

Epidemiology of Candidemia in Songklanagarind Hospital

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Objective: To study the epidemiology of candidemia patients in Songklanagarind Hospital.

Material and Method: A retrospective study examining the epidemiological data of candidemia patients in Songklanagarind Hospital, a referral center in southern Thailand, between January 2004 and December 2009.

Results: Two hundred six candidemia inpatients had an overall 54% mortality rate. The median age of the patients was 53 years (range: 1-98 years). Length of hospital stay was an average of 55 days. Most of them (129, 62.6%) were admitted in a non-intensive care unit (non-ICU). The most common associated condition was solid organ malignancy (67, 32.5%). Most of the patients (181, 88%) had a history of broad spectrum antibiotic usage; however, in the non-broad spectrum antibiotics group solid organ malignancy was still the most common associated condition. *Candida albicans* and non-*albicans Candida* accounted for 83 (40.3%) and 123 (59.7%) cases, respectively. Higher mortality rates were significantly related with intensive care unit (ICU) admission, elderly patients, and the presence of solid organ tumors, hematologic malignancies, and neutropenia, and influenced by intubation with a mechanical ventilator, central venous or urethral catheterization, surgical procedures, and administration of antibiotics.

Conclusion: Candidemia can cause a high mortality rate that is influenced with many independent risk factors including surgical and medical interventions. Non-*albicans Candida* is more common than *Candida albicans* whereas each mortality rate was not significantly different.

Keywords: Epidemiology, Candidemia, Songklanagarind Hospital

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Candidemia plays an important role in nosocomial infections, which are associated with longer hospital stays, higher health care costs, and higher mortality rates⁽¹⁾. It is ranked as the fourth most common cause of nosocomial bloodstream infections in the United States⁽²⁾. The main contributors to this increase are the growing number of invasive devices or procedures, immunosuppressive therapies and the usage of broad-spectrum antibiotics⁽³⁻⁵⁾. The epidemiology of candidemia is complicated and varies among the different groups of patients, especially in tertiary care hospitals or referral centers^(6,7). A recent shift from *Candida albicans* to other groups of *Candida* as the dominant causative pathogen has been found in many hospitals⁽⁸⁾. The authors have attributed the epidemiology of candidemia patients in Songklanagarind Hospital, a referral center in

Southern Thailand, and specifically demonstrated the difference in medical burden between *C. albicans* and non-*albicans Candida* groups of *Candida* and the present study has also identified the risk factors for developing candidemia and the risk factors for mortality of this disease.

Material and Method

The present retrospective study was performed in Songklanagarind Hospital, an 800-bed tertiary care hospital. All patients who had had at least one blood culture which had positive *Candida* spp., among specimen a collected within 48 hours of admission, were enrolled. Patients whose medical record was incomplete were excluded. Demographic data was reviewed including age, sex, underlying diseases (malignancies, diabetes mellitus, chronic renal failure, chronic liver diseases, chronic steroid usages, ruptured visceral organs and neutropenia), admitting ward, length of stay, primary site of infection, as well as interventions including previous antibiotic treatment, type of surgery, central venous catheterization, parenteral nutrition, urinary catheterization and

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endotracheal intubation with a mechanical ventilator. Univariate analysis was performed to identify individual risk factors associated with mortality by using the odds ratio and its corresponding 95% 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. Data was described by frequency percentage and or means and standard deviations.

Results

Between January 2004 and December 2009 there were 206 confirmed candidemia cases during admissions. The *C. parapsilosis* was the most common species (38%) associated with candidemia in the present patients, followed by *C. tropicalis* (32%) and *C. albicans* (28%). *C. grabata* and *C. krusei* were also found, but only in the last two years of the present study. These two species are known to be naturally resistant to azoles antifungal agents.

The average age of the present patients was 53 years, range of 1-98 years with a male-female ratio of 1.7:1. The length of stay (LOS) was an average of 55 days, with a 54% of mortality rate. The candidemia was commonly found in the non intensive care unit (non-ICU) settings, especially the highest proportion in the surgical wards. Solid organ tumors and hematologic malignancies were the two most common associated conditions (Table 1).

