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Major article

Invasive candidiasis in intensive care units in China: Risk factors and prognoses of *Candida albicans* and non–*albicans Candida* infections

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Background: To investigate the risk factors and prognoses of patients with invasive *Candida albicans* and non–*albicans Candida* (NAC) infection in intensive care units (ICUs) in China.
Methods: Between November 2009 and April 2011, we performed a prospective study of critically ill patients with invasive *Candida* infection from 67 ICUs across China to compare the risk factors and mortality between patients with *C albicans* and NAC infection.
Results: There were 306 patients with proven invasive *Candida*; 244 cases (a total 389 *Candida* isolates) were sent to laboratory for strain identification (*C albicans*, 40.1%; NAC, 59.9%). More patients admitted for surgery or trauma had NAC infection than *C albicans* infection. *C albicans* infection was more common in patients with subclavian vein catheters or peritoneal drainage tubes. Compared with patients with *C albicans* infection, patients with NAC infection had longer antifungal therapy ($P < .001$), longer ICU ($P = .004$) or hospital stay ($P = .002$), and slightly higher mortality (38.4% vs 29.6%), but the difference was not significant ($P = .17$).
Conclusions: *C albicans* remains the most common pathogen in candidiasis in critical care patients. However, the number of NAC infections exceeded *C albicans* infections. Compared with patients with *C albicans* infection, patients with NAC infection had heavier disease burdens.

Invasive *Candida* infection is very common in intensive care units (ICUs); the mortality rate is high. This is true especially in immunosuppressed patients or patients with severe diseases, in whom the mortality rate is 35%-80%.[1-4] Although difficult to diagnose, invasive *Candida* infection remains the third leading cause of ICU infections,[5] causing (responsible for) 17% of all ICU infections.[6] The major risk factors in critically ill patients with invasive fungal infections include age, underlying diseases,[7-12] multisite *Candida* colonization, invasive procedures,[13-16] medication, upper abdominal surgery,[13-16] and immunosuppressive diseases.[17-20] *Candida albicans* is one of the most common pathogens of invasive fungal infections, with an incidence of 40%-82%.[4,21-23] *C albicans* infections account for 50%-70% of ICU infections in the United States;[2,24] in Asia, South America, and Northern Europe, the incidence of non–*albicans Candida* (NAC) infection is higher.[3] In the last 20 years, *C albicans* has been the most common strain isolated from hospitalized patients; however, there is currently a growing trend of NAC infection. In many countries, *Candida glabrata* infections account for 15%-20% of *Candida* infections.[1,25] Fungal resistance has changed, and there is decreased fluconazole susceptibility in some *Candida* spp. Compared with *C albicans*, approximately 60% of NAC is less fluconazole-sensitive.[26-28] The rate of mortality caused by NAC

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infection is higher than that caused by *C albicans*.[1-4,26-28] Therefore, diagnosing *Candida* infections early, screening pathogens into *C albicans* or NAC, and early appropriate empirical therapy are crucial, especially for selecting NAC antifungal drugs. To our knowledge, the risk factors or large-scale surveys and analysis of *C albicans* and NAC infection prognoses in mainland China have not been reported. This was a prospective multicenter study of critically ill Chinese patients with invasive candidiasis in ICUs. The study has important implications and identifies empirical treatment strategies for clinicians.

METHODS

Patient identification and data collection

We conducted a multicenter, prospective, observational study between November 2009 and April 2011 that involved 67 ICUs across China (China-SCAN). We enrolled patients who were aged ≥18 years, with clinical signs of infection (in the treating physician's opinion) and at least 1 of the listed diagnostic criteria: (1) confirmation through histopathology, cytopathology, or direct microscopy of yeast cells in a needle aspiration or biopsy specimen from a normally sterile site (other than mucous membranes); (2) at least 1 *Candida*-positive peripheral blood culture; and (3) a *Candida*-positive culture from a sample obtained by a sterile technique from a normally sterile site (eg, cerebrospinal, pleural, peritoneal, peritoneal abscess fluid). The attending physicians, who also acted as the investigators for the study, managed the patients at their discretion; patients were followed until discharge or death, whichever occurred first. Demographic information, ICU type, clinical patient characteristics (admission diagnosis, ICU admission diagnosis, Acute Physiology and Chronic Health Evaluation score, sepsis-related organ failure assessment score) (Table 1), and medical interventions (total parenteral nutrition, surgery, mechanical ventilation, arterial and venous catheters, body cavity drainage tubes, catheters, antibiotics and antifungal treatment within 2 weeks before diagnosis) (Table 2) were recorded when the patients were admitted to the ICUs. Investigators evaluated both clinical and microbiologic outcomes for invasive candidiasis. Regarding clinical outcome, we defined complete cure as the disappearance of signs and symptoms caused by Invasive Candida Infections and infectious lesions on radiologic examination, partial cure as partial relief of clinical signs and symptoms and improved radiologic findings, and clinical ineffectiveness as persistent or worsened signs, symptoms, and radiologic lesions. The details have been described previously.[29] ICU or hospital stay duration and outcome were recorded.

