Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Journal of Medical Mycology 32 (2022) 101236

Contents lists available at ScienceDirect

Journal of Medical Mycology

journal homepage: www.elsevier.com

Case report

Invasive *Candida kefyr* infection presenting as pyelonephritis in an ICU hospitalized COVID-19 patient: Case report and review of the literature

Anastasia Spiliopoulou[a,*], Fevronia Kolonitsiou[a], Georgia Vrioni[b], Stamatia Tsoupra[c], Alexandra Lekkou[d], Fotini Paliogianni[a]

[a] *Department of Microbiology, University Hospital of Patras, Patras, Greece*
[b] *Department of Microbiology, Medical School, National and Kapodistrian University of Athens, Athens, Greece*
[c] *Department of Internal Medicine, University Hospital of Patras, Greece*
[d] *Department of Internal Medicine, Division of Infectious Diseases, University Hospital of Patras, Greece*

ARTICLE INFO

Article History:
Received 3 August 2021
Revised 19 December 2021
Accepted 20 December 2021
Available online 23 December 2021

Keywords:
Candida kefyr
Urinary tract infection
Pyelonephritis
Invasive candidiasis
COVID-19
ICU

ABSTRACT

Candida kefyr (*Kluyveromyces marxianus*), an ascomycetous environmental yeast, occasionally isolated from dairy products, represents an uncommon but emerging pathogen in immunocompromised patients. Herein, we present a case of *C. kefyr* pyelonephritis in a 41-year-old, previously immunocompetent, patient who was hospitalized in an COVID-19 ICU. Pyelonephritis was associated with caliectasis and obstruction due to possible fungus ball formation. Predisposing factors included ICU stay, use of broad spectrum antibiotics and steroids, central venous catheterization, mechanical ventilation and urologic manipulation. Susceptibility testing revealed high MIC values to amphotericin B. Infection was effectively controlled by prolonged administration of fluconazole without further surgical intervention. COVID-19 complicated with invasive candidiasis is an increasingly observed clinical situation that warrants high suspicion index and careful evaluation of laboratory data.

Introduction

Candida kefyr (formerly *C. pseudotropicalis*) is a yeast with its teleomorph currently recognized as *Kluyveromyces marxianus*. The latter was first isolated from kefir in 1909 and reported under the obsolete name *Saccharomyces fragilis* [1]. The yeast can be isolated from wide-ranging natural habitats such as fermented traditional dairy products, kefir grain, sewage from sugar industries, sisal leaves, and plants [2], and represents a rare but emerging pathogen in immunocompromised patients, especially patients with hematological malignacies [3–10]. Most studies refer to *C. kefyr* candidemia cases [3-4, 7-12], whereas, reports on well-defined *C. kefyr*-related upper urinary tract infections are very scarce [13–15]

Patients with severe COVID-19, such as those in an intensive care unit (ICU), are particularly vulnerable to invasive candidiasis [16]. Relevant clinical factors include prolonged ICU stay, central venous catheters' and broad-spectrum antibiotics' use [17]. In addition, dexamethasone has been found to improve survival in COVID-19 hospitalized patients who require supplemental oxygen, with the greatest benefit observed in patients under mechanical ventilation and therefore is increasingly used [18]. Unfortunately, corticosteroids may promote fungal growth in vitro and have been associated with increased risk for serious fungal diseases [19]. Finally, a disturbed immune response toward *C. albicans*, which may hint at an increased susceptibility toward *Candida* sp infection in critically ill COVID-19 patients has been recently described [20].

Herein we present a case of *C. kefyr* pyelonephritis successfully treated with a 30-days fluconazole regimen, in a 41-year-old COVID-19 patient.

