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ORIGINAL ARTICLE

Prognostic factors of candidemia among nonneutropenic adults with total parenteral nutrition

Chen-Chi Tsai [a,b], Chorng-Jang Lay [a,b], Chun-Lung Wang [a,b], Mei-Lin Lin [c,d], Su-Pen Yang [c,d,*]

[a] *Division of Infectious Diseases, Department of Medicine, Buddhist Dalin Tzu Chi General Hospital, Chiayi, Taiwan*
[b] *College of Medicine, Tzu Chi University, Hualien, Taiwan*
[c] *Division of Infectious Diseases, Department of Medicine, Taipei Veterans General Hospital, Taipei, Taiwan*
[d] *Department of Medicine, National Yang-Ming University, Taipei, Taiwan*

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KEYWORDS
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Background: Immediate removal of central venous catheters (CVCs) is not possible in patients with candidemia requiring total parenteral nutrition (TPN). This study analyzed the possible prognostic factors for survival time after onset of candidemia among nonneutropenic adults requiring TPN.
Methods: We conducted a retrospective analysis from September 2003 to August 2005.
Results: A total of 59 nonneutropenic adults with candidemia and requiring TPN were identified retrospectively. All Candida isolates were susceptible to flucytosine and amphotericin B. With the exception of one *C glabrata* isolate, all other isolates were susceptible to fluconazole and itraconazole. The only predictor of 30-day survival rate after onset of candidemia identified in our analysis was an Acute Physiology and Chronic Health Evaluation II (APACHE II) score of 23 points or less. Adults with higher APACHE II scores, who did not have their CVCs changed, did not receive antifungal treatment, or who had thrombocytopenia had shorter survival times after the onset of candidemia.
Conclusions: APACHE II scores, thrombocytopenia, antifungal agents, and CVCs changes are associated with survival time in nonneutropenic adults requiring TPN after the onset of candidemia.

* Corresponding author. Division of Infectious Diseases, Department of Medicine, Taipei Veterans General Hospital, No. 201, Section 2, Shih-Pai Road, Taipei, Taiwan.
E-mail address: antibody_1@msn.com (S.-P. Yang).

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Introduction

The frequency of Candida bloodstream infections has increased in recent decades. The risk factors for candidemia have been well documented and include total parenteral nutrition (TPN).[1–3] Several reports have revealed that the earlier a central venous catheter (CVC) is removed, the better the response is to antifungal therapy.[4,5] Retention of CVCs was shown to be a significant risk factor and was associated with higher mortality in patients with candidemia.[4,5] However, immediate removal of CVCs is not possible in patients requiring TPN after the onset of candidemia. We conducted a retrospective study to analyze the possible prognostic factors after the onset of candidemia among nonneutropenic adults requiring TPN.

Methods

Study population

A retrospective cohort study was performed from September 2003 to August 2005 at a 2,900-bed tertiary referral medical center where there were specialized units for bone marrow and solid organ transplantation, cardiac monitoring, burn care, and intensive care. We reviewed the medical records of adults who required TPN for nutritional support because they were not able to feed enterally. Among these patients, those who developed candidemia during administration of TPN were included in this study. Those patients with less than 500 cells/mm^3 of absolute neutrophil count at the onset of candidemia were excluded. If the patients could resume feeding enterally and their TPN could be discontinued within 1 week after the onset of candidemia, they were excluded. Information, including demographic characteristics, medical history, invasive procedures, medications, laboratory data, and outcome, were collected for analysis.

Definition of terms

Candidemia was defined as the presence of at least one blood culture yielding Candida species. Nosocomial candidemia was defined as symptoms associated with candidemia occurring 48 hours or more after admission. Chronic respiratory failure was defined by the presence of chronic obstructive pulmonary disease or chronic restrictive pulmonary disease diagnosed on the basis of history, physical examination, chest radiography, and respiratory function tests. Thrombocytopenia was defined as a platelet number below 150,000 cells/μL of blood. Recent intra-abdominal surgery was defined as intra-abdominal surgery performed within 1 month before onset of candidemia. Recent chemotherapy was defined as chemotherapy administered within 1 month before onset of candidemia. Chronic steroid treatment was defined as use of a dose equivalent to at least 20 mg prednisolone per day for more than 7 days within 1 month of the onset of candidemia.[6] Congestive heart failure was diagnosed by a cardiovascular physician according to the Framingham Heart Study criteria.[7] Shock was defined as a decrease in systolic blood pressure to less than 90 mmHg or a decrease of at least 40 mmHg below baseline blood pressure despite adequate fluid resuscitation. According to the Sepsis-related Organ Failure Score criteria, the diagnosis of acute respiratory failure was based on the ratio of arterial oxygen tension to fractional inspired oxygen of lower than 200 mmHg.[8] Acute renal failure was defined according the Risk, Injury, Failure, Loss, End stage classification of acute renal failure published by the Acute Dialysis Quality Initiative group in 2004.[9] Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation II (APACHE II) within 72 hours after the symptoms associated with candidemia occurred.[10] Acid-suppressant therapy was defined as the use of proton pump inhibitors or H_2 blockers for more than 7 days within 1 month before the onset of candidemia.

