Mediterranean Journal of Hematology and Infectious Diseases

Original Article

Increase in *Candida Parapsilosis* Candidemia in Cancer Patients

Mingyue Sun[1], Chunguang Chen[2], Weiqiang Xiao[1], Yanmin Chang[1], Cailin Liu[3] and Qingxia Xu[1].

[1] Department of Clinical Laboratory, Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital, Zhengzhou, Henan, People's Republic of China
[2] Department of Clinical Laboratory, The Sixth People's Hospital of Zhengzhou City, Zhengzhou, People's Republic of China.
[3] Department of Clinical Laboratory, The First Affiliated Hospital of Zhengzhou University, Zhengzhou, People's Republic of China.

Competing interests: The authors have declared that no competing interests exist.

Abstract. This study aimed to identify the risk factors of candidemia and asses possible clinically significant differences between *Candida parapsilosis* and other *Candida species* in a Chinese tertiary cancer center over six years. A total of 323 cancer patients were enrolled and analyzed from 2012 to 2018. Among the isolates, the species most frequently isolated was *C. parapsilosis* (37.15%, 120/323), and *C. albicans* only accounted for 34.37%. Based on statistical analysis, when candidemia patients who had *C. parapsilosis* were compared with other *Candida spp*., the following factors were found to be significantly associated with *C. parapsilosis* fungemia: parenteral nutrition ($p < 0.001$), neutropenia ($p < 0.001$), receipt of chemotherapy ($p = 0.002$), and previous antifungal use ($p < 0.001$). Parenteral nutrition was a factor that independently predicted *C. parapsilosis* candidemia (OR, 0.183; 95% CI, 0.098–0.340; $p < 0.001$).In short, *C. parapsilosis* as the leading non-albicans *Candida spp.* isolates in candidemia are posing a major threat for cancer patients. The study highlights the urgent need to evaluate the possibility of development of *C. parapsilosis* candidemia in cancer patients exposed to these risk factors effective and prevention strategies against this causative agent transmitted through nosocomial route should be implemented.

Keywords: Candidemia; malignancy; *C. parapsilosis*; *C. albicans*; non-*albicans Candida spp*.

Citation: Sun M., Chen C., Xiao W., Chang Y., Liu C., XU Q. Increase in Candida Parapsilosis Candidemia in Cancer Patients. Mediterr J Hematol Infect Dis 2019, 11(1): e2019012, DOI: http://dx.doi.org/10.4084/MJHID.2019.012

Published: January 1, 2019 **Received: July 20, 2018** **Accepted: November 26, 2018**

Correspondence to: Qingxia Xu. Department of Clinical Laboratory, Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital. Dongming Road No.127, Zhengzhou, Henan province, China. Tel +0371-65587147, Fax +0371-65587147. E-mail: qxiaxu@126.com

Introduction. Candida species are among the most important causes of nosocomial bloodstream infection (BSI).[1] Candidemia was cited as the fourth most prevalent nosocomial BSI in the United States and seventh to tenth in population-based studies with mortality of around 40%.[2-5] It is, therefore, a public health concern worldwide.[6]

Numerous surveillance programs have focused on candidemia and have documented the prevalence of different Candida species. Until recently, C. *albicans* was the predominant Candida spp. isolated from patients with nosocomial candidemia. However, in recent years, there has been an increase in the proportion of non-*albicans* Candida spp. (NAC) isolates, and in some European and Latin American centers, it has overtaken C. *albicans* as the predominant cause of nosocomial candidemia.[7-9] Considering the different worldwide distribution of Candida spp., some researchers have recommended that the epidemiology of Candida infections should be

studied at local levels rather than on a worldwide scale.[10]

There is a consensus that antifungal therapy should be initiated before candidemia ensues to avoid mortality,[8] considering that the incubation time has a statistically significant impact on in-hospital mortality,[1] and delaying empirical treatment for more than 12 h is associated with high mortality.[11] Duration of therapy is an important point.[12] What's more, NAC is associated with stronger biofilm production than C. *albicans* spp.[13-15] Thus, eradication of NAC candidemia is likely to require high doses of fluconazole or other effective agents (e.g., echinocandin or amphotericin B).[8,16] Epidemiological data that can help differentiate NAC from C. *albicans* infections may, therefore, be important in selecting the appropriate antifungal treatment.

