ISSN- O: 2458 - 868X, ISSN–P: 2458 – 8687
National Library of Medicine - ID: 101731606

International Journal of Medical Science and Innovative Research (IJMSIR)
IJMSIR : A Medical Publication Hub
Available Online at: www.ijmsir.com
Volume – 7, Issue – 4, August – 2022 , Page No. : 08 – 18

Non-albicans candida in critically ill patients in ICU of a tertiary care hospital - Indicator of failure of surveillance

[1]Vikas Saini, Department of Microbiology, University College of Medical Sciences, Delhi, India.
[2]Praveen Kumar Singh, Department of Microbiology, University College of Medical Sciences, Delhi, India.
[3]Gargi Rai, Department of Microbiology, University College of Medical Sciences, Delhi, India.
[4]Vishal Gaurav, Department of Dermatology and Venereology, All India Institute of Medical Sciences, Ansari Nagar, New Delhi, India.
[5]Asha Tyagi, Department of Anaesthesiology and critical care, University College of Medical Sciences, Delhi, India.
[6]Prerna Batra, Department of Paediatrics, University College of Medical Sciences, Delhi, India.
[7]Narendra Pal Singh, Department of Microbiology, University College of Medical Sciences, Delhi, India.
[8]Shukla Das, Department of Microbiology, University College of Medical Sciences, Delhi, India.
Corresponding Author: Shukla Das, Department of Microbiology, University College of Medical Sciences, Delhi, India.

Citation this Article: Vikas Saini, Praveen Kumar Singh, Gargi Rai, Vishal Gaurav, Asha Tyagi, Prerna Batra, Narendra Pal Singh, Shukla Das, " Non-albicans candida in critically ill patients in ICU of a tertiary care hospital - Indicator of failure of surveillance", IJMSIR- August - 2022, Vol – 7, Issue - 4, P. No. 08 – 18.
Type of Publication: Original Research Article
Conflicts of Interest: Nil

Abstract

Background: Bloodstream infections (BSIs) remain a cause of concern for clinicians and microbiologists. The incidence of septicaemia due to different Candida species is increasing with non-albicans Candida species accounting for approximately half of all Candida BSIs. Amongst non-albicans Candida species, Candida Auris has emerged as one of the most important, multi-drug resistant pathogens in critically ill patients.

Methods: The study is designed to evaluate the isolation of bloodstream Candida species and perform their antifungal susceptibility pattern from patients admitted to Medical, neonatal and Paediatric ICU in a tertiary care centre. An attempt to correlate the underlying risk factors with bloodstream Candida species. This retrospective study comprised a total of 45 patients with bloodstream infection investigated in the Department of Microbiology of University College of Medical Sciences (UCMS) and Guru Teg Bahadur Hospital (GTBH), Delhi from January 2019 to December 2019. Identification was done using Micros can and DNA sequencing.

Results: Of the 45 cases (out of 3024 strains) sent for strain identification by Micros can and DNA sequencing, Candida Auris was present in 26.66%, Wicker o my cesanomalus was present in 24.44%, C. tropicalis was present in 17.77%, C. parapsilosis was present in 15.55%, C. glabrata was present in 6.66% and other Candida was present in 8.88%. Overall, approximately 80% of our isolates were susceptible to all antifungals.

Conclusions: C. Auris is the leading pathogen in our patients, along with the rise in the incidence of Wicker o mycesanomala which is usually an environmental contaminant. Regular surveillance and infection control

practices are future ventures to reduce the burden of infection in ICU settings.

Keywords: Micros can, DNA sequencing, Candida Auris, Wicker o myces Anomal

Introduction

Bloodstream infections (BSIs) remain a cause of alarm for clinicians and a dilemma for diagnostic laboratories. Candida BSIs is increasingly being implicated as a major etiological agent in both immune-compromised and immunocompetent patients almost accounting for nearly 96% of all opportunistic mycoses[1–4]. The risk of Candida BSI in medical ICU patients has been attributed to various underlying factors with crude mortality, ranging from 35% to 67%[4–9].

Though regional and geographic differences exist in the incidence of the different Candida species, non-albicans Candida accounts for approximately half of all Candida BSIs with Candida Auris emerging as the multi-drug resistant pathogen in critically ill patients[4–6,10–13]. The treatment guidelines favour the use of echinocandins in patients who are moderate to severely ill and recommend fluconazole for patients with mild invasive candidiasis[14–18].

