Risk Factors for Candidemia in Intensive Care Unit: A Matched Case Control Study from North-Western India

Ekadashi Rajni, Ashish Jain, Shilpi Gupta*, Yogita Jangid, Rajat Vohra

ABSTRACT

Candidemia is one of the significant causes of mortality amongst critically ill patients in Intensive Care Units (ICUs). This study aimed to assess the incidence, risk factors and antifungal susceptibility pattern in candidemia cases admitted in ICU in a tertiary care hospital in Jaipur, Rajasthan from June 2021 to November 2021. *Candida* species isolated from blood culture of clinically suspected patients of sepsis were defined as candidemia cases. Blood culture and antifungal susceptibility testing were performed as per standard laboratory protocol. Analyses of risk factors was done between candidemia cases and matched controls in a ratio of 1 : 3. Forty-six candidemic cases and 150 matched controls were included in the study. *C. tropicalis* was the most prevalent species (22/46; 48%) followed by *C. auris* (8/46; 17%) and *C. albicans* (7/46; 15%). *Candida* species showed good sensitivity to echinocandins (97%) followed by amphotericin B (87%) and voriconazole (80%). In multivariate analysis, longer stay in ICU, presence of an indwelling device, use of immunosuppressive drugs and positive SARS-CoV-2 infection were associated with increased risk of candidemia. The constant evaluation of risk factors is required as prediction of risks associated with candidemia may help to guide targeted preventive measures with reduced morbidity and mortality.

KEYWORDS

candidemia; invasive candidiasis; antifungal susceptibility; ICU; risk factors

AUTHOR AFFILIATIONS

Mahatma Gandhi Medical University and Science Technology, Riico Institutional Area, Sitapura, Tonk Road, Jaipur, Rajasthan, India

* Corresponding author: Mahatma Gandhi Medical University and Science Technology, Riico Institutional Area, Tonk Rd, Sitapura, Jaipur, Rajasthan – 302020, India; e-mail: shilpigupta15nov@yahoo.com

Received: 29 July 2022
Accepted: 11 November 2022
Published online: 2 February 2023

Acta Medica (Hradec Králové) 2022; 65(3): 83–88
https://doi.org/10.14712/18059694.2022.23

© 2022 The Authors. This is an open-access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

INTRODUCTION

The last few decades have witnessed an unprecedented level of development in the healthcare industry. Both the therapeutic and diagnostic facilities have grown multi-fold, making saving lives a reality (1). The flip side to this development is there is an increased number of patients in intensive care units battling immunosuppression, either because of the disease itself or because of the potent broad-spectrum drugs and critical procedures being used (2, 3). All this has led to a humungous burden of patients at risk of invasive fungal infections. Bloodstream infections (BSIs) caused by *Candida* species have become a substantial threat in the hospital and are associated with high morbidity and mortality (4).

The profile of species involved in candidemia is continuously evolving and novel species are being described. Non *albicans candida* (NAC) are being isolated more frequently as compared to *C. albicans* (5). While *C. albicans* is being reported more frequently in the developed countries, *C. tropicalis* and *C. parapsilosis* dominate the epidemiology in developing nations (3, 6). *C. auris*, first described in 2009, has currently spread in several continents and is frequently associated with nosocomial infections and outbreaks. The resistance profile of *C. auris* and the high mortality associated with *C. auris* infections present quite a challenge for physicians. An increasing level of antifungal resistance to commonly used first and second-line antifungals is being observed on a global level (7, 8). Traditionally, invasive candidiasis has been associated with immunocompromised and chronic inflammatory states. The use of broad-spectrum antibiotics, recent surgery and indwelling central venous catheters (CVC), particularly those for total parenteral nutrition and prolonged hospital stay are known to be the other risk factors associated with candidemia (9).

Most of this data is limited by the fact that the large majority of studies have been retrospective in nature. Given the geographical variation and evolving epidemiology of candidemia, it is important to determine the predictors of candidemia in any particular set up (4). Also, a fresh perspective is needed to assess these factors in the light of currently pursuing pandemic. With this background the present matched case control study was conducted to assess the prevalence, risk factors and antifungal susceptibility pattern in invasive candidemia cases from medico-surgical intensive care unit (MS-ICU) of our hospital.

