Original Article

Epidemiology of Candidemia at King Chulalongkorn Memorial Hospital, Thailand

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ABSTRACT

The present study was conducted to evaluate the epidemiologic data of candidemia at King Chulalongkorn Memorial Hospital, a 1,200-bed tertiary hospital, from September 1991 to January 2003. A total of 235 episodes of candidemia were identified. Complete medical records were available in only 118 cases. The median age of the patients was 37 years (range: 8 months-85 years), and 70 (59.3%) cases were males. All patients had at least one identifiable risk factor. All infections were nosocomial. Most of them (74, 62.7%) were in intensive care units (ICUs) at the onset of candidemia. *Candida albicans* and non-*albicans Candida* accounted for 101 (42.9%) and 134 (57.1%) cases, respectively. Non-*albicans Candida* were the predominant species during two periods, before 1997 and after 2001. In contrast, *C. albicans* was the predominant species between 1997 and 2000. The species of non-*albicans Candida* was identified in only 16 isolates (12.2%). There were 13 *C. tropicalis* (9.9%), 2 *C. parapsilosis* (1.52%) and 1 *C. guilliermondii* (0.76%). The overall mortality was 50.8 percent (60 of 118 patients). The independent risk factor associated with mortality was the presence of a central venous catheter. (*J Infect Dis Antimicrob Agents 2005;22:59-69.*)

INTRODUCTION

Fungi have recently played an increasingly important role as pathogens in nosocomial infections, and nosocomial candidemia is associated with substantial mortality, longer hospital stays and higher health care costs.[1-7] The mortality among patients with candidemia remains high, at 30-80 percent[4-8], even though antifungal agents are widely used and therapeutic guidelines have been formulated.[9] The data from the National Nosocomial Infections Surveillance (NNIS) showed that *Candida* now rank as the fourth most common cause

of nosocomial bloodstream infections in the United

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States.[3,10] The main contributors to this increase include the severity of illness of hospitalized patients, the growing number of invasive devices or procedures, the aggressive immunosuppressive therapy and the widespread use of broad-spectrum antibiotics.[4,11-14]

Furthermore, a recent shift from *C. albicans* to non-*albican*s *Candida* as the dominant causative pathogens has been described in many hospitals.[15-17] Several studies have attributed this change to the increased use of azole prophylaxis in immuno-compromised patients.[18] Few studies are available from European hospitals[17,19-20], and showed different epidemiologic results between countries despite being conducted in the same study period. A Norwegian study conducted in the early 1990s showed a stable incidence of candidemia and a stable contribution of species of *Candida*.[21] In contrast, a Dutch survey conducted in the same period described an increased incidence of candidemia with non-*albicans Candida* as the dominant species.[19] An investigation of the European Confederation of Clinical Mycology between 1998 and 1999 showed the predominance of *C. albicans*.[17]

These observations suggest that the epidemiology of candidemia may be different between countries, and there are a few studies in Thailand. We thus conducted a retrospective study to evaluate the epidemiologic data of candidemia at King Chulalongkorn Memorial Hospital (KCMH), a 1,200-bed tertiary hospital, from September 1991 to January 2003.

MATERIALS AND METHODS

All records of blood culture isolates positive for *Candida* from the Department of Clinical Microbiology Laboratory were collected from September 1991 to January 2003. The medical records of these patients with candidemia were then identified and analyzed.

Definition

Candidemia was defined when a patient had compatible clinical manifestations and at least one blood culture positive for *Candida*. Episodes of candidemia were categorized as community-acquired or nosocomial infection, according to the definitions of the Center for Diseases Control and Prevention.[22] Potential risk factors were considered relevant if they were present within 30 days prior to the onset of candidemia. Neutropenia was defined when an absolute neutrophil count was <1,000 cells/µl. Death of patient was considered related or attributable to candidemic episode if it occurred during the phase of active infection. Only attributable or related mortality was used in the analysis in this study.

