Antibiotics exposure, risk factors, and outcomes with *Candida albicans* and non-*Candida albicans* candidemia

Results from a multi-center study

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ABSTRACT

الأهداف: التعرف على فرق التعرض للمضادات الحيوية، وعوامل الخطورة ونتائج المرضى المنومين المصابين بداء المبيضات البيضاء وغير البيضاء.

الطريقة: أجريت دراسة استعادية في مراكز متعددة على 132 مريض مصاب بمبيضات الدم من 5 مستشفيات تعليمية في شاندوغ، الصين خلال الفترة من يناير 2009م ويونيو 2010م. من بين 132 مريض 36 مريض 42.4% مصاب بداء المبيضات البيضاء و76 من 132 (57.6%) مصاب بداء المبيضات غير البيضاء.

النتائج: تلقى المرضى المصابين بداء المبيضات غير البيضاء عوامل لا هوائية في الغالب (23.7% في المقابل 8.9% , p=0.027) ومثبط أنزيم بيتالاكتاماز بشكل أقل (34.2% في المقابل 51.8%، p=0.043) بشكل أكثر من المصابين بداء المبيضات البيضاء. كانت عوامل الخطر لداء المبيضات غير البيضاء هي استعمال المضادات الفطرية ولا هوائية وتغير القسطرة الوريدية المركزية. بشكل عام، معدل الوفيات خلال مدة شهر كان عالياً للمرضى المصابين بداء المبيضات البيضاء بشكل أكثر من المصابين بداء المبيضات غير البيضاء (50% في المقابل 31.6%، p=0.032). أظهر تحليل الانحدار اللوجستي المتعدد أن داء المبيضات البيضاء، وتقدم العمر، وجرثومة المعدة مصاحبة للموت نتيجة داء المبيضات البيضاء.

خاتمة: أظهرت الدراسة أن المرضى الذين تلقوا العوامل المضادة للفطريات ولاهوائية اصيبوا بداء المبيضات غير البيضاء. بينما كان التهاب داء المبيضات البيضاء مصاحب لتوقعات سير المرض البطيئة. المزيد من التوعية بهذه المخاطر مهم لمعرفة العلاج والتقليل من معدل الوفاة العالية لداء المبيضات البيضاء.

Objectives: To define the differences in antibiotics exposure, risk factors, and outcome in hospitalized patients with *Candida albicans (C. albicans)* and non-*C. albicans* candidemia.

Methods: This is a multi-center retrospective study of 132 patients with candidemia from 5 tertiary-care educational hospitals in Shandong, China conducted between January 2009 and June 2010. Fifty-six of 132 (42.4%) patients had candidemia due to *C. albicans* and 76/132 (57.6%) had non-*C. albanians* candidemia.

Results: Patients with non-*C. albicans* candidemia received anti-anaerobic agents more often (23.7% versus 8.9%; p=0.027) and ß-lactam/ß-lactamase inhibitors less often (34.2% versus 51.8%; p=0.043) than those with *C. albicans* candidemia. Independent risk factors of non-*C. albicans* candidemia were prior anti-anaerobic and antifungal therapies and central venous catheter placement. Overall, 30-day mortality was higher for patients with *C. albicans* than non-*C. albicans* candidemia (50% versus 31.6%; p=0.032). Multivariate logistic regression analysis revealed that *C. albicans* candidemia, advanced age, and concomitant bacteremia were associated with death due to candidemia.

Conclusion: Patients who received anti-anaerobic or antifungal agents were likely to develop non-*C. albicans* candidemia. *Candida albicans* infection was associated with poorer prognosis. An awareness of these factors is needed to guide therapy and decrease the high mortality of candidemia.

