Journal of Critical Care 30 (2015) 862.e1–862.e5

Contents lists available at ScienceDirect

Journal of Critical Care

journal homepage: www.jccjournal.org

Risk factors for fluconazole-resistant invasive candidiasis in intensive care unit patients: An analysis from the China Survey of Candidiasis study☆

Xuelian Liao [a], Haibo Qiu [b], Ruoyu Li [c], Fengmei Guo [b], Wei Liu [c], Mei Kang [d], Yan Kang [a,*] on behalf of the China-SCAN Team

[a] Department of Critical Care Medicine, West China Hospital of Sichuan University, Chengdu, China
[b] Zhongda Hospital, Southeast University, Nanjing, China
[c] Peking University First Hospital, Research Center for Medical Mycology, Peking University, Beijing, China
[d] Department of Microbiology Laboratory, West China Hospital of Sichuan University, Chengdu, China

ARTICLE INFO

Keywords:
Invasive *Candida* infection
Invasive candidiasis
Intensive care unit
Fluconazole resistance

ABSTRACT

Purpose: To assess the risk factors for invasive *Candida* infection (ICI) caused by fluconazole-resistant (Flu-R) *Candida* species in intensive care unit (ICU) patients.
Materials and methods: Data from China Survey of Candidiasis study were analyzed. Patients with proven ICI were classified into fluconazole-sensitive (Flu-S) and Flu-R groups. Independent risk factors for Flu-R ICI were identified using a multivariate logistic regression.
Results: Forty-one percent of ICI patients were infected with Flu-R *Candida*. Significantly more patients had *Candida* colonization, intra-abdominal hypertension, and antifungal therapy at least 7 days before diagnosis; fewer patients had gastrointestinal perforation, systemic inflammatory response syndrome manifestation, and fluoroquinolone exposure in the Flu-R group. Furthermore, hospital or ICU stay before onset of infection was longer in the Flu-R group than in the Flu-S group (hospital or ICU stay: 19 vs 13 days or 10.5 vs 8 days, $P < .05$). Also, it was demonstrated as an independent risk factor for Flu-R *Candida* infection.
Conclusion: As many as 41% of ICI patients were infected with Flu-R *Candida*, and the main risk factor was longer ICU stay before onset of ICI, implying that caution should be exercised when treating patients who have been long stayed in ICU with fluconazole as the first-line drug before testing isolates for drug sensitivity.

1. Introduction

Invasive *Candida* infection (ICI) is the third most common cause of infection in intensive care units (ICUs) worldwide, and the occurrence of ICI is still showing an upward trend. The mortality of ICI remains high (35%-67%) despite improvements in clinical management over time. Invasive *Candida* infection greatly endangers patients' lives and increasingly consumes health resources [1–3].

Our previous study and others have confirmed that susceptibility to initial therapy is a factor determining lower mortality of ICI [4,5]. To date, fluconazole is the most commonly used first-line antifungal drug for ICI [4,6]. However, increasing ICI with fluconazole-resistant (Flu-R) species including Flu-R *Candida albicans*, non–albicans species, as well as some rare species, makes the initial choice of appropriate antifungal drugs extremely difficult. Therefore, early recognition of risk factors for patients who may experience drug-resistant ICI plays a vital role in improving the efficacy of antifungal therapy and the prognosis of patients with ICI.

Very few studies have focused on analyzing risk factors for a microbiologically proven Flu-R *Candida* infection, although many studies have been conducted to identify risk factors associated with invasive candidiasis by non–albicans *Candida* or potentially Flu-R species (such as *Candida glabrata* and *Candida krusei*) [7–11]. Different conclusions were also drawn from different studies [12–14]. For instance, prior fluconazole exposure was considered an independent risk factor in most of these studies, but various other risk factors were also reported, including use of specific antibiotics, history of gastrointestinal surgery, neutropenia, time of hospitalization, and so on. These inconsistent results may be derived from differences in the populations studied. In fact, previous studies primarily investigated hospitalized patients or patients with specific disease (such as cancer or liver transplantation), and few studies analyzed ICI in ICU patients whose prognosis is strongly correlated with appropriate initial treatment. In addition, a recent investigation revealed that candidiasis acquired before or after ICU admission had different risk factors [15]. Furthermore, previous studies relied on the old standards of clinical breakpoints (CBPs) for fluconazole, which could have possibly underestimated the number of patients infected with

☆ Conflict of interest: None declared.

