EPIDEMIOLOGY OF ADULT CANDIDEMIA AT CHIANG MAI UNIVERSITY HOSPITAL

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Abstract. A retrospective study was conducted between July 1, 2004 and June 30, 2009 at Chiang Mai University Hospital among 138 patients with candidemia; 85 patients (61.6%) were male and the mean age was 57.7±19.4 years. Seventy-eight patients (56.5%) had underlying medical conditions. *Candida albicans* and non-*albicans Candida* were identified in 42 (30.4%) and 96 (69.6%) patients, respectively. Not being admitted to the ICU was the only factor associated with non-*albicans* candidemia (p=0.018). Sixty patients (43.5%) had favorable outcomes. Factors independently associated with unfavorable outcomes included patients who were in the ICU (p=0.025), were intubated (p<0.001) or were on hemodialysis (p=0.031); prior abdominal surgery was associated with a favorable outcome (p=0.026). Candidemia is not a rare condition at this hospital. Early recognition and prompt empirical treatment are essential to improve outcomes of patients at risk for developing candidemia. Improvement of surveillance is crucial to recognizing emergence of highly resistant strains of *Candida* spp.

Keywords: candidemia, epidemiology, risk factors

INTRODUCTION

Candida species are the most common cause of nosocomial fungal infection (Fridkin and Jarvis, 1996). The incidence of *Candida* infections increased following the introduction of newer medical treatments, such as bone marrow and organ transplantation, chemotherapy for cancer patients and invasive medical procedures, including insertion of a central venous catheter, administration of broad spectrum antimicrobial therapy, and total parenteral nutrition (Solomkin and Simmono, 1980; Henderson *et al*, 1981; Karabinis *et al*, 1988; Bross *et al*, 1989; Castaldo *et al*, 1991; Goodrich *et al*, 1991; Pittet *et al*, 1994; Bow *et al*, 1995; Marr *et al*, 2000). In the United States, candidemia is the fourth leading cause of nosocomial bloodstream infections (Edmond *et al*, 1999; Wisplinghoff *et al*, 2004). Epidemiologic studies worldwide have shown the same trend toward increasing numbers of patients with candidemia over the past few decades (Lamagni *et al* 2001; Marchetti *et al*, 2004; Anunnatsiri *et al*, 2009; Yap *et al*, 2009). Candidemia causes high morbidity and mortality (40%), a prolonged hospital stay and high cost of treatment (Wey *et al*, 1989; Pittet and Wenzel, 1995). *Candida albicans* has been the most common isolated *Candida* species for several decades

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(Edmond *et al*, 1999; Marchetti *et al*, 2004; Anunnatsiri *et al*, 2009; Horn *et al*, 2009; Yap *et al*, 2009); however, a shift to non-*albicans Candida* species, such as *C. grabata*, *C. krusei*, and *C. parapsilosis*, has been observed (Edmond *et al*, 1999; Anunnatsiri *et al*, 2009; Yap *et al*, 2009). This might be the result of widespread use of fluconazole for treatment and prophylaxis (White, 1997; Viscoli *et al*, 1999).

There are several epidemiologic studies in Thailand from different time periods (Foongladda *et al*, 2004; Suankratay *et al*, 2005; Anunnatsiri *et al*, 2009). These studies confirmed the increasing number of non-*albicans Candida* species. We conducted the epidemiologic study to evaluate the incidence, risk factors, species identification, and outcomes of candidemia in a tertiary-care hospital in northern Thailand.

MATERIALS AND METHODS

A retrospective study was conducted among patients older than 15 years, who had at least 1 blood culture positive for *Candida* spp between July 1, 2004 and June 30, 2009, at Chiang Mai University Hospital, an 1,800-bed, tertiary-care hospital in northern Thailand.

The blood cultures were performed at a central diagnostic laboratory of the hospital. Conventional standard methods, such as germ tube test, morphology studies, and carbohydrate assimilation characteristics, were used to identify *C. albicans* and non-*albicans Candida* (*ie*, *C. tropicalis*, *C. grabata*, *C. parapsilosis*, *C. krusei*). These methods were not changed during the five-year period. Susceptibility tests for *Candida* spp are not routinely done at our hospital.

Patient-related clinical data were retrospectively collected using a preprinted data collection form.

