Heliyon 10 (2024) e31464

Contents lists available at ScienceDirect

Heliyon

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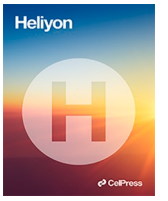

Case report

Case report and literature review of refractory fungemia caused by *Candida vulturna*

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A B S T R A C T

Candida vulturna is a recently discovered and not widely documented ascomycetous yeast phylogenetically related to the outbreak-causing and multidrug-resistant *Candida auris*. A middle-aged Japanese man with no discernible immunodeficiency was admitted to hospital with ileal diverticulitis. Following laparoscopic right hemicolectomy against abscess formation on postoperative day (POD) 7, continuous fungemia occurred due to *Candida haemulonii,* identified using a conventional method by confirming the biochemical phenotype. Micafungin was initiated; however, the fungus was persistently isolated from blood cultures. Eventually, the antifungal agent was changed to a combination of liposomal amphotericin B (L-AMB) and caspofungin (CPFG), which cleared the infection, and no pathogens were detected in the blood cultures on POD 31. Contrast-enhanced computed tomography showed septic emboli in the lungs and spleen; however, no evidence of vasculitis was observed. Moreover, sequential echocardiography did not reveal any signs of infectious endocarditis. Finally, CPFG and L-AMB were administered to the patient for 7 and 9 weeks, respectively, during which the patient's symptoms did not relapse. The strain was later genetically identified as *C. vulturna*. This case report illustrates a clinical presentation of *C. vulturna* and provides the diagnostic approach and treatment methods for this pathogen.

1. Introduction

Candida vulturna is an ascomycetous yeast that was discovered in flowers on Mindanao Island, Philippines, in 2016 [1]. This fungus is phylogenetically related to *Candida auris,* which poses a serious global threat and belongs to the *Candida haemulonii* species complex of the Metschnikowiaceae family. Human cases of *C. vulturna* have not been widely reported, and the epidemiology, diagnostic methods, and treatment strategies remain unclear [1–6]. Herein, we report a case of persistent fungemia in a 67-year-old man caused by *C. vulturna* that was resistant to antifungal agents.

CASE/CASE SERIES PRESENTATION: In August 2015, a 67-year-old man was admitted to National Hospital Organization Nagasaki Medical Center in Japan with a diagnosis of ileal diverticulitis. This patient presented with fever, chills, and right lower abdominal pain for two days. The patient was a heavy smoker (129 packs/year) with comorbidities, including hypertension, hyperuricemia, and

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https://doi.org/10.1016/j.heliyon.2024.e31464
Received 16 February 2024; Received in revised form 10 May 2024; Accepted 16 May 2024
Available online 19 May 2024