* Corresponding author at: Department of Critical Care Medicine, West China Hospital, Sichuan University, 37 Guo Xue lane, Chengdu 610041, China. Tel./fax: +86 28 85422508.
E-mail address: kang_yan_123@163.com (Y. Kang).

http://dx.doi.org/10.1016/j.jcrc.2015.04.002
0883-9441/

Flu-R species, because the breakpoint for the minimum inhibitory concentration (MIC) according to old standards is higher than that according to current standards.

In this study, we used the newly revised CBPs or Epidemiological Cutoff Values (ECVs), recommended by the Clinical and Laboratory Standards Institute (CLSI), for fluconazole to classify patients into Flu-R and fluconazole-sensitive (Flu-S) groups [16,17], and a multilogistic regression model was developed to identify risk factors for ICI by Flu-R *Candida* in an ICU population.

2. Materials and methods

2.1. Study design and patients

The China Survey of Candidiasis (China-SCAN) study is so far the largest prospective observational study on prevalence of ICI in China and was conducted between November 2009 and April 2011 in 67 participated ICUs distributed throughout China.

Adult patients (age ≥18 years) were consecutively enrolled when diagnosed as having proven ICI in each ICU. Patients with ICI diagnosed before ICU admission were excluded. The detailed inclusion or exclusion criteria were described in a previous report [4]. Demographic data, disease severity scores (Acute Physiology and Chronic Health Evaluation [APACHE] II and Sequential Organ Failure Assessment [SOFA] scores), recent history, ICI risk factors, clinical manifestations, diagnosis, microbiological information, treatment, and prognosis of studied patients were recorded (details have been published in our previous article [4]). The study was approved by the Ethics Committee of Zhongda Hospital of Southeast University, the lead investigation site.

Isolated *Candida* samples obtained after documentation of ICI were sent to the Research Center for Medical Mycology, Peking University First Hospital, Beijing, China, for species identification and in vitro susceptibility testing.

Candida isolates were identified by using chromogenic culture media (CHROMagar, Paris, France) and the API 20C AUX yeast identification kit (bioMérieux SA, Marcy l'E'toile, France). When necessary, sequencing of large-subunit (26S) ribosomal rRNA gene D1/D2 domain was undertaken. Some rare *Candida* species were also identified by sequencing. Antifungal susceptibility testing was performed using the CLSI M27-A3 microbroth dilution method. Fluconazole (Shouguang Fukang Pharmaceutical Ltd, Shan Dong, China; purity 99.5%) was prepared according to CLSI methods described previously. Minimum inhibitory concentrations for fluconazole were determined after growth at 35°C for 24 hours. Minimum inhibitory concentrations were read as the lowest drug concentration producing a prominent decrease in turbidity translating to 50% growth reduction compared with the drug-free control [18].

To standardize differentiation of Flu-R species, we only analyzed patients whose *Candida* isolates were sent to the central laboratory. Patients infected by rare *Candida* species whose CBPs or ECVs for fluconazole had not been established were also excluded. Patients who were infected by at least 1 non–Flu-S isolates were classified into the Flu-R group. Susceptible/susceptible dose-dependent (SDD)/resistant is defined as an MIC ≤2/4/≥8 mg/L of fluconazole for *C albicans*, *Candida tropicalis*, and *Candida parapsilosis*, and an MIC ≤32 and ≥64 mg/L of fluconazole is defined as SDD and resistant for *C glabrata*, respectively. ECVs used for *Candida guilliermondii* and *Candida pelliculosa* were greater than 8 and greater than 4 μg/mL, respectively. Isolates of *C krusei* were considered intrinsically resistant to fluconazole [16,17].

2.2. Statistical analysis

Continuous variables were described as mean ± SD, median, and range and compared by Student *t* test if normally distributed or by Wilcox on test if nonnormally distributed. Categorical variables were described as frequencies and percentage and compared by χ^2 test or Fisher exact test. Two-tailed test was used to determine statistical differences with $P < .05$. Multivariate analysis to identify independent risk factors was performed using logistic regression model after univariate analysis that included all variables with a *P* value less than .1 in the univariate test. Model calibration was assessed using Hosmer and Lemeshow goodness-of-fit test. All statistical analyses were performed using SAS 9.1 (SAS Institute, Cary, NC).