The data examining predisposing factors revealed that endotracheal intubation with a mechanical ventilator was the most common intervention associated with candidemia, followed by central venous catheterization and placement of a urethral catheter. Eighty-eight patients (42%) had received broad spectrum antibiotics before contracting candidemia, while solid organ tumor was the most common associated condition in patients that had not received broad spectrum antibiotics (Table 1).

ICU admission was the main significant independent risk factor associated with a higher rate of mortality, and solid organ tumors. Hematologic malignancies and neutropenic status were significantly associated conditions related to higher mortality rates. Most interventions, including intubation with a mechanical ventilator, central venous catheterization, urethral catheterization, surgical procedures and administration of antibiotics significantly influenced the mortality. There were no significant differences in

Table 1. Characteristics of candidemia patients

Variable (n = 206)	No. (%)
Age, mean (years), range	53, 1 to 98
Male:female proportion, ratio	130:76, 1.7:1
Length of stay, mean (days), range	55, 8 to 235
Admitting setting	
ICU	77 (37.4)
Non-ICU	129 (62.6)
Department affiliation	
Surgery	98 (45.6)
Medicine	74 (35.9)
Pediatrics	34 (16.5)
Associated condition	
Solid tumor	67 (32.5)
Hematologic malignancy	42 (20.4)
Neutropenia	30 (14.6)
Diabetes mellitus	32 (15.5)
Chronic renal failure	16 (7.8)
Chemotherapy	14 (6.8)
HIV	5 (2.4)
Chronic steroid usage	8 (3.9)
Intervention	
Intubation	118 (57.3)
Central venous catheter	100 (48.5)
Urinary catheter	88 (42.7)
Previous antibiotic treatment	85 (41.3)
Previous surgery	76 (36.9)
Parenteral nutrition	28 (13.6)

mortality rates between patients with and without administration of parenteral nutrition, or between patients with albican and non-albican candidemia. (Table 2).

Discussion

Candidemia rates have been increasing and causing associated higher rates of morbidity and mortality, especially in nosocomial infections as described in previous reports from the US, Europe and some countries in Asia⁽⁸⁻¹¹⁾. In Thailand, there have been three such reports, from Siriraj, Ramathibodi, and King Chulalongkorn Memorial Hospitals^(6,7,12). It was similar to previous studies that non-*albican* *Candida* species had predominated since 2004, the start of the present study^(7,12). *C. parapsilosis* and *C. tropicalis* became the first two most common species among non-*albican* *Candida* species similar to the previous study in Ramathibodi Hospital⁽⁷⁾. It was interesting to note that the incidence of *C. albicans* was rising in the most recent three years of the present study, but the authors also noticed the first appearance of *C. grabata*

Table 2. Factors influencing mortality of candidemia patients

Variable	Candidemia patients who died (n = 113)	Candidemia patients who survived (n = 93)	All patients (n = 206)	OR (95% CI)	p-value
Age (years), mean $\pm$ SD	58.29 $\pm$ 23.76	47.90 $\pm$ 26.90	53.60 $\pm$ 25.69		<0.001
Female/male proportion	75/38	63/30	138/68	0.88 (0.49-1.58)	0.662
ICU/non-ICU proportion	60/53	17/76	77/129	5.06 (2.66-9.62)	<0.001
Proportion of non-albican/albican	70/43	53/40	123/83	1.23 (0.70-2.15)	0.471
Candida					
Proportion of associated condition, with/without					
Solid tumor	55/58	12/71	67/139	5.61 (2.74-11.46)	<0.001
Hematologic malignancy	32/81	10/83	42/164	3.28 (1.51-7.10)	<0.001
Neutropenia	25/88	5/88	30/176	5.00 (1.83-13.65)	<0.001
Diabetes mellitus	19/94	13/80	32/174	1.24 (0.58-2.68)	0.575
Chronic renal failure	9/104	7/86	16/190	1.06 (0.38-2.97)	0.913
Chemotherapy	10/103	4/89	14/192	2.16 (0.66-7.12)	0.198
HIV	3/110	2/91	5/201	1.24 (0.20-7.59)	0.814
Chronic steroid usage	4/109	4/89	8/198	0.82 (0.20-3.36)	0.783
Proportion of associated intervention, with/without					
Intubation	97/16	21/72	118/88	20.79 (10.14-42.63)	<0.001
Central venous catheter	95/18	5/88	100/106	92.89 (33.08-260.81)	<0.001
Urinary catheter	85/28	3/90	88/118	91.07 (26.70-310.65)	<0.001
Previous antibiotic treatment	76/37	9/84	85/121	19.17 (8.69-42.32)	<0.001
Previous surgery	65/48	11/82	76/130	10.10 (4.86-20.98)	<0.001
Parenteral nutrition	16/97	12/81	28/178	1.11 (0.50-2.49)	0.789