bronchial asthma. Despite the initiation of sulbactam/ampicillin treatment, plain computed tomography (CT) showed new abscess formation around the diverticulum near the ileum on the 10th day of admission. The antimicrobial agent was changed to meropenem (MEPM) on the 11th day of admission, and laparoscopic right hemicolectomy was performed on the 17th day of admission (Fig. 1). The abdominal drain was removed on postoperative day (POD) 3, and no bacteria were detected in the drain. However, fever was noted on POD 7. No surgical site infection was suspected, and the source of the fever could not be determined by conducting a physical examination with no central line/total parenteral nutrition or urine catheter. Using the β-glucan single M30 test Wako, β-D glucan was found to be elevated at 37.28 pg/mL, peaking at 189.4 pg/mL on POD 14. The fever occurred while the patient was receiving broad-spectrum antimicrobial therapy, and considering the high levels of β-D glucan, invasive fungal infection was considered as a possible differential diagnosis [7]. Consequently, yeast-like fungi were detected in blood cultures on POD 7, but not in urine cultures, and 100 mg/day micafungin (MCFG) was initiated. As there was no improvement in the patient's condition, MCFG was changed to 3 mg/kg liposomal amphotericin B (L-AMB) on POD 12. Using VITEK 2 (software version 06.01), the yeast-like fungus was identified as *C. haemulonii*, and the patient was diagnosed to have candidemia. Drug sensitivity test was done based on the CLSI M27-A3 guidelines, using the ASTY colorimetric antifungal panel (Kyokuto Pharmaceutical Industrial Co., Ltd., Tokyo, Japan), which showed that the minimal inhibitory concentration (MIC) of L-AMB (1.0 μg/mL) and MCFG (0.125 μg/mL) remained low (Table 1). Blood cultures were submitted at POD 10, 16, and 24, and the fungus was persistently isolated from blood cultures. Periodic acid-Schiff and Grocott's staining of the surgically excised ileal site did not reveal any presence of fungi. Furthermore, enhanced magnetic resonance imaging (MRI) of the head showed no findings suggestive of intracranial infection, and contrast-enhanced CT on POD 25 revealed no vascular inflammatory lesions. Free air and increased mesenteric fatty tissue density around the resection site indicated a minor leak (Fig. 2). Additionally, a wedge-shaped area of poor contrast was observed in the spleen, and septic emboli were suspected. Results of transthoracic echocardiography, transesophageal echocardiography, and cardiac MRI showed no evidence of infective endocarditis. Consequently, caspofungin (CPFG, 70 mg/day) was administered on POD 19, followed by 50 mg/day thereafter; blood cultures yielded no pathogens on POD 31. The patient continued to have low-grade fever with a temperature consistently around 37 °C in the following days (Fig. 1). A contrast-enhanced CT scan conducted on POD 51 suggested further enhancement of the mesenteric fatty tissue density around the resection site (Fig. 2a). However, the free air disappeared with the conservative treatments, and the increase in fatty tissue concentration and embolization in the lung and spleen reduced on POD 72 (Fig. 2a and b). Additionally, mild vitreous opacity was observed in the left eye on POD 58, leading to suspicion of *Candida* endophthalmitis; however, this resolved by POD 69. The patient's fever eventually subsided, and MEPM administration was discontinued on POD 66. CPFG and L-AMB were administered for 7 and 9 weeks, respectively. Fortunately, despite of the extended use of L-AMB, renal dysfunction and electrolyte abnormalities were not observed. The patient's symptoms did not relapse, and the β-D glucan level rose to a maximum of 189.4 on POD 14, and then decreased to 18.02 on POD 73 (Fig. 1). He was discharged on POD 80 and had multiple repeat echocardiograms as an outpatient over the course of several years without recurrence. The strain was later identified as *Candida vulturna* with a 99.7 % match for the internal transcribed spacer (ITS) region and a 100 % match for the D1/D2 region of the *26S* rRNA gene.

DISCUSSION: *Candida auris* exhibits multidrug resistance and has been reported in nosocomial outbreaks; consequently, it has received increasing attention clinically and in research [8]. Here, we report a case of *C. vulturna*, which is phylogenetically related to *C. auris* and is rarely detected in clinical specimens [9]. *C. vulturna* has been isolated from blood, wounds, and other body fluids, and has been reported primarily in subtropical countries, such as China and the Philippines. This is the first study to report a *C. vulturna* case from Japan (Table 1). This patient had no history of travel abroad. Although he had regular contact with soil as a hobby, it was not of tropical origin; thus, the origin of the fungus in this case remains unknown. *C. vulturna* was originally discovered in 2016, and there were no reported cases prior to 2015.

C. vulturna is difficult to identify using conventional microbiological tests. CHROMagar Candida Plus, a specific medium for differentiating *C. auris*, cannot distinguish *C. auris* from *C. vulturna* and *Candida pseudohaemulonii* [10]. Phenotypic biochemical