Pathogen identification

Specimens were sent to the China-SCAN Central Laboratory (Peking University First Hospital) for pathogen detection. We used chromogenic medium (CHROMagar, Paris, France) and API 20C AUX yeast identification kit (bioMérieux, Marcy l'Etoile, France) for species identification. We used the large subunit (26S) ribosomal DNA gene D1/D2 sequences when necessary.[30,31]

Statistical analysis

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

Table 1
Characterization of patients with *Candida albicans* and NAC infection

Risk factor	*C albicans*	NAC	*P* value
Age (y)	62.2 ± 17.26	61.4 ± 21.36	.7644
Sex			
Female	37 (37.8)	40 (27.4)	.0937
Male	61 (62.2)	106 (72.6)	
Weight (kg)	61.8 ± 10.27	64.0 ± 11.78	.2086
ICU type			
Medical	1 (1.0)	6 (4.1)	.0570
Surgical	13 (13.3)	16 (11.0)	
Integrated	77 (78.6)	122 (83.6)	
Others	7 (7.1)	2 (1.4)	
Diagnosis for hospitalization			
Infection	44 (44.9)	56 (38.4)	.3531
Organ failure			
Single organ	4 (4.1)	13 (8.9)	.3700
Multiple organ	3 (3.1)	4 (2.7)	
Surgery and trauma			.0283
Surgery	3 (3.1)	18 (12.3)	
Trauma	11 (11.2)	19 (13.0)	
Diagnosis for ICU admission			
Infection	60 (61.2)	76 (52.1)	.1888
Organ failure			
Single organ	14 (14.3)	35 (24.0)	.1777
Multiple organ	6 (6.1)	9 (6.2)	
Surgery and trauma			.6158
Surgery	20 (20.4)	31 (21.2)	
Trauma	10 (10.2)	21 (14.4)	
APACHE II score	27.2 ± 7.1	26.7 ± 7.1	.6239
SOFA score	10.4 ± 3.4	11.2 ± 3.3	.0738
Underlying disease			
Solid tumor	17 (17.3)	29 (19.9)	.5669
Hematologic malignancy	1 (1.0)	2 (1.4)	>.9999
Diabetes	20 (20.4)	33 (22.6)	.9243
COPD	14 (14.3)	19 (13.0)	.8492
Chronic liver dysfunction	4 (4.1)	9 (6.2)	.5706
Chronic renal insufficiency	9 (9.1)	14 (9.6)	.4571
Chronic heart failure	19 (19.4)	30 (20.5)	.8189
Neutropenia within 2 wk (<500/mm^3)	3 (3.1)	2 (1.4)	.3934
Digestive dysfunction	55 (56.1)	86 (58.9)	.6930

NOTE. Values are mean ± SD, n (%), or as otherwise indicated. Count data between groups were compared using Fisher exact test. Quantitative data between groups were compared using analysis of variance. Data between groups of chronic heart failure (New York Heart Association classification) were compared using the Kruskal-Wallis rank-sum test. Other indicators were compared by Fisher exact test.
APACHE II, Acute Physiology and Chronic Health Evaluation; *COPD*, chronic obstructive pulmonary disease; *ICU*, intensive care unit; *NAC*, non–*albicans Candida*; *SOFA*, sepsis-related organ failure assessment.

Table 2
Comparison of medical intervention and treatment in *Candida albicans* and NAC groups

Risk factor	*C albicans*	NAC	*P* value
Total parenteral nutrition in recent 2 wk	43 (43.9)	60 (41.1)	.6930
Surgery	40 (40.8)	54 (37.0)	.5923
Mechanical ventilation			.3448
Noninvasive	2 (2.0)	6 (4.1)	
Invasive	76 (77.6)	113 (77.4)	
Both	2 (2.0)	—	
Intravascular catheter			
Internal jugular vein	17 (17.3)	17 (11.6)	.2580
Subclavian vein	23 (23.5)	18 (12.3)	.0351
Femoral vein	12 (12.2)	19 (13.0)	1.0000
Ductus arteriosus	7 (7.1)	7 (4.8)	.5759
Nonintravascular catheter			
Chest tube	4 (4.1)	5 (3.4)	1.0000
Peritoneal drainage tube	9 (9.2)	3 (2.1)	.0154
Subdural, intradural, or ventricular drainage tube	1 (1.0)	3 (2.1)	.6508
Urine catheter	15 (15.3)	19 (13.0)	.7067
Antibiotic treatment before diagnosis	76 (77.6)	121 (82.9)	.3234
Antifungal treatment before diagnosis	22 (22.4)	49 (33.6)	.0637

NOTE. Values are n (%) or as otherwise indicated. Count data between groups were compared using Fisher exact test.
NAC, non–*albicans Candida*.