Candidemia in Siriraj Hospital: Epidemiology and Factors Associated with Mortality

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Objective: *To study the epidemiology of candidemia and to identify risk factors for mortality among adult patients*
Material and Method: *Retrospective analysis of patients with candidemia in a 2400-bed tertiary-care university hospital in Bangkok, Thailand from June 2006 to May 2009.*
Results: *During the study period, 147 patients (50 % male) with clinically significant candidemia were identified, with a mean age of 61 years. The underlying conditions included renal failure (47%), abdominal surgery within 30 days (31%), diabetes (27%), hematologic malignancies (25%), solid malignancies (25%), neutropenia (23%), and liver disease (11%). Nearly all patients (98%) received antibacterial therapy within 30 days. The four most common Candida species were C. albicans (39%), C. tropicalis (28%), C. glabrata (22%) and C. parapsilosis (6%). Only sixty-nine patients (47%) received appropriate antifungal therapy within 72 hours. The 28-day all-cause mortality was 59%. By multivariate analysis, the independent risk factors associated with mortality were neutropenia from chemotherapy OR = 9.12 (2.94-28.31), septic shock OR = 3.66 (1.54-8.66), ICU admission OR = 3.18 (1.27-7.92), inappropriate antifungal therapy within 72 hours OR = 2.38 (1.07-5.28) and renal failure OR = 2.34 (1.07-5.13).*
Conclusion: *Adult patients with candidemia had a high mortality rate particularly those receiving an inappropriate antifungal therapy. Empirical antifungal therapy should be considered in selected patients on the basis of underlying conditions, severity of illness and risk factors for mortality.*

Keywords: *Candidemia, Candida albicans, Non-albicans Candida, Invasive candidiasis, Risk factor, Epidemiology, Inappropriate antifungal therapy*

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Candidemia is an important cause of morbidity and mortality in immunocompromised patients. The incidence of candidemia is increasing especially in preterm infants, neutropenic patients, patients with central venous catheter, critically ill patients, and burn patients. Candidemia also results in prolonged hospital stay and substantial healthcare costs[1-4]. Although antifungal agents are widely used and therapeutic guidelines have been formulated, candidemia carries a high mortality rate of 30-80%[1,2]. The major independent risk factors for mortality are non-*albicans Candida* infection and inadequate antifungal therapies[5,6]. However, few studies have specifically investigated the importance of timing of antifungal therapies with invasive candidiasis[7-11]. The authors thus conducted a retrospective study to evaluate the epidemiologic data of candidemia and risk factors for mortality at the largest university hospital in Thailand.

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Material and Method

A retrospective study was conducted among patients older than 15 years, who were diagnosed with candidemia and were admitted between June 2006 to May 2009 at Siriraj Hospital 2,400-bed tertiary-care university hospital in Bangkok, Thailand.This study was reviewed and approved by Siriraj Institutional Review Board (SiRB).

Definition

Candidemia was defined when a patient had both at least one blood culture positive for *Candida* and the presence of relevant clinical signs and symptoms. Inappropriate antifungal therapy was considered when the patient did not receive (1) at

least one in vitro active antifungal agent within a specific period of time (12 or 72 hours) after blood cultures were obtained or (2) standard recommended dosage of antifungal agent in accordance with the Clinical and Laboratory Standards Institute (CLSI) definitions for antifungal susceptibility testing of yeasts and the Infectious Diseases Society of America guidelines for the management of candidiasis 2009[12,13].

Data collection

The following data were recorded: age, sex, admission ward, comorbid diseases/conditions, indwelling central venous catheterization or Foley's catheter, treatment with corticosteroid ($\geq$ 20 mg/day for > 1 week), parenteral nutrition, surgical procedures, neutropenia (neutrophils < 0.5 x 10^9 cells/l) and stay in the intensive care unit (ICU). The severity of infection and concomitant bacteremia were also evaluated. Concomitant bacteremia was defined as the isolation of bacteria from the blood within 24 hours of the initial positive fungal culture.

For each patient with candidemia, the following were recorded: date and time of blood culture collection and date and time of administration of the first antifungal agent. These data were obtained using computerized records from the microbiology laboratory and nursing records for medication administration.