Case report

A 41-year-old man with a history of bronchial asthma was diagnosed with severe COVID-19 and was admitted to the ICU COVID-19 Department of Patras University Hospital, where he remained in enteral nutrition for 50 days. He received for 10 days the standard treatment, Remdesivir and Dexamethasone 6 mg/d. On admission his laboratory parameters were as follows: white blood cell count 5.3 $\times$ 10^9/L, neutrophil count 4.09 $\times$ 10^9/L, lymphocyte count 0.85 $\times$ 10^9/L, platelet count 175 $\times$ 10^9/L, albumin 3.7 g/dL, proalbumin 10.4 mg/dL, LDH 486 U/L, CRP 10.7 mg/dL (normal values

Abbreviations: Intensive, Care Unit (ICU)
* Corresponding author.

https://doi.org/10.1016/j.mycmed.2021.101236
1156-5233/

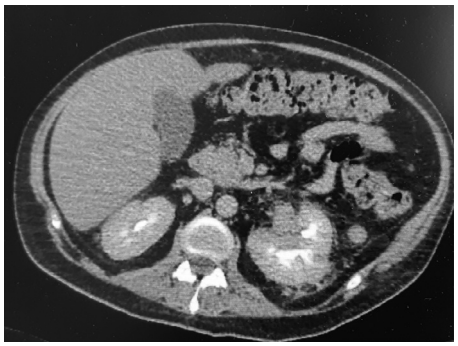

Fig 1. CT scan: Caliectasis of the left kidney.

<0.5 mg/dL), D-Dimer 1.09 mg/L, ferritin 1058 ng/mL. During his ICU stay, he has undergone several episodes of bacteremia due to *Enterococcus faecium*, *Acinetobacter baumannii* and *Klebsiella pneumoniae* that were treated appropriately. Two months after his admission, his condition was deteriorated again, whereas blood cultures were negative. CRP was elevated to 6.54 mg/dL, D-Dimer were slightly elevated 0.6 mg/L, albumin and total protein levels were low, 2.6 and 5 g/dL respectively, whereas white blood cell count remained at normal levels 6.14 $\times$ 10^9/L, neutrophil count at 4.1 $\times$ 10^9/L, lymphocyte count at 1.46 $\times$ 10^9/L and platelet count at 334 $\times$ 10^9/L, as well as LDH levels, 178 U/L. Due to persistent fever, a combination of antimicrobial regimens including liposomal amphotericin treatment was added. Whole-body CT work up revealed dilatation of the left renal pelvic system without obvious obstruction and a nephrostomy tube was placed. Because of respiratory failure, Methylprednisolone 80 mg/d was added. Under this treatment, his respiratory function improved and PCR SARS-CoV-2 turned negative, but a second CT revealed caliectasis of the left kidney, inflammatory elements around the renal pelvis reducing its lumen and no passage of the contrast agent through the renal pelvis (Fig. 1). At that time, culture of urine specimen collected from the nephrostomy grew yeast colonies (Fig. 2. 3) identified as *C. kefyr* by API 20C AUX (bioMerieux SA, France), VITEK2 YST (bioMerieux SA, France) and MALDI-TOF MS (Bruker Biotyper for identification of clinical yeast isolates, Bruker Daltonics, Bremen, Germany - Library database used was BDAL/ 8468 MSPs), whereas, blood cultures were negative. Antifungal susceptibility testing was performed using the concentration gradient diffusion assay (Etest; bioMérieux SA, France) and acquired values (mg/L) were as follows: amphotericin B >32, 5-flucytocine 2, fluconazole 0.38, itraconazole

Fig 2. *C. kefyr* colonies on Sabouraud Dextrose agar.

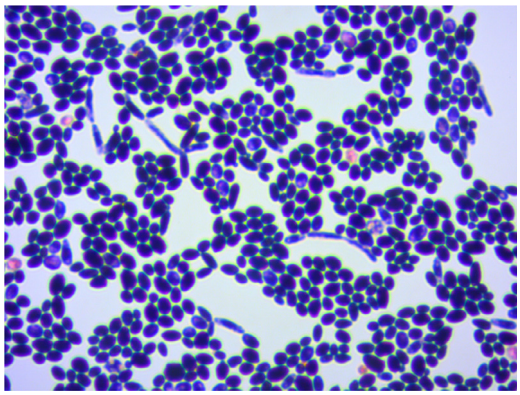

Fig 3. Gram stain. *C. kefyr* yeast cells. x100 magnification.