Although studies to date have sought to identify specific risk factors for nosocomial NAC candidemia, available data mostly come from Western countries.[8] Even though several studies had reported the epidemiology of Candida infections in China, they mainly focused on adults or special groups, such as neonates.[17,18] In China, investigations on C. *parapsilosis* compared with Candida non-*parapsilosis* and C. *albicans* compared with NAC candidemia in malignancy groups are limited. We performed this retrospective study to investigate the epidemiology of candidemia among cancer patients in central China. Our findings may facilitate the application of antifungal prophylaxis to patients at greatest risk and contribute to prognosis improvement.[5]

Material and methods. This retrospective study was carried out at Henan Cancer Hospital, a 2,991-bed special hospital located in Henan, China. From 1 March 2012 to 28 February 2018, all patients with positive blood culture for Candida species were identified.

Candidemia was defined as at least one positive blood culture for Candida spp. in patients hospitalized for more than 48 h. Those without complete case files were excluded. When a case of candidemia was identified, the following data were collected in a standardized case report form: demographics, underlying medical conditions, exposure to invasive medical procedures, immunosuppressive therapy, use of antibiotics and prophylaxis antifungal agent (fluconazole), and antifungal therapeutic duration (including the prophylaxis use of antifungal agent prior to the occurrence of candidemia and treatment during candidemia), use of H2 blockers and 30-day survival, presence of central venous catheter (CVC) and subsequent removal, the CVC was considered to be removed if this procedure was performed during the first 3 days following the first blood culture positive for Candida infection.

Catheter-related bloodstream infections were defined as 1) a colony count of blood obtained through the catheter hub that was >5-fold higher than that in blood obtained from a peripheral vein or 2) a catheter tip culture that was positive for Candida spp.[19] Delayed treatment was defined when treatment was started >2 days from blood culture or when treatment was not started because the patient was dead when the diagnosis was established. All clinical data were collected within 30 days prior to the first positive blood culture, and crude mortality referred to the ratio of death within 30 days after the first positive blood culture. This study obtained permissions from the Bioethics Committee of Affiliated Cancer Hospital of Zhengzhou University & Henan Cancer Hospital and participants (consent to participate was obtained from participants) to review patient records and use the data. Types of cancer were differentially diagnosed by pathological examination. Recurrent BSI was defined as an episode of infection occurring at least one month after the initial diagnosis. Neutropenia was defined as an absolute neutrophil count of $<1.5\times10^9$/L.

Blood samples were cultured in the BACTEC-FX system (BD, USA). All positive cultures were manually sampled and inoculated on CHROMagar Candida medium (Autobio, Zhengzhou, China) to ensure viability and purity. An aliquot was Gram-stained for preliminary identification of the microorganism. All species were identified using the API 20C AuX system (Biomérieux, France). Antifungal susceptibility tests were performed using the broth microdilution assay according to the Clinical and Laboratory Standards Institute (CLSI, formerly NCCLS), M27-A2 document.[20] Statistical analysis was performed using the SPSS 22 software (SPSS Inc., Chicago, IL, USA). Univariate analysis was performed using Fisher exact test or Chi-squared test (as appropriate) for categorical variables. All tests were two-tailed, and a level of significance of $p < 0.05$ was considered statistically significant. Parameters related to *C. parapsilosis* candidemia and *C. albicans* candidemia were analyzed by multivariate logistic regression.

Results. During the study period, 323 episodes of candidemia occurred in 323 patients, 58 with hematological malignancies (17.95%), and 265 (82.04%) with solid tumors (STs). The overall incidence rate was 1.3 episodes/1000 hospital admissions. The overall incidence rate of hematological malignancies was higher than STs (1.6 episodes/1000 hospital admissions vs. 0.6 episodes/1000 hospital admissions). *C. parapsilosis* was the most frequently isolated from blood cultures (37.15%, 120/323), followed by *C. albicans* (34.37%, 111/323), *C. tropicalis* (16.10%, 52/323), and *C. glabrata* (8.98%, 29/323). Other less common species

included *C. krusei*, *C. guilliermondii*, *C. dubliniensis*, and *C. lusitaniae*.