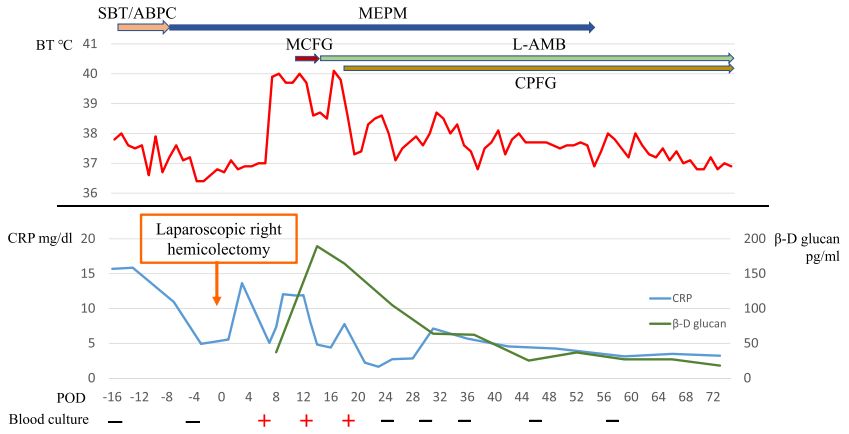

Fig. 1. The clinical course of the case. Following laparoscopic right hemicolectomy against abscess formation in the ileum site, on postoperative day 7, a high fever related to candidemia occurred. Dual treatment with liposomal amphotericin B and caspofungin restored the refractory fungemia accompanied by gradual suppression of CRP and β-D glucan.

Table 1
Clinical profiles from patients with *Candida vulturna* infection.

Table 1

Age	Sex	Specimen source	Underling diseases	Risk factor	MIC (μg/mL)										Region	Reference no.
					VRCZ	FLCZ	ITCZ	ISCZ	PSCZ	ANFG	CPFG	MCFG	AMB	5-FC		
NA	NA	Blood	Aspiration pneumonia	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA	Malaysia	[1]
4 month	Male	Blood	congenital megacolon	Antimicrobial agents, Rectal irrigation	0.25	4	NA	NA	NA	NA	0.5	0.5	8-12	NA	Philippines/ Korea	[2]
* 13-83	16Male/ 2Female	Blood and PICC tip	Hypertension, Brain surgery, et al	PICC	8-32	32-256	16-64	NA	16-64	0.125-0.25	0.06-0.25	0.25-0.5	4	0.06	China	[3]
83	Male	Blood	infected retroperitoneal cyst, Hypertension, Dyslipidemia	PICC, Antimicrobial agents, Age	<0.12	2	NA	NA	NA	NA	0.25	0.12	8	<1	Malaysia	[4]
69	Male	Leg Wound	Diabetes	NA	0.015	1	0.015	NA	0.008	<0.015	0.008	0.015	0.5	2	Ecuador	[5]
NA	NA	Endothelial secretion	NA	NA	0.03	8	0.06	0.125	0.016	0.5	16	0.06	24	NA	Panama	[6]
NA	NA	Mesh Wound	NA	NA	0.125	16	0.5	0.03	0.125	0.03	0.03	0.03	16	NA	Panama	[6]
NA	NA	Wound	NA	NA	0.06	8	0.5	0.03	0.06	0.06	0.03	0.06	>32	NA	Indiana, USA	[6]
NA	NA	Stomach acid	NA	NA	0.06	16	0.5	0.06	0.125	0.06	0.06	0.03	8	NA	Columbia	[6]
NA	NA	Blood	NA	NA	0.06	8	0.25	0.06	0.03	0.125	0.06	0.03	12	NA	Columbia	[6]
67	Male	Blood	Ileocecal diverticulitis	Antimicrobial agents, Surgery (gastrointestinal)	>8	>64	>8	NA	NA	NA	NA	0.125	1	0.25	Japan	present case

18 cases of *Candida vulturna* fungemia were reported from China at a single institution. The mean age was 58.6 years (13–83). 16 of the patients were male, and 2 were female. *Candida vulturna* was isolated from the blood cultures of all patients, and in four cases, the fungus was also isolated from a peripherally inserted central catheter (PICC) line tip. PICC line was implanted in all cases. Underlying diseases included traumatic injuries, hypertension, cancer, and blood and pulmonary infections.
PICC: peripherally inserted central catheter, CRBSI: Catheter-related bloodstream infection, VRCZ: voriconazole, FLCZ: fluconazole, ITCZ: itraconazole, ISCZ: isavuconazole, PSCZ: Posaconazole, ANFG: anidulafungin, CPFG: caspofungin, MCFG: micafungin, AMB: amphotericin B, 5-FC: 5-fluorocytosine.