0.125, posaconazole 0.125, voriconazole 0.023, isavuconazole 0.008, caspofungin 0.25, micafungin 0.047, anidulafungin 0.064. Antifungal susceptibility testing was also conducted by EUCAST broth microdilution method [21]. There was categorical agreement for all agents tested and all agents' MICs had a maximum difference of 1–3 dilutions with the exception of caspofungin and amphotericin B where a greater discrimination was observed. In specific, the following MICs were acquired: amphotericin B 2, 5-flucytocine 1, fluconazole 0.12, itraconazole 0.06, posaconazole 0.06, voriconazole 0.008, caspofungin 0.03, micafungin 0.12, andulafungin 0.12. The isolate was assessed for biofilm formation as previously described with slight modifications [22]. Biofilm staining (Fig. 4) and quantification was performed as previously described [23] and the isolate was classified as a strong biofilm producer [24].

Amphotericin was replaced by fluconazole 400 mg / day and corticosteroids were gradually discontinued. The patient remained for another 21 days in antifungal treatment as he refused endoscopic removal of a possible fungus ball. Since malignancy had been excluded based on three negative cytology results, nephrostomy catheter was removed after successful urine passage evaluation. Fluconazole treatment was continued for another 7 days. The patient remained fever-free, hemodynamically stable and a new imaging test did not reveal obstructive left kidney disease.

Discussion

C. kefyr (anamorph/asexual form) - and its teleomorph/sexual form *K. marxianus* - represents a rare isolate in cases of invasive candidiasis, accounting for 0.45% of invasive *Candida* isolates recorded by the SENTRY Program 1997–2016 [1] and has predominately associated with hematological and other malignancies [4–10].

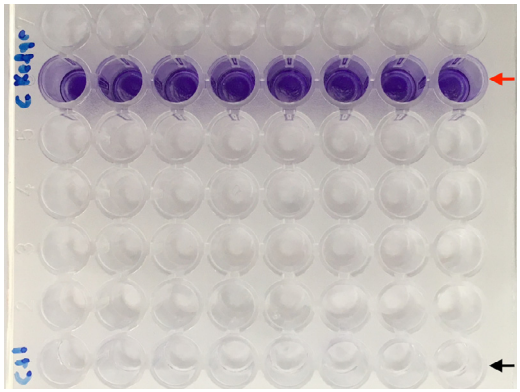

Fig 4. Crystal violet stain. Red arrow: wells containing *C. kefyr* biofilm, black arrow: wells without yeast cells (negative control).

Nevertheless, selected cases have been described in patients without profound immunosuppression, such as a patient with history of abdominal surgery and subsequent use of broad spectrum antibiotics [25]. In our case, the patient had no apparent immunosuppression until he got severe SARS-CoV-2 infection. Risk factors for fungal infection, included prolonged stay in ICU under broad spectrum antibiotics and corticosteroids, central venous catheterization, mechanical ventilation and urologic manipulation.

Rate of *C. kefyr* isolation from urine specimens extends between 2.5% to 3.57% [26–27]. In selected cases, *C. kefyr* isolation from urine has been associated with invasive candidiasis. These include two cases of renal transplant patients [28] and a case of disseminated disease originated from genitourinary tract in a patient with metastatic cancer [3]. *C. kefyr* associated fungus ball has been formed in the bladder of a patient with hematological malignancy [7] and a case of persistent calculus-associated *C. kefyr* cystitis has been reported [29].