MATERIALS AND METHODS

STUDY DESIGN, SETTINGS AND DATA COLLECTION

This single center matched case control observational study was conducted in a 1450 bedded tertiary care teaching hospital in Jaipur, Rajasthan from June 2021 to November 2021. Patients above 18 years of age with at least one blood culture positive for Candida spp. were included as cases in the study. The cases and controls were matched in a ratio of 1 : 3. The matching criteria included gender, admission in the ICU at about the same time as the candidemia patients and SOFA score of at least 5, at the day of admission in ICU.

The data concerning demographics (age, sex), comorbidities, length of ICU stay, presence of any indwelling device, use of steroids or chemotherapeutic drugs, presence of COVID 19 infection, laboratory tests (CRP, procalcitonin) and outcome was collected daily by dedicated nurses on a predesigned proforma and compiled on excel sheet for both cases and controls. Initial pilot study was done on 30 patients for the validation of proforma. After the successful completion of pilot study, all 196 study participants were assessed using this clinical proforma.

DEFINITION

All blood culture results of suspected sepsis cases during the study period at our centre were screened for candidemia cases. Candidemia was defined as the isolation of *Candida* sp. from at least one blood culture in patients with clinical signs and symptoms suggestive of sepsis. For patients with multiple positive blood culture, only the first case of candidemia was included, and furthermore a new episode of candidemia was defined if the duration between the two episodes was more than 30 days (4).

MICROBIOLOGICAL ANALYSIS

Blood culture was performed using automated blood culture system BactecTM FX (Becton Dickinson, Sparks, MD). Identification was done using VITEK-2 automated system (bioMèrieux, Marcy-l'Étoile, France) with VITEK 2 (YST) cards. *Candida* isolates that could not be identified conclusively by VITEK-2 were subjected to matrix-assisted laser desorption ionization- time of flight mass spectrometry (MALDI-TOF MS; Bruker Biotyper OC version 3.1, Daltonics, Bremen, Germany) using an ethanol formic acid extraction protocol. Antifungal susceptibility was performed using the broth microdilution assay according to the Clinical and Laboratory Standards Institute guidelines (10).

ETHICAL APPROVAL

Approval of the Institutional Ethics Committee was obtained prior to the commencement of this study (MGMC&H/IEC/JPR/2021/552).

STATISTICAL ANALYSIS

The data was entered in a Microsoft excel worksheet. The qualitative data was assessed using Chi-square test while quantitative data was assessed using t test for both cases and control group. P value less than 0.05 was considered as statistically significant.

RESULTS

Out of 811 blood cultures that tested positive during the study period, candidemia was detected in 46, incidence being 5.7%. Thereafter, these 46 cases of candidemia and 150 matched controls were included in the study. The median age (and IQR) was found to 52 (39–58) for candidemia cases and 51 (38–65) for non-candidemia patients.

Tab. 1 Invitro susceptibility profile of various *Candida* species against the antifungals tested.

Candida isolates (N = 46)	Azoles		Echinocandins			AMB Sensitive N (%)	Flucytosine Sensitive N (%)
	Fluconazole Sensitive N (%)	Voriconazole Sensitive N (%)	Anidulafungin Sensitive N (%)	Caspofungin Sensitive N (%)	Micafungin Sensitive N (%)		
Candida tropicalis (22)	20 (91%)	21 (96%)	22 (100%)	20 (91%)	22 (100%)	22 (100%)	21 (96%)
Candida auris (8)	0	2 (25%)	7 (88%)	8 (100%)	8 (100%)	2 (25%)	1 (13%)
Candida albicans (7)	7 (100%)	7 (100%)	7 (100%)	7 (100%)	7 (100%)	7 (100%)	6 (86%)
Candida parapsilosis (4)	3 (75%)	2 (50%)	4 (100%)	4 (100%)	4 (100%)	4 (100%)	4 (100%)
Candida famata (2)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)
Candida glabrata (2)	NA	2 (100%)	2 (100%)	2 (100%)	2 (100%)	2 (100%)	1 (50%)
Candida lusitaniae (1)	1 (100%)	1 (100%)	1 (100%)	0	0	1 (100%)	1 (100%)