Species identification and antifungal susceptibility testing

Blood samples were processed using a BACTEC NR-660 system (Becton Dickinson Diagnostic Instrument Systems, Spark, MD, USA). Organisms were initially identified by via germ tube analysis and colony morphology on brain heart infusion agar. If necessary, they were also assessed by standard biochemical testing using an ATB ID 32C system (bioMérieux, Marcy-l'Etoile, France) and Yeast Biochemical Cards (Vitek; bioMérieux, Marcy-l'Etoile, France).

Susceptibility of the isolates was evaluated for four antifungal agents, including flucytosine, itraconazole, fluconazole, and amphtericin B, using an ATB fungus 2 test (bioMérieux SA, Marcy-l'Etoile, France) according to the manufacturer's instructions. The cutoff point of minimal inhibitory concentration (MIC) for flucytosine, itraconazole, fluconazole, and amphotericin B was less than 4 mg/L, less than 0.125 mg/L, less than 8 mg/L, and less than 2 mg/L, respectively.[11,12]

Statistical analysis

Univariate analyses were used to identify the factors associated with 30-day survival rate. Pearson's χ^2 test or Fisher's exact two-tailed test was used to examine nominal data, and an unpaired Student t test was used for continuous data. A value of p less than 0.05 was considered statistically significant. The independent factors for 30-day survival were identified by stepwise logistic regression of multivariate analysis. The survival time after onset of candidemia was compared by Kaplan-Meier survival methods. Possible confounding factors were checked by Cox regression models. SPSS 11.5 software for MS Windows (SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

Results

Candidemia occurred in a total of 59 nonneutropenic adults requiring TPN from September 2003 to August 2005. Forty patients were males and the mean age was 66 years with a range of 23—89 years. All episodes of candidemia were nosocomial, and the time of infection was 3—126 days (median 38 ± 29.9 days) after admission. The mean

duration of hospitalization was 73 ± 50.5 days. The mean duration of antibiotic use before occurrence of symptoms related to candidemia was 28 ± 24.4 days. Nearly all patients had tachycardia (100.0%) and fever (98.3%). Severe complications, such as shock (44.1%), acute renal failure (33.9%), and thrombocytopenia (55.9%), were common, and the mean APACHE II score was 22 ± 7.1 points. Thirty-eight isolates were identified as *C albicans*, 9 were *C parapsilosis*, 7 were *C glabrata*, and 5 were *C tropicalis*. All Candida isolates were susceptible to flucytosine and amphotericin B. With the exception of one *C glabrata* isolate, all the other isolates were susceptible to fluconazole and itraconazole.

The overall 30-day survival rate was 45.8% (27/59) after the onset of candidemia. There were six patients who did not receive antifungal treatment and 53 patients who did receive antifungal treatment after the onset of candidemia. The median number of days from the onset of candidemia to administration of antifungal agents was 3 (range −9—22 days). There were six patients with breakthrough candidemia and all of these patients received fluconazole before the onset of candidemia. The mean cumulative dose of fluconazole among these patients was 2,000 mg (range 800—3,600 mg). Three of these patients continued fluconazole treatment because of susceptibility, and they all died within 30 days after the onset of candidemia. Amphotericin B replaced the use of fluconazole in the other three patients, and one of these patients survived more than 30 days. There were 43 patients who initially received fluconazole treatment after the onset of candidemia. Fluconazole was continued in 33 of these patients and was shifted to amphotericin B in the other 10 patients. Among the former, 17 of 33 patients survived more than 30 days, and among the latter, 7 of 10 patients survived more than 30 days. Among the patients initially receiving amphotericin B, two of four survived more than 30 days. No specific antifungal regimen was more effective than the others.

There were 50 patients who received a change in their CVC and 9 patients who did not receive a change in their CVC after the onset of candidemia. Among the latter, all died within 30 days after onset of candidemia. Among the former, the median number of days from the onset of candidemia to the change in CVC was 2 days (range 0—22 days). Sixteen of 32 patients whose CVCs were changed within 3 days after the onset of candidemia survived more than 30 days. Eleven of 18 patients whose CVCs were changed more than 3 days after the onset of candidemia survived more than 30 days. There was no statistically significant difference for 30-day survival rates between these two groups (16/32 *vs.* 11/18; $p = 0.645$).