The intestinal reservoir and translocation of Candida is a predictive risk of hematogenous candidiasis; however, the practice of antifungal prophylaxis has led to the emergence of non albicans Candida species as the dominant pathogens[1,2]. Moreover, the presence of Candida colonization otherkin and mucosa of the healthcare workers shows its potential to transmit among HCWs in the hospital[3,4]. These pathogens are reported to be frequently resistant to various antimicrobials. This raises a serious concern especially in overcrowded health care setups and tertiary care hospitals of India, where lack of regular surveillance and antimicrobial stewardship cause drug-resistant microbes to persist in critically ill patients[19]. The study was undertaken to find the pattern of isolation of bloodstream Candida species and the associated underlying risk factors from patients admitted to the Multidisciplinary intensive care unit (MICU), Neonatal intensive care unit (NICU) and Pediatric intensive care unit (PICU) of a tertiary care hospital in Delhi, India from January to December 2019.

Materials and methods

This retrospective study comprised a total of 45 Candida isolates obtained from8056 blood samples from patients with suspected bloodstream infection investigated in the Department of Microbiology of a tertiary care hospital, Delhi, India from January to December 2019. The study was initiated after obtaining institutional ethical clearance.

10-20 ml venous blood sample was collected from patients in BACTEC aerobic blood culture bottles using BD BACTEC system (Becton Dickinson and Company, USA) which was incubated up to 7 days at 37oC.Bottles flagged positive by the machine were withdrawn and subjected to gram staining. Subcultures were done on blood agar and Mac Conkey agar plates incubated overnight at 37^0C for the isolation of the pathogen. Growth was subjected to the microscopic examination of gram-stained smears prepared from the colonies. The yeast-like growth were further sub cultured on Sabouraud's Dextrose agar (SDA) with cycloheximide, 0.04% gentamicin and 0.005% chloramphenicol, (HI Media, India) at 37^0 C for 48 hours and on CHRO Magar medium (Hi media) at 30ºC for 48 hours, as per standard techniques. Growth on SDA with white, creamy and round colonies was subjected to urea hydrolysis, germ tube test, and thermotolerance at 45^0C[20].Further suspensions of yeast were prepared and calibrated against the Micros can turbidity standard. The substrate containing wells of the Rapid Yeast Identification (RYI)

panel were inoculated with 50 µl of the suspension, and the panel was incubated aerobically for 4 h at 37°C. The enzyme activities of each isolate were determined by a colour change in the chromogenic substrates or a pH indicator on Micro Scan (Bio Rad, California, USA)[21].

Molecular Identification

For molecular analysis, all the yeast isolates were subjected to DNA extraction using a commercially available extraction kit (Hi Yield Genomic DNA Kit, RBC, Taiwan). Extracted DNA was amplified using pan fungal primers; ITS1 (5′-TCC GTA GGT GAA CCT GCGG-3′) and ITS4 (3′-TCC TCC GCT TATT GATA TGC-5′). Purification of the PCR products and DNA sequencing was done commercially using ITS primers[22].The sequence analysis was performed and compared with the sequences deposited in GenBank by using the BLAST program (https://www.ncbi.nlm. nih. Gov /blast/ Blast. CGI). The identification of species was defined by 99% sequence similarity with 99% query coverage.

Antifungal susceptibility testing

Antifungal susceptibility was performed against Amphotericin B, Fluconazole, Voriconazole, Itraconazole and Posaconazole using E-strip agar diffusion method (Hi - Media, Mumbai Ltd.).

Due to financial constraint, Caspofungin was not included in antifungal susceptibility testing. The criteria for interpretation of susceptibility was based on the new criteria laid down by CLSI M27-A3[23].As the breakpoints for C. Auris were not defined, the breakpoints suggested for yeast in CLSI M27-A3 were used to interpret the MICs for yeast, and other Candida species the CLSI M27-S4 was followed[24,25].

Statistical analysis

We performed statistical analysis using SAS 9.1 software (SAS Institute, Cary, NC). Categorical variables were described using frequencies and 95% confidence intervals. Skewed distribution was described using medians, interquartile ranges, and maximums and minimums. The significance threshold was 0.05. Based on the pathogen detection results, the fungal isolates were classified as C. albicans alone or NAC (non-albicans Candida).

Results

A total of 8056 blood samples from various ICUs were received in the Microbiology department from January 2019 to December 2019, of which 3024 were blood culture positive by BACTEC system. There were 45 isolates of non-albicans Candida (NAC) as identified on Micros can / molecular methods accounting for 1.4% of the total isolates. Among the 45 isolates, the majority of the patients admitted were from NICU (n = 21; 46.66%); MICU (n=17; 37.77%) followed by PICU (n=7; 15.55%) (Figure 1). The median duration of ICU stay in cases with NAC infection was 17 ± 5 days.

