericin B, while in the second patient, micafungin was used in combination with amphotericin B. Conservative treatment alone was not enough to control the infection, in one case due to persistent candidemia and in the other due to development of heart failure. Thus, both patients underwent valve replacement and were subsequently treated with antifungals for 6 weeks. Furthermore, both patients were put on long-term antifungal suppression treatment. As shown in the literature, both valve replacement surgery and chronic therapy reduce the risk of death both in NVE and in PVE due to *Candida* species.^{4,22} Hence, even though there is a lack of prospective trials in the field of CE treatment, the combination of valve replacement surgery and prolonged antifungal suppressive treatment should be used. This is supported by a recent study that showed reduced risk of relapse of CE in patients treated with maintenance antifungal therapy.²⁰ However, the duration of treatment, whether it should be indefinite or not, as well as the type of the appropriate antifungal agent are not yet clear, and should be addressed in future studies.

Conclusions

We have described two patients with prosthetic valve *Candida* endocarditis successfully

treated. Both patients underwent prosthetic valve replacement and were put on long-term antifungal treatment.

Consent: Written informed consent was obtained from the patients for publication of these case reports and the associated images.

Authors' contributions statement: PI, MV, VM, IP and AM collected the data and wrote the manuscript. GS and DPK critically reviewed the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of interest: All authors – none to declare.

Funding: None to declare.