and *C. krusii*, two species that have a natural resistance to the azole antifungal agents used to treat Candida. However, the authors cannot make any definite assertions regarding this shift from *C. albicans* to non-*albicans* Candida species, as specific species identifications and antifungal susceptibility of identified Candida species were not routinely recorded or examined in Songklanagarind Hospital prior to 2004.

The demographics of Candidemia patients in the present study were generally similar to previous studies^(1-7,12). Males were more frequently affected than females, and the mean age was high. The average age of the present patients was 50 years, which was higher than in previous studies^(2,4,6,7,12). The frequency of neutropenia, hematologic malignancy and solid organ tumors increased^(6,7,12). Diabetes, chronic renal failure, HIV infection and chronic steroid usages were less frequent than in previous studies^(4,6,7,12). More Candidemia patients in the present study came from the general medical, surgical, and pediatric wards than intensive care units and general wards. The surgical wards had the highest numbers of these patients. The high frequency of non-ICU patients in the present study might be because of different ICU admission capacities or admission criteria than in studies from different institutes^(6,7).

Preexisting illnesses and interventions predisposing patients to candidemia have been well described in previous studies^(6,7,13-15). Therefore, our study focused more on the presented frequency of these predisposing factors and correlating them with mortality and different species of Candida. The mortality of candidemia patients in the present study was 55%. Although the frequency of ICU-based patients in the present study was quite lower than in previous studies, the mortality of this group of patients was significantly higher than patients admitted in the general ward, similar to previous studies^(1-7,12). The present study also identified a significantly higher mortality of Candidemia patients with neutropenia and hematologic malignancy ($p\text{-value} < 0.05$), while the other related conditions such as solid organ tumor, HIV infection and diabetes seemed to be related to higher mortality but not significantly, as was also described in the study of Tritipwanit et al⁽⁶⁾. Predisposing interventions that were also found to be related with significantly higher mortality included intubation with a mechanical ventilator, TPN applications, Foley catheterization, any surgical procedures and central venous cauterizations, ($p\text{-value} < 0.05$) as earlier described and correlated in the study of Bassetti

et al⁽³⁾. Non-*albicans* Candida and *C. albicans* were not significantly different in mortality rates ($p\text{-value} = 0.128$).

Most patients (88%) in the present study had received antibiotics before the onset of candidemia while only 80 patients (38%) received broad-spectrum antibiotics of the group including carbapenems and cephalosporin or penicillin with betalactamase inhibitors. The authors found that in patients without a history of broad-spectrum antibiotic exposure, solid organ tumor was the most common risk factor for candidemia.

Empirical antifungal agents were reflected in the mortality rates. Fifty patients (23.8%) did not receive any antifungal agents and the mortality rate in this group of patients was 97%. The authors found that patients who received antifungal agents had a mortality rate less than in the no-antifungal agents' patients ($p\text{-value} < 0.05$). However, there was no significant difference between empirical antifungal agents based on fluconazole and those based on Amphotericin-B. These non-significant differences might be related to the small number of patients who received antifungal agents (160 patients). Fluconazole is the recommended antifungal agent in non-critically-ill patients and is the standard agent for empirical treatment of candidemia in Songklanagarind Hospital. However, the authors would emphasize that they did not evaluate the severity of these patients and antifungal susceptibility was not routinely examined. Amphotericin-B or Caspofungin were still reserved for critically-ill patients with candidemia.