A favorable outcome was defined as a patient who survived and an unfavorable outcome was defined as a patient who died or had clinical deterioration.

Statistical analysis

Clinical data were presented as percents, means with standard deviations (SD), and medians with ranges where appropriate. Comparisons of variables between patients infected with *C. albicans* and non-*albicans Candida* and between patients who died and survived were performed using the Student's *t*-test, Mann-Whitney *U* test, chi-square test, or Fisher's exact test where appropriate. Variables with a p-value <0.10 on univariable analysis were then tested in multivariable models using a forward stepwise procedure. Variables with a p-value <0.05 were included in the final model. All statistical analyses were performed using Stata statistical software (Stata Statistical Software: Release 10.0, Stata Corporation, College Station, TX). A two-sided test was used to indicate statistical significance at a p-value of <0.05.

RESULTS

Demographic data

There were 148 episodes of candidemia among 206,043 hospitalized patients during the 5 years study period, giving a cumulative incidence of 7.2 cases/10,000 hospital admissions. Medical records were not available for review in 10 patients. Of the 138 patients included for the analysis, 74 (53.6%), 61 (44.2%), 2 (1.5%), and 1 (0.7%) were hospitalized in the Surgery, Internal Medicine, Orthopedics, and Obstetrics-Gynecology units, respectively. Thirty-seven patients (26.8%) were in the intensive care unit (ICU) during the episodes of candidemia. The

median length of hospitalization from admission to the episode of candidemia was 21.5 days (range 11-34 days). Eighty-five patients (61.6%) were male and the mean age was 57.7±19.4 years. Seventy-eight patients (56.5%) had underlying medical conditions, including hematologic malignancies (21 patients, 15.2%), non-hematologic malignancies (37 patients, 26.8%), chronic renal failure (18 patients, 13.0%), HIV infection (1 patient, 0.7%), and post-renal transplantation (1 patient, 0.7%). One-hundred thirty-five patients (97.8%) had received antimicrobial therapy within 1 month prior to the candidemia episode. The most common antimicrobials prescribed were ceftriaxone (24.6%), ciprofloxacin (16.0%), and ceftazidime (11.8%). Other clinical characteristics are shown in Table 1.

Among the 138 patients with candidemia, *Candida* of the same species as the positive blood culture was also isolated from other sites in 36 patients: urine (10 patients, 7.3%), skin lesions (5 patients, 3.6%), sputum (3 patients, 2.3%) and 2 or more sites (12 patients, 8.7%). Fifty-five patients had concurrent bacteremia (34 with gram-negative bacteria, 16 with gram-positive bacteria, and 5 with both gram-negative and gram-positive bacteria).

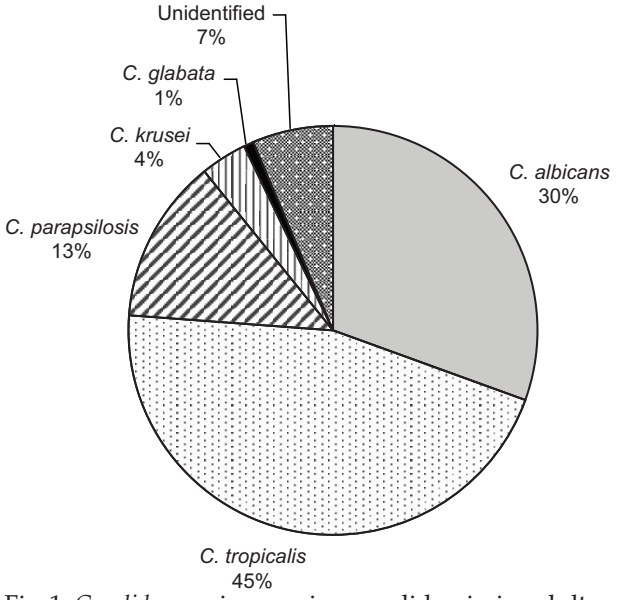

Fig 1–*Candida* species causing candidemia in adult patients between 1 July 2004 and 30 June 2009.

