Journal of Microbiology, Immunology and Infection (2015) 48, 552—558

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

# Antimicrobial susceptibility and clinical outcomes of *Candida parapsilosis* bloodstream infections in a tertiary teaching hospital in Northern Taiwan

Chih-Chen Lin [a], Chang-Pan Liu [a,b,c,d,**], Feng-Chih Hsieh [d], Chun-Ming Lee [a,b,c], Wei-Sheng Wang [a,b,c,*]

[a] *Division of Infectious Diseases, Department of Internal Medicine, Mackay Memorial Hospital, Taipei, Taiwan*
[b] *Department of Medicine, Mackay Medical College, Taipei, Taiwan*
[c] *Mackay Junior College of Medicine, Nursing, and Management, Taipei, Taiwan*
[d] *Microbiology Section, Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan*

Received 3 June 2014; received in revised form 3 July 2014; accepted 3 July 2014
Available online 12 October 2014

**KEYWORDS**
*Candida parapsilosis* bloodstream infection;
candidemia

*Background: Candida parapsilosis* is an emerging non-*albicans Candida* that is associated with central line-associated infection. *C. parapsilosis* has higher minimal inhibitory concentration to echinocandin than *Candida albicans*, and the effects of echinocandin on *C. parapsilosis* are ambiguous. Therefore, in this study, we aimed to investigate the susceptibility and the correlation between incidence and drug consumption.
*Methods:* This retrospective study was conducted in a tertiary teaching hospital in northern Taiwan between 2008 and 2012. The *Candida* species distribution, the correlation between the use of antifungal agents and the incidence of *C. parapsilosis* bloodstream infection, demographic information, clinical characteristics, mortality rate, and *in vitro* susceptibility of *C. parapsilosis* were analyzed.
*Results:* A total of 77 episodes from 77 patients were included for analysis. The overall 90-day mortality rate was 41.6%. The incidence of *C. parapsilosis* bloodstream infection showed a moderate positive correlation with the increased defined daily dose of echinocandin. The risk factors associated with mortality included malignancy or a metastatic tumor. Multivariate logistical regression analysis showed that patients with malignancy had higher odds ratios in

* Corresponding author. Division of Infectious Diseases, Department of Internal Medicine, Mackay Memorial Hospital, Number 92, Section 2, Zhongshan North Road, Taipei, Taiwan.
** Corresponding author. Microbiology Section, Department of Medical Research, Mackay Memorial Hospital, Taipei, Taiwan.
*E-mail addresses:* cpliu@mmh.org.tw (C.-P. Liu), mediator8332@gmail.com, fireman8800@gmail.com (W.-S. Wang).

http://dx.doi.org/10.1016/j.jmii.2014.07.007

terms of mortality. The rate of *C. parapsilosis* resistance to fluconazole was 3%, whereas the susceptibility rate was 95.5%.
*Conclusion:* Underlying comorbidity and malignancy were factors leading to death in patients with *C. parapsilosis* bloodstream infection. Catheter removal did not influence the mortality rate. The survival rate of patients receiving echinocandin was lower than the group receiving fluconazole. Fluconazole remains the drug of choice to treat *C. parapsilosis* bloodstream infections.


## Introduction

*Candida parapsilosis* was the third most isolated pathogen among *Candida* species in both North America and Taiwan.[1,2] According to an epidemiological study in North America, *C. parapsilosis* accounted for 15.9% of all isolated organisms from 3648 patients.[2] It is higher in some hospital services, such as neonatal intensive care units, where it accounts for 30.6% of all isolated *Candida* species from neonatal intensive care unit patients in North America.[2] In the epidemiological study in Taiwan, *C. parapsilosis* remains the third most frequent *Candida* species. *Candida albicans* accounts for 50% of candidemia, whereas *C. parapsilosis* accounts for about 10% of the candidemia.[1] In addition, *C. parapsilosis* accounts for 47.8% of neonatal candidemia, based on a study that enrolled 46 neonates in Taiwan from 1994 to 1997.[3] According to a review article published in 2008, the mortality rate of *C. parapsilosis* bloodstream infections was 28.5%.[4]

*C. parapsilosis* is a normal human commensal, which is often isolated from hand skin. It presents an oval, round, or cylindrical shape while appearing creamy, white, shiny, and smooth or wrinkled on Sabouraud dextrose agar.[5] Intact human skin limits the pathogenicity of *C. parapsilosis*. It is notorious for its affinity for catheter or prosthetic materials, capacity for forming biofilm and ability to grow in hyperalimentation solution.[6] A study in Spain revealed that the risk factors of *C. parapsilosis* infection include vascular catheterization, previous antibiotics history, previous immunosuppressive therapy, malignancy, transplant receipt, neutropenia, and previous colonization.[7] Several articles described the outbreak of *C. parapsilosis* infections either in neonate or adult intensive care units. Molecular typing methods revealed a link between hand carriage of *C. parapsilosis* from health care workers and the pathogen of the patients. Hand hygiene thus plays an important role in the prevention of the outbreak of *C. parapsilosis* infections.[4,6,8,9] With regard to the increasing incidence of *C. parapsilosis*, its correlation with a high mortality rate and association with hand hygiene, it is important to conduct further research regarding *C. parapsilosis*.