3. Results

Between November 2009 and April 2011, a total of 306 proven ICI cases were included in China-SCAN; 389 isolates from 244 patients were sent to the central laboratory for fluconazole sensitivity testing. Among them, isolated from 25 patients infected by rare *Candida* species (such as *C guilliermondii* and *C pelliculosa*) were excluded because their CBPs or ECVs for fluconazole have not been established. The data from 219 patients, 129 in the Flu-S group and 90 in the Flu-R group, were eligible for analysis.

3.1. Patients' characteristics at ICU admission

Average age was 61.69 ± 20.06 years, and 73.6% of patients had severe comorbidity. Their average APACHE II score was 27.08 ± 7.005. At the same time, they presented with severely impaired organ function (SOFA score was 10.87 ± 3.387). Digestive, respiratory, and neurologic diseases (32.4%, 29.7%, and 16.4%, respectively) accounted for the top 3 reasons for ICU admission. Overall, there were no significant differences between the Flu-S group and Flu-R groups in terms of baseline characteristics (Table 1).

3.2. Distribution of pathogenic Candida species in 219 patients

Approximately 41.09% of the whole population was infected by a Flu-R species or SDD isolates, which is a relatively high percentage. In patients infected by mono–*Candida* isolates, *C parapsilosis*, *C tropicalis*, and *C albicans* accounted for 51.92%, 37.5%, and 17.02% of Flu-R or SDD species, respectively, in addition to *C glabrata* and *C krusei* that are regarded as species intrinsically resistant or SDD to fluconazole. Among 6 patients with mixed infection, 5 were infected with at least 1 Flu-R/SDD species (Table 2).

3.3. Risk factors for Flu-R Candida infection

Using the predefined risk factors associated with ICI infection or prognosis, we analyzed them for possibly correlation to Flu-R *Candida* infection, including clinical manifestation, invasive procedures, and anti-infection therapy within 2 weeks before diagnosis or at diagnosis of ICI (Table 3).

In the unadjusted univariate analysis (Table 3), *Candida* colonization, antifungal therapy at least 7 days before diagnosis, and intra-abdominal hypertension were more commonly observed in the Flu-R group (34.4%, 18.9%, and 24.4%, respectively) than in the Flu-S group (21.7%, 9.3%, and 7.8%, respectively; $P < .05$), whereas prior use of fluoroquinolone, gastrointestinal perforation, and systemic inflammatory response syndrome (SIRS) were more likely to occur in the Flu-S group (21.8%, 18.6%, and 82.9%, respectively, in the Flu-S group vs 9.6%, 9.3%, and 71.9%, respectively, in the Flu-R group; $P < .05$). Hospital and ICU stays before diagnosis were significantly longer in the Flu-R group (19 and 10.5 days, respectively, in the Flu-R group vs 13 and 8 days, respectively, in the Flu-S group; $P < .05$). There were no differences in azole exposure, disease severity, and invasive procedures between the 2 groups ($P > .05$).

A multivariate logistic regression of risk factors associated with Flu-R/SDD *Candida* infection (Table 4) indicated that only increased ICU stay before diagnosis of ICI was a risk factor predicting Flu-R/SDD *Candida* infection (odds ratio, 1.016; $P = .0003$).

Table 1
Demographic and clinical characteristics of patients on admission to ICUs