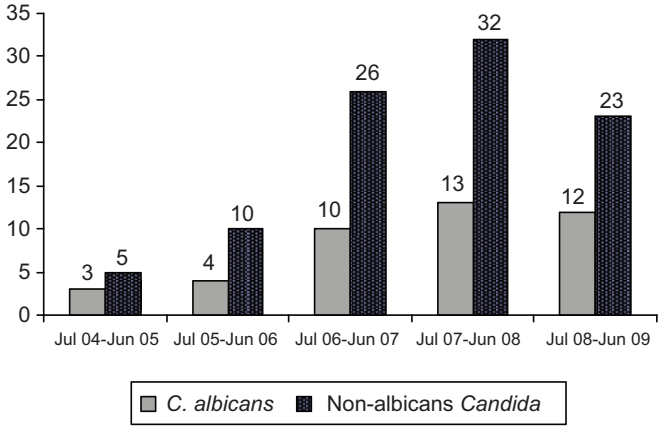

Fig 2–Number of patients with candidemia due to *Candida albicans* and non-albicans *Candida* spp between 1 July 2004 and 30 June 2009.

Identification of *Candida* species

C. albicans and non-*albicans Candida* were identified in 42 (30.4%) and 96 (69.6%) patients, respectively. Of the non-*albicans Candida*, 63 were *C. tropicalis* (45.7%), 18 were *C. parapsilosis* (13.0%), 5 were *C. krusei* (3.6%), 1 were *C. glabata* (0.7%), and 9 were unidentified species (6.5%) (Fig 1). The number of patients with candidemia increased over the 5-year study period; however, the proportions of *C. albicans* and non-*albicans Candida* did not differ over time (Fig 2).

Table 1
Clinical characteristics of patients with candidemia due to *Candida albicans* and non-*albicans Candida* spp.

Characteristics	Total $N = 138$	*C. albicans* $N = 42$	Non-*albicans Candida* spp $N = 96$	*p*-value
Age (years) (mean ± SD)	57.7 ± 19.4	64.4 ± 17.5	54.8 ± 19.6	0.007
Age ≥ 60 years old	66 (47.8)	14 (33.3)	52 (54.2)	0.024
Male	85 (61.6)	25 (59.5)	60 (62.5)	0.741
Hospitalized unit				0.363
Medicine	61 (44.2)	19 (45.2)	42 (43.7)	
Surgery	74 (53.6)	22 (52.4)	52 (54.2)	
Intensive care unit	37 (26.8)	17 (40.5)	20 (20.8)	0.017
Hospital stay prior to candidemia episode (median, range)	21.5 (11-34)	17.5 (10-34)	23.5 (12-35.5)	0.092
Underlying diseases				
Hematologic malignancy	21 (15.2)	4 (9.5)	17 (17.7)	0.218
Non-hematologic malignancy	37 (26.8)	10 (23.8)	27 (28.1)	0.598
HIV infection	1 (0.7)	0 (0)	1 (1.0)	0.507
Post-renal transplantation	1 (0.7)	0 (0)	1 (1.0)	0.507
Chronic renal failure	18 (13.0)	7 (16.7)	11 (11.5)	0.403
Co-morbidity condition/ invasive procedure				
Neutropenia	11 (7.9)	2 (4.8)	9 (9.4)	0.357
Corticosteroids	42 (30.2)	14 (33.3)	28 (29.2)	0.625
Prior abdominal surgery	56 (40.6)	20 (47.6)	36 (37.5)	0.407
Chemotherapy	21 (15.2)	8 (19.1)	13 (13.5)	0.288
Central venous catheter	112 (81.2)	35 (83.3)	77 (80.2)	0.836
Total parenteral nutrition	50 (36.2)	12 (28.6)	38 (39.6)	0.216
Foley catheter	104 (75.4)	34 (80.9)	70 (72.9)	0.313
Endotracheal intubation	89 (64.5)	31 (73.8)	58 (60.4)	0.130
Hemodialysis	24 (17.4)	9 (21.4)	15 (15.6)	0.408
Prosthetic instrument	2 (1.5)	1 (2.4)	1 (1.0)	0.545
Clinical presentation				
Altered consciousness	19 (13.8)	7 (16.7)	12 (12.5)	0.513
Respiratory failure	21 (15.2)	5 (11.9)	16 (16.7)	0.474