To assess the risk factors associated with 30-day survival, univariate analysis was performed and the result is presented in Table 1. Recent chemotherapy, an APACHE score of 23 points or higher, absence of antifungal therapy, and not changing CVCs were demonstrated to be associated with 30-day survival. After multivariate logistic regression, the only independent factor for 30-day survival was an APACHE II score of 23 points or higher (odds ratio 4.643; 95% confidence interval 1.355—15.908; $p = 0.009$).

Survival times after the onset of candidemia were compared by Kaplan-Meier survival methods. In the univariate analysis of 30-day survival, the factors with a p value less than 0.5 were considered as probable confounding factors for survival time after onset of candidemia and were included in multivariate Cox regression models. The non-neutropenic adults requiring TPN with higher APACHE II scores, no change of their CVCs, absence of antifungal therapy, or thrombocytopenia demonstrated shorter survival times after the onset of candidemia (Table 2).

Discussion

CVCs have extensive clinical application in intensive care but are often related to infectious complications. Several reports revealed that the earlier CVCs are removed, the better the response is to antifungal therapy.[4,5] In addition, candidemia was prolonged by a median of 3 days when CVCs were not removed immediately in neonates.[5] Candida was shown to produce biofilms in high-glucose medium and colonize indwelling CVCs.[13] The large size of Candida hyphae and pseudohyphae may preclude macrophages from phagocytosis and invasion of vascular structures, facilitating dissemination of Candida.[14] When the catheters are retained, it is difficult to eradicate intravenous Candida. Immediate removal of CVCs has been advised in clinical practice guidelines for the management of candidiasis, but it is impossible in some patients, such as patients requiring TPN.[15]

In this study, all the patients who did not have their CVCs changed died within 28 days. The patients whose CVCs were changed had a longer survival time. Changing of CVCs could decrease biofilm formation and then subsequently increase the efficacy of antifungal agents. However, the correct time to change CVCs is unknown for these patients. In our study, change of CVCs within 3 days after the onset of candidemia did not demonstrate a beneficial effect on 30-day survival rates. Recolonization of Candida species in new CVCs is a problem when intravenous Candida are not eradicated by antifungal agents in those patients whose CVCs were changed immediately after onset of candidemia. Temporary use of peripheral parenteral nutrition to replace TPN may be more suitable for the treatment of candidemia in these patients. However, peripheral lines are difficult to assess in some patients and changing CVCs is very risky in patients with bleeding tendencies. An *in vitro* study has shown that doxycyline-based antifungal agents are effective for the treatment of *C albicans* biofilms.[16] Liposomal amphotericin B and amphotericin B lipid complex all have been shown to be effective against Candida biofilms *in vitro*,[17,18] and caspofungin was demonstrated to be effective for the treatment and prevention of *C albicans* biofilms in mice.[19] Although there have been no clinical studies in humans, these new antifungal agents might be considered in patients with candidemia whose CVCs cannot be removed or changed.

The APACHE II score is the most important prognostic factor associated with survival rate in patients with candidemia.[3,20—23] In our study, APACHE II scores were related to survival time and 30-day survival rates in patients requiring TPN. Among our patients, several had breakthrough infections. Although clinical isolates were susceptible to fluconazole *in vitro*, continuous use of fluconazole was not effective for the treatment of this kind of

Table 1 Characteristics associated with 30-day survival after onset of candidemia according to univariate analysis among patients requiring TPN

Variable	Survival ($n = 27$)	Death ($n = 32$)	p
Age 65 yr or older	17 (63.0)	22 (68.8)	0.848
Gender, male	17 (63.0)	23 (71.9)	0.653
Candida albicans	17 (63.0)	21 (65.6)	1.000
Onset of candidemia in the intensive care unit	15 (55.6)	14 (43.8)	0.521
Underlying disease			
Recent intra-abdominal surgery	17 (63.0)	18 (56.3)	0.797
Ventilator support	9 (33.3)	14 (43.8)	0.583
Recent chemotherapy	0 (0.0)	7 (21.9)	0.012*
Chronic steroid therapy	5 (18.5)	8 (25.0)	0.777
Chronic respiratory failure	5 (18.5)	7 (21.9)	1.000
Congestive heart failure	3 (11.1)	2 (6.3)	0.652
Diabetes mellitus	4 (14.8)	4 (12.5)	1.000
Acid suppressant therapy	16 (59.3)	25 (78.1)	0.199
End-stage renal disease	2 (7.4)	1 (3.1)	0.593
Signs			
Shock	10 (37.0)	16 (50.0)	0.462
Acute renal failure	7 (25.9)	13 (40.6)	0.362
Conscious change	4 (14.8)	11 (34.4)	0.156
Thrombocytopenia	12 (44.4)	21 (65.6)	0.171
APACHE score of 23 points or higher	7 (25.9)	20 (62.5)	0.011*
Therapy			
No use of antifungal therapy	0 (0.0)	6 (18.8)	0.027*
No change of CVCs	0 (0.0)	9 (28.1)	0.003*
Fluconazole therapy	25/27 (92.6)	24/26 (92.3)	1.000
Antifungal therapy was started within 3 d after onset of candidemia	21/27 (77.8)	19/26 (73.1)	0.938
Change of CVCs within 3 d after onset of candidemia	16/27 (59.3)	16/23 (69.6)	0.645