Cases of *C. kefyr* upper urinary tract infection are scarce. The first published case involves a 74-year-old patient with diabetes and hypertrophic obstructive cardiomyopathy. The patient presented with haematuria and CT scan revealed a hemorrhagic mass at the kidney [14]. The second case involves a neonate with anal atresia, colostomy surgery, and vesico-ureteral-reflux grade V. The neonate developed initially bacterial urinary tract infection and afterwards, *C. kefyr* pyelonephritis. The yeast was isolated from urine cultures [13]. The third case refers to a 60-year-old patient with a history of uncontrolled diabetes and consumption of broad spectrum antibiotics. The patient presented with sepsis, pleural effusion and a perinephric collection. *C. kefyr* was isolated from both urine and aspirate of the perinephric mass [15].

Assessment of yeast isolation in urine specimens remains a controversial issue in patient management. This is due to the fact that it is indicative of a wide spectrum of conditions including asymptomatic candiduria; in this case administration of antifungal agents may not be required. Current recommendations suggest that candiduria should be treated regardless the presence of symptoms in patients that are at high risk for disseminated disease, such as neutropenic patients, low-birth weight infants (<1500 g) and patients who will undergo urologic manipulations. On the other hand, symptomatic *Candida* cystitis, symptomatic ascending *Candida* pyelonephritis, as well as *Candida* urinary tract infection associated with fungus balls, require treatment [30].

Treatment approaches include removal or replacement of urinary tract instruments, such as stents and Foley catheters, and use of antifungal agents, mainly fluconazole at 200–400 mg/d for 2 weeks and liposomal amphotericin B, 3–5 mg/kg/d for 1–7 days. In cases of *Candida* urinary tract infection, imaging of the urinary tract by ultrasound or CT scan is helpful in defining structural abnormalities, hydronephrosis, abscesses, emphysematous pyelonephritis, and fungus ball formation. Aggregation of mycelia and yeasts in fungus balls in bladder or kidney leads to obstruction and precludes successful treatment of infection with antifungal agents alone [30]. Fungus balls are an uncommon complication of *Candida* urinary tract infections in adults and surgical intervention along with long lasting treatment is strongly recommended [30].

Taking into account that many isolates are capable of biofilm formation, additional obstacles in efficient treatment plan are posed. Fluconazole may demonstrate diminished activity on mature biofilms, whereas use of traditional biofilm active antifungal agents, such as amphotericin B and echinocandins, may be disabled by high MIC values, inability to achieve appropriate concentrations at the site of infection- echinocandins in urine - or diminished activity against planktonic cells eg caspofungin [31].

Since there are no established clinical breakpoints for *C. kefyr* by EUCAST or CLSI, MIC values could be assessed in accordance with respective breakpoints of *C. albicans* or in respect to epidemiological cut-off values (ECVs &ECOFFs). Based on EUCAST ECOFFs the isolate was wild-type to fluconazole and non-wild-type to amphotericin B [32]. In addition, according to proposed Etest-based ECVs the isolate was wild-type to fluconazole, voriconazole and anidulafungin and non-wild-type to amphotericin B [33]. High MIC values to amphotericin have been already documented in other studies [10, 11]. In a large collection of bloodstream isolates, the authors observed that 52% (15 out of 29) of the isolates had MIC values >1 μg/mL [34]. However, in two studies concerning various clinical specimens, only 8% (5 out of 63) and none (0 out of 33) of the isolates had elevated MIC values [12, 35]. In this case, although the isolate was evaluated as amphotericin non-wild type by both EUCAST and Etest methodology, a major discrepancy regarding MIC values was observed. In a previous study regarding a collection of amphotericin B resistant *C. haemulonii* and *C. pseudohaemulonii* isolates, the authors suggested that Etest method on Mueller Hinton agar plates provided superior discrimination between amphotericin B-resistant and -susceptible isolates and noted that EUCAST as well as CLSI method generated narrow ranges of amphotericin B MICs [36]. Also, in a recent paper, Berkow *et al.* denoted the advantage of gradient diffusion strips versus broth microdilution methods for testing of amphotericin B. They suggest that broth microdilution testing reveals MIC values which are tightly clustered within a range of 0.25 to 1 μg/ml, whereas gradient diffusion strips provide a more reliable discrimination between susceptible and resistant isolates as far as a molecular target for resistance is lacking [37]. Nevertheless, amphotericin B resistance of this isolate can be indirectly claimed, since the present case appears to be a breakthrough infection due to prior use of amphotericin B regimen. Along with other *Candida* sp., *C. kefyr* has been reported to develop resistance upon exposure to antifungals and is considered one of the emerging multi-drug resistant *Candida* [38].