## Materials and methods

### Study population

A retrospective study was conducted at a 2200-bed tertiary teaching hospital with burn care and solid organ transplantation facilities, but without bone marrow transplantation facilities in northern Taiwan. We enrolled the patients whose blood culture yielded *C. parapsilosis* during hospitalization from June 2008 to June 2012. The medical records of patients were reviewed, and data such as demographic characteristics, medical history, invasive procedures, medications, laboratory data, and outcomes were collected for analysis. We also have reviewed medical literature for comparison of *C. parapsilosis in vitro* antimicrobial susceptibility.

### Inclusion criteria

*C. parapsilosis* bloodstream infection was defined as the presence of a positive blood culture of *C. parapsilosis* with concomitant signs and symptoms of infection.[10] *C. parapsilosis* bloodstream infection was considered to be health care-associated infections if it occurred more than 48 hours after admission.[11] If multiple episodes of *C. parapsilosis* bloodstream infection occurred in the same patient during the study period, the patient was included as a study participant using only the first episode of candidemia.[12] In the study period, a total of 77 patients whose blood culture yielding *C. parapsilosis* met the inclusion criteria.

### Definition of terms

Death was considered to be attributable to *C. parapsilosis* bloodstream infection if any of the following was noted during the same hospital stay: death within 7 days after a positive blood culture for *C. parapsilosis*; absence of any cause of fatality; death in the presence of clinical evidence of persistent candidiasis (e.g., persistent fever, hypotension, or positive cultures for *C. parapsilosis* at clinically involved sites, such as peritoneal fluid, renal abscess, or endophthalmitis); autopsy evidence of disseminated candidiasis; or cause of death as *C. parapsilosis* bloodstream infection on the death certificate.[13,14]

The patient was considered a survivor of *C. parapsilosis* bloodstream infection if either of the following was noted regarding the same hospital stay: survival at discharge or improvement of *C. parapsilosis* bloodstream infection associated symptoms without recurrence within 30 days.

The incidence of candidemia was defined as the number of cases of candidemia per 1000 inpatient-days.[15] Defined daily dose is a statistical measure of drug consumption, defined by the World Health Organization. It is used to standardize the comparison of drug usage between

different drugs or between different health care environments.

### Species identification and antifungal susceptibility testing

Blood samples were tested daily for microbial growth using the BACTEC FX system (Becton Dickinson Diagnostic Instrument Systems, Sparks, MD, USA). Organisms were initially identified by germ tube analysis and colony morphology on Sabouraud dextrose agar. If necessary, they were determined using a VITEK 2 yeast identification card (bioMérieux SA, Marcy-l'Etoile, France). In this study, susceptibility testing of isolates was performed using eight antifungal agents (voriconazole, posaconazole, itraconazole, fluconazole, caspofungin, micafungin, anidulafungin, and amphotericin B) with a Sensititre YeastOne Colorimetric Antifungal Panel used according to the manufacturer's instructions. Susceptibilities of *C. parapsilosis* to the above antifungal agents were read according to the interpretative breakpoints approved by the European Committee on Antimicrobial Susceptibility Testing and the Clinical Laboratory Standards Institute for susceptibility testing of *Candida* species.[16]

### Statistical analysis

Univariate analyses were used to identify the risk factors associated with candidemia-related death. A Pearson's Chi square test or Fisher's exact two-tailed test was used to examine nominal data, and the unpaired Student *t* test was used for continuous data. A $p$ value of $<0.05$ was considered statistically significant. The independent predictors of candidemia-associated mortality were identified by stepwise logistic regression of multivariate analysis for the significant risk factors on the univariate analyses. SPSS for Windows version 21.0 (SPSS Inc., Chicago, IL, USA) software was used for statistical analysis. Linear regression analysis was used to analyze the trend in annual consumption of antifungal agents and the incidence of patients with candidemia over time. Pearson's product moment correlation coefficient was used to determine the relationship between annual consumption of antifungal agents and the trend in candidemia incidence. A $p$ value of $<0.05$ was considered statistically significant.

## Results

In Table 1, the incidence levels of candidemia in our hospital from 2008 to 2012 are listed. The overall incidence of candidemia showed a significant increase ($p < 0.05$). The incidence of individual *Candida* species did not significantly increase by year. However, the incidence of *C. parapsilosis* showed a mild decrease although it did not reach statistical significance.