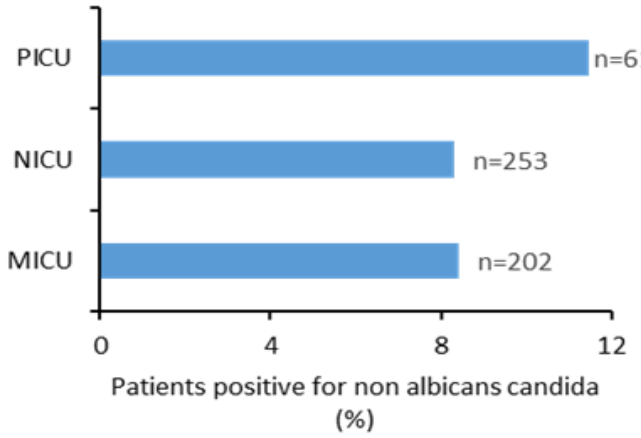

Figure 1: Distribution of isolates in blood culture (Jan-Dec 2019)

The demographic profile of patients is described in Table 1. Underlying sepsis was reported in 33.33%(n=15) of cases followed by low birth weight and respiratory distress syndrome 28.88%(n=13) amongst pediatric cases; while abdominal infection in 20% and hypo

glycaemia in 8.88% of neonates was observed. History of diabetes mellitus and post-hysterectomy sepsis was noted in 2.22% of adults admitted to MICU.

All patients admitted to the ICU had received injectable meropenem as an empirical management for sepsis. The administration of other antimicrobials to the patients were amikacin (73.33%), vancomycin (62.22%), amoxicillin–clavulanic acid (55.55%), piperacillin-tazobactam (55.55%), ceftriaxone (48.88%), linezolid (26.66%), colistin (22.22%), clindamycin (8.88%), levofloxacin (8.88%), ciprofloxacin (6.66%) and tigecycline (4.44%) (Table1).

Table 1: Baseline patient characteristics grouped by bloodstream infection

	Non albicanscandida(n=45)
Adults (no. %)	19(42%)
Paediatrics (no. %)	26(58%)
Male (no., %)	21 (47%)
Female (no., %)	24 (53%)
ICU settings	Mean number of days
MICU	17
NICU	19
PICU	17
Clinical spectrum	(no. %)
LBW and RDS	13(28.88%)
Sepsis	15(33.33%)
Abdominal infection	9(20%)
Term neonate with hypoglycaemia	4(8.88%)
Neonatal jaundice	2(4.44%)
Diabetes mellitus	1(2.22%)
Post Hysterectomy sepsis	1(2.22%)
Previous intake of Antibiotics	(no. %)
Amikacin	73.33%
Vancomycin	62.22%
Amoxicillin–clavulanic acid	55.55%
Piperacillin-Tazobactam	55.55%
Ceftriaxone	48.88%
Linezolid	26.66%
Colistin	22.22%
Clindamycin	8.88%
Levofloxacin	8.88%
Ciprofloxacin	6.66%
Tigecycline	4.44%
Empirical Fluconazole Prophylaxis	MICU (no.%) Total Patients-9 Death-1
	NICU (no.%) Total Patients-16 Death-1
	PICU (no.%) Total Patients-5 Death-0

On molecular identification amongst 45 isolates, Candida Auris was isolated primarily in 26.66% cases, Wicker Hamo myces anomalus in 24.44%, C. tropicalis in 17.77%, followed by C. parapsilosis 15.55% and C. glabrata in 6.66% and others in 8.88%. (Table 1). Most of the patients were administered fluconazole monotherapy on basis of our preliminary report. All the isolates were 100% susceptible to amphotericin B, Itraconazole, posaconazole though reduced susceptibility was observed for fluconazole. Unlike the others, C. Auris demonstrated lower susceptibility (45%) to all the drugs. While C tropicalis showed 87.5% susceptibility to fluconazole; C glabrata was 33.3% susceptibile to fluconazole and C. krusei with 66.66% susceptibility to voriconazole.

In our study, out of 45 patients with bloodstream infection, non-albicans candid aspp was predominant, a

total of 11 patients with candida BSI died of sepsis. Those patients admitted toI CUs and were administered antifungal treatment demonstrated low death rate, which is in concordance with previously published study Chakrabarti et al.[26]. Table 2 and 3 depicts the isolation of Candida albicans as the most common species globally unlike in India.

Table 2: Isolation of candida sp. in various international studies.