Variables	Total (n = 219)	Flu-S (n = 129)	Flu-R (n = 90)	*P*
Age (y), mean (SD)	61.69 (20.1)	62.40 (19.5)	60.68 (20.9)	.5324
Sex, male (%)	149 (68.0)	88 (68.2)	61 (67.8)	.9453
Weight (kg), mean (SD)	62.97 (11.147)	61.56 (10.187)	64.70 (12.072)	.0940
Origin, n (%)				.6767
Emergency or outpatient department	44 (20.1)	24 (18.6)	20 (22.2)	
Ward or operating room	136 (62.1)	80 (62.0)	56 (62.2)	
Other hospital	39 (17.8)	25 (19.4)	14 (15.6)	
ICU category, n (%)				.6167
Mix ICU	175 (79.9)	100 (77.5)	75 (83.3)	
Surgical ICU	28 (12.8)	17 (13.2)	11 (12.2)	
Medical ICU	7 (3.2)	5 (3.9)	2 (2.2)	
Other	9 (4.1)	7 (5.4)	2 (2.2)	
APACHE II score, mean (SD)	27.08 (7.005)	26.77 (7.045)	27.51 (6.966)	.4453
SOFA score, mean (SD)	10.87 (3.387)	10.83 (3.635)	10.92 (3.018)	.8405
Chronic comorbid diseases, n (%)				
Diabetes mellitus	48 (22.0)	22 (17.1)	26 (28.9)	.0527
Chronic obstructive pulmonary disease	29 (13.2)	19 (14.7)	10 (11.1)	.4371
Chronic hepatic insufficiency	12 (5.5)	6 (4.7)	6 (6.7)	.5190
Chronic renal insufficiency	22 (10.1)	11 (8.5)	11 (12.2)	.6700
Chronic cardiac dysfunction	47 (21.5)	30 (23.3)	17 (18.9)	.2295
Immunodeficiency[a]	14 (6.4)	11 (8.5)	3 (3.3)	.1221
Cancer	43 (19.6)	21 (16.3)	22 (24.4)	.1667
No comorbid conditions, n (%)	55 (25.1)	34 (26.4)	21 (23.3)	.6382
Main reason for admission, n (%)				
Respiratory disease	65 (29.7)	32 (24.8)	33 (36.7)	
Digestive disease	71 (32.4)	42 (32.6)	29 (32.2)	
Neurologic disease	36 (16.4)	22 (17.1)	14 (15.6)	
Cardiovascular disease	4 (1.8)	3 (2.3)	1 (1.1)	
Urinary system disease	9 (4.1)	7 (5.4)	2 (2.2)	
Hematologic disease	2 (0.9)	1 (0.8)	1 (1.1)	
Multiple trauma	16 (7.3)	10 (7.8)	6 (6.7)	
Burn	3 (1.4)	3 (2.3)	0	
Other	10 (4.6)	9 (7.0)	4 (4.4)	
Invasive mechanical ventilation, n (%)	171 (78.1)	97 (75.2)	74 (82.2)	.21
Vasopressors, n (%)	83 (37.9)	52 (40.3)	31 (34.4)	.3989

[a] Definition of immunodeficiency: patients who had received immunosuppression therapy, including chemotherapy, radiotherapy, and high doses of glucocorticoid in the previous 3 months, or patients who had immune system diseases, such as malignant lymphoma, leukemia, or acquired immunodeficiency virus infection.

3.4. Treatment strategies and outcomes for the 2 groups

Understandably, patients in the Flu-R group were more likely to experience a change in antifungal therapy than the patients in the Flu-S group (61.1% in the Flu-R group vs 35.7% in the Flu-S group; $P = .0006$). Monoantifungal therapy was more frequently prescribed in the Flu-S group than in the Flu-R group (64.5% vs 48.4%, respectively), but this difference was not statistically significant ($P = .0579$). There was no difference in mortality between the 2 groups (41.1% in the Flu-R group and 31.8% in the Flu-S group; $P = .1561$). Patients in the Flu-R group did have longer ICU and hospital stays than those in the Flu-S group (29 and 48 days, respectively, in the Flu-R group vs 22.5 and 34.5 days, respectively, in the Flu-S group; $P < .05$; Table 5). The findings from clinical and microbiologic evaluations at the end of antifungal therapy were also similar between the 2 groups (all $P > .05$).

Table 2
Classification of pathogenic *Candida* isolates in 219 patients

Variables	Total (n = 219)	Flu-S (n = 129)	Flu-R (n = 90)
Monoinfection (n)[a]	213	128	85
C albicans	94	78	16
C tropicalis	40	25	15
C parapsilosis	52	25	27
C glabrata	26	0	26
C krusei	1	0	1
Mixed infection (n)[b]	6	1	5
C albicans + *C parapsilosis*	2	1	1
C albicans + *C glabrata*	1	0	1
C albicans + *C tropicalis*	1	0	1
C glabrata + *C parapsilosis*	1	0	1
C glabrata + *C tropicalis*	1	0	1

[a] Monoinfection is defined as 1 *Candida* species, including single *Candida* culture positive or repetitiously culture positive with the same *Candida*.
[b] Mix infection is defined as more than 1 *Candida* species.