Laboratory findings (Mean ± SD)				
Hemoglobin (g/dl)	10.4 ± 2.4	10.5 ± 2.1	10.4 ± 2.5	0.927
White blood cell count (cells/mm^3)	11,098.1 ± 7,101.5	10,429.2 ± 6,719.2	12,126.9 ± 7,674.4	0.817
Platelet count (/mm^3)	245,836.4 ± 161,636.8	223,426.8 ± 151,893.7	255,407.1 ± 165,464.1	0.291
Serum creatinine (mg/dl)	2.0 ± 2.8	2.3 ± 3.0	2.0 ± 2.5	0.551
Serum albumin (g/dl)	3.0 ± 0.8	2.8 ± 0.8	3.1 ± 0.7	0.006
Serum albumin > 3 g/dl	77 (55.8)	18 (42.7)	59 (61.5)	0.043
Bacterial co-infection				0.528
Gram-positive cocci	16 (11.6)	7 (16.7)	9 (9.4)	
Gram-negative bacilli	34 (24.6)	11 (26.2)	23 (24.0)	
Other sites of infection/colonization	5 (3.6)	3 (7.1)	2 (2.1)	0.356
Skin	16 (11.6)	5 (11.9)	11 (11.5)	
Urinary tract	3 (2.3)	2 (4.8)	1 (1.0)	
Sputum	12 (8.7)	2 (4.8)	10 (10.4)	
Two or more sites	84 (60.9)	20 (47.6)	64 (66.7)	
Received fluconazole prior to candidemia	78 (56.5)	29 (69.1)	47 (49)	0.376

Predictive factors for non-*albicans* candidemia

Univariate analysis showed patients ≥ 60 years old, not in the intensive care unit, or who had a serum albumin >3 g/dl were more likely to have non-albicans candidemia (Table 1). However, not being admitted to the ICU was the only factor associated with non-albicans candidemia (OR 2.58; 95% CI 1.17-35.69, p=0.018) on multivariate analysis. Receiving fluconazole prior to the candidemia episode was not associated with non-*albicans* candidemia.

Treatments and outcomes

Eighty-four patients (60.9%) received systemic antifungal therapy: amphotericin B, fluconazole, and echinocandins were prescribed in 64 (76.2%), 13 (15.5%), and 7 (8.3%) patients, respectively. There were no reasons noted for not prescribing antifungal therapy in the remaining 54 patients. Of the 84 patients who received antifungal therapy, 41 (48.8%) improved clinically and were discharged home, 29 patients (34.5%) died and 14 patients had clinical deterioration and left the hospital against medical advice. These 14 patients did not return to the hospital during the 5 year study period and their statuses were unknown at the time of the study. Of the 54 patients who did not receive antifungal therapy, 19 patients (35.2%) had clinical improvement and were discharged home, 29 patients (38.9%) died and 14 patients (25.9%) had clinical deterioration and left the hospital against medical advice. These 14 patients did not return to the hospital during the 5 year study period and their statuses were unknown at the time of study.

Predictive factors for unfavorable outcomes

Univariate analysis showed patients ≥ 60 years old, who were in the Internal

Table 2
Clinical characteristics of patients who had favorable and unfavorable outcomes.