Sn.	Study	Place	Year	Isolates
1	Ngamchokwathana et al.[43])	Bangkok	2021	C. tropicalis (49.4%) C. albicans (28.8%) C. glabrata (16.7%) C. parasilosis (5.1%)
2	Chaves et al [44]	Brazil	2021	C. Guillaumond (70%) C. famata (20%) C. pellicullosa (10%)
3	Silva et al[45]	Brazil	2020	C. albicans (35.6%) C. parasilosis (30%) C. tropicalis (16.7%)
4	Raja et al. [46]	United Kingdom	2020	C. albicans (46.45%) C. parasilosis (22%) C. glabrata (16%)
5	Ahangarkani et al. [47]	Iran	2020	C. albicans (49%) C. Guillaumond (10.9%) C. tropicalis (9%) C. parapsilosis (7.27%)
6	Brunette et al(32)	Italy	2019	C. albicans (31.21%) C. parasilosis (24.35%) C. glabrata (4.08%)
7	Israel et al(33)	Israel	2019	C. albicans (39.4%) C. glabrata (18.8%) C. tropicalis (18%)
8	Zhang et al[48]	China	2019	C. parapsilosis (38.3%) C. albicans (35.6%) C. glabrata (13.9%)
9	Lin et al. [49]	China	2018	Candida albicans (37.3%) C. parapsilosis (24.1%) C. tropicalis (22.8%) C. glabrata (14.5%)
10	Lee et al. [50]	Taiwan	2018	C. parapsilosis (50.3%) C. glabrata (11.1%) C. tropicalis (11.7%) C. Guillaumond (7.0%)
11	Bal desi et al [51]	France	2017	C. albicans (61.4%) C. glabrata (14.3%) C. parasilosis (8%)

Table 3: Isolation of candida sp. in various Indian studies

Sn.	Study	Place	Year	Isolates
1.	Sowmya sridharan[52]	India	2021	C.tropicalis (37%) C.glabrata (18%) C.albicans (17%) C.parasilosis (11%)
2	Chakrabarti et al.[26]	India	2020	C.tropicalis (27.4%) C.albicans (22.8%) C.parasilosis (14.4%) C.auris (7.4%) C.krusei (7.4%)
3	Shilpeekumar et al [53]	India	2018	C.tropicalis (40.8%) C.albicans (29.6%) C.glabrata (18.5%)
4.	Mathur et al[34]	India	2018	C.glabrata (16%) C. Auris(17.5%) C.albicans (14%)
5.	Shivaprakash et al[28]	India	2017	C.tropicalis (43.3%) C.albicans (25.2%) C.auris (6.4%)

Discussion

The global status of non-albicans Candida as the emerging pathogen in health care facilities is a major cause of concern with limited options available for treatment[27].Patients at risk for candidemia are increasing and often misuse of antifungals results in the selection of rarer yeast as pathogens. Various underlying factors like the use of indwelling medical devices, underlying malignancy, growing number of immunocompromised patients, long-term immunosuppressive/cytotoxic therapy in transplant or cancer patients and prolonged duration of hospital stay increases the susceptibility to hospital-acquired pathogens.

In the present study, empirical use of carbapenem antibiotics, uncontrolled diabetes, post-surgical sepsis and abdominal infections, increased the risk of development of Candida septicemia in adults. On the other hand, in neonates admitted to ICU, low birth weight, neonatal sepsis, respiratory distress syndrome and parenteral nutrition that resulted in prolonged hospital stay were noted as significant risk factors.

Earlier Candida albicans was considered as an important threat amongst BSIs but the use of prophylactic antifungal therapy has serendipitously led to a paradigm shift to NAC, eventually leading to fatal invasive fungal infections. Candidiasis has been reported to have a crude mortality rate of 30-50% especially in low-birth-weight neonates[8,9]

Furthermore, conventional techniques of isolation and identification procedures often lead to the mistaken identity of the species, which poses a potential threat to the critically ill patients in ICU. The overwhelming number of non-albicans Candida in fections will pose great challenges to the existing infection control measures followed in tertiary health care facilities. Additionally overcrowding, compounded by lack of proper surveillance, can eventually lead to the un controlled proliferation, persistence and circulation of Candida species in hospital environment and amongst the HCW. Ironically, we did not isolate C. albic Ansin our study, a complete replacement with NAC reflects upon the endogenous colonization of non albicans candida species in the critically ill patients admitted to our hospital.

Several co-morbidities like sepsis (33.33 %), low birth weight and respiratory distress syndrome (28.88%), abdominal infections (20%), term neonate with hypoglycaemia (8.88%,) were observed amongst patients but the SE & CI calculated of the various comorbidities were not statistically associated with isolation of NAC. However, the average duration of ICU stay was an important factor, found significantly associated with NAC (28,29). We observed that an average ICU stay of 17 days led to an increased risk of NAC septicemia, which may have allowed colonization and migration of Candida species from various anatomical sites or long indwelling intravenous catheters causing bloodstream infections. We also observed that empirical Fluconazole was administered to patients harbour ing NAC, which is often the practice in tertiary care hospitals without performing prior antifungal susceptibility testing. The non-availability of an automated identification system or lack of an updated database in commercial platforms poses difficulty to correctly identify the pathogen and guide clinicians for proper antifungal usage.