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Candidemia is a life-threatening infection with high morbidity and mortality.[1,2] It is the fourth most common nosocomial bloodstream infection in the United States.[3] Although *Candida albicans* (*C. albicans)* continues to be the most common cause of Candida bloodstream infections, infection with non-*C. albicans* species, which can be resistant to fluconazole, is increasing in frequency.[3-7] Species identification and data on antifungal susceptibility are usually unavailable when antifungal therapy is initiated. Hence, knowledge of risk factors associated with infection with *C. albicans* and non-*C. albicans* species could guide selection of the appropriate initial antifungal regimen pending further microbiologic results.[8] Several studies of patients in intensive care units (ICUs) have aimed to identify differences in risk factors associated with *C. albicans* and non-*C. albicans* candidemia.[9-12] However, the burden of candidemia is shifting from the ICU to general hospital wards, so research involving all hospitalized patients is necessary.[13] Moreover, consensus is lacking on the following issues: the role of exposure to antibiotics in *C.albicans* and non-*C.albicans* candidemia, and the differences in prognosis in *C.albicans* and non-*C. albicans* candidemia.[10,12,14-17] In this study, we retrospectively examined differences in antibiotics exposure, risk factors, and outcome for patients with *C. albicans* and non-*C. albicans* candidemia based on a whole-hospital population in multiple centers in Shandong, China. We aimed to provide guidance on deciding anti-Candida therapy.

Methods. This was a multi-center retrospective study of patients with candidemia admitted to hospital from January 2009 to June 2010 in 5 tri-service general hospitals in Shandong, China: Qilu Hospital of Shandong University (Jinan, Shandong, 2000 beds), Jinan Military General Hospital (Jinan, Shandong, 2000 beds), Qianfoshan Hospital affiliated with Shandong University (Jinan, Shandong, 1500 beds), Jinan Center Hospital affiliated with Shandong University (Jinan, Shandong, 1000 beds), and Liaocheng Hospital affiliated with Taishan Medical College (Liaocheng, Shandong, 2000 beds). We included patients >16 years old who had candidemia, defined as at least one blood culture positive for Candida species, with signs or symptoms of infection, and hospitalization for more than 48 hours. All episodes of candidemia were identified via the laboratory computer system. For patients with multiple candidemic episodes, only the first episode was analyzed. Patients with candidemia caused simultaneously by different Candida species were excluded from the analysis. The study was approved by the Ethics Committee of Qilu Hospital of Shandong University and carried out with the ethical standards set forth in the Helsinki Declaration of 1975.

The search for prior related literature was initiated by defining the key words, synonyms, and combination search words, which were identified as candidemia, candida, bloodstream infection, risk factors, outcome, antibiotic, and antifungal therapy. The electronic resources available on the website of Shandong University were used to access most databases, including MEDLINE, PubMed, Elsevier Science Direct, Springer, Wiley Online Library, Web of Science via Web of Knowledge. Google scholar was also used as a search tool. Trained study team members collected demographic and clinical data by chart review. Demographic data, microbiological data, underlying diseases, predisposing factors, exposure to antibiotic and antifungal therapy, laboratory data, concomitant infection, and outcomes were evaluated and recorded on standardized case report forms. Underlying diseases, including solid organ tumor, hematologic malignancy, neutropenia, diabetes mellitus and chronic renal failure were recorded. Predisposing factors that occurred within 30 days before the onset of candidemia were evaluated. These included stay in an ICU, surgery, exposure to antibiotic, antifungal or immunosuppressive therapy, total parenteral nutrition, receipt of mechanical ventilation, and central venous catheter (CVC) placement. Antibiotic agents used for ≥3 days during the 2 weeks before the onset of candidemia were recorded. The severity of the initial presentation of candidemia was assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) II score after the occurrence of candidemia. Patient mortalities at the thirtieth day after the onset of candidemia were determined. Candida species were identified by use of the VITEK-32 system (BioMerieux Vitek, St. Louis, MO, USA).