Microbiologic study

BacT/Alert FA aerobic hemoculture bottles (bioMerieux, Durham, NC) were used to detect both yeasts and bacteria. Blood cultures were taken according to Clinical and Laboratory Standards Institute (CLSI) guidelines. The BacT/Alert FA vials were incubated in the BacT/Alert 3D automated blood culture systems for a maximum period of 14 days for fungus and 5 days for bacteria, according to the recommendations from the manufacturers. Fungal isolates that have a germ tube formation and chlamydoconidia production were identified as *C. albicans*. The species of non-*albicans Candida* was identified using Candi-select test[14] and Rapid ID™ Yeast Plus System (Remel, USA). Susceptibility testing of *Candida spp.* is not routinely done at our hospital. If the test is ordered, commercially prepared dried color imetric micro dilution panel (Sensititre® Yeast One, TREK Diagnostic Systems, Cleveland, Ohio) will be performed. The MICs of all eight agents (itraconazole, fluconazole, voriconazole, ketoconazole, posaconazole, 5-flucytosine, caspofungin and amphotericin B) were read with the aid of a reading mirror.

Statistical analysis

Variables were expressed as mean, ranges and standard deviation (SD) for numerical variables and as frequencies and percentages for categorical variables. Characteristics of patients were analyzed according to the factors associated with 28-day mortality. Comparison of categorical data between groups were performed using the Mann-Whitney U and Chi-square or Fisher's exact test as appropriate. The authors performed a multivariate stepwise logistic regression analysis among the factors that were significant at the 20% level in univariate regressions. Kaplan-Meier survival analysis was done to compare survival between the two groups stratified by appropriate antifungal drug within 72 hours. Curves were compared by means of the log rank test. All tests were based on two-tailed tests and p-values < 0.05 were considered significant. Data were analyzed using Predictive Analytics Software 17.0.1 (SPSS Inc., Chicago Ill).

Results

During the study period, a total of 147 distinct episodes of candidemia were identified. The average age of the studied patients was 61.3 $\pm$ 18.6 years, range of 15-98 years. Patients were admitted on medical ward 74.8%, surgical ward 21.8%, ENT ward 2.0% and OB/Gyn ward 1.4%. Forty-one patients (27.9%) were admitted ICU at the time of candidemia. One third of patients are associated with the development of septic shock at the time of blood culture extraction. The patient characteristics and univariate analysis of factors associated with mortality of candidemic patients are provided in Table 1.

Mycological data

C. albicans was the most common species (38.8%), followed by *C. tropicalis* (27.9%), *C. glabrata* (21.8%). *C. parapsilosis* (6.1%) and *C. krusei* were also found, but only 1.4%. Unfortunately, susceptibility testing of *Candida spp.* is not routinely done at our hospital. Antifungal susceptibility testing was done only in 25 of 147 patients (17%), the results were shown on Table 2. Fluconazole resistance occurred in 2 (8%) isolates, including 1 isolate of *C. glabrata* and 1 of *C. krusei*; six cases (24%) were classified as SDD to fluconazole (5 case of *C. glabrata*, 1 of *C. parapsilosis*). One *Candida albicans* isolate exhibited a MIC of 2 μg/ml to amphotericin B, but this *C. albicans* isolate was not resistant to fluconazole and

Table 1. Demographic features and univariate analysis of factors associated with 28-day all-cause mortality of candidemia patients (n = 147)