AMB – Amphotericin B

The distribution of various *Candida* species isolated from blood culture is shown in figure 1. *C. tropicalis* was the most common isolated *Candida* sp. (22/46; 48%) followed by *C. auris* (8/46; 17%) and *C. albicans* (7/46; 15%). Table 1 shows the antifungal susceptibility pattern to various antifungals tested. *C. albicans* isolates were 100% sensitive to almost all antifungals except for 5-flucytosine (5-FC) which showed resistance in 14% (1/7) of the isolates. Amongst the NAC, maximum resistance was seen against fluconazole (11/39; 28%) followed by voriconazole (9/39; 23%) and 5-flucytosine (9/39; 23%). *C. auris* was found to be most resistant speciesamongst all with 75–88% resistance against azoles, amphotericin B and 5-FC.

A summary of clinico-demographic characteristics of cases and matched controls is presented in Table 2. The univariate comparison (candidemia vs non-candidemia patients), longer stay in ICU for more than 20 days (39% vs 12%), presence of central venous catheter (61% vs 17%), raised C reactive protein (CRP) levels (76% vs 7%) and presence of SARS-CoV-2 infection (15% vs 1%) were associated with the development of candidemia. Hypertension, diabetes and chronic lung disease were the most common comorbidities associated with patients admitted in the ICU in both case and control groups and were not found to be statistically significant in development of candidemia. All patients who developed candidemia (46/46; 100%) were on immunosuppressants and was found to be statistically significant risk factor in comparison to the control group (61/150; 41%). Almost all patients had previous history of exposure to broad spectrum antibiotics in previous 30 days and 9 (9/46; 19.6%) patients had history of empirical use of antifungal drug in past 90 days (data not shown in table). The overall, mortality rate was found to be 28% in candidemia patients and did not show any statistical correlation when compared to non-candidemia (36%) patients.

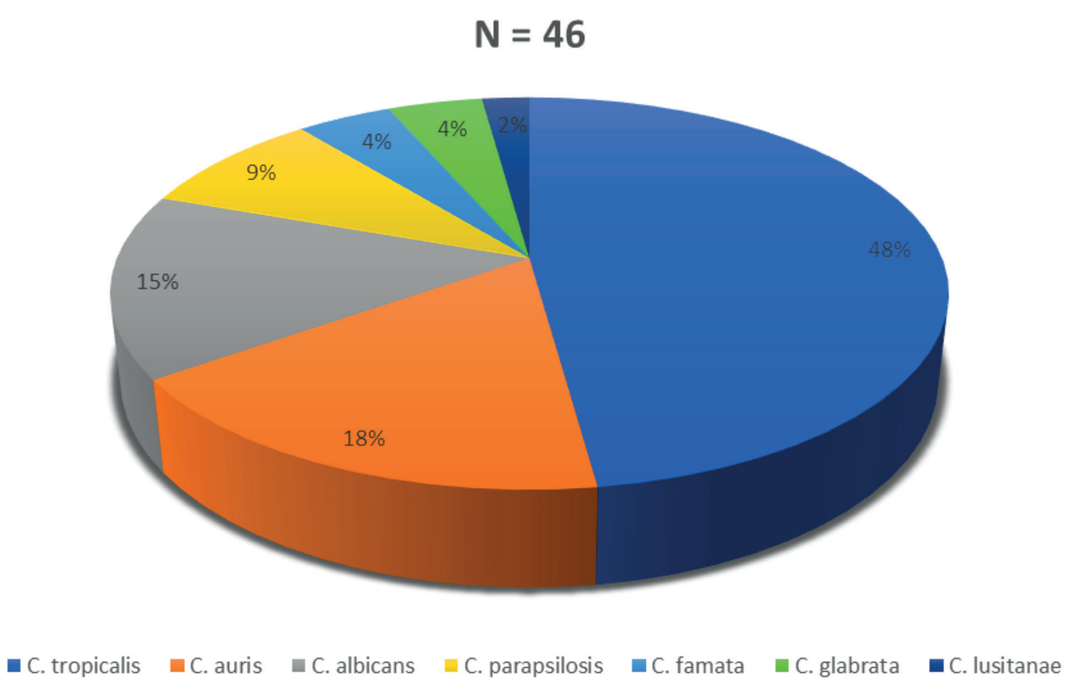

Fig. 1 Distribution of *Candida* species isolated from blood culture.