Regarding MIC determination for caspofungin by EUCAST broth microdilution method, significant inter-laboratory variation in MIC ranges have been recorded. This fact excludes so far establishment of ECOFFs or clinical breakpoints. Alternatively, susceptibility to caspofungin can be presumed according to susceptibility to micafungin and anidulafungin [21, 39].

Moreover, *Candida* pyelonephritis can be a sign of concurrent *Candida* bloodstream infection as far as it can develop either as an ascending infection arising from the lower urinary tract, or because of hematogenous spread to the kidneys in a patient with candidemia. Even though in many cases the yeast is not isolated from the blood, candidemia cannot be excluded as approximately as high as 50% of cases of invasive candidiasis are not identified by blood culture [17]. Moreover, the vast majority of *C. kefyr* upper urinary tract infections retrieved from literature have been complicated with disseminated disease [14, 15]. Only in one case of *C. kefyr* pyelonephritis in a neonate, the yeast was isolated solely from urine; nevertheless, the authors considered the case as systemic infection and speculated that hematogenous spread was preceded to renal involvement [13].

In our case the origin of infection is unclear, although catheterization could be suspected. In a recent study, two cases of invasive candidiasis due to *Saccharomyces cerevisiae* in COVID-19 patients were described upon receiving a probiotic supplement [40]. Considering that *C. kefyr* is associated with dairy products and that this is the first isolate in our settings, we could speculate a possible yeast translocation from the patient's digestive tract into the bloodstream, possibly due to damaged intestinal mucosal barrier. Association between *C. kefyr* candidemia and consumption of dairy products, such as yogurt, has been documented in reports concerning hematological patients [4, 7].

Fungal infections in COVID-19 patients have increased. A study from Spain reported a rate of 0.7% (7/989) of fungal super-infections complicating hospitalized COVID-19 patients: four of them were caused by molds and three by *Candida*, in specific one each of candidemia, candiduria, and complicated intraabdominal candidiasis [17]. In another study from Spain, a great increase in candidaemia cases

along with a shift from other *Candida* sp to *C. auris* prevalence is described [41]. Moreover, invasive yeast infections are associated with a higher mortality in COVID-19 cases not receiving antifungal treatment compared to those receiving [17]. Therefore, high suspicion index and careful evaluation of all available laboratory data are of paramount importance to these patients.

Although yeast and mold infections are more common in COVID-19 ICU patients, this is the first – to the best of our knowledge- case of invasive *C. kefyr* urinary tract infection in a COVID-19 patient. In addition, pyelonephritis associated with fungus ball formation is a rare entity and is more commonly managed with removal of the obstruction by radiological or surgical intervention along with systemic antifungal agents. In this case, resolution of the infection was achieved by solely prolonged intravenous antifungal therapy and removal of nephrostomy catheter without surgical intervention.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial or not-for-profit sectors

Declaration of Competing Interest

None

References

[1] Pfaller MA, Diekema DJ, Turnidge JD, Castanheira M, Jones RN. Twenty Years of the SENTRY Antifungal Surveillance Program: results for Candida Species From. Open Forum Infect Dis 2019;6(Suppl 1):1997–2016 S79-S94. doi: 10.1093/ofid/ofy358.

[2] Karim A, Gerliani N, Aïder M. Kluyveromyces marxianus: an emerging yeast cell factory for applications in food and biotechnology. Int J Food Microbiol 2020;333:108818. doi: 10.1016/j.ijfoodmicro.2020.108818.