References

- Baddley JW, Benjamin DK Jr, Patel M, et al. *Candida* infective endocarditis. *Eur J Clin Microbiol Infect Dis*. 2008;27:519-29. <https://doi.org/10.1007/s10096-008-0466-x>
- Bor DH, Woolhandler S, Nardin R, Brusch J, Himmelstein DU. Infective endocarditis in the U.S., 1998-2009: a nationwide study. *PLoS One*. 2013;8:e60033. <https://doi.org/10.1371/journal.pone.0060033>
- Benjamin DK Jr, Miro JM, Hoen B et al. *Candida* endocarditis: contemporary cases from the International Collaboration of Infectious Endocarditis Merged Database (ICE-mD). *Scand J Infect Dis*. 2004;36:453-5. <https://doi.org/10.1080/00365540410020703>
- Giuliano S, Guastalegname M, Russo A, et al. *Candida* endocarditis: systematic literature review from 1997 to 2014 and analysis of 29 cases from the Italian Study of Endocarditis. *Expert Rev Anti Infect Ther*. 2017;15:807-18. <https://doi.org/10.1080/14787210.2017.1372749>
- Nasser RM, Melgar GR, Longworth DL, Gordon SM. Incidence and risk of developing fungal prosthetic valve endocarditis after nosocomial candidemia. *Am J Med*. 1997;103:25-32. [https://doi.org/10.1016/S0002-9343\(97\)90050-4](https://doi.org/10.1016/S0002-9343(97)90050-4)
- Pappas PG, Kauffman CA, Andes DR, et al. Executive summary: Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. *Clin Infect Dis*. 2016;62:409-17. <https://doi.org/10.1093/cid/civ1194>
- Ammannaya GKK, Sripad N. Fungal endocarditis: what do we know in 2019? *Kardiolog Pol*. 2019;77:670-3. <https://doi.org/10.33963/KP.14869>
- Pfaller MA, Diekema DJ, Rinaldi MG, et al. Results from the ARTEMIS DISK Global Antifungal Surveillance Study: a 6.5-year analysis of susceptibilities of *Candida* and other yeast species to fluconazole and voriconazole by standardized disk diffusion testing. *J Clin Microbiol*. 2005;43:5848-59. <https://doi.org/10.1128/JCM.43.12.5848-5859.2005>
- Paramythiotou E, Frantzeskaki F, Flevari A, Armaganidis A, Dimopoulos G. Invasive fungal infections in the ICU: how to approach, how to treat. *Molecules*. 2014;19:1085-119. <https://doi.org/10.3390/molecules19011085>
- Tóth R, Nosek J, Mora-Montes HM, et al. *Candida parapsilosis*: from genes to the bedside. *Clin Microbiol Rev*. 2019;32:e00111-18. <https://doi.org/10.1128/CMR.00111-18>
- Pammi M, Holland L, Butler G, Gacser A, Bliss JM. *Candida parapsilosis* is a significant neonatal pathogen: a systematic review and meta-analysis. *Pediatr Infect Dis J*. 2013;32:e206-16. <https://doi.org/10.1097/INF.0b013e3182863a1c>
- Harrington R, Kindermann SL, Hou Q, Taylor RJ, Azie N, Horn DL. Candidemia and invasive candidiasis among hospitalized neonates and pediatric patients. *Curr Med Res Opin*. 2017;33:1803-12. <https://doi.org/10.1080/03007995.2017.1354824>
- Meletiadi J, Curfs-Breuker I, Meis JF, Mouton JW. In vitro antifungal susceptibility testing of *Candida* isolates with the EUCAST methodology, a new method for ECOFF determination. *Antimicrob Agents Chemother*. 2017;61:e02372-16. <https://doi.org/10.1128/AAC.02372-16>
- Pfaller MA, Moet GJ, Messer SA, Jones RN, Castanheira M. *Candida* bloodstream infections: comparison of species distributions and antifungal resistance patterns in community-onset and nosocomial isolates in the SENTRY Antimicrobial Surveillance Program, 2008-2009. *Antimicrob Agents Chemother*. 2011;55:561-6. <https://doi.org/10.1128/AAC.01079-10>
- Govender NP, Patel J, Magobo RE, et al. Emergence of azole-resistant *Candida parapsilosis* causing bloodstream infection: results from laboratory-based sentinel surveillance in South Africa. *J Antimicrob Chemother*. 2016;71:1994-2004. <https://doi.org/10.1093/jac/dkw091>
- Lupetti A, Tavanti A, Davini P, et al. Horizontal transmission of *Candida parapsilosis* candidemia in a neonatal intensive care unit. *J Clin Microbiol*. 2002;40:2363-9. <https://doi.org/10.1128/JCM.40.7.2363-2369.2002>
- Garzoni C, Nobre VA, Garbino J. *Candida parapsilosis* endocarditis: a comparative review of the literature. *Eur J Clin Microbiol Infect Dis*. 2007;26:915-26. <https://doi.org/10.1007/s10096-007-0386-1>
- Muñoz P, Vena A, Valerio M, et al. Risk factors for late recurrent candidaemia. A retrospective matched case-control study. *Clin Microbiol Infect*. 2016;22:277.e11-277.e2.77E20. <https://doi.org/10.1016/j.cmi.2015.10.023>
- Russo A, Falcone M, Picciarella A, Giuliano S, Raponi G, Venditti M. Candidaemia after heart valve replacement surgery: recurrence as prosthetic valve endocarditis is an expected over one-year complication. *Clin Microbiol Infect*. 2016;22:466-7. <https://doi.org/10.1016/j.cmi.2016.01.019>
- Rivoisy C, Vena A, Schaeffer L, et al. Prosthetic valve *Candida* spp. endocarditis: new insights into long-term

-
- prognosis-the ESCAPE study. Clin Infect Dis. 2018;66:825-32. <https://doi.org/10.1093/cid/cix913>
21. Pai MP. Antifungal combinations against simulated *Candida albicans* endocardial vegetations. Antimicrob Agents Chemother. 2009;53:2629-31. <https://doi.org/10.1128/AAC.01026-08>
22. Smego RA Jr, Ahmad H. The role of fluconazole in the treatment of *Candida* endocarditis: a meta-analysis. Medicine (Baltimore). 2011;90:237-49. <https://doi.org/10.1097/MD.0b013e3182259d38>

Please cite this article as:

Ioannou P, Volosyraki M, Mavrikaki V, Papakitsou I, Mathioudaki A, Samonis G, Kofteridis DP. *Candida parapsilosis* endocarditis. Report of cases and review of the literature. GERMS. 2020;10(3):254-259. doi: 10.18683/germs.2020.1214