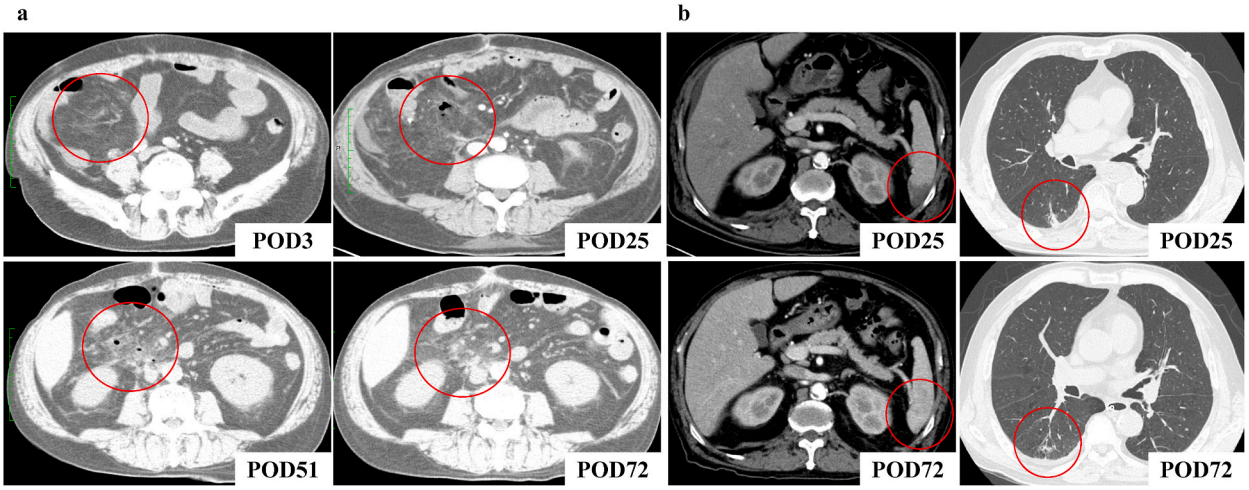

Fig. 2. The enhanced computed tomographies on specified time points are shown. a. On POD 25, free air and increased mesenteric fatty tissue density around the resection site indicated a minor leak, compared to POD 3. On POD 51, further enhancement of the mesenteric fatty tissue density around the resection site was suggested. On POD 72, the free air and fatty tissue density were diminished. b. A wedge-shaped area of poor contrast was observed in the spleen and lung on POD 25 and disappeared on POD 72. POD; postoperative day.

identification methods, such as Vitek 2 (software versions before 8.01), API 20C, BD Phoenix, MicroScan, and mass spectrometry methods such as MALDI-TOF-MS may misidentify *C. vulturna* as the *Candida haemulonii* species complex [2,4,5,11]. This case was initially misidentified as *C. haemulonii*, and similar difficulty in identification may have contributed to the paucity of reported cases of *C. vulturna*. Accurate identification requires direct sequencing of the ITS region between the *18S* and *26S* rRNA genes, and the D1/D2 region of the *26S* rRNA gene [2].

Known risks for candidemia include the long-term use of antimicrobial agents, immunosuppressive drugs, malignancies, central venous catheters, and gastrointestinal surgery [12]. The use of peripherally inserted central catheter lines, trauma, hypertension, cancer, as well as blood and lung infections may also be implicated in the development of *C. vulturna* infections [3]. The *C. haemulonii* species complex is known to cause catheter-related bloodstream infections by forming biofilms, similar to *C. vulturna* [3,13]. In this case, the patient did not have a central venous catheter during his hospitalization; therefore, the placement of a peripheral intravascular catheter without apparent signs of infection, prolonged use of broad-spectrum antimicrobials, and gastrointestinal surgery with postoperative suture failure may have led to *C. vulturna* fungemia.

Clinical breakpoints based on CLSI are not available for *C. vulturna*, but previous reports have shown high MICs for azole antifungals

and amphotericin B (AMPH-B), as well as low MICs for echinocandin antifungals [3,6]. However, the *C. vulturna* detected in this case showed high MICs against azole antifungals, but relatively low MICs against AMPH-B (Table 1). As with this case, other cases with low MICs for AMPH-B have also been reported, which indicates that drug susceptibility testing results should be confirmed [5].