[3] Morgan MA, Wilkowske CJ, Roberts GD. Candida pseudotropicalis fungemia and invasive disease in an immunocompromised patient. J Clin Microbiol 1984;20(5):1006–7. doi: 10.1128/jcm.20.5.1006-1007.1984.

[4] Reuter CW, Morgan MA, Bange FC, Gunzer F, Eder M, Hertenstein B, et al. Candida kefyr as an emerging pathogen causing nosocomial bloodstream infections in neutropenic leukemia patients. Clin Infect Dis 2005;41:1365–6. doi: 10.1086/497079.

[5] Sendid B, Lacroix C, Bougnoux ME. Is Candida kefyr an emerging pathogen in patients with oncohematological diseases? Clin Infect Dis 2006;43:666–7. doi: 10.1086/506573.

[6] Kalkanci A, Saracli MA, Guzel O, Yildiran ST, Senol E, Kustimur S. Clustering of nosocomial Candida kefyr infections among hematological patients in a university hospital: molecular typing of the strains by PFGE and RAPD. J Mycol Med 2007;17:250–5.

[7] Dufresne SF, Marr KA, Sydnor E, Staab JF, Karp JE, Lu K, et al. Epidemiology of Candida kefyr in patients with hematologic malignancies. J Clin Microbiol 2014;52:1830–7. doi: 10.1128/JCM.00131-14.

[8] Jung DS, Farmakiotis D, Jiang Y, Tarrand JJ, Kontoyiannis DP. Uncommon Candida Species Fungemia among Cancer Patients, Houston, Texas, USA. Emerg Infect Dis. 2015;21:1942–50. doi: 10.3201/eid2111.150404.

[9] Seth-Smith HMB, Büchler AC, Hinic V, Medinger M, Widmer AF, Egli A. Bloodstream infection with Candida kefyr/Kluyveromyces marxianus: case report and draft genome. Clin Microbiol Infect 2020;26:522–4. doi: 10.1016/j.cmi.2019.11.014.

[10] Wang E., Farmakiotis D., Yang D., McCue D.A., Kantarjian H.M., Kontoyiannis D.P. et al. The ever-evolving landscape of candidaemia in patients with acute leukaemia: non-susceptibility to caspofungin and multidrug resistance are associated with increased mortality. J Antimicrob Chemother. 2015;70:2362−2368. doi: 10.1093/jac/dkv087 5/69

[11] Dagi HT, Findik D, Senkeles C, Arslan U. Identification and antifungal susceptibility of Candida species isolated from bloodstream infections in Konya, Turkey. Ann Clin Microbiol Antimicrob 2016 May 31;15:36. doi: 10.1186/s12941-016-0153-1.

[12] Ahmad S, Khan Z, Al-Sweih N, Alfouzan W, Joseph L, Asadzadeh M. Candida kefyr in Kuwait: prevalence, antifungal drug susceptibility and genotypic heterogeneity. PLoS ONE 2020;15:e0240426. doi: 10.1371/journal.pone.0240426.

[13] Weichert S, Reinshagen K, Zahn K, Geginat G, Dietz A, Kilian AK, et al. Candidiasis caused by Candida kefyr in a neonate: case report. BMC Infect Dis 2012;12:61. doi: 10.1186/1471-2334-12-61.

[14] Chopra T, Bhargava A, Kumar S, Chopra A, Dhar S, Afonso L, et al. Candida kefyr endocarditis in a patient with hypertrophic obstructive cardiomyopathy. Am J Med Sci 2010;339:188–9. doi: 10.1097/MAJ.0b013e3181c0d945.

[15] Madhyastha SP, Acharya RV, Banerjee B, Prakashini K. Huge fungal perinephric abscess masquerading as malignancy. BMJ Case Rep 2018;11:e226753. doi: 10.1136/bcr-2018-226753.

[16] CDC. Fungal infections and COVID-19. https://www.cdc.gov/fungal/covid-fungal.html

[17] Arastehfar A, Carvalho A, Nguyen MH, Hedayati MT, Netea MG, Perlin DS, et al. COVID-19-Associated Candidiasis (CAC): an Underestimated Complication in the Absence of Immunological Predispositions? J Fungi (Basel) 2020;6:211. doi: 10.3390/jof6040211.