Tab. 2 Clinico-demographic characteristics of patients with and without candidemia.

Variables		Patients with candidemia (N = 46) (%)	Patients without candidemia (N = 150) (%)	Chi square (df)	p value
Age	≤ 60 ≥ 61	38 (83) 8 (17)	91 (61) 59 (39)	7.533 (1)	0.006
Gender	Male	30 (65)	97 (65)	0.012 (1)	0.914
Gender **Duration of hospital stay**	Female	16 (35)	53 (35)	0.012 (1) 15.520 (1)	0.914 < 0.0001
	< 20 days	28 (61)	132 (88)		
Duration of hospital stay **Presence of indwelling device**	≥ 20 days	18 (39)	18 (12)	15.520 (1) 26.751 (3)	< 0.0001 < 0.0001
	CVC	27 (61)	25 (17)		
Presence of indwelling device **Comorbidities**	Mechanical ventilation	37 (80)	77 (51)	26.751 (3) 11.543 (6)	< 0.0001 0.073
	Urinary catheter	43 (94)	126 (84)		
	Dialysis line/drains	3 (7)	44 (29)		
	Hypertension	11 (24)	49 (33)		
Comorbidities **C Reactive Protein (Positive)**	Diabetes	11 (24)	55 (37)	11.543 (6) 92.031 (1)	0.073 < 0.0001
	Lung disease	13 (28)	49 (33)		
	Renal disease	3 (12)	46 (31)		
	Liver disease	1 (2)	13 (9)		
	Malignancy	5 (11)	19 (13)		
	History of previous surgery	0	26 (17)		
	Yes	35 (76)	10 (7)		
C Reactive Protein (Positive) **Procalcitonin (Positive)**	No	11 (24)	140 (93)	92.031 (1) 13.338 (1)	< 0.0001 < 0.0001
	Yes	15 (33)	14 (9)		
Procalcitonin (Positive) **Use of steroids/immunosuppressive drugs**	No	31 (67)	136 (91)	13.338 (1) 47.630 (1)	< 0.0001 < 0.0001
	Yes	46 (100)	61 (41)		
Use of steroids/immunosuppressive drugs **History of COVID 19 infection**	No	0	89 (59)	47.630 (1) 15.503 (1)	< 0.0001 < 0.0001
	Yes	7 (15)	1 (1)		
History of COVID 19 infection **Final disease outcome**	No	39 (89)	149 (99)	15.503 (1) 0.088 (1)	< 0.0001 0.766
	Deceased	13 (28)	48 (32)		
Final disease outcome	Survived	33 (72)	102 (68)	0.088 (1)	0.766

df – degree of freedom; CVC – Central venous catheter

DISCUSSION

The present study provides an insight into the current epidemiology of candidemia in an adult ICU of a tertiary care teaching hospital in Jaipur with the incidence rate of 5.7%. A multicentric observational study conducted nationwide at 27 ICUs documented an overall incidence of 6.51 cases/1,000 ICU admission (4). This variation may be due to the timing of our observation which is done during pandemic era while the previous mentioned Indian data is from pre-pandemic period. Routsi et al., and several other researchers have observed that the incidence of candidemia increased significantly during the COVID-19 pandemic in comparison to pre-COVID era (11). More than three-fourth of the patients (83%) with candidemia were more than 60 years of age similar to most other studies (5, 12). Invasive candidiasis is not directly related to the virulence of the pathogen rather attributed to the subsidence of the host immune system. Thus, increased incidence in ICUs is encountered due to various factors including age related comorbidities which accentually compromise defence mechanism in patients enhancing chances of *Candida* invasion (5, 9).