4. Discussion

This study was intended to identify risk factors associated with the occurrence of ICI by Flu-R *Candida* in ICUs. There were 2 main novel features of this study: (a) the resistant strains were microbiologically ascertained; and (b) the newly revised CBPs or ECVs for fluconazole were used. To our knowledge, our study is a first to represent such an investigation in ICU patients. Our analysis suggests that a longer stay in ICU is an independent risk factor for the occurrence of ICI by Flu-R *Candida*.

Many studies have confirmed that susceptibility to initial antifungal therapy is associated with reduced mortality of ICI. Thus, the use of more sensitive cutoff CBPs or ECVs to identify potential Flu-R *Candida* infection would yield lifesaving benefits to critically ill patients treated in the ICU. Previous studies [10,11] showed that the new epidemiologic CBPs provided by the CLSI are a more sensitive tool for the detection of emerging *Candida* spp infection with reduced susceptibility to antifungals than the previous CBPs, and thus, we selected this standard to define Flu-S and Flu-R infections.

Our finding that a longer stay in the ICU before onset of ICI was the independent risk factor for Flu-R *Candida* infection is similar to the finding of Lee et al [12], who studied risk factors for Flu-R infections in patients with *C glabrata* bloodstream infection. In their case-control study, they found that an increased hospitalized time, but not earlier use of fluconazole, was the independent risk factor for Flu-R *C glabrata* BSI (odds ratio, 1.03; 95% confidence interval, 1.004-1.06). Other similar

Table 3
Unadjusted univariate analysis for potential risk factors for Flu-R *Candida* infection

Risk factor	Flu-S (n = 129)	Flu-R (n = 90)	*P*
Within 2 wk before or at diagnosis			
Candida colonization, n (%)	28 (21.7)	31 (34.4)	.0366
Antibiotic related factors, n (%)			
Antibiotic use ≥5 d	101 (78.3)	73 (81.1)	.7341
Monoantibiotic therapy	32 (31.7)	26 (35.6)	.7474
Penicillin	26 (25.7)	20 (27.4)	1.000
Cephalosporin	53 (52.5)	37 (50.7)	.760
Carbapenem	41 (40.6)	25 (34.2)	.437
Fluoroquinolone	22 (21.8)	7 (9.6)	.0463
Aminoglycoside	2 (2.0)	4 (5.5)	.455
Glycopeptide	18 (17.8)	16 (21.9)	.570
Other	27 (26.7)	21 (28.8)	1.000
Antifungal related factors, n (%)			
Antifungal therapy before diagnosis	32 (24.8)	30 (33.3)	.1741
Antifungal therapy ≥7 d before diagnosis	12 (9.3)	17 (18.9)	.0446
Azole exposure	22 (68.8)	22 (73.3)	.7830
Neutropenia, n (%)	4 (3.1)	1 (1.1)	.6509
Invasive procedures, n (%)			
Surgery	52 (40.3)	31 (34.4)	.3787
Abdominal surgery	36 (27.9)	18 (20.0)	.1816
Invasive mechanical ventilation	95 (73.6)	74 (82.2)	.2667
Deep venous catheter[a]	107 (82.9)	72 (80.0)	.5788
Arterial catheter	25 (19.4)	13 (14.4)	.3427
Urinary catheter	94 (72.9)	70 (77.8)	.4098
Drainage tube			
Gastrointestinal dysfunction, n (%)	75 (58.1)	47 (52.2%)	.3857
Gastrointestinal perforation	24 (18.6)	3 (3.3)	.0007
Intra-abdominal hypertension	10 (7.8)	22 (24.4)	.0006
Total parental nutrition	53 (41.1)	41 (45.6%)	.5108
At the onset of ICI time of diagnosis			
Hospital stay before onset of ICI, Median (Q1-Q3)	13.00 (6.0-26.0)	19.00 (8.0-43.0)	.0299
ICU stay before onset of ICI, (Q1-Q3)	8.00 (3.0-17.0)	10.50 (4.0-27.0)	.0347
Clinical presentation			
Fever, n (%)	117 (90.7)	80 (88.9)	.6560
Chills, n (%)	41 (31.8)	26 (28.9%)	.6585
White blood cells ($\times 10^9$/L)	13.6 (9.65)	12.3 (6.96)	.310
SIRS, n (%)	107 (82.9%)	64 (71.1%)	.0373
Septic shock, n (%)	40 (31.0%)	20 (22.2%)	.1515
Disease severity scores, mean (SD)			
APACHE II score	26.83 (7.089)	27.06 (6.753)	.8131
SOFA score	10.59 (3.687)	10.17 (3.077)	.3732