A total of 77 episodes were identified retrospectively in 77 patients with *C. parapsilosis* candidemia. The univariate analysis of risk factors of *C. parapsilosis* candidemia-associated mortality in 77 patients is summarized in Table 2. About 58% (45/77) were male, and the mean age was 50.5 $\pm$ 30.9 years. About 25% (19/77) of the patients

**Table 1** The incidence and *Candida* species distribution of candidemia from 2008 to 2012

| Annual inpatient days | | 2008<br>565,839 | 2009<br>595,288 | 2010<br>589,075 | 2011<br>605,233 | 2012<br>578,422 | *p* |
|---|---|---|---|---|---|---|---|
| Species identification | | Number of isolates (%) | | | | | |
| *Candida albicans* | | 66 (55.9) | 58 (47.5) | 71 (51.1) | 77 (47.5) | 79 (45.1) | 0.434 |
| | Incidence | 0.12 | 0.10 | 0.12 | 0.13 | 0.14 | |
| *Candida glabrata* | | 19 (16.1) | 12 (9.8) | 20 (14.4) | 30 (18.5) | 28 (16.0) | 0.363 |
| | Incidence | 0.03 | 0.02 | 0.03 | 0.05 | 0.05 | |
| *Candida parapsilosis* | | 13 (11.0) | 14 (11.4) | 10 (7.2) | 22 (13.6) | 18 (10.3) | 0.509 |
| | Incidence | 0.02 | 0.02 | 0.01 | 0.04 | 0.03 | |
| *Candida tropicalis* | | 14 (11.8) | 23 (18.9) | 27 (19.4) | 19 (11.7) | 28 (16.0) | 0.226 |
| | Incidence | 0.02 | 0.04 | 0.05 | 0.03 | 0.05 | |
| *Candida krusei* | | 0 | 3 (2.5) | 1 (0.7) | 0 | 3 (1.7) | 0.136 |
| | Incidence | 0 | 0.01 | 0.00 | 0 | 0.01 | |
| *Candida dubliniensis* | | 1 (0.8) | 0 | 1 (0.7) | 0 | 1 (0.5) | 0.775 |
| *Candida famata* | | 0 | 0 | 0 | 2 (1.2) | 0 | 0.144 |
| *Candida guilliermondii* | | 1 (0.8) | 0 | 1 (0.7) | 5 (3.1) | 3 (1.7) | 0.261 |
| *Candida haemulonii* | | 0 | 0 | 0 (0) | 2 (1.2) | 0 | 0.144 |
| *Candida lusitaniae* | | 1 (0.8) | 0 | 1 (0.7) | 1 (0.6) | 0 | 0.683 |
| *Candida pelliculosa* | | 0 | 0 | 1 (0.7) | 1 (0.6) | 0 | 0.794 |
| *Candida rugosa* | | 0 | 1 (0.8) | 0 | 0 | 1 (0.5) | 0.706 |
| *Candida utilis* | | 0 | 1 (0.8) | 0 | 0 | 0 | 0.335 |
| *Candida lipolytica* | | 0 | 0 | 1(0.7) | 0 | 0 | 0.529 |
| *Candida norvegensis* | | 0 | 0 | 0 | 0 | 1 (0.5) | $p > 0.999$ |
| *Candida* species | | 3 (2.5) | 10 (8.2) | 5 (3.6) | 3 (1.9) | 13 (7.4) | 0.031 |
| Total | | 118 | 122 | 139 | 162 | 175 | 0.002 |