There were 186 males and 137 females. The average age was 52.81 ± 18.38 years. The median time from admission to the first positive blood specimen was 19 days. There were 155 patients from surgical wards (47.99%), 141 patients from medical wards (43.65%), and 27 patients from the ICU (8.36%). Common underlying diseases and risk factors 30 days prior to the first positive blood culture are listed in **Table 1**. Most of the cases patients with candidemia had received antibiotic therapy (91%) and had an indwelling CVC (83.3%) at the time of infection. CVCs were removed within 72hours from the onset of candidaemia in 96 patients (29.7%). CVC-related candidaemia was more likely to occur in non-*albicans Candida spp*. isolates. Advanced age, STs, abdominal surgery, and ICU stay at diagnosis were related with C. *albicans* candidemia.

Table 1. Characteristics of 323 cancer patients with candidemia caused by Candida albicans and C. parapsilosis.

Characteristics	Univariate analysis *n* (%)/Median (range)/Mean (range)						
	Total(n=323)	C.albicans (n = 111)	NAC[a] (n= 212)	*P*	C. parapsilosis (n = 120)	Candida non-parapsilosis (n= 203)	P
Age	57(2-89)	60(11-89)	55(2-84)	<0.001	55.5(2-84)	58.0(4-89)	<0.001
Fever	38.5(36-42)	38.5(36.1-40.2)	38.5(36-42)	0.129	38.5(36-40.2)	38.5(36.1-42)	0.460
Male	186(57.6)	62(55.9)	124(58.5)	0.618	65(54.2)	121(59.6)	0.318
N° of days in hospital until candidemia	19(1-184)	20(3-184)	19(1-147)	0.543	21(2.5-90)	19(1-184)	0.163
Hematologic malignancy	58(18.0)	4(3.6)	54(25.5)	<0.001	41(34.2)	17(8.4)	<0.001
Solid tumors	265(82.0)	107(96.4)	158(74.5)		79(65.8)	186(91.6)	
In the ICU at diagnosis	27(8.4)	10(9.0)	17(8.02)	0.032	6(5.0)	21(10.3)	0.001
Mechanical ventilation	114(35.3)	40(36.0)	74(34.9)	0.864	44(36.7)	70(34.5)	0.716
Parenteral nutrition	199(61.6)	66(59.5)	133(62.7)	0.535	90(75.0)	109(53.7)	<0.001
Neutropenia	68(21.1)	8(7.2)	60(28.3)	<0.001	42(35.0)	26(12.8)	<0.001
Previous surgery (last 3 months)	186(57.6)	72(64.9)	114(53.8)	0.062	52(43.3)	134(66.0)	<0.001
Abdominal surgery	146(45.2)	63(56.8)	83(39.2)	0.003	30(46.7)	116(57.1)	<0.001
Receipt of dialysis	19(5.9)	5(4.5)	17(8.0)	0.417	7(5.8)	12(5.9)	0.969
CVC	269(83.3)	96(86.5)	173(81.6)	0.162	107(89.2)	162(79.8)	0.790
CVC-related candidaemia	143(44.3)	36(32.4)	107(50.5)	0.003	67(55.8)	76(37.4)	0.952
Receipt of corticosteroids	231(71.5)	74(66.7)	157(74.1)	0.143	91(75.8)	140(69.0)	0.202
Receipt of chemotherapy[2]	174(53.9)	45(40.5)	129(60.8)	<0.001	78(65.0)	106(52.2)	0.002
Receipt of antibiotics	294(91.0)	100(90.1)	194(91.5)	0.588	111(92.5)	183(90.1)	0.549
Antibiotic therapeutic duration (d)	5.48(0-14)	5.20(0-14)	5.64(0-14)	0.175	5.23(0-10)	5.64(0-14)	0.182
Receipt of H2 blocker	190(58.8)	59(53.2)	131(61.8)	0.122	76(63.3)	114(56.2)	0.222
Previous antifungal use	90(27.9)	16(14.4)	74(34.9)	<0.001	53(44.2)	37(18.2)	<0.001
Antifungal therapeutic duration (d)	0.73(0-6)	0.32(0-5)	0.94(0-6)	<0.001	1.08(0-5)	0.52(0-6)	<0.001
Removal of CVC (<72h)	96(29.7)	32(28.8)	64(30.2)	0.671	39(32.5)	57(28.1)	0.113
Crude mortality	47(14.6)	18(16.2)	29(13.7)	0.561	21(17.5)	26(12.8)	0.257

ICU = intensive care unit; CVC = central venous catheter; NAC = Candida *non-albicans*.