In India, Biswalet al observed 21% of patients screened to be colonized by C. Auris (30). The species of Candida isolated from BSI in India has observed a change from C. albicans to C. tropicalis and now to C. Auris (Table 3). Though C. albicans is often associated with serious invasive fungal infections, other NAC species have emerged as clinically important pathogens causing

opportunistic infections. For instance, Wicker hamomyces are associated with outbreaks in pediatric cases and occasionally in adults (31).

Our study revealed high prevalence of C. Auris (26.66 %) while Wicker Hamo my cesanomalus sand C. tropicalis affected only 24.44% and 17.77 % of cases respectively which is contrary to other studies where C. tropicalis and C. albicans were the dominant species (28,32–34). The rise in Wicker Hamo my cesanomalus (formerly Pichia anomalus and C. pellicullosa) as a cause of fungemia has been associated with oropharyngeal and rectal colonization in children, often causing outbreaks. W. anomalus has been reported as the causative agent of nosocomial cerebral ventriculitis, endocarditis in intravenous drug abusers and urinary tract infections in renal transplant patients.

Cross-contamination with the hands of hospital personnel and survival on inanimate surfaces are implicated as potential reservoirs of such pathogens in the hospital. Further, frequent blood sampling and poor venepuncture care are well-identified risk factors for colonization by Candida (35–37).

C.auris being multidrug-resistant, a persistent colonizer amongst patients in ICU, is often responsible for high mortality in up to 30-60% of cases. The limitation of our study was the low number of isolates and short study period of 1 year, we could not find any significant association with the comorbidities. It poses a tremendous challenge to clinicians and health care providers in public health sectors (38).

Worldwide, the preferred drug of choice for treating resistant Candida species in BSI remains echinocandins, though amphotericin B deoxycholate remains the preferred drug as per the CDC (Centers for Disease Control and Prevention) guidelines in neonates (39–42).

Ours is 1500 bedded tertiary care hospital catering to patients with direct admissions and referred from private sectors residing in Delhi and also from adjoining states. Frequently, every year during the months from May to June, NICU admissions are estimated to be the highest, when an investigation in NICU (data not shared) led to the isolation of Wicker hamomyces causing BSI. On multiple sampling, the probable reservoir was traced to a source of water used for the preparation of infant oral feeds. It is has been established that W. anomalus fungemia causes outbreaks in pediatric units as they frequently survive in food and organic compounds. Supplemented by overcrowding, poor hand hygiene, inadequate infection control measures and various other activities like the use of mobile phones, X-ray machine, ventilators add to environmental contamination and promote the persistence of these pathogens in ICU. Lack of manpower and poor vigilance on infection control policy in ICU and high dependency units makes them the epicenters of emerging drug-resistant pathogens in these vulnerable zones of hospitals. The Covid-19 pandemic has provided valuable lessons on hygiene and social distancing. Therefore, if we continue to adhere to simple practices like hand hygiene, wearing masks and/or PPE in ICUs as a part of infection control programme likeSARSCoV-2 preventive protocols, the burden of infection by emerging drug-resistant pathogens may certainly see a downfall.

Conclusion

This study differentiated several factors promoting environmental survival and transmission of non-albicans Candida species, in hospital ICU. C.auris remains a predominant pathogen in patients admitted to medical and neonatal ICU, along with a rise in the incidence of Wicker hamomyces anomalus. Though an environmental contaminant, it frequently causes outbreaks. It is time to

switch over to molecular tools for correct identification and provide specific antifungals as per the resistance profile and avoid over usage of azoles. Regular surveillance, care of venepuncture and intravenous lines and infection control practices to be strictly followed in tertiary care hospitals to reduce the survival of these microbes in the hospital environment and ensure the favorable patient outcome in ICU settings.

Acknowledgement

We thank the Multi-Disciplinary Research Units (MRUs) of the University College of Medical Sciences for use of instrumentation facilities.