**Table 2** Univariate analysis of risk factors of *Candida parapsilosis* candidemia-associated mortality

| Variable (%) | Survival ($n$ = 45) | Death ($n$ = 32) | $p$ |
|---|---|---|---|
| Sex, male | 25 (55.6) | 20 (62.5) | 0.542 |
| Age < 8 y | 16 (35.6) | 3 (9.4) | 0.009 |
| Onset of candidemia in ICU | 16 (35.6) | 3 (9.4) | 0.009 |
| *Underlying disease* | | | |
| Recent intra-abdominal surgery | 13 (28.9) | 9 (28.1) | 0.942 |
| Recent chemotherapy | 8 (17.8) | 12 (37.5) | 0.052 |
| Chronic steroid therapy | 3 (6.7) | 3 (9.4) | 0.688 |
| Diabetes mellitus | 8 (17.8) | 12 (37.5) | 0.913 |
| End-stage renal disease | 3 (6.7) | 1 (3.1) | 0.637 |
| COPD | 1 (2.2) | 4 (12.5) | 0.154 |
| Chronic liver disease | 7 (15.6) | 7 (21.9) | 0.479 |
| Any maligency | 17 (37.8) | 26 (81.3) | <0.001 |
| Leukemia | 1 (2.2) | 2 (6.3) | 0.567 |
| Gastrointestinal malignancy | 8 (17.8) | 10 (31.3) | 0.169 |
| Metastatic solid tumor | 5 (11.1) | 11 (34.4) | 0.013 |
| Neutropenia | 6 (13.3) | 5 (15.6) | >0.999 |
| *Catheter* | | | |
| Hickmann catheter | 4 (8.9) | 1 (3.1) | 0.395 |
| Port-A | 12 (26.7) | 14 (50) | 0.118 |
| CVC | 28 (62.2) | 16 (50) | 0.285 |
| Femoral CVC | 12 (26.7) | 6 (18.8) | 0.419 |
| Catheter all | 44 (91.1) | 31 (93.8) | >0.999 |
| Remove CVC | 26 (33.8) | 26 (33.8) | 0.410 |
| TPN | 4 (8.9) | 2 (6.3) | >0.999 |
| PPN | 13 (28.9) | 15 (46.9) | 0.106 |
| TPN + PPN | 17 (37.8) | 17 (53.1) | 0.181 |
| Fluconazole | 26 (59.1) | 18 (40.9) | 0.894 |
| Echinocandin | 6 (46.2) | 7 (53.8) | 0.324 |
| Amphotericin B | 9 (81.8) | 2 (18.2) | 0.089 |
| Voriconazole | 3 (50) | 3 (50) | 0.894 |

COPD = chronic obstructive pulmonary disease; CVC = central venous catheter; ICU = intensive care unit; PPN = partial parenteral nutrition; TPN = total parenteral nutrition.

were younger than 18 years. The overall mortality attributable to *C. parapsilosis* candidemia was about 42% (32/77). Risk factors of mortality in the univariate analysis included patients with malignancy ($p < 0.001$) or a metastatic tumor ($p = 0.013$). By contrast, patients younger than 18 years and or whose candidemia was discovered in the intensive care unit showed a better survival rate ($p = 0.009$). A multivariate logistic regression analysis, the results of which are listed in Table 3, showed that patients with malignancy had a higher odds ratio in terms of mortality ($p = 0.045$).

A total of 75 patients (75/77) had a central line-associated route when they acquired a *C. parapsilosis* bloodstream infection. Five patients had a Hickman catheter, 26 patients had a port-A, and 44 patients had a central venous catheter (CVC), which included 18 patients with femoral CVC. However, the kind of catheter used did not contribute to mortality (Table 2).

The minimal inhibitory concentration (MIC) of 67 *C. parapsilosis* in our study, which were identified by YeastOne commercial disk, is summarized in Table 4. The $MIC_{50}/MIC_{90}$ of fluconazole was 1/2 (range 0.25–8), amphotericin B was 1/1 (range 0.25–1), anidulafungin was 1/2 (range 0.12–2), micafungin was 1/2 (range 0.25–4), caspofungin was 0.5/1 (range 0.25–1), voriconazole was 0.008/0.15 (range 0.008–0.15), posaconazole was 0.03/0.06 (range 0.015–0.12), and itraconazole was 0.06/0.12 (range 0.015–0.25). The *C. parapsilosis* susceptibility rate to fluconazole was 95.5%, whereas the resistance rate was 3%. We included papers mentioning the fluconazole resistance rate of *C. parapsilosis* and those giving full coverage of antifungal agents. The result is also listed in Table 4.

The correlation between the annual consumption of antifungal agents and the incidence of *C. parapsilosis* bloodstream infection was calculated using Pearson's product moment correlation coefficient (results shown in Table 5). The incidence of *C. parapsilosis* bloodstream infection increased, whereas the annual consumption of echinocandin increased during the study period. *C. parapsilosis* bloodstream infection showed a moderate positive correlation with the use of echinocandin, but this correlation was not statistically significant (Pearson correlation = 0.614, $p = 0.271$).

## Discussion

The incidence of all candidemia cases in the hospital was 0.25 per 1000 patient-days, which shows a significant increase from 2008 to 2012; the incidence also increased significantly from 0.10 to 0.15 per 1000 patient-days from 1999 to 2006 in Taiwan.[1] In the meantime, the incidence of candidemia ranged from 0.45 to 0.46 per 1000 admission-days in America and ranged from 0.2 to 0.38 in Europe.[17] Ruan and Hsueh[17] mentioned that the incidence of candidemia from 1980 to the end of 1990s increased. This was followed by a relatively stable period in Taiwan, but it continued to increase significantly in the 2000s.[17]