Neutropenia was defined as absolute neutrophil count $<0.5\times10^9$/l. Immunosuppressive drugs received included glucocorticoids (≥20 mg/day of prednisone or equivalent doses of other corticosteroids for more than one week), chemotherapy drugs, or other

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immunosuppressive agents. Septic shock was defined as systolic blood pressure <90 mm Hg, diastolic blood pressure <60 mm Hg, or fluid/inotrope required to maintain blood pressure above these levels. Advanced age was defined as >65 years old.

Statistical analysis. Results for categorical variables are expressed as percentages, and continuous variables as mean (SD). Chi-square or Fisher's exact test (2-tailed) was used for categorical variables and unpaired Student's t test for continuous variables. Multivariate, backwards, stepwise, and logistic regression analyses was used to identify independent variables associated with non-*C. albicans* candidemia and risk factors associated with mortality; the results are presented as odds ratios (ORs) with 95% confidence intervals (95% CIs) and *p*-values. All statistical analyses involved use of the Statistical Package for Social Sciences Version 15.0 for Windows (SPSS Inc., Chicago, IL, USA). *P*<0.05 was considered statistically significant.

Results. During the study period, 137 cases of candidemia were detected. Five episodes of polyfungal candidemia were excluded, and the remaining 132 episodes in 132 patients (98 men) were examined. The mean age was 54.40 ± 23.82 years. Most patients were from the ICU (44/132; 33.3%), 41/132 (31.1%) from medical wards and 30/132 (22.7%) from surgical wards. A total of 56/132 (42.4%) patients had *C. albicans* and 76/132 (57.6%) had non-*C. albicans* candidemia. The non-*C. albicans* species included *Candida tropicalis (C. tropicalis)* (30/132; 22.7%), *Candida parapsilosis (C. parapsilosis)* (23/132; 17.4%), *Candida glabrata (C. glabrata)* (14/132; 10.6%), *Candida krusei (C. krusei)* (6/132; 4.5%), and *Candida famata (C. famata), Candida guilliermondii* (*C. guilliermondii)* and *Candida rugosa (C. rugosa)* (1/132 each; 2.3%). The characteristics of patients with *C. albicans* and non-*C. albicans* candidemia are in **Table 1**. As compared with *C. albicans*-infected patients, those with non-*C. albicans* infection received mechanical ventilation less often but more often underwent surgery, received prior antifungal therapy and fluconazole therapy, and had CVC placement.

Patients with non-*C. albicans* candidemia received anti-anaerobic agents more often and ß-lactam/ß-lactamase inhibitors less often than those with *C. albicans* candidemia (**Table 2**). The 2 groups did not differ in prior receipt of cephalosporins, aminoglycosides, quinolones, carbapenems, or glycopeptides. Nearly all patients in both groups received antibiotics before the onset of candidemia (100% versus 98.7%, *p*=0.389); approximately 80% of both groups received more than one antibiotic (43/56 [76.8%] with *C. albicans* and 61/76 [80.3%] with non-*C. albicans* candidemia; *p*=0.629) (**Table 2**). On multivariate analysis, factors associated with non-*C. albicans* candidemia were receipt of anti-anaerobic agents (OR 1.276; 95% CI: 1.132-

Table 1 - Demographics and clinical characteristics of patients with *Candida albicans (C. albicans)* and non-*Candida albicans* candidemia (N=132).