Table 2. Factors associated with Candida non-*parapsilosis* and *C. parapsilosis* candidemia.[a]

Factors	OR (95% CI)	*P* value
In the ICU at diagnosis	2.883 (1.501-5.539)	0.001
Parenteral nutrition	0.183(0.098-0.340)	<0.001
Abdominal surgery	4.066 (1.777-9.300)	0.004

[a]By backward stepwise multiple logistic regression.

Table 3. Factors associated with non- C. albicans and C. albicans candidemia.[a]

Factors	OR (95% CI)	*P* value
Type of cancer	0.164 (0.030-0.899)	0.036

[a]By backward stepwise multiple logistic regression.

When C. *parapsilosis* was compared with Candida non-*parapsilosis* candidemia (**Table 2**), the cases of C. *parapsilosis* BSI were exposed more frequently to parenteral nutrition and CVC and less frequently to surgery. As regards the underlying diseases, both neutropenia and previous antifungal use were associated with *C. parapsilosis* candidemia, whereas STs and ICU stay at diagnosis were related to non-C. *parapsilosis* candidemia. Moreover, parenteral nutrition and receipt of chemotherapy were associated with *C. parapsilosis* candidemia. However, advanced age and surgery were correlated with non-*C. parapsilosis* candidemia. In a model of multivariate independently predicting *C. parapsilosis* candidemia (OR, 0.183; 95% CI, 0.098–0.340; p < 0.001). Another factor that predicted *C. albicans* candidemia was type of cancer (OR, 0.164; 95% CI, 0.030–0.899; p = 0.036). In other words, solid malignancy is a factor independently predicting *C. albicans*, and hematologic malignancy occurs more frequently with C. *parapsilosis* candidemia (**Table 3**).

As shown in **Table 4**, the susceptibility test of antifungal drugs was performed for four mainly isolates of Candida species. Concern need be addressed on *C. albicans*, *C. tropicals* and *C. glabrata* which had higher MICs to fluconazole than *C.parapsilosis.*

The overall mortality among affected patients was 14.6%. *C. albicans* and *C. parapsilosis* were associated with a mortality rate of 16.2% and 17.5%, respectively.

There was no significance between the two groups, *C. albicans* and non-*albicans* Candida (p = 0.561) and *C. parapsilosis* and non-*C. parapsilosis* (p = 0.257). Univariate predictors of poor outcome in candidemia of cancer patients are shown in **Table 5**. The variables associated with 30-day mortality were as follows: older age, in the ICU at diagnosis and mechanical ventilation. Factors associated with 30-day survival were as follows: CVC-related candidaemia and removal of CVC (<72h). As shown in **Table 6**, factors associated with 30-day mortality by multivariate analysis among candidemia with cancer patients

Table 4. In vitro antifungal susceptibility test results of the mainly Candida species.

Candida species	Strains (n)	Antifungal agent	MIC Range (µg/ml)	MIC 50 (µg/ml)	MIC 90 (µg/ml)	No. (%) of susceptibility
C.albicans	111	Flucytosine	0.125-4	0.125	0.125	111(100%)
		Amphotericin B	0.125-1	0.125	0.125	ND
		Fluconazole	1-64	1	2	110(99.1%)
		Itraconazole	0.125-0.25	0.125	0.125	110(99.1%)
		Voriconazole	0.03-0.06	0.03	0.06	111(100%)
C.parapsilosis	120	Flucytosine	0.125-1	0.125	0.25	120(100%)
		Amphotericin B	0.5-1	0.5	0.5	ND
		Fluconazole	1-8	1	1	120(100%)
		Itraconazole	0.125-0.25	0.125	0.125	120(100%)
		Voriconazole	0.03-0.5	0.03	0.03	120(100%)
C.tropicalis	52	Flucytosine	0.125-4	0.125	0.125	52(100%)
		Amphotericin B	0.125-1	0.125	0.25	ND
		Fluconazole	0.25-32	1	8	50(96.2%)
		Itraconazole	0.125-0.25	0.125	0.125	52(100%)
		Voriconazole	0.03-0.5	0.03	0.5	52(100%)
C.glabrata	29	Flucytosine	0.125-0.5	0.125	0.125	29(100%)
		Amphotericin B	0.25-1	0.25	0.25	ND
		Fluconazole	2-64	4	8	25(86.2%)
		Itraconazole	0.125-1	0.125	0.25	21(72.4%)
		Voriconazole	0.06-0.5	0.25	0.5	29(100%)