[18] Therapeutic Management of Adults With COVID-19. COVID-19 treatment guidelines. https://www.covid19treatmentguidelines.nih.gov.

[19] Riche CVW, Cassol R, Pasqualotto AC. Is the Frequency of Candidemia Increasing in COVID-19 Patients Receiving Corticosteroids? J Fungi (Basel) 2020;6:286. doi: 10.3390/jof6040286.

[20] Moser D, Biere K, Han B, Hoerl M, Schelling G, Choukér A, et al. COVID-19 Impairs Immune Response to Candida albicans. Front Immunol 2021;12:640644. doi: 10.3389/fimmu.2021.640644.

[21] Arendrup MC, Meletiadis J, Mouton JW, Lagrou K, Hamal P. Guinea J and the Subcommittee on Antifungal Susceptibility Testing of the ESCMID European Committee for Antimicrobial Susceptibility Testing. EUCAST Definitive Document E.DEF 7.3.2: method for the determination of broth dilution minimum inhibitory concentrations of antifungal agents for yeasts. EUCAST April 2020 https://www.eucast.org/astoffungi/methodsinantifungalsusceptibilitytesting/susceptibility_-testing_of_yeasts/).

[22] Melo AS, Colombo AL. Arthington-Skaggs BA. Paradoxical growth effect of caspofungin observed on biofilms and planktonic cells of five different Candida species. Antimicrob Agents Chemother 2007;51:3081–8. doi: 10.1128/AAC.00676-07.

[23] Júnior ACV, de Castro Nogueira Diniz Pontes M, Barbosa JP, Höfling JF, Araújo RM, Boniek D, et al. Antibiofilm and Anti-Candidal Activities of the Extract of the Marine Sponge Agelas dispar. Mycopathologia 2021;186:819–32. doi: 10.1007/s11046-021-00591-9.

[24] Stepanović S, Vuković D, Hola V, Di Bonaventura G, Djukić S, Cirković I, Ruzicka F. Quantification of biofilm in microtiter plates: overview of testing conditions and practical recommendations for assessment of biofilm production by staphylococci. APMIS 2007;115:891–9. doi: 10.1111/j.1600-0463.2007.apm_630.x.

[25] Khan Z, Ahmad S, Al-Obaid K, Joseph L, Chandy R. Candida kefyr as a cause of bloodstream infection and adjunctive role of biomarkers in its diagnosis. J Mycol Med 2015;25:71–5. doi: 10.1016/j.mycmed.2014.04.002.

[26] Ortiz B, Pérez-Alemán E, Galo C, Fontecha G. Molecular identification of Candida species from urinary infections in Honduras. Rev Iberoam Micol 2018;35:73–7. doi: 10.1016/j.riam.2017.07.003.

[27] Mishra M, Agrawal S, Raut S, Kurhade AM, Powar RM. Profile of yeasts isolated from urinary tracts of catheterized patients. J Clin Diagn Res 2014;8:44–6. doi: 10.7860/JCDR/2014/6614.4003.

[28] Diba K, Makhdoomi K, Nasri E, Vaezi A, Javidnia J, Gharabagh DJ, et al. Emerging Candida species isolated from renal transplant recipients: species distribution and susceptibility profiles. Microb Pathog 2018;125:240–5. doi: 10.1016/j.micpath.2018.09.026.

[29] Hodgin Jr. UG. Cystitis due to Candida pseudotropicalis. A persistent case secondary to bladder calculus. Rocky Mt Med J. 1969;66:30–2.

[30] Pappas PG, Kauffman CA, Andes DR, Clancy CJ, Marr KA, Ostrosky-Zeichner L, et al. Clinical Practice Guideline for the Management of Candidiasis: 2016 Update by the Infectious Diseases Society of America. Clin Infect Dis 2016;62:e1–e50. doi: 10.1093/cid/civ933.