Microbiologic study

Blood cultures were processed at the Clinical Microbiology Laboratory using the conventional method (Sabouraud dextrose broth) from September 1991 to December 2002, and the Bactec 9240 system (Becton Dickinson, USA) in 2003. 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 the analytical profile index (API) 20 AUX system (bioMerieux Vitek, USA).

Statistics

A univariate analysis was performed to identify individual risk factors associated with mortality, using the odds ratio and its corresponding 95 percent confidence interval (95% CI). Factors significantly associated with mortality in the univariate analysis were further evaluated in a stepwise logistic regression model. All tests were based on two-tailed tests, and P values <0.05 were considered significant. Statistical analyses were performed using SPSS software, version 12.0.

RESULTS

During the 13-year study period, the prevalence of candidemia in KCMH was 6.14 percent (235 of

3,827 blood cultures). Only 118 had complete medical records available, and thus were eligible for epidemiologic study.

Demographic data

Complete medical records were available in only 118 cases. The demographic characteristics and associated conditions of all the patients are shown in Table 1. All infections were nosocomial. The median length of hospital stays before the onset of candidemia was 55.8 days (range: 2-551 days). The median age of the patients was 37 years (range: 8 months-85 years), and 70 (59.3%) were males.

Predisposing factors

At the onset of candidemia, all cases had at least one predisposing illness or intervention (Table 1). The preexisting illnesses included neutropenia (27, 23%), diabetes (21, 17.8%), hematologic malignancy (21, 17.8%), solid tumor (16, 13.6%) and human immu-nodeficiency virus (HIV) (8, 6.8%). Other interventions predisposing to infection included previous antibiotic treatment (110, 93.2%), previous surgery (36, 30.5%), total parenteral nutrition (52, 44.1%) and the presence of indwelling catheters or prosthesis including central venous catheter (78, 66%), urinary catheter, endotracheal tube (5, 4.2%) and prosthesis (4, 3.4%). The patients were hospitalized at the Department of Medicine (60, 50.8%), Pediatrics (37, 31.4%) and Surgery (21, 17.8%). Most of them (74, 62.7%) were in intensive care units (ICUs) at the onset of candidemia.

Table 1. Demographic characteristics and associated illnesses of 118 patients with candidemia.

Variable	No. (%) of episodes (n = 118)
Age (mean, range)	37 y (8 mo-85 y)
Sex	
Male	70 (59.3)
Female	48 (40.7)
Acquistion	
Nosocomial	118 (100)
Community	0
Admitting ward	
Non-ICU	44 (37.3)
ICU	74 (62.7)
Department	
Medicine	60 (50.8)
Surgery	21 (17.8)
Pediatrics	37 (31.4)
Associated conditions	
Preexisting illness	
Neutropenia	23 (19.5)
Hematologic malignancy	21 (17.8)
Diabetes	21 (17.8)
Solid tumor	16 (13.6)
HIV infection	8 (6.8)
Transplantation	1 (0.8)
Interventions	
Previous antibiotic treatment	110 (93.2)
Previous surgery	36 (30.5)
Central venous catheter	78 (66.1)
Parenteral nutrition	52 (44.1)
Urinary catheter and endotracheal tube	5 (4.2)
Prosthesis	4 (3.4)

Mycologic data

During the 13-year study period, the prevalence of candidemia in KCMH was 6.14 percent (235 of 3,827 blood cultures). *C. albicans* and non-*albicans Candida* accounted for 101 (42.9%) and 134 (57.1%) episodes, respectively. The evolution of distribution of *Candida* from September 1991 to January 2003 is shown in Figure 1. In addition, the distribution of *C. albicans* and non-*albicans Candida* according to adult and pediatric patients is shown in Table 2. Non-*albicans Candida* were the predominant species during two periods, before 1997 (6 of 9 in 1991-1992, 9 of 9 in 1993-1994 and 12 of 16 in 1995-1996) and after 2001 (47 of 72). In contrast, *C. albicans* was the predominant species between 1997 and 2000 (25 of 51 in 1997-1998 and 44 of 78 in 1999-2000). The species of non-*albicans Candida* was identified in only 16 isolates (12.2%). These included *C. tropicalis* (13), *C. parapsilosis* (2) and *C. guilliermondii* (1).