Characteristic	No. (%) of patients (n = 147)	Survived (n = 61)	Died (n = 86)	p-value
Age ≥ 65 yr	78 (53.1)	30 (49.2)	48 (55.8)	0.43
Male	74 (50.3)	31 (50.8)	43 (50.0)	0.92
No. of cases of underlying diseases				
Renal failure	69 (46.9)	22 (36.1)	47 (54.7)	0.03
Diabetes mellitus	39 (26.5)	22 (36.1)	17 (19.8)	0.03
Lymphoma	19 (12.9)	5 (8.2)	14 (16.3)	0.15
GI malignancy	17 (11.6)	9 (14.8)	8 (9.3)	0.31
Significant liver disease (liver failure or cirrhosis)	16 (10.9)	6 (9.8)	10 (11.6)	0.73
Autoimmune Disease/vasculitis	12 (8.2)	6 (9.8)	6 (7.0)	0.55
Burns	6 (4.1)	5 (8.2)	1 (1.2)	0.08
Transplantation	5 (3.4)	2 (3.3)	3 (3.5)	1.00
HIV infection	1 (0.7)	1 (1.6)	0 (0.0)	0.41
No. of patients with characteristic				
Neutropenia	34 (23.1)	7 (11.5)	23 (26.7)	0.02
Required mechanical ventilation	65 (44.2)	23 (37.7)	42 (48.8)	0.18
Indwelling urinary catheter	107 (72.8)	39 (63.9)	68 (79.1)	0.04
Central venous catheter	50 (34.0)	22 (36.1)	28 (32.6)	0.66
Recent abdominal surgery within 30 days	45 (30.6)	20 (32.8)	25 (29.1)	0.63
Salvage chemotherapy	37 (25.2)	1 (1.6)	9 (10.5)	0.05
Lipid-based parenteral nutrition	34 (23.1)	15 (24.6)	19 (22.1)	0.72
Antibacterial therapy within 30 days	144 (98.0)	58 (95.1)	86 (100)	0.07
Antifungal therapy within 30 days	6 (4.1)	3 (4.9)	3 (3.5)	0.69
Prednisolone > 20 mg/day (equivalence) ≥ 7 days within 30 days	21 (14.3)	5 (8.2)	16 (18.6)	0.08
Concomitant bacteremia	14 (9.5)	7 (11.5)	7 (8.1)	0.50
Severity of illness				
Septic shock*	52 (35.4)	13 (21.3)	39 (45.3)	0.003
ICU admission	41 (27.9)	12 (19.7)	29 (33.7)	0.06
Candida species				
C. albicans	57 (38.8)	27 (44.3)	30 (34.9)	0.25
non-*albicans Candida*	90 (61.2)	34 (55.7)	56 (65.1)	0.25
C. tropicalis	41 (27.9)	12 (19.7)	29 (33.7)	0.06
C. glabrata	32 (21.8)	11 (18.0)	21 (24.4)	0.36
C. parapsilosis	9 (6.1)	5 (8.2)	4 (4.7)	0.49
Antifungal treatment				
Inappropriate antifungal therapy within 12 hours	140 (95.2)	58 (95.1)	82 (95.3)	1.00
Inappropriate antifungal therapy within 72 hours	78 (53.1)	26 (42.6)	52 (60.5)	0.03

***** At the time of collecting the first positive Candida blood culture

voriconazole.

Treatment and outcomes

Antifungal therapy was given to 101 patients (68.7%). Approximately half of candidemic patients (46.9%) received appropriate antifungal therapy within 72 hours (68% received amphotericin B, 28% received fluconazole, and 4% received caspofungin). Only 7 patients (4.8%) received appropriate antifungal therapy within 12 hours. The reasons that antifungal use was in appropriate were as follows: treatment delay of ≥ 72 hours from candidemia onset (94%), using a resistant in vitro antifungal drug (4%), inadequate loading dose of fluconazole (1%), and no dose adjustment in renal impairment (1%).

Unfortunately, 28-day all-cause mortality was

Table 2. In vitro susceptibilities of blood stream *Candida spp.* isolates at Siriraj Hospital from June 2006 to May 2009

Species	N*	Susceptibility+ (N)							
		Amphotericin B	Fluconazole			Voriconazole			Caspofungin
			S	S-DD	R	S	S-DD	R	
C. albicans	8	7++	8	-	-	8	-	-	8
C. tropicalis	8	8	8	-	-	8	-	-	8
C. glabrata	6	6	-	5	1	-	-	-	6
C. parapsilosis	2	2	1	1	-	2	-	-	2
C. krusei	1	1	-	-	1	1	-	-	1
All species	25	24	17	6	2	25	-	-	25

+ S indicates susceptible; S-DD, susceptible dose dependent; R, resistant
++ MIC of Amphotericin B-resistant *C. albicans* = 2 μg/ml

Table 3. Multivariate analysis of factors associated with 28-day all-cause mortality of candidemic patients (n = 147)