The distribution of *Candida* species shows regional differences.[18] In this study, C. *albicans* (49.0%) was the most frequently isolated species, followed by *C. tropicalis* (15.5%), *C. glabrata* (15.2%), and *C. parapsilosis* (10.8%). The rate of isolated *C. parapsilosis* was 13.3%, which is close to the average rate in the Asia-Pacific area (13.7%), but lower than the global average (17.2%) from 2008 to 2009.[19] Three studies during 1994 to 2000 from northern Taiwan reported the rate of isolated *C. parapsilosis* to be around 11.2–17.5%.[20–22] Pfaller et al[23,24] reported global data showing that the rate of isolated *C. parapsilosis* from 1992 to 2001 was 13.1% and 15%. The distribution in the

**Table 3** Multivariate logistic regression analysis of risk factors associated with mortality in episodes of candidemia

| | Odds ratio | 95% CI | $p$ |
|---|---|---|---|
| Age < 18 y | 0.39 | 0.09–1.79 | 0.227 |
| Onset of candidemia in ICU | 0.77 | 0.13–4.39 | 0.767 |
| Any malignancy | 4.08 | 1.03–16.14 | 0.045 |
| Metastatic solid tumor | 1.72 | 0.46–6.45 | 0.419 |

CI = confidence interval; ICU = intensive care unit.

**Table 4** *In vitro* activities of antifungal agents against *Candida parapsilosis*

| Author | Time | Location | $MIC_{50}/MIC_{90}$ | | | | | | | Fluconazole |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Fluconazole | Caspofungin | Micafungin | Anidulafungin | Amphotericin B | Voriconazole | Posaconazole | Itraconazole | Susceptible/resistant% |
| Lin | 2008—2012 | Taiwan | 1/2 | 0.5/1 | 1/2 | 1/2 | 1/1 | 0.008/0.15 | 0.03/0.06 | 0.06/0.12 | 95.5/3 |
| Hsueh | 1981—2000 | Taiwan | | | | | 0.5/1 | 0.12/0.12 | | 0.12/0.25 | 98/0 |
| Yang | 1999—2002 | Taiwan | | | | | | | | | 100/0 |
| Hsueh | 2003 | Taiwan | | | | | | | | | 100/0 |
| Ruan | 2005—2007 | Taiwan | | 1/2 | 2/2 | 1/2 | 1/1 | 0.03/0.06 | 0.03/0.06 | 0.06/0.25 | 98/0 |
| Wei Liu | 2009—2011 | China | 4/8 | 0.25/0.25 | | | 0.5/0.5 | 0.03/0.125 | | 0.5/1 | 40/16 |
| Fang Li | 2006—2011 | China | 1/1 | 1/1.5 | | | 0.5/0.5 | 0.064/0.064 | | 0.125/0.125 | */0 |
| Ostrosky-Zeichner | 1995—1999 | America | | 2/2 | 1/2 | 2/2 | 0.13/0.5 | 0.03/0.06 | 0.03/0.13 | | |
| Cuenca-Estrella | 2001—2006 | Europe | | 0.5/1 | | | 0.12/0.25 | 0.02/0.03 | 0.02/0.03 | | |
| Pfaller | 2001—2004 | Global | | 0.5/1 | 1/2 | 2/4 | | | | 0.25/0.5 | */3.2 |
| Eike | 2008 | Global | | */0.5—4 | | | | */0.03—0.25 | */0.03—0.25 | | |

**Table 5** Correlation between the use of the antifungal agents and the incidence of *Candida parapsilosis* bloodstream infection

| | | *C. parapsilosis* |
|---|---|---|
| Fluconazole total | Pearson correlation | −0.643 |
| | Sig. (2-tailed) | 0.241 |
| Fluconazole IV | Pearson correlation | −0.486 |
| | Sig. (2-tailed) | 0.407 |
| Fluconazole oral | Pearson correlation | −0.586 |
| | Sig. (2-tailed) | 0.299 |
| Echinocandin total | Pearson correlation | 0.614 |
| | Sig. (2-tailed) | 0.271 |
| Caspofungin | Pearson correlation | −0.086 |
| | Sig. (2-tailed) | 0.891 |
| Micafungin | Pearson correlation | 0.800 |
| | Sig. (2-tailed) | 0.104 |
| Anidulafungin | Pearson correlation | 0.390 |
| | Sig. (2-tailed) | 0.516 |
| Voriconazole | Pearson correlation | −0.162 |
| | Sig. (2-tailed) | 0.795 |
| Amphotericin B | Pearson correlation | −0.787 |
| | Sig. (2-tailed) | 0.114 |

hospital was similar to that reported in the Asia-Pacific area, and although *C. tropicalis* was higher than *C. glabrata*, the rates of the following three non-*albicans Candida* spp. were close.