Treatment and outcome

Antifungal therapy was given to only 45 of 118 (38%) patients. These agents included amphotericin B (34), fluconazole (8), itraconazole (2) and ketoconazole (1). Treatment and clinical outcome are shown in Table 3. The mortality rate was 50.8 percent (60 of 118). The associated risk factors for mortality in the univariate analysis included admission in the ICUs (59% vs. 36%, $p<0.05$) and the presence of central venous catheter (60% vs. 32%, $p<0.05$) (Table 4). In the multivariate analysis, only the presence of central venous catheter was associated with mortality (adjusted odds ratio: 3.03 with 95% CI: 1.03-8.9, p=0.04).

DISCUSSION

Bloodstream infections due to *Candida* have become an increasingly important cause of morbidity and mortality in hospitalized patients, and a number of studies have documented the increased incidence of systemic candidiasis in recent decades.[1-7,23-25] Our study demonstrated an increasing trend of candidemia, from 9 patients during 1991-1992 to 72 patients during 2001-

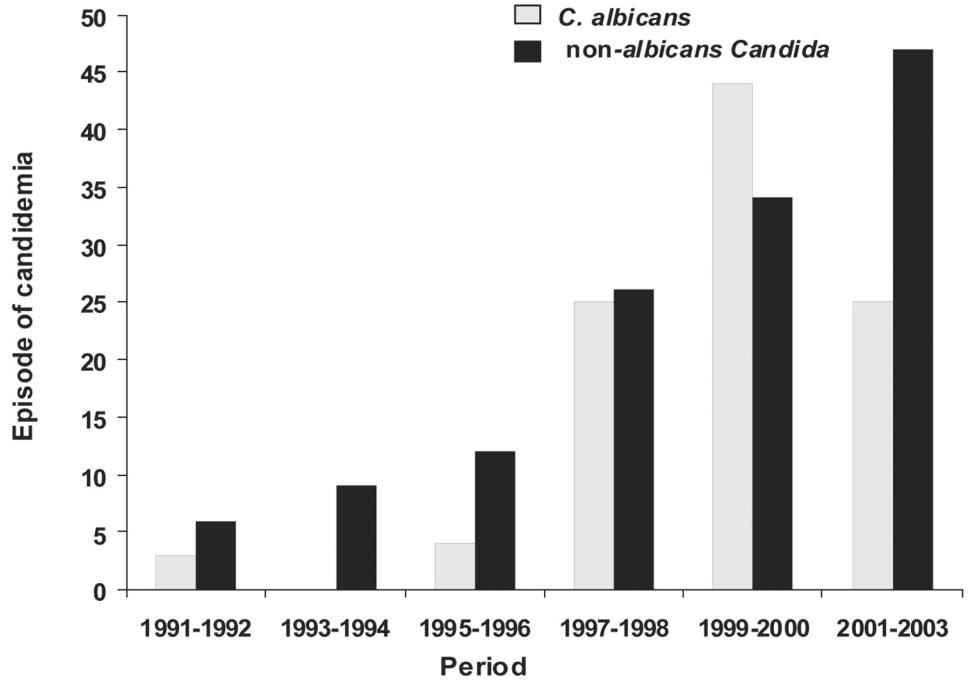

Figure 1. Evolution of *Candida* species in King Chulalongkorn Memorial Hospital from September 1991 to January 2003.

Table 2. The distribution of *C. albicans* and non-*albicans Candida* according to 235 adult and pediatric patients with candidemia from 1991 to 2003.