As a new member of the *C. haemulonii* species complex, *C. auris* was first reported in 2009 as a multidrug-resistant yeast [14] and has since caused outbreaks of nosocomial infections worldwide [15]. Nosocomial transmission of *C. haemulonii* and *C. duobushaemulonii* was detected in a Panamanian hospital, indicating that these species can cause outbreaks in healthcare settings. Colombian isolates showed amplified azole resistance associated with *ERG11* gene substitution [6]. In contrast, *C. vulturna* is phylogenetically related to *C. auris* and shares several pathogenicity-related traits including adhesion to prosthetic materials, phenotypic switching, and multidrug resistance [16]. It remains unclear whether *C. vulturna* can be transmitted through a nosocomial environment. Prior to this case, there were no reports of infections caused by *C. haemulonii* species complex at our hospital. Furthermore, outbreaks of *C. vulturna* have only been reported at a single facility in China [3]. *C. vulturna* cases were not detected by environmental screening, but a significant decrease in infection rates was observed during the COVID-19 pandemic period, indicating that enhanced disinfection methods may help to prevent the transmission of *C. vulturna* [3].

2. Conclusion

In conclusion, we report a case of persistent fungemia caused by *Candida vulturna*. This organism may have previously been misidentified as other *Candida haemulonii* species complexes in general microbiology laboratories. Accurate identification of the organism and drug susceptibility testing are required because of its resistance to some antifungal agents. Only a few clinical reports have been published on this organism, and further evidence regarding the risk factors for disease development and treatment strategies should be investigated.

Ethics statement

Ethical approval was not required for the publication of this manuscript. The authors obtained informed consent from the patient.

Data availability statement

Data will be made available on request.

CRediT authorship contribution statement

Daichi Setoguchi: Writing – review & editing, Writing – original draft, Visualization, Validation, Data curation. **Naoki Iwanaga:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Project administration, Investigation, Data curation, Conceptualization. **Yuya Ito:** Writing – review & editing, Data curation. **Tatsuro Hirayama:** Writing – review & editing, Methodology, Data curation. **Masataka Yoshida:** Writing – review & editing, Data curation. **Kazuaki Takeda:** Writing – review & editing, Data curation. **Shotaro Ide:** Writing – review & editing, Investigation, Data curation. **Yohsuke Nagayoshi:** Writing – review & editing, Data curation. **Akira Kondo:** Writing – review & editing, Data curation. **Masato Tashiro:** Writing – review & editing, Data curation. **Takahiro Takazono:** Writing – review & editing, Data curation. **Kosuke Kosai:** Writing – review & editing, Data curation. **Koichi Izumikawa:** Writing – review & editing, Supervision, Data curation. **Katsunori Yanagihara:** Writing – review & editing, Supervision, Data curation. **Hiroshi Mukae:** Writing – review & editing, Validation, Supervision, Data curation, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

The authors are grateful to Makiko Mori for performing a genetic testing in this case. This study did not receive any specific grants from funding agencies in the public, commercial, or non-profit sectors.

References

[1] M. Sipiczki, R.M. Tap, Candida vulturna pro tempore sp. nov., a dimorphic yeast species related to the Candida haemulonis species complex isolated from flowers and clinical sample, Int. J. Syst. Evol. Microbiol. 66 (2016) 4009–4015, https://doi.org/10.1099/ijsem.0.001302.

[2] Y.B. Oh, H.J. Lim, S.A. Byun, M.J. Choi, H.J. Choi, M.G. Shin, S.Y. Lee, J.H. Shin, Candida vulturna fungemia in an infant with congenital megacolon from the Philippines, Ann. Lab Med. 43 (2023) 395–397, https://doi.org/10.3343/alm.2023.43.4.395.

[3] H. Du, J. Bing, X. Xu, Q. Zheng, T. Hu, Y. Hao, S. Li, C.J. Nobile, P. Zhan, G. Huang, Candida vulturna outbreak caused by cluster of multidrug-resistant strains, China, Emerg. Infect. Dis. 29 (2023) 1425–1428, https://doi.org/10.3201/eid2907.230254.

[4] A. Muthusamy, M. Rao, A. Chakrabarti, R.D. Velayuthan, Case report: catheter related blood stream infection caused by Candida vulturna, Med. Mycol. Case Rep. 36 (2022) 27–30, https://doi.org/10.1016/j.mmcr.2022.04.001.