The present study observed that NAC (85%) outnumbered *C. albicans* (15%). The steadily increased occurrence of NAC in comparison to *C. albicans* in ICU settings has been documented in various Indian as well as in western literature in the past few years. This shift has been attributed to rampant use of fluconazole which has led to selection and increased survival of resistant strains (13, 14, 16). According to a review on epidemiology of invasive candidiasis incidence of NAC has increased and *C. albicans* has decreased worldwide though distribution of candida species is variable region wise. As documented by same review the incidence of C. glabrata is high in USA while most frequently observed species in Asia-Pacific countries and Latin America are *C. tropicalis* and *C. parapsilosis* (2). Amongst NAC, the predominant *Candida* species in our study was *C. tropicalis* (48%) followed by *C. auris* (17%). It is interesting to note that observation on candidemia from the same setting during August 2020 to Jan 2021 had shown *C. auris* being the most common isolate. The study highlighted the fact of anticipation of *C. auris* outbreak during COVID-19 pandemic, which was documented worldwide (7).

It is an important observation to note that the earlier study on candidemia was conducted during the first pandemic wave in our country while the present study was conducted after the decline of second wave wherein epidemiology of candidemia seems to be shifting back steadily to the pre-pandemic period. The sudden increase in frequency of *C. auris* in ICU during COVID pandemic waves is multifactorial. It is attributed to mainly rampant and irrational use of steroids, broad-spectrum antibiotics and breach in infection control practices which contributed to sudden widespread of *C. auris* amongst patients where this species was already prevalent in hospital environment (15). This finding is in contrast to studies reported from other parts of the world including European countries where still *C. albicans* is the predominant species in ICU even during the ongoing pandemic (6, 9, 16).

In concordance with other studies across the country, we observed an overall higher invitro resistance in NAC isolates compared to *C. albicans* (7, 17, 18). Azoles including fluconazole showed 100% susceptibility against *C. albicans* thus implying it can be used as drug of choice in our ICU settings. The present study documents a high degree of antifungal resistance amongst *C. auris* isolates, a fact which has been apprised in previous studies from our centre (3, 7).

In our cohort, *C. auris* strains (n = 8) were resistant to azoles (75–100%), 75% and 88% were resistant to AMB and flucytosine respectively. Minimal resistance was shown against anidulafungin (13%) while sparing other echinocandins (Table 2). *C. auris* is known for its unfavourable antifungal susceptibility profile with most of the isolates being multi drug resistant. Implementation of adequate infection control measures and continuous surveillance remain the mainstay to prevent colonization of *C. auris* in a way to reduce development of invasive candidiasis rather treating the MDR strain (8).

The traditional risk factors associated with candidemia known since decades are characterised under demographic factors, co-morbid conditions, medical interventions and usage of broad-spectrum antibiotics and steroids (6). A systematic review had identified 29 risk factors extracted from 34 studies worldwide for invasive candidiasis. This review highlights significant association with comorbid conditions especially HIV and use of invasive devices. Other important risk factors with strong odds ratio, documented were patients on broad-spectrum antibiotics, total parenteral nutrition and previous *Candida* colonization (19).

Several studies in literature can be searched which have evaluated the risk factors for development of candidemia. However, majority of them were conducted on specific patient cohorts and did not use case control design. The present study used matched case-control methodology to identify multiple risk factors associated with candidemia in the critical care unit. Overall, the present study confirmed the strong association with increased length of ICU stay, presence of invasive devices, use of steroids and COVID-19 infection in comparison to patients who did not develop candidemia (p value < 0.001) (Table 2) which is in sync with other studies (6, 20). A sudden upsurge in candidemia cases ranging from two to upto ten folds have been noted during and after COVID 19 pandemic all over the globe (7, 21, 22). In an analysis by Rouitsi et al., the risk factors for severe COVID-19 disease and development of candidemia are almost similar (11). However, the commonest risk factor for increased incidence of candidemia in COVID-19 patients being the rampant use of antimicrobials empirically for suspected as well as for confirmed secondary bacterial infections which was stressed upon by various studies (7, 11, 23).