Year	*C. albicans*	Non-*albicans Candida*	Total
1991-1992			
Adults	3	2	5
Children	0	4	4
1993-1994			
Adults	0	4	4
Children	0	5	5
1995-1996			
Adults	4	7	11
Children	0	5	5
1997-1998			
Adults	15	19	34
Children	10	7	17
1999-2000			
Adults	36	27	63
Children	8	7	15
2001-2003			
Adults	10	28	38
Children	15	19	34
Total	**101**	**134**	**235**

Table 3. Treatment and outcome of 118 patients with candidemia.

Treatment	Number of treatment	Number of deaths	Mortality rate (%)
Amphotericin B	34	15	44.1
Itraconazole	2	2	100
Ketoconazole	1	0	0
Fluconazole	8	6	75

2003. This increase is similar to other previous reports. The incidence of candidemia increased in the United States in the 1980s[10,26], and accounted for 10 percent of all bloodstream infections in the 1990s.[7,24,26] There are contrasting data of candidemia in Europe.[19,21] The incidence increased in the Netherlands[19], but remained stable in Norway[21] and Switzerland[17,27] in the 1990s. In Asia, there is also an increased trend of candidemia in several countries.[28-33] In Thailand, two previous studies of candidemia were conducted in Siriraj[34] and Ramathibodi Hospitals.[35] The incidence of candidemia was reported to be stable in Siriraj Hospital from 1999 to 2002, with 79 isolates in 1999 and 33 isolates in 2002. The study of Ramathibodi Hospital was conducted in one year in 1996, and only adult patients were included. Fifty-four patients with candidemia were identified, accounting for 2.6 infections per 1,000 hospitalized patients (Table 5).

Overall, *C. albicans* remains the most commonly isolated species of candidemia in our study, accounting for 42.9 percent of all isolates. This is similar to several other reports in the United States[7,12,36-37] and Europe.[17,21,38-39] *C. albicans* comprised 44.55 percent and 34.5 percent of all candidemia episodes in the studies of Siriraj and Ramathibodi Hospitals, respectively (Table 5). Surprisingly, non-*albicans Candida* were the predominant species before 1997 in our study, probably attributable to the fact that most isolates were from pediatric patients. *C. parapsilosis* has been described to constitute more than one-third of blood isolates recovered from children due to its propensity to

Table 4. Factors influencing mortality of 118 patients with candidemia in the univariate analysis.

Factor	Number of deaths (n=60)/ number of patients (n = 118)	Crude odds ratio (95% CI)	P value[a]
1. Demographic data			
Sex			
Female	24/48	1[b]	
Male	36/70	1.1 (0.6-2.2)	1.0
ICU			
No	16/44	1[b]	
Yes	44/74	2.6 (1.9-5.5)	0.015
2. Associated conditions			
Preexisting illness			
Neutropenia			
No	47/95	1[b]	
Yes	13/23	1.3 (0.5-3.3)	0.7
Hematologic malignancy			
No	49/97	1[b]	
Yes	11/21	1.1 (0.4-2.8)	1.0
Diabetes			
No	50/97	1[b]	
Yes	10/21	0.9 (0.3-2.2)	0.9
Solid tumor			
No	53/102	1[b]	
Yes	7/16	0.7 (0.2-2.0)	0.7
HIV infection			
No	57/110	1[b]	
Yes	3/8	0.6 (0.1-2.5)	0.7
Transplantation			
No	60/117	-[c]	
Yes	0/1	-	-
Interventions			
Previous antibiotic therapy			
No	2/8	1[b]	
Yes	58/110	3.3 (0.06-17.3)	0.25
Previous surgery			
No	20/36	1[b]	
Yes	40/82	1.3 (0.6-2.9)	0.6
Central venous catheter			
No	13/40	1[b]	
Yes	47/78	3.1 (1.4-7.0)	0.008
Parenteral nutrition			
No	31/66	1[b]	
Yes	29/52	1.4 (0.7-3.0)	0.45
Urinary catheter and endotracheal tube			
No	58/113	1[b]	
Yes	2/5	0.6 (0.1-3.9)	1.0
Prosthesis			
No	59/114	1[b]	
Yes	1/4	0.3 (0.03-3.1)	0.6
3. Mycologic data			
Non-*albicans Candida*	36/74	1[b]	
Candida albicans	24/44	1.3 (0.6-2.7)	0.7