References

1. Richardson MD. Changing patterns and trends in systemic fungal infections. J Antimicrob Che mother. 2005; 56 Suppl 1: i5-i11. doi: 10. 1093/ Jac/ dki218

2. Muñoz P, Burillo A, Bouza E. Environmental surveillance and other control measures in the prevention of nosocomial fungal infections. Clin Microbiol Infect. 2001;7 (s2): 38-45. doi: https:// doi.org/10.1111/j.1469-0691. 2001.tb00008.x

3. Clark TA, Hajjeh RA. Recent trends in the epidemiology of invasive mycoses. Curr Opin Infect Dis. 2002;15(6):569-574.

4. Wisplingh off H, Bischoff T, Talent SM, Seifert H, Wenzel RP, Edmond MB. Nosocomial bloodstream infections in US hospitals: analysis of 24,179 cases from a prospective nationwide surveillance study. Clin Infect Dis. 2004;39(3):309-317.

5. Garbino J, Kolar ova L, Rohner P, Lew D, Pichna P, Pittet D. Secular Trends of Candidemia Over 12 Years in Adult Patients at a Tertiary Care Hospital. Medicine (Baltimore). 2002;81(6):425-433.

6. Leleu G, Aegerter P, Guidet B. Systemic candidiasis in intensive care units: A multicenter, matched-cohort study. J Crit Care. 2002;1 7(3) :168-175. doi:10.1053/ jcrc.2002.35815

7. Choi HK, Jeong SJ, Lee HS, et al. Blood Stream Infections by Candida glabrata and Candida krusei: A Single-Center Experience. Korean J Intern Med. 2009;24(3):263-269. doi:10.3904/ kjim. 2009.24.3.263

8. Marriott DJ, Playford EG, Chen S, et al. Determinants of mortality in non-neutropenic ICU patients with candidemia. Crit Care. 2009;13(4):1-8.

9. Moran C, Grussemeyer CA, Spalding JR, Benjamin DK, Reed SD. Comparison of costs, length of stay, and mortality associated with Candida glabrata and Candida albicans bloodstream infections. Am J Infect Control. 2010; 38 (1): 78-80. doi: 10.1016 /j. ajic. 2009. 06. 014

10. Horn DL, Fishman JA, Steinbach WJ, et al. Presentation of the PATH Alliance® registry for prospective data collection and analysis of the epidemiology, therapy, and outcomes of invasive fungal infections. Diagn Microbiol Infect Dis. 2007; 59 (4): 407- 414. doi: 10.1016/j. diag microbio.2007 .06.008

11. Almirante B, Rodríguez D, Park BJ, et al. Epidemiology and Predictors of Mortality in Cases of Candida Bloodstream Infection: Results from Population-Based Surveillance, Barcelona, Spain, from 2002 to 2003. J Clin Microbiol. 2005; 43 (4):1829-1835. doi: 10. 1128/ JCM.43.4.1829-1835. 2005

12. P faller MA, Boy ken L, Hollis RJ, et al. In Vitro Susceptibility of Invasive Isolates of Candida spp. to Anidulafungin, Caspofungin, and Micafungin: Six Years of Global Surveillance. J Clin Microbiol. 2008;46(1):150-156. doi:10.1128/JCM.01901-07

13. P faller MA, Messer SA, Hollis RJ, et al. Variation in Susceptibility of Bloodstream Isolates of Candida glabrata to Fluconazole According to Patient Age and Geographic Location in the United States in 2001 to

2007. J Clin Microbiol. 2009; 47 (10): 3185-3190. doi: 10. 1128/ JCM. 00946-09

14. Pappas PG, Kauffman CA, Andes D, et al. Clinical Practice Guidelines for the Management of Candidiasis: 2009 Update by the Infectious Diseases Society of America. Clin Infect Dis Off Publ Infect Dis Soc Am. 2009;48(5):503-535. doi:10.1086/596757

15. Mora-Duarte J, Betts R, Rotstein C, et al. Comparison of Caspofungin and Amphotericin B for Invasive Candidiasis. N Engl J Med. 2002; 347 (25):2020-2029. doi:10.1056/NEJMoa021585

16. Kuse E-R, Chetchotisakd P, da Cunha CA, et al. Micafungin versus liposomal amphotericin B for candidaemia and invasive candidosis: a phase III randomised double-blind trial. The Lancet. 2007; 369 (9572):1 519-1527. doi:10.1016/S0140-6736 (07)60605-9

17. Pappas PG, Rotstein CMF, Betts RF, et al. Micafungin versus Caspofungin for Treatment of Candidemia and Other Forms of Invasive Candidiasis. Clin Infect Dis. 2007;45(7):883-893. doi:10.1086/520980

18. Reboli AC, Rotstein C, Pappas PG, et al. Anidulafungin versus Fluconazole for Invasive Candidiasis. N Engl J Med. 2007; 35 6(24): 2472-2482. doi: 10 .1056/ NEJMoa066906

19. Vincent J-L, Rello J, Marshall J, et al. International Study of the Prevalence and Outcomes of Infection in Intensive Care Units. JAMA. 2009; 30 2(21): 2323 - 2329. doi: 10. 1001/ jama.2009.1754

20. Das S, Tigga R, Rai G, et al. Candida auris colonization in an immunocompetent patient: A new threat in medical ICU. Med Mycol Case Rep. 2018; 21:54-56. doi: 10. 1016/ j. mmcr. 2018. 05.004

21. Germain GS, Beauchesne D. Evaluation of the Micros can Rapid Yeast Identification panel. J Clin Microbiol. 1991;29(10):2296-2299.