[a] Deep venous catheter includes catheter inserted through subclavian vein, internal jugular vein and femoral vein.

studies [15,19] have considered fluconazole exposure as an independent risk factor, suggesting that the resistant strains were likely antifungal drug induced. The findings from our study as well as the one conducted by Lee et al [12], which indicated that longer hospital or ICU stay played a pivotal role in developing Flu-R ICI, do not deny that fluconazole exposure is a factor inducing fluconazole resistance, but rather suggest an additional source for the resistant species. In addition to facilitating acquisition of the resistant strains, a longer ICU stay also could contribute many other factors to the development of Flu-R ICI, such as invasive procedures, long-term antibiotic use, and host immunosuppression in patients with hospital- or ICU-acquired infection. All these factors would produce a compounding effect with prolonged ICU stay.

Table 5
Impact of Flu-R *Candida* infection on patients' treatment strategy and prognosis

Variables	Flu-S (n = 129)	Flu-R (n = 90)	*P*
Monoantifungal therapy, n (%)	69 (64.5)	40 (48.8)	.0579
Fungal drug adjustment, n (%)	46 (35.7)	55 (61.1)	.0006
Clinical evaluation, n (%)[a]			.3687
Completely improved	37 (34.6)	23 (28.0)	
Partially improved	42 (39.3)	30 (36.6)	
No improvement	28 (26.2)	29 (35.4)	
Microbiology evaluation, n (%)[b]			.9751
Candida eradication	51 (47.2)	38 (45.8)	
Candida persistence	9 (8.3)	7 (8.4)	
Not known	48 (44.4)	38 (45.8)	
Hospital mortality, n (%)	41 (31.8)	37 (41.1)	.1561
ICU stay, median (Q1, Q3)	22.5 (10, 40)	29.0 (17, 59)	.0056
Hospital stay, median (Q1, Q3)	34.5 (18, 65)	48.0 (21, 90)	.0296

[a] The proportion of clinical evaluation were calculated in 189 patients who had been received antifungal therapy and evaluated at the end of treatment.
[b] The proportion of microbiology evaluation were calculated in 191 patients who had been received antifungal therapy.

There were additional interesting findings in our unadjusted analysis. First, we found that the rate of abdominal surgery was similar between the 2 groups (27.9% in the Flu-S group vs 20% in the Flu-R group; $P = .1816$). This was different from the rates in a study of patients with cancer, which reported that gastrointestinal tract surgery was one of the independent risk factors associated with Flu-R candidemia [15]. In this study, we found that there were more patients with gastrointestinal perforation in the Flu-S group (18.6% in the Flu-S group vs 3.3% in the Flu-R group; $P = .0007$) and fewer patients with intra-abdominal hypertension (7.8% in the Flu-S group vs 24.4% in the Flu-R group; $P = .0007$). From a clinical perspective, patients with gastrointestinal perforation could often be cured with surgery immediately, whereas patients with intra-abdominal hypertension were more difficult to treat and often experienced persistence of the condition for a relatively longer period, which supports the conclusion described before that a longer ICU stay is associated with Flu-R ICI. The median intervals between ICU admission and ICI onset in patients with gastrointestinal perforation and intra-abdominal hypertension were 5 days and 9.5 days, respectively ($P = .0149$). Second, more patients in the Flu-S group used fluoroquinolone before diagnosis (21.8% in the Flu-S group vs 9.6% in the Flu-R group; $P = .0463$), whereas the uses of other antibiotics were similar between the 2 groups. We could not sufficiently explain this finding, which requires further investigation. A few studies have indicated that antibiotic usage can influence fluconazole resistance, but their results were inconsistent. For example, Ben-Ami et al [16] reported that metronidazole use was associated with *C glabrata* BSI (odds ratio, 3.2; $P < .001$), whereas Maldonado et al [13] considered antituberculosis therapy to be an independent risk factor associated with Flu-R species. As most patients with ICI were exposed to multiple classes of antibacterials, either concomitantly or sequentially,