[a] Chi-square two-tailed P values, [b]reference category, [c]cannot be computerized
CI: confidence interval, ICU: intensive care unit

Table 5. Summary of three studies of candidemia in Thailand.

Data[1]	Present study (N = 235, 1991-2002)	Siriraj Hospital (N = 202, 1999-2002)	Ramathibodi Hospital (N = 54, 1996)
1. Demographic data			
Age (median, range)	37, 8 mo-85 y	NA	55.8 (mean), 16-92 y
Sex			
Male	70, 59.3%	115, 59.2%	30, 56.6%
Female	48, 40.7%	87, 40.8%	23, 43.4%
Ward			
ICU	74, 62.7%	NA	
Non-ICU	44, 37.3%	NA	NA
Length of stays (median, range)	55.8, 2-551 d	47.1 (mean), 4-235 d	NA
2. Associated conditions			
Preexisting illness			
Neutropenia	23, 19.5%	NA	NA
Hematologic malignancy	21, 17.8%	50, 43.9%	4, 7.6%
Diabetes	21, 17.8%	18, 15.8%	11, 20.8%
Solid tumor	16, 13.6%	16, 14%	14, 26.4%
HIV infection	8, 6.8%	10, 8.8%	1, 1.9%
Transplantation	1, 0.8%	NA	1, 1.9%
Interventions			
Previous antibiotic treatment	110, 93.2%	NA	50, 94.3%
Previous surgery	36, 30.5%	NA	31, 58.5%
Central venous catheter	78, 66.1%	NA	33, 71.3%
Total parenteral nutrition	52, 44.1%	NA	NA
Urinary catheter and endotracheal tube	5, 4.2%	NA	NA

adhere to foreign material commonly used in critically ill neonates.[40 - 41] In addition, our study showed a shift from *C. albicans* isolates between 1997 and 2000 toward non-*albicans Candida* isolates after 2001 as dominant pathogens of candidemia. This may reflect the aggressive use of intravascular devices favoring the colonization of *C. parapsilosis*, the increased use of azoles both as therapeutic and prophylactic purposes in immunocompromised hosts especially neutropenic and transplant patients, the changing of infection control policy, or the improved diagnostic tests for fungus.

The emergence of non-*albicans Candida* as major causes of candidemia was observed recently in the United States[15,16], comprising about one-half of all isolates recovered from blood cultures. *C. glabrata* comprised more than 20 percent of blood isolates recovered from adult patients in the survey by the NNIS.[7,10,16] However, *C. parapsilosis* was observed in more than one-third of blood isolates recovered from pediatric patients.[42] The distribution of non-*albicans Candida* as the predominant species of candidemia was not observed in the studies from Canada, Latin