Variables	*C. albicans* (n = 56)	Non-*C. albicans* (n = 76)	*P*-value
Age (years), mean±SD*	58.01±22.18	51.74±25.21	0.151
Gender (Males) (%)	43 (76.8)	55 (72.4)	0.566
Hospital location of patients (%)			
ICU	18 (32.1)	26 (34.2)	0.803
Medical ward	17 (30.4)	24 (31.6)	0.881
Surgical ward	10 (17.9)	20 (26.3)	0.252
Other	11 (19.6)	6 (7.9)	0.046
Underlying diseases (%)			
Solid tumor	6 (10.7)	12 (15.8)	0.401
Hematological malignancy	7 (12.5)	9 (11.8)	0.909
Neutropenia	9 (16.1)	12 (15.8)	0.965
Diabetes mellitus	13 (23.2)	19 (25.0)	0.813
Chronic renal failure	10 (17.9)	21 (27.6)	0.190
Predisposing factors (%)			
ICU stay ≥7 days	11 (19.6)	12 (15.8)	0.564
Surgery	12 (21.4)	29 (38.2)	0.040
Total parenteral nutrition	12 (21.4)	22 (28.9)	0.329
Mechanical ventilation	25 (44.6)	20 (26.3)	0.028
CVC placement	23 (41.1)	48 (63.2)	0.012
Prior immunosuppressive drugs	14 (25.0)	30 (39.5)	0.081
Prior antifungal exposure	12 (21.4)	31 (40.8)	0.019
Prior fluconazole therapy	8 (14.3)	22 (28.9)	0.047

ICU - intensive care unit, CVC - central venous catheter
*Two-independent samples t-test, Unspecified: chi-square test

Table 2 - Previous antibiotics therapy for patients with *Candida albicans (C. albicans)* and non-*Candida albicans* candidemia.

Variables	*C. albicans* (n = 56)	Non-*C. albicans* (n = 76)	*P*-value
Prior antibiotics exposure (%)*	56 (100.0)	75 (98.7)	0.389
Cephalosporins	28 (50.0)	27 (35.5)	0.096
Beta-lactam/beta-lactamase inhibitors	29 (51.8)	26 (34.2)	0.043
Aminoglycosides	9 (16.1)	18 (23.7)	0.284
Quinolones	8 (14.3)	12 (15.8)	0.812
Carbapenems	38 (67.9)	49 (64.5)	0.685
Glycopeptides	14 (25.0)	25 (32.9)	0.326
Anti-anaerobic agents	5 (8.9)	18 (23.7)	0.027
No. of prior antibiotics (%)			
1	13 (23.2)	15 (19.7)	0.629
2	17 (30.4)	34 (44.7)	0.094
≥3	26 (46.4)	27 (35.5)	0.207

Anti-anaerobic agents included metronidazole and tinidazole,
*Fisher's exact test, Unspecified: chi-square test

9.708; *p*=0.034) and antifungal agents (OR1.902; 95% CI: 1.250-4.685; *p*=0.026) and CVC placement (OR 3.437; 95% CI: 1.269-17.323; *p*=0.011).

The APACHE II score, incidence of concomitant bacteremia, and septic shock were higher, but not significantly, for patients with *C. albicans* than non-*C. albicans* candidemia, but overall 30-day mortality was significantly greater (**Table 3**). On univariate analysis, factors associated with death due to candidemia were older age (>65 years), *C. albicans* candidemia, solid tumors, and concomitant bacteremia; fewer patients who died than did not die had received prior fluconazole therapy (**Table 4**). On multivariate analysis, factors associated with mortality were advanced age (OR 1.794; 95% CI: 1.113-2.890; *p*=0.016), *C. albicans* candidemia (OR 2.491; 95% CI: 1.001-20.809; *p*=0.048), and concomitant bacteremia (OR 5.984; 95% CI: 1.739-48.456; *p*=0.025).

Table 3 - Outcome of patients with *Candida albicans (C. albicans)* and non-*Candida albicans*.

Variables	*C. albicans* (n = 56)	Non-*C. albicans* (n = 76)	*P*-value
Length of hospital stay, mean±SD*	37.28±17.14	43.42±18.67	0.055
APACHE II score, mean±SD*	17.28±8.97	15.88±9.84	0.403
Concomitant bacteremia (%)	12 (21.4)	11 (14.5)	0.298
Septic shock (%)	21 (37.5)	20 (26.3)	0.170
Overall 30-day mortality (%)	28 (50.0)	24 (31.6)	0.032

APACHE, Acute Physiology and Chronic Health Evaluation, *Two-independent samples t-test, Unspecified: chi-square test

Table 4 - Univariate analysis of factors associated with death for patients with candidemia.