Charateristics	Unfavorable outcomes $N = 78$	Favorable outcomes $N = 60$	p-value
Age (years) (Mean ± SD)	63.3 ± 15.8	50.5 ± 18.3	<0.001
Male	44 (51.8)	41 (64.2)	0.153
Medicine unit	45 (57.7)	16 (26.7)	0.001
Intensive care unit	33 (42.3)	4 (6.7)	<0.001
Hospital stay prior to candidemia episode (median, range)	20.5 (9-34)	23 (12-45)	0.503
Underlying medical conditions			
Hematologic malignancy	12 (15.4)	9 (15.0)	0.950
Non-hematologic malignancy	19 (24.4)	18 (30.0)	0.458
HIV infection	0 (0)	1 (1.67)	0.252
Postrenal transplantattion	1 (1.3)	0	0.379
Chronic renal failure	16 (20.5)	2 (3.3)	0.003
Co-morbidity condition/invasive procedure			
Neutropenia	4 (5.1)	7 (11.7)	0.160
Corticosteroids	30 (38.5)	12 (28.6)	0.019
Prior abdominal surgery	24 (30.8)	32 (57.1)	0.005
Chemotherapy	14 (18.0)	7 (33.3)	0.308
Central venous catheter	68 (87.2)	44 (73.3)	0.039
Total parenteral nutrition	18 (23.1)	32 (53.3)	<0.001
Foley catheter	70 (89.7)	34 (56.7)	<0.001
Endotracheal intubation	67 (85.9)	22 (36.7)	<0.001
Hemodialysis	23 (29.5)	1 (1.7)	<0.001
Prosthetic instrument	2 (2.6)	0	0.212
Clinical presentation			
Alteration of consciousness	17 (21.8)	2 (3.3)	0.002
Respiratory failure	17 (21.8)	4 (6.7)	0.014
Laboratory findings (Mean ± SD)			
Hemoglobin (g/dl)	10.3 ± 2.2	10.5 ± 2.5	0.578
White blood cell count (cells/mm^3)	11,799.3 ± 7,953.5	10,186.6 ± 180,633.2	0.429
Platelet count (/mm^3)	214,919.5 ± 138,605.3	285,513 ± 180,633.2	0.040
Serum creatinine (mg/dl)	2.7 ± 3.2	1.2 ± 3.1	0.005
Serum albumin (g/dl)	2.9 ± 0.7	3.2 ± 0.8	0.003
Serum albumin >3 g/dl	38 (48.7)	39 (65.0)	0.056
Bacterial co-infection	28 (35.9)	27 (45.0)	0.279
Other sites of candidal infection/colonization			0.630
Skin	3 (3.9)	2 (3.3)	
Urinary tract	9 (11.5)	7 (11.7)	
Sputum	1 (1.3)	2 (3.3)	
Two or more sites	9 (11.5)	3 (5)	
Received antifungal therapy	43 (55.1)	41 (68.3)	0.115
C. albicans	49 (62.8)	47 (78.3)	0.050

Medicine Unit, were in the ICU, had chronic renal failure, had altered mental status, had respiratory failure, were receiving corticosteroids, had no prior abdominal surgery, were on endotracheal intubation, had received dialysis, had a medical instrument in place, had thrombocytopenia, had a high serum creatinine level or had a serum albumin <3 mg/dl were more likely to have an unfavorable outcome (Table 2). However, multivariate analysis showed the factors associated with an unfavorable outcome were: 1) patients who were in the ICU (OR 4.07; 95%CI 1.19-13.92, p=0.025), 2) had no prior abdominal surgery (OR 2.70; 95% CI 1.13-6.46, p=0.026), 3) who were intubated (OR 5.67; 95% CI 2.26-14.25, p<0.001) or 4) who were on hemodialysis (OR 10.57; 95% CI 1.24-87.32, p=0.031). The median length of hospital stay after diagnosis of candidemia was 47.5 days (range 35.5-78) for patients with favorable outcomes and 32.5 days (range 20-45) for those with unfavorable outcomes (p=0.001).

DISCUSSION

Our study showed that the number of patients with candidemia has increased over the period of 5 years. Males and females were equally affected, similar to other reports (Wiwattanachang and Sathapatayavongs, 1999; Foongladda *et al*, 2004; Suankratay *et al*, 2005; Anunnatsiri *et al*, 2009; Horn *et al*, 2009). The majority of patients had underlying medical conditions, invasive medical devices in place or had received immunosuppressive agents during episodes of candidemia. More than 90% of patients had received antimicrobial therapy prior to the episodes of candidemia. These are well-known risk factors for candidemia as reported in previous studies (Henderson *et al*, 1981; Karabinis *et al*, 1988; Bross *et al*, 1989; Castaldo *et al*, 1991; Goodrich *et al*, 1991; Pittet *et al*, 1994; Bow *et al*, 1995; Marr *et al*, 2000). Only one-third of patients in our study were in the ICU during their episode of candidemia; this corresponds with other reports (Marchetti *et al*, 2004; Anunnatsiri *et al*, 2009) and highlights the importance of early recognition of patients who are at risk even if they are not in a critical care unit.