While evaluating candidemia cases it was found that markers of systemic inflammation like C reactive protein (CRP) was increased in majority of cases (35/46; 76%) while levels of procalcitonin (PCT) were increased only in 33% (15/46) cases. An interesting finding by Yin et al., among immunocompromised children have suggested that high CRP and low PCT levels help to differentiate invasive fungal infection from bacterial blood stream infection which is in favour with our findings. However, further studies with larger data in adults are required to establish this fact taking time of testing also under consideration (24).

The mortality rate found in our study was found to be 28.3% which is slightly lower than the previously reported studies (35–80%). This could possibly due to the fact that all the patients included in our study were not critically ill as suggested by low SOFA score during time of admission (9). Invasive devices constitute an important and unavoidable part of patient care. At the same time, they have an undisputed role to play in the genesis of nosocomial infections. They are invariably found to be the nidus of infection in patients requiring critical care (2, 4). Repeated and religious reinforcement is required for infection control practices including strict compliance to hand hygiene. The five moments of hand hygiene as endorsed by WHO must be adhered to. Also, a culture of "device intolerance" needs to be developed as propounded by Gopal P (25).

The strength of our study lies in its prospective matched case control design, taking care of many confounding variables along with collection of a sufficient amount of information to properly model potential risk factors of candidemia. Also, biochemical parameters like CRP and procalcitonin have been included as potential factors influencing the situation, thus enlarging the domain of risk factors studied.

However, there are certain limitations of the study which need to be brought forth. The correlation of few important risk factors like *Candida* score, correlation of candidemia cases with exact duration and specific class of antimicrobial use have been missed. Further studies on continuous surveillance of patients admitted in critical care for *Candida* colonization should be undertaken to establish its role in development of invasive candidiasis.

CONCLUSION

C. tropicalis followed by *C. auris* were the most frequently isolated candida species from candidemia patients in critical care unit. Age group more than 50 years, longer stay in ICU, presence of an indwelling device, use of steroids or immunosuppressive drugs and presence of SARS-CoV-2 infection were significant risk factors associated with candidemia patients in comparison to the control group. The continuous change in epidemiology and emergence of acquired resistance to antifungals necessitate regular monitoring to develop local guidelines for strengthening antifungal stewardship. Constant evaluation of risk factors in any particular set up is mandated to help intensivists to assess distribution and trends of candidemia.

ACKNOWLEDGEMENTS

The authors thank Dr Anuradha Chowdhary, Professor, Department of Medical Mycology, Vallabhbhai Patel Chest Institute, Delhi, for contributing in identification of isolates by MALDI-TOF MS and antifungal susceptibility testing. Additionally, she provided valuable suggestions for this manuscript.