Variables	Died (n=52)	Survived (n=80)	*P*-value
*Age (years), mean±SD**	61.03±21.77	50.09±24.01	0.009
Advanced age (>65 years) (%)	29 (55.8)	26 (32.5)	0.008
Gender (male) (%)	38 (73.1)	60 (75.0)	0.805
Underlying diseases (%)			
Solid tumor	11 (21.2)	7 (8.8)	0.042
Hematological malignancy	3 (5.8)	13 (16.3)	0.071
Neutropenia	5 (9.6)	16 (20.0)	0.111
Diabetes mellitus	13 (25.0)	19 (23.8)	0.870
Chronic renal failure	14 (26.9)	17 (21.3)	0.452
Predisposing factors (%)			
ICU stay ≥7 days	13 (25.0)	10 (12.5)	0.064
Surgery	16 (30.8)	25 (31.3)	0.953
Prior antifungal exposure	12 (23.1)	31 (38.8)	0.060
Prior fluconazole therapy	7 (13.5)	23 (28.8)	0.041
Receipt of mechanical ventilation	18 (34.6)	27 (33.8)	0.918
CVC placement	25 (48.1)	46 (57.5)	0.289
Prior antibiotics†	52 (100.0)	79 (98.8)	0.418
Candida albicans candidemia (%)	28 (53.8)	28 (35.0)	0.032
APACHE II score, mean±SD*	17.85±10.63	15.58±9.00	0.203
Concomitant bacteremia (%)	15 (28.8)	8 (10.0)	0.005
Septic shock (%)	20 (38.5)	21 (26.3)	0.138

ICU - intensive care unit, APACHE - Acute Physiology and Chronic Health Evaluation, CVC - central venous catheter, *Two-independent samples t-test, †Fisher's exact test, Unspecified: chi-square test

Discussion. The species distribution of candidemia differs considerably in various parts of the world. In this study, *C. albicans* accounted for 42.4% of all candidemia cases, which is close reports from Japan (40.7%) and Singapore (37%).[18,19] The most common non-*C. albicans* species we found was *C. tropicalis* (22.7%), followed by *C. parapsilosis* (17.4%), *C. glabrata* (10.6%), and *C. krusei* (4.5%). Similarly, studies in other Asian regions, including India, and Korea also found high proportions of *C. tropicalis,* and *C. parapsilosis* and low proportions of *C. krusei*.[20,21]

Early institution of antifungal therapy appears important for favorable clinical outcomes.[22,23] The clinical characteristics associated with non-*C. albicans* pathogens may support appropriate empiric antifungal therapy before the species' identification and results of antifungal susceptibility testing. A retrospective analysis of candidemia in a US cohort reported no differences in clinical characteristics with *C. albicans* or non-*C. albicans* infection.[24] Nonetheless, we found several differences between patients with non-*C. albicans* and *C. albicans* candidemia: the former patients more often had had surgery, multiple blood product transfusion, CVC placement, and prior antifungal exposure and less often mechanical ventilation than the latter patients. Several publications also reported differences in clinical features between patients with non-*C. albicans* and *C. albicans* candidemia and identified risk factors. In a prospective study performed in the ICU of a hospital in Athens,[9] independent risk factors associated with non-*C. albicans* candidemia were administration of glucocorticoids, CVC placement, and candiduria. In a 6-year retrospective research in the US,[25] non-*C. albicans* candidemia was associated with lack of antibiotic use at the onset of candidemia, recent history of solid tumors, and male gender.[25] The inter-study variations in risk factors might result from the heterogeneity of pathogens and study populations.