ND Not Defined.

Table 5. Factors associated with 30-day mortality by univariate analysis in candi-demic patients with cancer patients.

Characteristics	Univariate analysis *n* (%)/Median (range)/Mean (range)		
	Survived(n = 276)	Died(n= 47)	*P*
Age	56(2-84)	58.2(4-89)	0.025
Fever	38.5(36-40.2)	38.4(36.2-42)	0.378
Male	159(57.6)	27(57.5)	0.528
N° of days in hospital until candidemia	19(2.5-184)	27.3(1-147)	0.168
Hematologic malignancy	54(19.6)	14(29.8)	0.786
Solid tumors	222(80.4)	33(70.2)	0.893
In the ICU at diagnosis	12(4.4)	15(31.9)	<0.001
Mechanical ventilation	88(31.9)	26(55.3)	0.018
Parenteral nutrition	167(60.5)	32(68.1)	0.329
Neutropenia	54(19.6)	14(29.8)	0.236
Previous surgery (last 3 months)	162(58.7)	24(51.1)	0.128
Abdominal surgery	128(46.4)	18(38.3)	0.063
Receipt of dialysis	16(5.8)	3(6.4)	0.763
CVC	240(86.9)	29(61.7)	0.388
CVC-related candidaemia	139(50.4)	4 (8.5)	<0.001
Receipt of corticosteroids	199(72.1)	32(68.1)	0.265
Receipt of chemotherapy[2]	149(54.0)	25(53.2)	0.819
Receipt of antibiotics	254(92.0)	40(85.1)	0.096
Antibiotic therapeutic duration (d)	6(0-14)	5(0-12)	0.353
Receipt of H2 blocker	156(56.5)	34(72.3)	0.080
Previous antifungal use	68(24.6)	22(46.8)	
Antifungal therapeutic duration (d)	0(0-6)	0(0-5)	0.070
Removal of CVC (<72h)	93(33.7)	3 (6.4)	<0.001
Delayed treatment	20(7.2)	2(4.3)	0.312

Table 6. Factors associated with 30-day mortality by multivariate analysis.[a]

Factors	OR (95% CI)	P value
Removal of CVC (<72h)	0.248 (0.067-0.915)	0.036
In the ICU at diagnosis	5.487 (1.139-6.441)	0.034

[a]By backward stepwise multiple logistic regression.

was in the ICU at diagnosis (OR 5.487; 95% CI 1.139-6.441), whereas candidemia due to removal of CVC (<72h) (OR 0.248; 95% CI 0.067-0.915) was associated with 30-day survival.

Discussion. The percentage of NAC isolates varies considerably from region to region.[21,22]

In our study there was an increase in cases of candidemia caused by *C.* parapsilosis, consistent with the results of studies from Spain, Italy, and Turkey.[23,24] However, to our knowledge, many studies in China indicated that candidemia is mainly caused by *C. albicans*.[5,8,17,18] In this report, we found that *C. parapsilosis* is the most common cause for the occurrence of candidemia.

C. parapsilosis is an emerging major human pathogen that has dramatically increased in significance and prevalence over the past two decades. It causes invasive candidal disease in patients at high risk of severe infection, especially ICU patients.[25] *C. parapsilosis* is frequently linked to an exogenous source, such as the hands of healthcare providers, or can be part of the normal flora of the human skin, appearing to be directly introduced into the bloodstream.[26,27] High rates of candidemia due to *C. parapsilosis* can be attributed to nosocomial transmission. In addition, infections due to *C. parapsilosis* are especially associated with parenteral nutrition and indwelling catheters.[25-28] Our findings are in agreement with previous epidemiological studies showing that *C. parapsilosis* infections are more frequent in patients with parenteral nutrition.