Table 4
Multivariate analyses for Flu-R *Candida* infection

Variables	Estimate	SE	χ^2	*P*	OR	Lower 95% CI	Upper 95% CI
Intercept	−1.0034	0.3662	7.5090		–	–	–
Diabetes mellitus	0.1824	0.1770	1.0612	.3029	1.440	0.720	2.882
Candida colonization	0.2841	0.1683	2.8500	.0914	1.765	0.913	3.414
Gastrointestinal perforation	−0.0495	0.2383	0.0432	.8354	0.906	0.356	2.305
Intra-abdominal hypertension	−0.0429	0.2180	0.0387	.8441	0.918	0.390	2.157
Antifungal therapy ≥7 d before diagnosis	−0.0405	0.2256	0.0322	.8577	0.922	0.381	2.233
Increased time between onset of ICI and ICU admission	0.0156	0.0043	13.1104	.0003	1.016	1.007	1.024
SIRS	0.2721	0.1921	2.0059	.1567	1.723	0.811	3.660

Hosmer and Lemeshow goodness-of-fit test: $\chi^2 = 7.7283$, $P = .4604$.

it is difficult to pinpoint any one antibiotic responsible for the antibiotics-induced fluconazole resistance.

It is worth noting that the overall fluconazole resistance/SDD infection rate was as high as 41.09% in this study. This occurrence was not only much higher than that in previous studies of hospitalized populations or cancer patients (18.2% [14] and 27.43% [15], respectively), but also higher than that among ICU patients in Spain (20.8%) [5]. This difference could be explained by 3 possible reasons: first, fluconazole, a first-line antifungal drug, was most commonly used for ICI in our patient population (41.1% patients received fluconazole), which increased the possibility to introduce the resistance to fluconazole. In a study of patients admitted to ICUs in Spain, the first-line antifungal drugs were echinocandins in 50% of cases initially treated with an antifungal drug; second, most of the patients (78.5%; 172/219) in this study were diagnosed as having ICI beyond 48 hours after admission to the ICU, suggesting that they had ICU-acquired ICI; and third, the new cutoffs for CBPs or ECVs for fluconazole would result in increased recognition of Flu-R species.

In the prognosis analysis, hospital mortality was higher in the Flu-R group (Flu-R: 41.1% vs Flu-S: 31.8%), but this difference was not statistically significant ($P = .1561$). The median interval between ICI diagnosis and occurrence of death in this study population was 15 (Q1-Q3, 7-33) days, indicating that patients might have died of other causes other than ICI. However, the significantly longer lengths of ICU stays and hospital stays in the Flu-R group, in addition to the more frequent changes of their antifungal therapy (Table 5), suggest a worse prognosis and heavier disease burden for Flu-R ICI.

There are a few limitations in this study. First, patients infected with rare *Candida* species were excluded because the CBPs or ECVs of these species for fluconazole have not been established. In addition, as in the China-SCAN study, not all proven ICI samples were sent to the central laboratory, and the data analysis in this study based on ICI confirmed by the central laboratory might not be fully representative of all ICU patients infected with invasive candidiasis. These 2 exclusion criteria reduced the population size and potentially the statistical power of this study.

In conclusion, this study showed that as many as 41% of patients with ICI were infected by a Flu-R strain in the tested ICU population, and a longer stay in the ICU is an independent risk factor for ICI by Flu-R *Candida* species.

References

[1] Wisplinghoff H, Bischoff T, Tallent 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;39:309–17.

[2] Vincent JL, Rello J, Marshall J, Silva E, Anzueto A, Martin CD, et al. International study of the prevalence and outcomes of infection in intensive care units. JAMA 2009;302:2323–9.

[3] Kett DH, Azoulay E, Echeverria PM, Vincent JL. Candida bloodstream infections in intensive care units: analysis of the extended prevalence of infection in intensive care unit study. Crit Care Med 2011;39:665–70.

[4] Guo F, Yang Y, Kang Y, Zang B, Cui W, Qin B, et al. Invasive candidiasis in intensive care units in China: a multicentre prospective observational study. J Antimicrob Chemother 2013;68:1660–8.

[5] Puig-Asensio M, Peman J, Zaragoza R, Garnacho-Montero J, Martin-Mazuelos E, Cuenca-Estrella M, et al. Impact of therapeutic strategies on the prognosis of candidemia in the ICU. Crit Care Med 2014;42:1423–32.