There are a few limitations to the present study. First, the data are incomplete as the present study includes a time when electronic medical records were being introduced to Songklanagarind Hospital and not everything was transferred to the electronic system for various reasons, including incomplete species identification of organisms. Secondly, there was no antifungal agents' susceptibility an important factor influencing the success of treatment and related directly to mortality rates. Third, there was no data indicating the severity of these patients that might be independent factors influencing mortality. Finally, there was no information concerning any changes of antifungal agents after failure of the first choice of antifungal agent or after antifungal susceptibility was revealed. Candidemia is known to cause high mortality rates with increased economic burdens from a prolonged length of stay in the hospital. Early diagnosis in highly suspicious patients and appropriate treatment

can decrease mortality and shorten duration of admission. Routine prompt antifungal susceptibility studies can improve clinical outcomes and increase more epidemiologic data while conventional severity assessments are still important to independently determine treatment outcomes. Well-designed prospective studies and routine complete epidemiologic and clinical information collection are needed to assess these factors.

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Potential conflicts of interest

None.

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การศึกษาระบาดวิทยาของภาวะเชื้อราแคนดิดาในเลือดในโรงพยาบาลสงขลานครินทร์

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วัตถุประสงค์: เพื่อศึกษาระบาดวิทยาของผู้ป่วยภาวะเชื้อราในเลือดในโรงพยาบาลสงขลานครินทร์

วัสดุและวิธีการ: ศึกษาย้อนหลังข้อมูลระบาดวิทยาของผู้ป่วยภาวะเชื้อราแคนดิดาในเลือดในโรงพยาบาลสงขลานครินทร์ โรงพยาบาลรับส่งต่อแห่งหนึ่งในภาคใต้ของประเทศไทย ระหว่างเดือนมกราคม พ.ศ. 2547 ถึงเดือนธันวาคม พ.ศ. 2552

ผลการศึกษา: มีผู้ป่วยในภาวะแคนดิดาในเลือด 206 คน อัตราตายโดยรวมร้อยละ 54 อายุเฉลี่ย 53 ปี (พิสัย 1 ถึง 98 ปี) ระยะอยู่โรงพยาบาลเฉลี่ย 55 วัน ส่วนใหญ่จำนวน 129 ราย (ร้อยละ 62.6) ไม่อยู่ในหอบริบาลผู้ป่วยหนัก ภาวะเกี่ยวข้องที่พบบ่อยมากที่สุดคือมะเร็งอวัยวะสืบพันธุ์ 67 ราย (ร้อยละ 32.5) ผู้ป่วยส่วนใหญ่ 181 ราย (ร้อยละ 88) มีประวัติการเข้ายาปฏิชีวนะช่วงกว้างในกลุ่มที่ไม่ได้เข้ายาปฏิชีวนะ ช่วงกว้างมะเร็งอวัยวะสืบพันธุ์ก็ยังเป็นภาวะเกี่ยวข้องที่พบบ่อย ภาวะเชื้อราในเลือดจากแคนดิดาและไม่ใช้แคนดิดาเท่ากับ 83 ราย (ร้อยละ 40.3) และ 123 ราย (ร้อยละ 59.7) ตามลำดับ ปัจจัยต่ออัตราตายสูงได้แก่ ผู้ป่วยอยู่ในหอบริบาลผู้ป่วยหนัก ผู้ป่วยสูงอายุ และมะเร็งอวัยวะสืบพันธุ์ มะเร็งโลหิต และภาวะเม็ดเลือดขาวนิวโทรฟิลต่ำ รวมถึงอิทธิพลจากการใส่สายในหลอดลมและใช้เครื่องช่วยหายใจ การใส่สายในท่อปัสสาวะ การใส่สายในหลอดเลือดดำกลาง วิธีการผ่าตัดทางศัลยกรรม และการได้รับยาปฏิชีวนะ

สรุป: ภาวะเชื้อราแคนดิดาในเลือดเป็นเหตุให้อัตราเสียชีวิตสูง ซึ่งมีอิทธิพลจากหลายเหตุปัจจัย รวมทั้งวิธีปฏิบัติทางอายุรศาสตร์และศัลยศาสตร์ เชื้อราที่ไม่ใช่แคนดิดาพบบ่อยกว่าแคนดิดาขณะที่อัตราการตายไม่แตกต่างกันอย่างมีนัยสำคัญ