We observed a stable predominance (approximately 70%) of non-*albicans Candida* species over the study period, similar to other reports from the United States (2004-2008) (Horn *et al*, 2009) and Thailand (1999-2003) (Anunnatsiri *et al*, 2009). However, studies from Taiwan (1994-1995) (Hung *et al*, 1996), (2003-2005) (Tsai *et al*, 2008), Hong Kong (1998-2006) (Yap *et al*, 2009), Switzerland (1991-2000) (Marchetti *et al*, 2004), France (1990-2000) (Charles *et al*, 2003), and United States (1995-1997) (Edmond *et al*, 1999) found that *C. albicans* remained the most common isolated *Candida* species. Of the non-*albicans Candida* species; *C. tropicalis*, followed by *C. parapsilosis*, were the two most common species, which was also observed in many studies from Thailand (Wiwattanachang and Sathapatayavongs, 1999; Foongladda *et al*, 2004; Anunnatsiri *et al*, 2009). *C. tropicalis*, followed by *C. glabrata*, were the two most common isolates in a study from Hong Kong (Yap *et al*, 2009), whereas in Western countries, *C. glabrata* was most common (Edmond *et al*, 1999; Marchetti *et al*, 2004; Horn *et al*, 2009). *C. krusei*, which is intrinsically resistant to fluconazole, was rare in our study as was reports in other studies (Hung *et al*, 1996; Edmond *et al*, 1999; Marchetti *et al*, 2004; Horn *et al*, 2009; Yap *et al*, 2009).

Previous studies found receiving fluconazole and central venous catheter exposure were associated with non-

albicans candidemia (Weems *et al*, 1987; Almirante *et al*, 2006; Chow *et al*, 2008), but we failed to demonstrate this association in our study. Only 9% of our patients received fluconazole prior to episodes of candidemia. Total parenteral nutrition was inconsistently associated with non-*albicans* candidemia (Almirante *et al*, 2006; Chow *et al*, 2008a). Some studies found no difference in risk factors between *albicans* candidemia and non-*albicans* candidemia (Chow *et al*, 2008b; Dutta and Palazzi, 2011). The only independent predictive risk factor for non-*albicans* candidemia in our study was not being admitted to the ICU during the episode of candidemia.

The overall in-hospital mortality rate in this study was 36.2%. However, 56.5% of patients had unfavorable outcomes. The crude mortality rate in other studies ranges from 30% to 80% depending on the study population (Charles *et al*, 2003; Almirante *et al*, 2006; Anunnatsiri *et al*, 2009; Horn *et al*, 2009; Yap *et al*, 2009). Sixty percent of our patients received systemic antifungal therapy, including amphotericin B, fluconazole or echinocandins. Factors independently associated with unfavorable outcomes included patients who were in the intensive care unit, who were intubated or who were on hemodialysis, similar to the findings of some other studies (Voss *et al*, 1996; Anunnatsiri *et al*, 2009). We found prior abdominal surgery was associated with poor clinical outcomes, similar to another report (Charles *et al*, 2003). Other studies have reported the association between prior surgery and a poor outcome (Nieto-Rodriguez *et al*, 1996). We found no other factors associated with survival, such as antifungal treatment, the absence of neutropenia or a lower APACHE II score (Charles *et al*, 2003; Anunnatsiri *et al*, 2009).

Candidemia is a leading cause of nosocomial bloodstream infection and has a high mortality. This is not a rare condition in either developed or developing countries. The majority of patients had underlying medical conditions and exposure to medical devices or other therapeutic modalities. Although we observed the predominance of non-*albicans* candidemia, but most of these isolates were *C. tropicalis* and *C. parapsilosis*, which were generally sensitive to amphotericin B and fluconazole. Early recognition and prompt empirical treatment are essential to improve outcomes of patients who are at risk for developing candidemia. Improved surveillance is crucial to recognize the emergence of highly resistant strains of *Candida* spp that may lead to a change in practice guidelines.

This study has several limitations. First, this was a retrospective study; therefore, the data were not complete. We failed to explore the reason for not receiving antifungal therapy and outcomes in some patients which could affect the mortality rate. Second, our laboratory, cannot identify all species of non-*albicans Candida*. We were unable to identify 9 isolates. Third, we cannot perform drug susceptibility testing for fungi. Therefore, we lack data about drug susceptibilities, which is important for guiding physicians in empiric systemic antifungal therapy. This is the first report of the epidemiology of candidemia at a tertiary-care hospital in northern Thailand. Prospective data collection is needed to avoid the above limitations and lead to a meaningful surveillance program with proper clinical practice guidelines for management of this important nosocomial blood stream infection.

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