*C. parapsilosis* is a common skin colonizer. It is most often isolated from neonates and children and related to intravenous instrumentation. The risk factors of patients who developed *C. parapsilosis* bloodstream infections include prolonged use of catheter or indwelling device, hyperalimentation solution infusion, gastrointestinal surgery, presence of immune compromising conditions such as AIDS, recent chemotherapy or use of immune compressive agents, previous colonization, previous antibiotics treatment, or previous antifungal agent treatment.[4] Chen et al[25] found that patients with *C. parapsilosis* bloodstream infections had higher blood albumin levels, lower Sequential Organ Failure Assessment scores, and frequently those who had total parental nutrition infusions would have lower mortality rates. In our study, the mortality rate was 41.6%, which is higher than that (28.5%) reported in a review article in 2008 or in 2012 (30%).[2,4] The risk factors of mortality included those patients with any malignancy or presence of a metastatic tumor. By contrast, patients younger than 18 years had lower mortality rates. Furthermore, in multivariate logistical regression analysis, patients with malignancy had a higher odds ratio in terms of mortality. However, the drug selection, total parental nutrition infusion, type of catheter, or the site of CVC did not increase the risk of mortality. Andes et al[26] report that echinocandin, CVC removal, and Acute Physiology and Chronic Health Evaluation II score were independently associated with mortality in non-*albicans Candida* species infections, but only disease severity predicted the survival of patients with *C. parapsilosis* and *C. tropicalis* infections. In our study, the results supported similar conclusions—that underlying comorbidity and malignancy

were the factors leading to death. *C. parapsilosis* bloodstream infection was merely a confounding accident.

The Infectious Diseases Society of America guidelines for the management of candidiasis in 2009 suggested fluconazole for nonneutropenic patients with *C. parapsilosis* infections, and fluconazole or liposomal amphotericin B for neutropenic patients. The susceptibility of *C. parapsilosis* to echinocandin was susceptible to resistance, even though *in vitro* resistance was uncommon.[27] The *in vitro* activity of antifungal agents against *C. parapsilosis* from this study and other articles are summarized in Table 4.[28–37] About 3% of isolated *C. parapsilosis* in our study were resistant to fluconazole. This rate is similar to the global data. However, a high resistance rate of fluconazole was noted in China. The authors of two articles mentioned the cross resistance between fluconazole and voriconazole, and suggested using non-azole antifungal agents and consistently monitoring susceptibility.[32,33] Echinocandin is a new class of antifungal agents. The echinocandin MICs of *C. parapsilosis* are higher than those of other *Candida* species. In our study, only one isolated *C. parapsilosis* was intermediate to micafungin. The other isolates were susceptible to *in vitro* echinocandin. However, the survival rate of patients receiving echinocandin was lower than that of patients receiving fluconazole (46.2% vs. 59.1%). Amphotericin B was traditionally the most commonly prescribed antifungal agent. The reported resistance rate of *C. parapsilosis* to amphotericin B was 2–3%.[4] In our study, no isolated *C. parapsilosis* was resistant to amphotericin B *in vitro*. The clinical response was better compared with other agents. However, because of its nephrotoxicity and the high cost of liposomal amphotericin B, their annual consumption was on the decrease. In our study, fluconazole remains the drug of choice to treat *C. parapsilosis* bloodstream infections.

Caspofungin was introduced to our hospital in 2003, followed by micafungin in 2009, and then anidulafungin in 2011. It is hypothesized that the increasing use of antifungal agents, such as fluconazole, increases the selection pressure on non-*albicans Candida* species. However, conflicting results have been reported, and thus the hypothesis remains controversial.[17] Given the high MIC of *C. parapsilosis*, some articles mention the selection pressure associated with the increasing use of echinocandin.[2] However, Lai et al[15] reported a significant negative correlation between the incidence of *C. parapsilosis* infection and the use of echinocandin and voriconazole. In our study, *C. parapsilosis* bloodstream infection showed a moderate positive correlation with the use of echinocandin, but this correlation was not statistically significant. Many factors influence the incidence of *C. parapsilosis* bloodstream infection. The advocacy of hand hygiene campaign started in our hospital in 2009. Furthermore, the CVC care bundle was launched in the intensive care unit in our hospital in 2010. The reinforcement of infection control would reduce the infection rate of *C. parapsilosis*. Although the use of antifungal agents is not the only factor influencing the incidence of *C. parapsilosis* infection, our study does not support the hypothesis that increasing use of echinocandin increases the incidence of *C. parapsilosis* infection.

Underlying comorbidity and malignancy were factors leading to death in patients with *C. parapsilosis* bloodstream infection. Catheter removal did not influence the mortality rate. The survival rate of patients receiving echinocandin was lower than that in the group receiving fluconazole. Fluconazole remains the drug of choice to treat *C. parapsilosis* bloodstream infections.