	Survived (n = 61)	Died (n = 86)	Odd Ratio (95% CI)	p-value
Neutropenia	7 (11.5)	23 (26.7)	9.12 (2.94-28.31)	< 0.001
Septic shock*	13 (21.3)	39 (45.3)	3.66 (1.54-8.66)	0.003
ICU admission	12 (19.7)	29 (33.7)	3.18 (1.27-7.92)	0.013
Inappropriate antifungal therapy within 72 hours*	26 (42.6)	52 (60.5)	2.38 (1.07-5.28)	0.033
Renal failure	22 (36.1)	47 (54.7)	2.34 (1.07-5.13)	0.034

* the time of collecting the first positive Candida blood culture

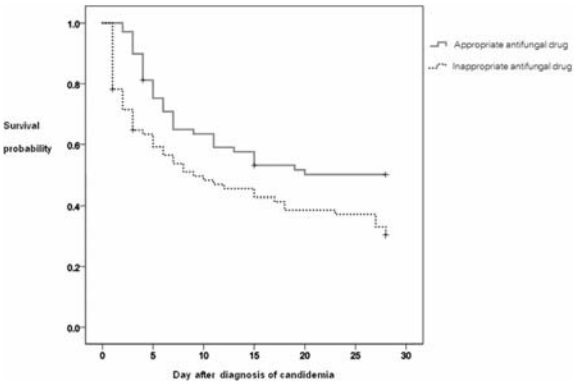

Fig. 1 Kaplan-Meier survival curve of candidemic patients receiving early (< 72 hr) or late (≥ 72 hr) appropriate antifungal therapy (p-value = 0.009)

relatively high, as it was 58.5%. Independent factors associated with mortality of candidemic patients are shown on Table 3. From survival analysis, delay in appropriate antifungal therapy of greater than 72 hours from the time when the first positive *Candida* blood culture was drawn was associated with an increase in mortality as shown in Kaplan-Meier survival curves (Fig. 1).

Discussion

The demography and associated conditions predisposing to candidemia in the present study are similar to those described in previous reports, such as elderly, diabetes, neutropenia, hematologic malignancy, solid tumor, previous antibiotic treatment, total parenteral nutrition and the presence of indwelling catheters or central venous catheter[4-6,15-19].

C. albicans remains the most commonly isolated species of candidemia in the present study, accounting for 38.8 percent of all isolates. This is similar to several other reports in the United States, Europe, and Thailand[3,4,20-26]. The three most common species of non-*albicans Candida* in the present study were *C. tropicalis* (28%), *C. glabrata* (22%) and *C. parapsilosis* (6%). The predominance of *C. tropicalis* in Thailand was interesting and is in contrast to several studies in the USA and UK, which show a predominance of *C. glabrata*[5,6,10,15,26-31]. Publications from India and

Singapore also show similar trends in a shift towards *C. tropicalis* as the primary cause of non-*albicans* candidemia[32,33]. A plausible explanation for *C. tropicalis* predominance in the tropics that it is a geographic variation in candida epidemiology[32].

Although *C. albicans* and *C. tropicalis* are generally susceptible to azole antifungal agents, *C. glabrata and C. krusei* are more often resistant to fluconazole. The authors do not recommend fluconazole for empirical therapy in candidemic patients. According to the 2009 Infectious Diseases Society of America (IDSA) candidias is guidelines and epidemiological studies in Thailand, the choice of empirical antifungal therapy should be echinocandins, or amphotericin B[5,6,13,26].

The overall 28-day mortality of 59% is higher than a recent report from the USA and Europe which is 30-49%[9,34,35]. Independent factors associated with mortality in the present study were neutropenia, renal failure, septic shock, ICU admission, and in appropriate antifungal therapy within 72 hours. Approximately half of candidemic patients (53.1%) did not receive any antifungal therapy within 72 hours. Physicians in the study only infrequently considered candidemia to be a cause of sepsis. This observation is consistent with results from other studies involving patients with candidemia[36-38].

The present study has a number of limitations. This is a retrospective observational study of patients in a single institution. Consequently, the authors had insufficient information about the severity of the illness and antifungal susceptibility test that might be independent factors influencing mortality. However, the results of our study were consistent with several studies[5,6,26,39,40].

In conclusion, the overall mortality rate among candidemic patients was high. Timely and effective antimicrobial therapy is crucial for successful management of candidemia. The addition of an antifungal agent to the initial empiric antimicrobial regimen should be strongly considered in septic, hospitalized patients, especially among those with known multiple risk factors for candidemia.