America and most of Europe.[21,43,44] Only the studies from the Netherlands[19] and the Invasive Fungal Infections Group of the European Organization for the Research and Treatment of Cancer[17] showed non-*albicans Candida* as the predominant species of candidemia. *C. tropicalis* was the second most common blood isolates, as described in the studies of Siriraj Hospital[34], Saudi Arabia[28], Singapore[29] and Taiwan.[31] There were 91 *C. tropicalis* (45%), 12 *C. parapsilosis* (6%), 8 *C. glabrata* (4%) and 1 *C. krusei* (0.5%) of non-*albicans Candida* blood isolates in the study of Siriraj Hospital. The study of Ramathibodi Hospital showed 15 *C. parapsilosis* (27.3%), 13 *C. tropicalis* (23.6%), 7 *C. glabrata* (12.7%) and 1 *C. intermedia* (1.8%).[35] In our study, there were 13 *C. tropicalis* (9.9%), 2 *C. parapsilosis* (1.5%) and 1 *C. guilliermondii* (0.8%). Unfortunately, our result is analyzed from a sample size that is too small. The difference in the distribution of species of non-*albicans Candida* as major causes of candidemia in different hospitals may be explained by different ecology, types of patients, factors predisposing infections, intravascular devices, use of azole prophylaxis or infection control policy. Generally, *C. glabrata* is predominant in adult patients, compared to *C. parapsilosis* in pediatric patients.[42,44] Some investigators suggest that the predominance of *C. parapsilosis* in children may be due to the aggressive use of intravascular devices in neonatal ICUs. The role of azole treatment and prophylaxis in the shift to *C. krusei* and some strains of *C. glabrata* has remained controversial because of conflicting results from the studies conducted in different hospitals.[18]

In our study, the demography and associated conditions predisposing to candidemia are similar to those described in previous reports.[4,11-14,16,37] Candidemia was more prevalent in males than females. The mean age was high, but some were in a group of young patients possibly reflecting the impact of neoplastic disease, HIV infection or the use of intravascular devices. All episodes of candidemia were nosocomial infections which were more frequent in ICU patients.

Important risk factors for candidemia have been well described.[4,16,37] In our study, all patients had at least one identifiable risk factor. The preexisting illnesses predisposing patients to *Candida* infections included neutropenia, hematologic or solid malignancy, diabetes and HIV infection, in agreement with other studies. Other predisposing interventions which may reflect the primary site of candidemia included the presence of central venous catheter, total parenteral nutrition and other indwelling catheters. Furthermore, previous antibiotic use especially with broad-spectrum antibacterial activity, is known to affect the protection of bacterial gut flora against the fungal overgrowth. Most patients in our study had received broad-spectrum antibiotics before the onset of candidemia.

In our study, 61.8 percent of patients received no antifungal treatment, and some of them survived. This probably reflects the intact or recovering host immunity, transient rather than persistent candidemia or successful response to catheter removal in some patients with catheter-related bloodstream infection.

The mortality of candidemia in our study was 50.8 percent, comparable to those reported in the literature.[1-8] The mean duration of admission was 42.5 days in the non-survivor group and 62.5 days in the survivor group (data not shown). The factor influencing mortality in the multivariate analysis was the presence of central venous catheter. This probably reflects the primary site of *Candida* bloodstream infection or the greater severity of these patients in our study. Indwelling central venous catheter is a well established risk for mortality in most studies.[45-47]

The choice of antifungal treatment was not found to correlate with outcome in our study. We did not

observe any difference in survival among patients with *C. albicans* and non-*albicans Candida* who received fluconazole or amphotericin B (data not shown). This non-significant difference may be due to the small number of patients analyzed. In addition, most non-*albicans Candida* isolates in our study were probably fluconazole-sensitive strains. According to the recommendations of the Infectious Diseases Society of America, amphotericin B, fluconazole, caspofungin or the combination of fluconazole plus amphotericin B is the preferred treatment of candidemia. Empirical amphotericin B is reserved for patients admitted in hospitals with high prevalence of fluconazole-resistant strains.[9]

The limitations of our study are mainly from the retrospective nature, incomplete clinical data from unavailable medical records, and incomplete species identification of non-*albicans Candida*. Despite these limitations, our study represents the largest series of candidemia in Thailand. It provides a longitudinal overview of the epidemiologic data over a 13-year period. There was an increasing trend of candidemia, and a shift from *C. albicans* toward non-*albicans Candida* from 1991 to 2003. Given the substantial influence of candidemia on morbidity and mortality and the difficulty in diagnosis, awareness, high index of suspicion and prompt treatment of high-risk patients will become much more important to improve the clinical outcome. In addition, a well-designed prospective study is needed to confirm the observation in our study.

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