REFERENCES

1. Dasgupta S, Das S, Chawan NS, Hazra A. Nosocomial infections in the intensive care unit: incidence, risk factors, outcome and associated pathogens in a public tertiary teaching hospital of Eastern India. Indian J Crit Care Med 2015; 19: 14–20.
2. Yapar N. Epidemiology and risk factors for invasive candidiasis. Ther Clin Risk Manag 2014 Feb 13; 10: 95–105.
3. Rajni E, Chaudhary P, Garg VK, Sharma R, Malik M. A complete clinico-epidemiological and microbiological profile of candidemia cases in a tertiary-care hospital in Western India. Antimicrobial Stewardship & Healthcare Epidemiology. Cambridge University Press 2022; 2(1): e37.
4. Chakrabarti A, Sood P, Rudramurthy SM, et al. Incidence, characteristics and outcome of ICU-acquired candidemia in India. Intensive Care Med 2015; 41(2): 285–95.
5. Ahmad S, Kumar S, Rajpal K, et al. Candidemia Among ICU Patients: Species Characterisation, Resistance Pattern and Association with Candida Score: A Prospective Study. Cureus 2022; 14(4): e24612.
6. Poissy J, Damonti L, Bignon A, et al. Risk factors for candidemia: a prospective matched case-control study. Crit Care 2020; 24(1): 109.
7. Rajni E, Singh A, Tarai B, et al. A High Frequency of Candida auris Blood Stream Infections in Coronavirus Disease 2019 Patients Admitted to Intensive Care Units, Northwestern India: A Case Control Study. Open Forum Infect Dis 2021; 8(12): ofab452.
8. Briano F, Magnasco L, Sepulcri C, et al. Candida auris Candidemia in Critically Ill, Colonized Patients: Cumulative Incidence and Risk Factors. Infect Dis Ther 2022; 11(3): 1149–60.
9. Xiao Z, Wang Q, Zhu F, An Y. Epidemiology, species distribution, antifungal susceptibility and mortality risk factors of candidemia among critically ill patients: a retrospective study from 2011 to 2017 in a teaching hospital in China. Antimicrob Resist Infect Control 2019; 8: 89.
10. Clinical and Laboratory Standards Institute. Reference Method for Broth Dilution Anti-Fungal Susceptibility Testing of Yeasts. CLSI Document M27. 4th ed. Wayne, PA: Clinical and Laboratory Standards Institute 2017.
11. Routsi C, Meletiadis J, Charitidou E, et al. Epidemiology of Candidemia and Fluconazole Resistance in an ICU before and during the COVID-19 Pandemic Era. Antibiotics 2022; 11: 771.
12. Tortorano AM, Peman J, Bernhardt H, et al.: Epidemiology of candidaemia in Europe: results of 28-month European Confederation of Medical Mycology (ECMM) hospital-based surveillance study. Eur J Clin Microbiol Infect Dis 2004; 23: 317–22.
13. Giri S, Kindo AJ, Kalyani J. Candidemia in intensive care unit patients: a one year study from a tertiary care center in South India. J Postgrad Med 2013; 59(3): 190–5.
14. Kaur H, Singh S, Rudramurthy SM, et al. Candidaemia in a tertiary care centre of developing country: Monitoring possible change in spectrum of agents and antifungal susceptibility. Indian J Med Microbiol 2020; 38(1): 110–6.
15. Chowdhary A, Sharma A. The lurking scourge of multidrug resistant Candida auris in times of COVID-19 pandemic. J Glob Antimicrob Resist 2020; 22: 175–6.
16. Macauley P, Epelbaum O. Epidemiology and Mycology of Candidaemia in non-oncological medical intensive care unit patients in a tertiary center in the United States: Overall analysis and comparison between non-COVID-19 and COVID-19 cases. Mycoses 2021; 64(6): 634–40.
17. Sabhapandit D, Lyngdoh WV, Bora I, Prasad A, Debnath K, Elantamilan D. Prevalence of non-albicans candidemia in a tertiary-care hospital in Northeast India. Int J Med Sci Public Health 2017; 6: 1620–5.
18. Kothari A, Sagar V. Epidemiology of candida bloodstream infections in a tertiary care institute in India. Indian J Med Microbiol 2009; 27(2): 171–2.
19. Thomas-Rüddel DO, Schlattmann P, Pletz M, Kurzai O, Bloos F. Risk Factors for Invasive Candida Infection in Critically Ill Patients: A Systematic Review and Meta-analysis. Chest 2022; 161(2): 345–55.
20. Li D, Xia R, Zhang Q, Bai C, Li Z, Zhang P. Evaluation of candidemia in epidemiology and risk factors among cancer patients in a cancer center of China: an 8-year case-control study. BMC Infect Dis 2017; 17(1): 536.
21. Nucci M, Barreiros G, Guimaraes LF, Deriquehem VAS, Castineiras AC, Nouer SA. Increased incidence of candidemia in a tertiary care hospital with the COVID-19 pandemic. Mycoses 2021; 64: 152–6.
22. Riche CVW, Cassol R, Pasqualotto AC. Is the frequency of candidemia increasing in COVID-19 patients receiving corticosteroids? J Fungi 2020; 6: 286.
23. Segala FV, Bavaro DF, Di Gennaro F, et al. Impact of SARS-CoV-2 Epidemic on Antimicrobial Resistance: A Literature Review. Viruses 2021; 13: 2110.
24. Liu Y, Zhang X, Yue T, et al. Combination of C-Reactive Protein and Procalcitonin in Distinguishing Fungal from Bacterial Infections Early in Immunocompromised Children. Antibiotics 2022; 11(6): 730.
25. Gopal P. Providencial Progression: Time tobe Intolerant. Indian J Crit Care Med 2022; 26(4): 409–10.