22. White TJ, Bruns T, Lee S, Taylor J, others. Amplification and direct sequencing of fungal ribosomal RNA genes for phylogenetics. PCR Protoc Guide Methods Appl. 1990;18(1):315-322.

23. P faller MA, Rhomb erg PR, Messer SA, Jones RN, Castanheira M. Isavuconazole, micafungin, and 8 comparator antifungal agents' susceptibility profiles for common and uncommon opportunistic fungi collected in 2013: temporal analysis of antifungal drug resistance using CLSI species-specific clinical breakpoints and proposed epidemiological cutoff values. Diagn Microbiol Infect Dis. 2015; 82 (4):303-313. doi: 10. 1016 /j. diagmicrobio.2015.04.008

24. Wayne P. Clinical and Laboratory Standards Institute (CLSI): Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi. Carol Stream IL Allured Publ Corp. Published online 2008.

25. Sanitá PV, de Oliveira Mima EG, Pavarina AC, Jorge JH, Machado AL, Vergani CE. Susceptibility profile of a Brazilian yeast stock collection of Candida species isolated from subjects with Candida-associated denture stomatitis with or without diabetes. Oral Surg Oral Med Oral Pathol Oral Radiol. 2013;116(5):562-569. doi: 10.1016/j.oooo.2013.07.002

26. Chakrabarti A, Sood P, Rudra Murthy SM, et al. Characteristics, outcome and risk factors for mortality of paediatric patients with ICU-acquired candidemia in India: A multicentre prospective study. Mycoses. 2020;63(11):1149-1163.

27. Chakrabarti A, Sood P, Rudra Murthy SM, et al. Incidence, characteristics and outcome of ICU-acquired candidemia in India. Intensive Care Med. 2015;41(2):285-295.

28. Rudra Murthy SM, Chakrabarti A, Paul RA, et al. Candida Auris candidaemia in Indian ICUs: analysis of

risk factors. J Antimicrob Che mother. 2017;72(6):1794-1801.

29. Borman AM, Szekely A, Johnson EM. Comparative pathogenicity of United Kingdom isolates of the emerging pathogen Candida auris and other key pathogenic Candida species. MS phere. 2016;1(4).

30. Biswal M, Rudra Murthy SM, Jain N, et al. Controlling a possible outbreak of Candida auris infection: lessons learnt from multiple interventions. J Hosp Infect. 2017; 97 (4): 363-370. doi: 10.1016 /j. jhin. 2017.09.009

31. Yılmaz Semerci S, Demirel G, Taştekin A. Wickerhamomyces anomalus blood stream infection in a term newborn with pneumonia. Published online 2017. Accessed April 2, 2021. http:// acikerisim. medipol. edu.tr/ xmlui/ handle/20.500.12511/3978

32. Brunetti G, Navazio AS, Giuliani A, et al. Candida blood stream infections observed between 2011 and 2016 in a large Italian University Hospital: A time-based retrospective analysis on epidemiology, biofilm production, antifungal agents consumption and drug-susceptibility. PLOS ONE. 2019; 14 (11): e0224678. doi: 10. 1371/ journal. pone.0224678

33. Israel S, Amit S, Israel A, Livneh A, Nir-Paz R, Korem M. The Epidemiology and Susceptibility of Candidemia in Jerusalem, Israel. Front Cell Infect Microbiol. 2019;9. doi: 10.3389/ fcimb. 2019.00352

34. Mathur P, Hasan F, Singh PK, Malhotra R, Walia K, Chowdhary A. Five-year profile of candidaemia at an Indian trauma centre: High rates of Candida auras blood stream infections. Mycoses. 2018;61(9):674-680. doi: https:// doi. org/10.1111/myc.12790

35. Russotto V, Cortegiani A, Raineri SM, Giarratano A. Bacterial contamination of inanimate surfaces and equipment in the intensive care unit. J Intensive Care. 2015;3(1):1-8.