Prior antifungal exposure was significantly associated with non-*C. albicans* candidemia in a prospective nationwide study in Australia.[10] The same finding in our study agrees with previous reports that widespread fluconazole use results in infection with yeast species that are less susceptible to this antifungal agent, such as *C. tropicalis, C. glabrata,* and *C. krusei*.[10,12]

However, the isolation of *C. parapsilosis*, a species that is almost always susceptible to fluconazole, is not explained by the increase in antifungal agent use; this finding may be associated with the widespread use of intravascular devices and parenteral feeding.[26,27] In our study, *C. parapsilosis* accounted for 30% (23/76) of non-*C. albicans* infections, and CVC placement was a risk factor for non-*C. albicans* candidemia.

Although recent exposure to azole antifungal agents was identified as an important risk factor of infection with certain *Candida spp*., little is known on the role of antibacterial drug exposure.[10,28] Davis et al[25] found reduced development of non-*C. albicans* candidemia in patients who received antibiotics at candidemia onset. However, we did not find this relationship, because nearly all patients with candidemia due to *C. albicans* (100%) and non-*C. albicans* (98.7%) received antibiotic therapy before candidemia onset. An estimated 30% of antibiotics prescribed for hospitalized patients are unnecessary, with anaerobically active drugs representing one third of the redundant antibiotic use.[29] Metronidazole use was found associated with fluconazole-susceptible *C. glabrata* candidemia, and linezolid exposure was a risk factor for fluconazole-resistant *C. glabrata* infection.[14] The underlying mechanisms of exposure to certain antibiotics promoting infection with certain Candida strains remain unclear. Marked effects of antibiotics treatment on the composition of the gastrointestinal microbiome have been demonstrated.[30] By altering the resident gut flora, antibiotics may selectively impair colonization resistance to favor gastrointestinal colonization with certain Candida species, which may translocate to normally sterile body sites and lead to invasive Candida infection.[31]

Several studies sought to identify differences in outcome between *C. albicans* and non-*C. albicans* candidemia and yielded different results.[10,12,16,17] In the US, Chow et al[12] reported no difference in in-hospital mortality between the 2 groups (57% versus 58%). However, in prospective studies in Australia, mortality was higher in patients with non-*C. albicans* than *C. albicans* infection (53% versus 41%).[10] In contrast, a study from Taiwan[16] reported a higher crude mortality, although not statistically significant, with *C. albicans* than non-*C. albicans* candidemia (44.3% versus 29.8%). We found a greater association of *C. albicans* candidemia than non-*C. albicans* candidemia with mortality (50% versus 31.6%, $p<0.05$), and the former was an independent risk factor of mortality among candidemic patients. Although *C. albicans* is known to be more virulent than non-*C. albicans*, candidemia are not only related to the virulence of the Candida species but also to the underlying diseases, comorbidities, and a damage in host-defense mechanisms.[32] Patients with severe disease are at increased risk of Candida infection and have a poorer prognosis. In this study, critical illness was more associated, but not significantly, with *C. albicans* than non-*C. albicans* infection as reflected by a higher APACHE II score, higher incidence of septic shock, and concomitant bacteremia. Advanced age and concomitant bacteremia were significantly associated with mortality, which highlights the need for awareness of candidemia and prompt initiation of antifungal therapy in these groups.

A major strength of this study is that our data represented 5 centers and included patients from different hospital settings. However, our observations are subject to the limitations of a retrospective cohort design. In addition, we considered only the presence or absence of risk factor exposure, not the duration of exposure. Because the study was not designed to quantify the length of exposure, this variable was not available for analysis and its associated bias could not be assessed.

In conclusion, we found a significant difference in antibiotics exposure, risk factors, and outcome between patients with *C. albicans* and non-*C. albicans* candidemia. Receipt of anti-anaerobic or antifungal agents was associated with non-*C. albicans* candidemia. As a risk factor of mortality, *C. albicans* candidemia was associated with poorer prognosis. Increased awareness of these specific characteristics can guide antifungal therapy and reduce the high mortality of candidemia.

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