Girmenia et al. showed an overall decrease in isolation of *C. albicans* with a concomitant increase in isolation of *C. parapsilosis* among adult patients with cancer,[29] which is accord with this report. In other studies, *C. albicans* was more frequently associated with STs of the gastrointestinal and genitourinary tracts and breast, whereas NAC was most frequently

recovered from hematologic patients.[30] The results of our study were consistent with previous studies, wherein 12.7% of patients with *C. parapsilosis* and 16.7% non-*albicans* candidemia had a hematologic malignity. In solid cancer patients, *C. albicans* candidemia accounted for 32.8%. Moreover, in the present study, there was a significant difference in age between the patients with C. *parapsilosis* candidemia and those with other Candida spp.

The crude mortality of candidemia shows slight differences when it comes to species and not consistent in different studies. Our data show lower overall mortality in candidemia. The possible reasons are as follows: firstly, the majority of isolates were fluconazole susceptible, therefore, this antifungal drug is a reasonable alternative for the treatment of candidemia; furthermore, our study introduces an important observation of a relatively high proportion (44.3%) of CVC-related candidaemia episodes, however, the rate of removal CVC within 72h was higher than another study;[31] what's more, it is known that a delay in the treatment start has a negative impact on survival, but the incidence of delayed treatment was particularly low in the report. Finally, different study period and underlying diseases might contribute to the conflicting conclusions.

Conclusions. The emergence of *C. parapsilosis* as the leading NAC species is posing a major threat for cancer patients. Similarly, studies reported an increase in cases of candidemia due to *C. parapsilosis*. Given the incidence of disease and the unacceptably high morbidity and mortality associated with *C. parapsilosis*, the study highlights the urgent need to evaluate the possibility of development of C. *parapsilosis* candidemia in cancer patients exposed to these risk factors. Much emphasis must also be given on the early implementation of a medical intervention to reduce the incidences of candidemia in malignancy. In light of the results of this study, it can be suggested that effective prevention strategies against this causative agent transmitted through nosocomial route should be implemented. However, Candida species may vary with geographic regions, and local risk factors in cancer patients can be different. Therefore, local risk factors and epidemiological trends specific to cancer patients should be investigated.

References:

1. Morii D, Seki M, Binongo JN, et al. Distribution of Candida species isolated from blood cultures in hospitals in Osaka, Japan. Journal of Infection and Chemotherapy 2014; 20(9): 558-562. https://doi.org/10.1016/j.jiac.2014.05.009 PMid:25009091
2. Kullberg BJ, Campion EW, Arendrup MC. Invasive Candidiasis. New England Journal of Medicine 2015; 373(15): 1445-1456. https://doi.org/10.1056/NEJMra1315399 PMid:26444731
3. Magill SS, Edwards JR, Bamberg W, et al. Multistate Point-Prevalence Survey of Health Care–Associated Infections. New England Journal of Medicine 2014; 370(13): 1198-1208. https://doi.org/10.1056/NEJMoa1306801 PMid:24670166 PMCid:PMC4648343
4. Chowdhary A, Cleveland AA, Harrison LH, et al. Declining Incidence of Candidemia and the Shifting Epidemiology of Candida Resistance in Two US Metropolitan Areas, 2008–2013: Results from Population-Based Surveillance. Plos One 2015; 10(3): e0120452 https://doi.org/10.1371/journal.pone.0120452 PMid:25822249 PMCid:PMC4378850
5. Li D, Xia R, Zhang Q, et al. Evaluation of candidemia in epidemiology and risk factors among cancer patients in a cancer center of China: an 8-year case-control study. BMC Infectious Diseases 2017; 17(1). https://doi.org/10.1186/s12879-017-2636-x
6. Pfaller MA, Diekema DJ. Epidemiology of Invasive Candidiasis: a Persistent Public Health Problem. Clinical Microbiology Reviews 2007; 20(1): 133-163. https://doi.org/10.1128/CMR.00029-06 PMid:17223626 PMCid:PMC1797637
7. Pappas PG, Rex JH, Lee J, et al. A Prospective Observational Study of Candidemia: Epidemiology, Therapy, and Influences on Mortality in Hospitalized Adult and Pediatric Patients. Clinical Infectious Diseases 2003; 37(5): 634-643. https://doi.org/10.1086/376906 PMid:12942393
8. Ding X, Yan D, Sun W, et al. Epidemiology and risk factors for nosocomial Non-Candida albicans candidemia in adult patients at a tertiary care hospital in North China. Medical Mycology 2015; 53(7): 684-690. https://doi.org/10.1093/mmy/myv060 PMid:26229153
9. Montagna MT, Caggiano G, Lovero G, et al. Epidemiology of invasive fungal infections in the intensive care unit: results of a multicenter Italian survey (AURORA Project). Infection 2013; 41(3): 645-653. https://doi.org/10.1007/s15010-013-0432-0 PMid:23463186 PMCid:PMC3671106
10. Mikulska M, Bassetti M, Ratto S, et al. Invasive Candidiasis in Non-Hematological Patients. Mediterranean Journal of Hematology and Infectious Diseases 2011; 3(1): e2011007. https://doi.org/10.4084/mjhid.2011.007 PMid:21625311 PMCid:PMC3103237
11. Morrell M, Fraser VJ, Kollef MH. Delaying the Empiric Treatment of Candida Bloodstream Infection until Positive Blood Culture Results Are Obtained: a Potential Risk Factor for Hospital Mortality. Antimicrobial Agents and Chemotherapy 2005; 49(9): 3640-3645 https://doi.org/10.1128/AAC.49.9.3640-3645.2005 PMid:16127033 PMCid:PMC1195428
12. Wilson Dib, R., Hachem, R., Chaftari, A.-M., & Raad, I. (2018). Appropriate duration of intravenous treatment of candidemia and timing of step down to oral therapy in non-neutropenic patients. Mediterranean Journal of Hematology and Infectious Diseases, 10(1), e2018028. https://doi.org/10.4084/mjhid.2018.028
13. Hajjeh RA, Sofair AN, Harrison LH, et al. Incidence of Bloodstream Infections Due to Candida Species and In Vitro Susceptibilities of Isolates Collected from 1998 to 2000 in a Population-Based Active Surveillance Program. Journal of Clinical Microbiology 2004; 42(4): 1519-1527. https://doi.org/10.1128/JCM.42.4.1519-1527.2004 PMid:15070998 PMCid:PMC387610
14. Tumbarello M, Posteraro B, Trecarichi EM, et al. Biofilm Production by Candida Species and Inadequate Antifungal Therapy as Predictors of Mortality for Patients with Candidemia. Journal of Clinical Microbiology 2007; 45(6): 1843-1850. https://doi.org/10.1128/JCM.00131-07 PMid:17460052 PMCid:PMC1933062
15. Melo AS, Bizerra FC, Freymüller E, et al. Biofilm production and evaluation of antifungal susceptibility amongst clinicalCandidaspp. isolates, including strains of the Candida parapsilosis complex. Medical Mycology 2011; 49(3): 253-262. https://doi.org/10.3109/13693786.2010.530032 PMid:21039308
16. Serefhanoglu K, Timurkaynak F, Can F, et al. Risk factors for candidemia with non-albicans Candida spp. in intensive care unit patients with end-stage renal disease on chronic hemodialysis. Journal of the Formosan Medical Association 2012; 111(6): 325-332 https://doi.org/10.1016/j.jfma.2011.03.004 PMid:22748623
17. Fu J, Ding Y, Wei B, et al. Epidemiology of Candida albicans and non-C.albicans of neonatal candidemia at a tertiary care hospital in western China. BMC Infectious Diseases 2017; 17(1). https://doi.org/10.1186/s12879-017-2423-8