36. Chakrabarti A, Singh K, Narang A, et al. Outbreak of Pichia Anomal Infection in the Pediatric Service of a Tertiary-Care Center in Northern India. J Clin Microbiol. 2001; 39 (5):1702-1706. doi: 10.1128/ JCM.39.5.1702-1706.2001

37. Pasqual Otto A, Sukiennik T, Severo L, Amorim C, Colombo A. An Outbreak of Pichia Anomal Fungemia in a Brazilian Pediatric Intensive Care Unit.; 2005:558.

38. Arastehfar A, Bakhtiari M, Daneshnia F, et al. First fungemia case due to environmental yeast Wicker hamomyces myanmarensis: detection by multiplex qPCR and antifungal susceptibility. Future Microbiol. 2019;14 (4):267-274.

39. Pappas PG, Kauffman CA, Andes DR, et al. Clinical practice guideline for the management of candidiasis: 2016 update by the Infectious Diseases Society of America. Clin Infect Dis. 2016;62(4): e1-e50.

40. Sears D, Schwartz BS. Candida Auris: An emerging multidrug-resistant pathogen. Int J Infect Dis. 2017; 63:95-98. doi: 10. 1016/ j. ijid.2017.08.017

41. Clancy CJ, Nguyen MH. Emergence of Candida Auris: An International Call to Arms. Clin Infect Dis. 2017; 64 (2): 141- 143. doi: 10. 1093/ cid/ciw696

42. Strich JR, Palmore TN. Preventing transmission of multidrug-resistant pathogens in the intensive care unit. Infect Dis Clin. 2017;31(3):535-550.

43. Ngamchokwathana C, Chongtrakool P, Waesamaae A, Chayakulkeeree M. Risk Factors and Outcomes of Non-albicans Candida Bloodstream Infection in Patients with Candidemia at Siriraj Hospital-Thailand's Largest National Tertiary Referral Hospital. J Fungi Basel Switz. 2021;7(4):269. doi:10.3390/jof7040269

44. Chaves ALS, Trilles L, Alves GM, et al. A case-series of bloodstream infections caused by the Meyerozyma Guillaumond species complex at a

reference center of oncology in Brazil. Med Mycol. 2020; 59 (3):2 35-243. doi: 10. 1093/ mmy /myaa 044

45. Paixao de Sousa da Silva AM, de Moraes-Pinto MI, Teofilo Pignati L, et al. Candida spp bloodstream infections in a Latin American Pediatric Oncology Reference Center: Epidemiology and associated factors. Mycoses. 2020; 63 (8): 812-822.

46. Raja NS. Epidemiology, risk factors, treatment and outcome of Candida bloodstream infections because of Candida albicans and Candida non-albicans in two district general hospitals in the United Kingdom. Int J Clin Pract. 2021; 75 (1): e13655. doi: https:/ /doi. org/ 10.1111/ijcp.13655

47. Ahangarkani F, Shokohi T, Rezai MS, et al. Epidemiological features of nosocomial candidaemia in neonates, infants and children: A multicentre study in Iran. Mycoses. 2020; 63 (4): 382-394. doi: https:// doi. org/ 10.1 111/ myc. 13053

48. Zhang M, Jiang L, Li F, Xu Y, Lv S, Wang B. Simultaneous dermatophytosis and keratomycosis caused by Trichophyton interdigitale infection: a case report and literature review. BMC Infect Dis. 2019; 19 (1):9 83-983. doi:10.1186/s12879-019-4612-0

49. Lin S, Chen R, Zhu S, et al. Candidemia in Adults at a Tertiary Hospital in China: Clinical Characteristics, Species Distribution, Resistance, and Outcomes. Mycopathologia. 2018; 183 (4):679—689. doi:10.1007/ s11046-018-0258-5

50. Lee W-J, Hsu J-F, Lai M-Y, et al. Factors and outcomes associated with candidemia caused by non-albicans Candida spp versus Candida albicans in children. Am J Infect Control. 2018; 46 (12) :1387- 1393. doi: 10. 1016/ j. ajic. 2018. 05.015

51. Bal desi O, Bailly S, Ruckly S, et al. ICU-acquired candidaemia in France: epidemiology and temporal trends, 2004–2013–a study from the REA-RAISIN network. J Infect. 2017;75(1):59-67.

52. Sridharan S, Gopalakrishnan R, Nambi PS, Kumar S, Sethuraman N, Rama Subramanian V. Clinical Profile of Non-neutropenic Patients with Invasive Candidiasis: A Retrospective Study in a Tertiary Care Center. Indian J Crit Care Med Peer-Rev Off Publ Indian Soc Crit Care Med. 2021;25(3):267.

53. Kumar S, Sen P, Gaind R, et al. Prospective surveillance of device-associated health care–associated infection in an intensive care unit of a tertiary care hospital in New Delhi, India. Am J Infect Control. 2018;46(2):202-206.