[31] Nagy F, Bozó A, Tóth Z, Daróczi L, Majoros L, Kovács R. In vitro antifungal susceptibility patterns of planktonic and sessile Candida kefyr clinical isolates. Med Mycol 2018;56:493–500. doi: 10.1093/mmy/myx062.

[32] Arendrup MC, Friberg N, Mares M, Kahlmeter G, Meletiadis J, Guinea J. How to interpret MICs of antifungal compounds according to the revised clinical breakpoints v. 10.0 European committee on antimicrobial susceptibility testing (EUCAST). Clin Microbiol Infect 2020;26:1464–72. doi: 10.1016/j.cmi.2020.06.007.

[33] Salsé M, Gangneux JP, Cassaing S, Delhaes L, Fekkar A, Dupont D, et al. Multicentre study to determine the Etest epidemiological cut-off values of antifungal drugs in Candida spp. and Aspergillus fumigatus species complex. Clin Microbiol Infect 2019;25:1546–52. doi: 10.1016/j.cmi.2019.04.027.

[34] Pfaller MA, Diekema DJ, Messer SA, Boyken L, Hollis RJ, Jones RN. In vitro susceptibilities of rare Candida bloodstream isolates to ravuconazole and three comparative antifungal agents. Diagn Microbiol Infect Dis 2004;48:101–5. doi: 10.1016/j.diagmicrobio.2003.09.009.

[35] Gomez-Lopez A, Pan D, Cuesta I, Alastruey-Izquierdo A, Rodriguez-Tudela JL, Cuenca-Estrella M. Molecular identification and susceptibility profile in vitro of the emerging pathogen Candida kefyr. Diagn Microbiol Infect Dis 2010;66:116–26. doi: 10.1016/j.diagmicrobio.2009.06.007.

[36] Shin JH, Kim MN, Jang SJ, Ju MY, Kim SH, Shin MG, Suh SP, Ryang DW. Detection of amphotericin B resistance in Candida haemulonii and closely related species by use of the Etest, Vitek-2 yeast susceptibility system, and CLSI and EUCAST broth microdilution methods. J Clin Microbiol 2012;50:1852–5. doi: 10.1128/JCM.06440-11.

[37] Berkow EL, Lockhart SR, Ostrosky-Zeichner L. Antifungal Susceptibility Testing: current Approaches. Clin Microbiol Rev 2020;33:e69–79. doi: 10.1128/CMR.00069-19.

[38] Colombo AL, Júnior JNA, Guinea J. Emerging multidrug-resistant Candida species. Curr Opin Infect Dis 2017;30:528–38. doi: 10.1097/QCO.0000000000000411.

[39] Arendrup MC, Rodriguez-Tudela J-L, Park S, Garcia-Effron G, Delmas G, Cuenca-Estrella M, Gomez-Lopez A, Perlin DS. Echinocandin susceptibility testing of Candida spp. using EUCAST EDef 7.1 and CLSI M27-A3 standard procedures: analysis of the influence of bovine serum albumin supplementation, storage time, and drug lots. Antimicrob. Agents Chemother. 2011;55:1580–7. doi: 10.1128/AAC.01364-10.

[40] Ventoulis I, Sarmourli T, Amoiridou P, Mantzana P, Exindari M, Gioula G, Vyzantiadis TA. Bloodstream Infection by Saccharomyces cerevisiae in Two COVID-19 Patients after Receiving Supplementation of Saccharomyces in the ICU. J Fungi (Basel) 2020;6:98. doi: 10.3390/jof6030098.

[41] JV Mulet Bayona, N Tormo Palop, C Salvador García, B Fuster Escrivá, M Chanzá Aviñó, P Ortega García, al et. Impact of the SARS-CoV-2 Pandemic in Candidaemia, Invasive Aspergillosis and Antifungal Consumption in a Tertiary Hospital. J Fungi (Basel) 2021;7:440. doi: 10.3390/jof7060440.