18. Li C, Wang H, Yin M, et al. The Differences in the Epidemiology and Predictors of Death between Candidemia Acquired in Intensive Care Units and Other Hospital Settings. Internal Medicine 2015; 54(23): 3009-3016. https://doi.org/10.2169/internalmedicine.54.3744 PMid:26631884
19. Jung DS, Farmakiotis D, Jiang Y, et al. Uncommon CandidaSpecies Fungemia among Cancer Patients, Houston, Texas, USA. Emerging Infectious Diseases 2015; 21(11) https://doi.org/10.3201/eid2111.150404
20. Bergamasco MD, Garnica M, Colombo AL, et al. Epidemiology of candidemia in patients with hematologic malignancies and solid tumours in Brazil. Mycoses 2013; 56(3): 256-263 https://doi.org/10.1111/myc.12013 PMid:23043234
21. Pfaller MA, Boyken L, Hollis RJ, et al. In Vitro Susceptibilities of Candida spp. to Caspofungin: Four Years of Global Surveillance. Journal of Clinical Microbiology 2006; 44(3): 760-763. https://doi.org/10.1128/JCM.44.3.760-763.2006 PMid:16517851 PMCid:PMC1393154
22. Pfaller MA, Boyken L, Hollis RJ, et al. Global Surveillance of In Vitro Activity of Micafungin against Candida: a Comparison with Caspofungin by CLSI-Recommended Methods. Journal of Clinical Microbiology 2006; 44(10): 3533-3538. https://doi.org/10.1128/JCM.00872-06 PMid:17021079 PMCid:PMC1594802
23. Horasan EŞ, Ersöz G, Göksu M, et al. Increase in Candida parapsilosis Fungemia in Critical Care Units: A 6-Years Study. Mycopathologia 2010; 170(4): 263-268. https://doi.org/10.1007/s11046-010-9322-5 PMid:20524154
24. Almirante B, Rodriguez D, Cuenca-Estrella M, et al. Epidemiology, Risk Factors, and Prognosis of Candida parapsilosis Bloodstream Infections: Case-Control Population-Based Surveillance Study of Patients in Barcelona, Spain, from 2002 to 2003. Journal of Clinical Microbiology 2006; 44(5): 1681-1685. https://doi.org/10.1128/JCM.44.5.1681-1685.2006 PMid:16672393 PMCid:PMC1479182
25. Trofa D, Gacser A, Nosanchuk JD. Candida parapsilosis, an Emerging Fungal Pathogen. Clinical Microbiology Reviews 2008; 21(4): 606-625. https://doi.org/10.1128/CMR.00013-08 PMid:18854483 PMCid:PMC2570155
26. Bonassoli LA, Bertoli M, Svidzinski TIE. High frequency of Candida parapsilosis on the hands of healthy hosts. Journal of Hospital Infection 2005; 59(2): 159-162. https://doi.org/10.1016/j.jhin.2004.06.033 PMid:15620452
27. Clark TA, Slavinski SA, Morgan J, et al. Epidemiologic and Molecular Characterization of an Outbreak of Candida parapsilosis Bloodstream Infections in a Community Hospital. Journal of Clinical Microbiology 2004; 42(10): 4468-4472. https://doi.org/10.1128/JCM.42.10.4468-4472.2004 PMid:15472295 PMCid:PMC522355
28. Bassetti M, Righi E, Costa A, et al. Epidemiological trends in nosocomial candidemia in intensive care. BMC Infectious Diseases 2006; 6(1). https://doi.org/10.1186/1471-2334-6-21 PMid:16472387 PMCid:PMC1379648
29. Girmenia C, Martino P, De Bernardis F, et al. Rising Incidence of Candida parapsilosis Fungemia in Patients with Hematologic Malignancies: Clinical Aspects, Predisposing Factors, and Differential Pathogenicity of the Causative Strains. Clinical Infectious Diseases 1996; 23(3): 506-514. https://doi.org/10.1093/clinids/23.3.506 PMid:8879773
30. Sabino R, Verissimo C, Brandao J, et al. Epidemiology of candidemia in oncology patients: a 6-year survey in a Portuguese central hospital. Medical Mycology 2009: 1-10. https://doi.org/10.1080/13693780903161216 PMid:19657956
31. Gamaletsou MN, Walsh TJ, Zaoutis T, et al. A prospective, cohort, multicentre study of candidaemia in hospitalized adult patients with haematological malignancies. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2014; 20(1): O50-7.