[5] J. Zurita, Y.M.A. Paz, M.B. Solís, G. Sevillano, Failed identification of Candida vulturna using the updated Vitek 2 yeast identification system, version 9.02 and CHROMagar Candida Plus, New Microbes New Infect. 48 (2022) 101012, https://doi.org/10.1016/j.nmni.2022.101012.
[6] L. Gade, J.F. Muñoz, M. Sheth, D. Wagner, E.L. Berkow, K. Forsberg, B.R. Jackson, R. Ramos-Castro, P. Escandón, M. Dolande, R. Ben-Ami, A. Espinosa-Bode, D. H. Caceres, S.R. Lockhart, C.A. Cuomo, A.P. Litvintseva, Understanding the emergence of multidrug-resistant Candida: using whole-genome sequencing to describe the population structure of Candida haemulonii species complex, Front. Genet. 11 (2020) 554, https://doi.org/10.3389/fgene.2020.00554.
[7] Y. Bamba, K. Nagano, H. Moro, H. Ogata, M. Hakamata, S. Shibata, T. Koizumi, N. Aoki, Y. Ohshima, S. Watanabe, T. Nakamura, S. Kobayashi, Y. Hoshiyama, T. Koya, T. Takada, T. Kikuchi, Efficacy of the new β-D-glucan measurement kit for diagnosing invasive fungal infections, as compared with that of four conventional kits, PLoS One 16 (2021) e0255172, https://doi.org/10.1371/journal.pone.0255172.
[8] S. Schelenz, F. Hagen, J.L. Rhodes, A. Abdolrasouli, A. Chowdhary, A. Hall, L. Ryan, J. Shackleton, R. Trimlett, J.F. Meis, D. Armstrong-James, M.C. Fisher, First hospital outbreak of the globally emerging Candida auris in a European hospital, Antimicrob. Resist. Infect. Control 5 (2016) 35, https://doi.org/10.1186/s13756-016-0132-5.
[9] B.R. Jackson, N. Chow, K. Forsberg, A.P. Litvintseva, S.R. Lockhart, R. Welsh, S. Vallabhaneni, T. Chiller, On the origins of a species: what might explain the rise of Candida auris? J Fungi (Basel) 5 (2019) https://doi.org/10.3390/jof5030058.
[10] A.W. de Jong, C. Dieleman, M. Carbia, R. Mohd Tap, F. Hagen, Performance of two novel chromogenic media for the identification of multidrug-resistant Candida auris compared with other commercially available formulations, J. Clin. Microbiol. 59 (2021), https://doi.org/10.1128/jcm.03220-20.
[11] J.C. Navarro-Muñoz, A.W. de Jong, B. Gerrits van den Ende, P.J. Haas, E.R. Then, R. Mohd Tap, J. Collemare, F. Hagen, The high-quality complete genome sequence of the opportunistic fungal pathogen Candida vulturna CBS 14366(T), Mycopathologia 184 (2019) 731–734, https://doi.org/10.1007/s11046-019-00404-0.
[12] M.A. Pfaller, D.J. Diekema, Epidemiology of invasive candidiasis: a persistent public health problem, Clin. Microbiol. Rev. 20 (2007) 133–163, https://doi.org/10.1128/cmr.00029-06.
[13] L.S. Ramos, T.P. Mello, M.H. Branquinha, A.L.S. Santos, Biofilm formed by Candida haemulonii species complex: structural analysis and extracellular matrix composition, J Fungi (Basel) 6 (2020), https://doi.org/10.3390/jof6020046.
[14] K. Satoh, K. Makimura, Y. Hasumi, Y. Nishiyama, K. Uchida, H. Yamaguchi, Candida auris sp. nov., a novel ascomycetous yeast isolated from the external ear canal of an inpatient in a Japanese hospital, Microbiol. Immunol. 53 (2009) 41–44, https://doi.org/10.1111/j.1348-0421.2008.00083.x.
[15] J. Rhodes, M.C. Fisher, Global epidemiology of emerging Candida auris, Curr. Opin. Microbiol. 52 (2019) 84–89, https://doi.org/10.1016/j.mib.2019.05.008.
[16] U. Francoise, M. Desnos-Ollivier, Y. Le Govic, K. Sitbon, R. Valentino, S. Peugny, T. Chouaki, E. Mazars, A. Paugam, M. Nicolas, N. Desbois-Nogard, O. Lortholary, G. French Mycoses Study, Candida haemulonii complex, an emerging threat from tropical regions? PLoS Neglected Trop. Dis. 17 (2023) e0011453 https://doi.org/10.1371/journal.pntd.0011453.