## References


1. Liu C-Y, Liao C-H, Chen Y-C, Chang S-C. Changing epidemiology of nosocomial bloodstream infections in 11 teaching hospitals in Taiwan between 1993 and 2006. *J Microbiol Immunol Infect* 2010;**43**:416–29.
2. Pfaller M, Neofytos D, Diekema D, Azie N, Meier-Kriesche HU, Quan SP, et al. Epidemiology and outcomes of candidemia in 3648 patients: data from the Prospective Antifungal Therapy (PATH Alliance(R)) registry, 2004–2008. *Diagn Microbiol Infect Dis* 2012;**74**:323–31.
3. Huang YC, Lin TY, Lien RI, Chou YH, Kuo CY, Yang PH, et al. Candidaemia in special care nurseries: comparison of albicans and parapsilosis infection. *J Infect* 2000;**40**:171–5.
4. Trofa D, Gacser A, Nosanchuk JD. *Candida parapsilosis*, an emerging fungal pathogen. *Clin Microbiol Rev* 2008;**21**:606–25.
5. Laffey SF, Butler G. Phenotype switching affects biofilm formation by *Candida parapsilosis*. *Microbiology* 2005;**151**:1073–81.
6. Clark TA, Slavinski SA, Morgan J, Lott T, Arthington-Skaggs BA, Brandt ME, et al. Epidemiologic and molecular characterization of an outbreak of *Candida parapsilosis* bloodstream infections in a community hospital. *J Clin Microbiol* 2004;**42**:4468–72.
7. Almirante B, Rodriguez D, Cuenca-Estrella M, Almela M, Sanchez F, Ayats J, 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. *J Clin Microbiol* 2006;**44**:1681–5.
8. Huang YC, Lin TY, Leu HS, Peng HL, Wu JH, Chang HY. Outbreak of *Candida parapsilosis* fungemia in neonatal intensive care units: clinical implications and genotyping analysis. *Infection* 1999;**27**:97–102.
9. Lin HC, Lin HY, Su BH, Ho MW, Ho CM, Lee CY, et al. Reporting an outbreak of Candida pelliculosa fungemia in a neonatal intensive care unit. *J Microbiol Immunol Infect* 2013;**46**:456–62.
10. Bone RC, Sibbald WJ, Sprung CL. The ACCP–SCCM consensus conference on sepsis and organ failure. *Chest* 1992;**101**:1481–3.
11. Tsai CC, Lay CJ, Wang CL, Lin ML, Yang SP. Prognostic factors of candidemia among nonneutropenic adults with total parenteral nutrition. *J Microbiol Immunol Infect* 2011;**44**:461–6.
12. Dotis J, Prasad PA, Zaoutis T, Roilides E. Epidemiology, risk factors and outcome of *Candida parapsilosis* bloodstream infection in children. *Pediatr Infect Dis J* 2012;**31**:557–60.
13. Pfaller MA, Diekema DJ, Gibbs DL, Newell VA, Ellis D, Tullio V, et al. Results from the ARTEMIS DISK Global Antifungal Surveillance Study, 1997 to 2007: a 10.5-year analysis of susceptibilities of *Candida* species to fluconazole and voriconazole as determined by CLSI standardized disk diffusion. *J Clin Microbiol* 2010;**48**:1366–77.
14. Tortorano AM, Peman J, Bernhardt H, Klingspor L, Kibbler CC, Faure O, 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.
15. Lai CC, Chu CC, Wang CY, Tsai HY, Cheng A, Lee YC, et al. Association between incidence of candidaemia and