[6] Leroy O, Gangneux JP, Montravers P, Mira JP, Gouin F, Sollet JP, et al. Epidemiology, management, and risk factors for death of invasive *Candida* infections in critical care: a multicenter, prospective, observational study in France (2005-2006). Crit Care Med 2009;37:1612–8.

[7] Leroy O, Mira JP, Montravers P, Gangneux JP, Lortholary O. Comparison of albicans vs. non-albicans candidemia in French intensive care units. Crit Care 2010;14:R98.

[8] Chi HW, Yang YS, Shang ST, Chen KH, Yeh KM, Chang FY, et al. Candida albicans versus non-albicans bloodstream infections: the comparison of risk factors and outcome. J Microbiol Immunol Infect 2011;44:369–75.

[9] Tapia GG, Razonable RR, Eckel-Passow JE, Lahr BD, Afessa B, Keegan MT, et al. A scoring model of factors associated with *Candida glabrata* candidemia among critically ill patients. Mycoses 2012;55:228–36.

[10] Cisterna R, Tellería O, Hernaez S, Ezpeleta G. Impact of the new clinical breaking points proposed by the Clinical and Laboratory Standards Institute (CLSI) in the antifungal susceptibility profile of clinical strains isolated from invasive bloodstream *Candida* spp. infections in Spain. Clin Med Insights 2012;4:19–27.

[11] Orasch C, Marchetti O, Garbino J, Schrenzel J, Zimmerli S, Mühlethaler K, et al. The Fungal Infection Network of S. Candida species distribution and antifungal susceptibility testing according to European Committee on Antimicrobial Susceptibility Testing and new vs. old Clinical and Laboratory Standards Institute clinical breakpoints: a 6-year prospective candidaemia survey from the fungal infection network of Switzerland. Clin Microbiol Infect 2014;20:698–705.

[12] Lee I, Fishman NO, Zaoutis TE, Morales KH, Weiner MG, Synnestvedt M, et al. Risk factors for fluconazole-resistant *Candida glabrata* bloodstream infections. Arch Intern Med 2009;169:379–83.

[13] Maldonado NA, Cano LE, De Bedout C, Arbelaez CA, Roncancio G, Tabares AM, et al. Association of clinical and demographic factors in invasive candidiasis caused by fluconazole-resistant *Candida* species: a study in 15 hospitals, Medellin, Colombia 2010-2011. Diagn Microbiol Infect Dis 2014;79:280–6.

[14] Garnacho-Montero J, Diaz-Martin A, Garcia-Cabrera E, Ruiz Perez de Pipaon M, Hernandez-Caballero C, Aznar-Martin J, et al. Risk factors for fluconazole-resistant candidemia. Antimicrob Agents Chemother 2010;54:3149–54.

[15] Slavin MA, Sorrell TC, Marriott D, Thursky KA, Nguyen Q, Ellis DH, et al. Candidaemia in adult cancer patients: risks for fluconazole-resistant isolates and death. J Antimicrob Chemother 2010;65:1042–51.

[16] Ben-Ami R, Olshtain-Pops K, Krieger M, Oren I, Bishara J, Dan M, et al. Antibiotic exposure as a risk factor for fluconazole-resistant *Candida* bloodstream infection. Antimicrob Agents Chemother 2012;56:2518–23.

[17] Ylipalosaari P, Ala-Kokko TI, Karhu J, Koskela M, Laurila J, Ohtonen P, et al. Comparison of the epidemiology, risk factors, outcome and degree of organ failures of patients with candidemia acquired before or during ICU treatment. Crit Care 2012;16:R62.

[18] Pfaller MA, Messer SA, Woosley LN, Jones RN, Castanheira M. Echinocandin and triazole antifungal susceptibility profiles for clinical opportunistic yeast and mold isolates collected from 2010 to 2011: application of new CLSI clinical breakpoints and epidemiological cutoff values for characterization of geographic and temporal trends of antifungal resistance. J Clin Microbiol 2013;51:2571–81.

[19] Shah DN, Yau R, Lasco TM, Weston J, Salazar M, Palmer HR, et al. Impact of prior inappropriate fluconazole dosing on isolation of fluconazole-nonsusceptible *Candida* species in hospitalized patients with candidemia. Antimicrob Agents Chemother 2012;56:3239–43.