APACHE = Acute Physiology and Chronic Health Evaluation; CVCs = central venous catheters; SD = standard deviation; TPN = total parenteral nutrition.
Data are presented as n (%) or mean ± SD.
*$p < 0.05$.

candidemia. One study showed that the MICs of Candida isolates to fluconazole correlated with daily and cumulative doses of fluconazole in the patients with breakthrough infections,[24] and the patients with a higher cumulative dose of fluconazole were more likely to be infected with isolates of Candida with higher MICs to fluconazole. In addition to fluconazole, breakthrough candidemia can also occur with amphotericin B and caspofungin.[25,26] It is possible that the

Table 2 Hazard ratios of all probable confounding factors for the survival time after onset of candidemia among patients requiring TPN by multivariate Cox regression models

Probable variables	Hazard ratio	95% confidence interval	p
APACHE II score of 23 points or higher	2.793	1.333—5.851	0.006*
No change of central venous catheters	9.013	3.160—25.702	<0.001*
No use of antifungal therapy	33.509	6.822—164.580	<0.001*
Thrombocytopenia	2.988	1.372—6.510	0.006*
Shock	1.691	0.769—3.717	0.191
Acute renal failure	1.502	0.693—3.257	0.303
Conscious change	1.142	0.481—2.711	0.763
Age 65 yr or older	0.663	0.287—1.528	0.334
Acid-suppressant therapy	1.480	0.679—3.225	0.324
Recent chemotherapy	0.745	0.305—1.822	0.519

APACHE = Acute Physiology and Chronic Health Evaluation; TPN = total parenteral nutrition.
*$p < 0.05$.

MIC to fluconazole is higher in isolates from patients with breakthrough candidemia, who wound require a higher dose of fluconazole. However, most of clinical laboratories are not able to provide MICs of Candida species. As such, a change in antifungal agents seems to be a reasonable alternative for the treatment of breakthrough infections in these situations.

All those patients who did not receive antifungal therapy died within 2 weeks. In most cases, they died before blood cultures yielded Candida, and this resulted in these patients having more severe candidemia. In some reports, a better survival rate was demonstrated in the patients treated early with antifungal agents.[27,28] Although a better survival rate was noted in our study after controlling for APACHE II score, this was not statistically significant because of the small study population. Empirical use of antifungal agents before a positive blood culture should be considered earlier in patients requiring TPN, especially for those with higher APACHE II scores. In our study, thrombocytopenia was also associated with a lower survival time in patients with candidemia requiring TPN. Some reports have also shown that thrombocytopenia is an independent predictor of death attributable to candidemia.[21,29] Thrombocytopenia is a marker for disseminated intravascular coagulopathy in patients with severe infections. The retention of CVCs can lead to thrombophlebitis with seeding of Candida into the clots, which would affect the efficacy of antifungal agents, prolong candidemia, and then cause disseminated intravascular coagulopathy.[30] When disseminated intravascular coagulopathy develops, patients would be expected to demonstrate a lower survival time.

A better outcome for patients requiring TPN with fungemia because of *C parapsilosis* had been noted.[31] Some patients survived in spite of the fact that their main treatment was only removal of the catheter. However, this phenomenon was not observed in our study. Six of nine patients with *C parapsilosis* candidemia survived more than 30 days after onset of candidemia, and they all received antifungal agents and their CVCs were changed after the onset of candidemia. Of the other three patients not surviving more than 30 days, one did not receive antifungal agents and one did not receive a change in the CVC. Compared with the patients with *C albicans* candidemia (30-day survival rate: 17/38), a better outcome was found in patients with *C parapsilosis* candidemia, but this was not shown to be statistically different because of the small sample size.

Our study had several limitations. First, the lack of statistical power resulting from the small sample size may have contributed to concealing some differences among these patients. Second, because of the retrospective design of this study, we could not control for all confounding variables effecting survival. Prospective studies involving large numbers of patients are required before any firm recommendations for changing CVCs in these patients can be made. In conclusion, our study results indicated that APACHE II scores are an independent prognostic factor for 30-day survival rates in patients requiring TPN after the onset of candidemia. Thrombocytopenia, antifungal agents, APACHE II scores, and changing of CVCs are associated with total survival time after the onset of candidemia. Empirical antifungal agents may be considered earlier in patients requiring TPNs, especially in the patients with higher APACHE II scores. Also, changing CVCs to decrease colonization of Candida spices appears to be important for prolonging the survival time in these patients.

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