consumption of antifungal agents at a medical centre in Taiwan. *Int J Antimicrob Agents* 2012;**40**:349—53.
16. Cuenca-Estrella M, Verweij PE, Arendrup MC, Arikan-Akdagli S, Bille J, Donnelly JP, et al. ESCMID* guideline for the diagnosis and management of Candida diseases 2012: diagnostic procedures. *Clin Microbiol Infect* 2012;**18**(Suppl. 7):9—18.
17. Ruan SY, Hsueh PR. Invasive candidiasis: an overview from Taiwan. *J Formos Med Assoc* 2009;**108**:443—51.
18. Simon J, Sun HY, Leong HN, Barez MY, Huang PY, Talwar D, et al. Echinocandins in invasive candidiasis. *Mycoses* 2013;**56**:601—9.
19. Pfaller MA, Moet GJ, Messer SA, Jones RN, Castanheira M. Geographic variations in species distribution and echinocandin and azole antifungal resistance rates among Candida bloodstream infection isolates: report from the SENTRY Antimicrobial Surveillance Program (2008 to 2009). *J Clin Microbiol* 2011;**49**:396—9.
20. Cheng MF, Yu KW, Tang RB, Fan YH, Yang YL, Hsieh KS, et al. Distribution and antifungal susceptibility of *Candida* species causing candidemia from 1996 to 1999. *Diagn Microbiol Infect Dis* 2004;**48**:33—7.
21. Chen YC, Chang SC, Luh KT, Hsieh WC. Stable susceptibility of Candida blood isolates to fluconazole despite increasing use during the past 10 years. *J Antimicrob Chemother* 2003;**52**:71—7.
22. Lu JJ, Lee SY, Chiueh TS. In vitro antifungal susceptibility testing of Candida blood isolates and evaluation of the E-test method. *J Microbiol Immunol Infect* 2004;**37**:335—42.
23. Pfaller MA, Diekema DJ. International Fungal Surveillance Participant G. Twelve years of fluconazole in clinical practice: global trends in species distribution and fluconazole susceptibility of bloodstream isolates of Candida. *Clin Microbiol Infect* 2004;**10**:11—23.
24. Pfaller MA, Diekema DJ, Jones RN, Messer SA, Hollis RJ, Group SP. Trends in antifungal susceptibility of *Candida* spp. isolated from pediatric and adult patients with bloodstream infections: SENTRY Antimicrobial Surveillance Program, 1997 to 2000. *J Clin Microbiol* 2002;**40**:852—6.
25. Chen LY, Kuo SC, Wu HS, Yang SP, Chan YJ, Chen LK, et al. Associated clinical characteristics of patients with candidemia among different *Candida* species. *J Microbiol Immunol Infect* 2013;**46**:463—8.
26. Andes DR, Safdar N, Baddley JW, Playford G, Reboli AC, Rex JH, et al. Impact of treatment strategy on outcomes in patients with candidemia and other forms of invasive candidiasis: a patient-level quantitative review of randomized trials. *Clin Infect Dis* 2012;**54**:1110—22.
27. Pappas PG, Kauffman CA, Andes D, Benjamin Jr DK, Calandra TF, Edwards Jr JE, et al. Clinical practice guidelines for the management of candidiasis: 2009 update by the Infectious Diseases Society of America. *Clin Infect Dis* 2009;**48**:503—35.
28. Hsueh PR, Teng LJ, Yang PC, Ho SW, Luh KT. Emergence of nosocomial candidemia at a teaching hospital in Taiwan from 1981 to 2000: increased susceptibility of *Candida* species to fluconazole. *Microb Drug Resist* 2002;**8**:311—9.
29. Tsai MS, Yang YL, Wang AH, Wang LS, Lu DC, Liou CH, et al. Susceptibilities to amphotericin B, fluconazole and voriconazole of Trichosporon clinical isolates. *Mycopathologia* 2012;**174**:121—30.
30. Yang YL, Li SY, Cheng HH, Lo HJ, Hospitals T. The trend of susceptibilities to amphotericin B and fluconazole of *Candida* species from 1999 to 2002 in Taiwan. *BMC Infect Dis* 2005;**5**:99.
31. Ruan SY, Chu CC, Hsueh PR. In vitro susceptibilities of invasive isolates of *Candida* species: rapid increase in rates of fluconazole susceptible-dose dependent *Candida glabrata* isolates. *Antimicrob Agents Chemother* 2008;**52**:2919—22.
32. Li F, Wu L, Cao B, Zhang Y, Li X, Liu Y. Surveillance of the prevalence, antibiotic susceptibility, and genotypic characterization of invasive candidiasis in a teaching hospital in China between 2006 to 2011. *BMC Infect Dis* 2013;**13**:353.
33. Liu W, Tan J, Sun J, Xu Z, Li M, Yang Q, et al. Invasive candidiasis in intensive care units in China: in vitro antifungal susceptibility in the China-SCAN study. *J Antimicrob Chemother* 2014;**69**:162—7.
34. Ostrosky-Zeichner L, Rex JH, Pappas PG, Hamill RJ, Larsen RA, Horowitz HW, et al. Antifungal susceptibility survey of 2,000 bloodstream Candida isolates in the United States. *Antimicrob Agents Chemother* 2003;**47**:3149—54.
35. Cuenca-Estrella M, Gomez-Lopez A, Mellado E, Buitrago MJ, Monzon A, Rodriguez-Tudela JL. Head-to-head comparison of the activities of currently available antifungal agents against 3,378 Spanish clinical isolates of yeasts and filamentous fungi. *Antimicrob Agents Chemother* 2006;**50**:917—21.
36. Pfaller MA, Diekema DJ. Epidemiology of invasive candidiasis: a persistent public health problem. *Clin Microbiol Rev* 2007;**20**:133—63.
37. Hollenbach E. Invasive candidiasis in the ICU: evidence based and on the edge of evidence. *Mycoses* 2008;**51**:25—45.