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Potential conflicts of interest

None.

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การติดเชื้อราแคนดิดาในกระแสเลือดในโรงพยาบาลศิริราช: ปัจจัยเสี่ยงในการเสียชีวิต

อธิรัฐ บุญญาศิริ, จุรี เจียรนัยศิลาวงศ์, สุสัณห์ อาศนะเสน

วัตถุประสงค์*: เพื่อศึกษาระบาดวิทยาของการติดเชื้อราแคนดิดาในกระแสเลือดและปัจจัยที่มีผลต่อการเสียชีวิตในผู้ใหญ่*

วัสดุและวิธีการ*: คณะผู้นิพนธ์ทำการศึกษาข้อมูลย้อนหลังในผู้ป่วยทั้งหมดที่แยกเชื้อราแคนดิดาได้จากเลือดในโรงพยาบาลตติยภูมิขนาด 2,400 เตียงแห่งหนึ่งในกรุงเทพมหานครระหว่าง 1 มิถุนายน พ.ศ. 2549 ถึง 31 พฤษภาคม พ.ศ. 2552*

ผลการศึกษา*: ผู้ป่วยทั้งหมดจำนวน 147 ราย เข้าเกณฑ์ในการศึกษานี้ ผู้ป่วยครึ่งหนึ่งเป็นเพศชาย อายุเฉลี่ยประมาณ 61 ปี ปัจจัยที่พบกับภาวะนี้ ได้แก่ ภาวะไตวาย (ร้อยละ 47), ได้รับการผ่าตัดช่องท้องภายใน 30 วัน (ร้อยละ 31), โรคเบาหวาน (ร้อยละ 27), โรคมะเร็งทางโลหิตวิทยา (ร้อยละ 25), โรคมะเร็ง (ร้อยละ 25), ภาวะเม็ดเลือดขาวนิวโตรฟิลต่ำ (ร้อยละ 23), และโรคตับ (ร้อยละ 11) ผู้ป่วยเกือบทั้งหมด (ร้อยละ 98) ได้รับยาต้านเชื้อแบคทีเรียภายใน 30 วัน เชื้อก่อโรคที่พบบ่อยที่สุด 4 อันดับแรกได้แก่ C. albicans (ร้อยละ 39), C. tropicalis (ร้อยละ 28), C. glabrata (ร้อยละ 22), และ C. parapsilosis (ร้อยละ 6) ผู้ป่วยเพียง ร้อยละ 47 ได้รับยาต้านเชื้อราอย่างเหมาะสมภายใน 72 ชั่วโมง อัตราการเสียชีวิตรวมภายใน 28 วัน พบสูงถึงร้อยละ 59 ปัจจัยอิสระที่สัมพันธ์กับอัตราการเสียชีวิตจากการวิเคราะห์ทางสถิติแบบพหุตัวแปร (Multivariate Analysis) คือภาวะเม็ดเลือดขาวนิวโตรฟิลต่ำจากยาเคมีบำบัด OR = 9.12 (2.94-28.31), ภาวะช็อกในขณะที่สงสัยการติดเชื้อในกระแสเลือด OR = 3.66 (1.54-8.66), เข้ารับการรักษาตัวในหอผู้ป่วยวิกฤต OR = 3.18 (1.27-7.92), การได้รับยาต้านเชื้อราอย่างไม่เหมาะสมภายใน 72 ชั่วโมงแรก OR = 2.38 (1.07-5.28) และภาวะไตวาย OR = 2.34 (1.07-5.13)*

สรุป*: จากการศึกษานี้ผู้ป่วยที่มีการติดเชื้อราแคนดิดาในกระแสเลือดมีอัตราการเสียชีวิตค่อนข้างสูง โดยเฉพาะผู้ป่วยที่ได้รับยาต้านเชื้อราอย่างไม่เหมาะสม แพทย์ควรพิจารณาการให้ยาต้านเชื้อราในการรักษาเบื้องต้นที่เหมาะสมก่อนที่จะทราบผลเพาะเชื้อ ในผู้ป่วยที่สงสัยว่ามีการติดเชื้อในกระแสเลือดที่อาการรุนแรงและมีปัจจัยเสี่ยงในการติดเชื้อรา*