Effects of Nosocomial Candidemia on Outcomes of Critically Ill Patients

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PURPOSE: To determine whether nosocomial candidemia is associated with increased mortality in intensive care unit (ICU) patients.

SUBJECTS AND METHODS: We performed a retrospective (1992 to 2000) cohort study of 73 ICU patients with candidemia and 146 matched controls. Controls were matched based on disease severity as measured by the Acute Physiology and Chronic Health Evaluation (APACHE) II score (± 1 point), diagnostic category, and length of ICU stay before onset of candidemia.

RESULTS: In comparison with the control group, patients with candidemia developed more acute respiratory failure (97% [n = 71] vs. 88% [n = 129], $P = 0.03$) during their ICU stay. They were mechanically ventilated for a longer period (29 ± 26 days vs. 19 ± 19 days, $P<0.01$) and had a longer stay in the ICU (36 ± 33 days vs. 25 ± 23 days, $P = 0.02$) as well as in the hospital (77 ± 81 days vs. 64 ± 69 days, $P = 0.04$). There was no difference in in-hospital mortality between the groups (48% [n = 35] vs. 43% [n = 62], $P = 0.44$), a difference of 5% (95% confidence interval [CI]: −8% to 19%). In a multivariate analysis, older age (hazard ratio [HR] = 1.13 per 10 years; 95% CI: 1.04 to 1.23; $P = 0.004$), acute renal failure (HR = 1.4; 95% CI: 1.1 to 2.0; $P = 0.02$), and unfavorable APACHE II scores (HR = 1.10 per 5 points; 95% CI: 1.00 to 1.20; $P = 0.05$) were independent predictors of mortality. Candidemia was not associated with mortality in a model that adjusted for these factors (HR = 0.9; 95% CI: 0.7 to 1.2; $P = 0.53$).

CONCLUSION: Nosocomial candidemia does not adversely affect the outcome in ICU patients in whom mortality is attributable to age, the severity of underlying disease, and acute illness. **Am J Med. 2002;113:480–485.** ©2002 by Excerpta Medica, Inc.

In intensive care units (ICUs), candidemia most often occurs in patients who have survived a critical illness. Following an excessive systemic inflammatory response, ICU patients often have prolonged cellular immune dysfunction, with down-regulated monocyte and granulocyte function. This makes patients vulnerable to opportunistic infections like candidemia, which most often occurs after an ICU stay of 14 to 30 days (1). The emergence of candidemia among hospitalized patients is also associated with the use of immunosuppressive therapy and broad-spectrum antibiotics, as well as the increasing number of patients with long ICU stays (2–4).

Candidemia generally occurs in patients who are debilitated (5); other risk factors are prior antibiotic use, the use of central venous catheters, renal impairment requiring hemodialysis, and multisite candidal colonization (5), all of which are common in ICU patients. In non-ICU patients, candidemia is associated with increased mortality (6). In ICUs, mortality in patients with candidemia ranges from 36% to 63% (7–13). The aim of our study was to determine whether candidemia per se was associated with increased mortality in ICU patients.

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SUBJECTS AND METHODS

Setting and Design

The study was conducted at the 1060-bed Ghent University Hospital, Belgium. The ICU has 54 beds and includes a surgical and medical ICU, an ICU for cardiac surgery, and a unit for severely burned patients. Approximately 3300 patients are admitted to the ICU each year, including solid organ and bone marrow transplant recipients. Isolation rows are available for immunocompromised patients or patients colonized or infected with epidemiologically important microorganisms. The burn unit has six isolation rooms with shower and bath installations.

We conducted a retrospective, matched (1:2 ratio) cohort study in adult, non-neutropenic, critically ill patients admitted to the ICU during a 9-year period (January 1992 through December 2000). Each ICU patient with microbiologically documented candidemia was matched with 2 other ICU patients without clinical or microbiological evidence of candidemia (controls). Since September 1991, all positive blood cultures were screened for infection control. This hospital-wide case-based surveillance program was used to identify candidemic ICU patients.

Matching Procedure

Control patients were selected from the same time frame. Matching was based on the Acute Physiology and Chronic Health Evaluation (APACHE) II score (± 1 point) and the same principal diagnosis leading to ICU admission (14–18); control patients were also required to have had an ICU stay at least as long as the matched case's

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length of stay before the onset of candidemia. The APACHE II score is calculated from chronic health conditions and acute physiologic parameters during the first 24 hours of ICU observation. The expected in-hospital mortality can be calculated from the APACHE II score and the diagnostic category (surgical vs. nonsurgical admission diagnosis, elective or emergency surgery, major vital organ system of failure, and the principal diagnosis leading to ICU admission). Selection of controls was made without knowledge of outcome. If there were more than 2 potential controls, matching was based on the nearest admission date to the patients with candidemia.

Definitions

Candidemia was defined as at least one blood culture that grew *Candida* organisms. Blood cultures were obtained routinely (as a guideline) when a patient's temperature was >38.4°C. They were usually collected by venous puncture and processed following the BacT/Alert (Organon Teknika Corp., Durnham, North Carolina) procedure. A 10-mL blood culture inoculum was standard. There were no changes in microbiological laboratory techniques during the study. The time of onset of candidemia was defined as the date of the first positive blood culture. Candidemia was considered nosocomial when it first occurred more than 48 hours after hospital admission. The source of candidemia was determined by both intensivists and microbiologists based on isolation of *Candida* from the presumed portal of entry and confirmed by clinical evaluation.

Antifungal treatment was left to the discretion of the attending intensivists. During the study, antifungal therapy consisted of intravenous amphotericin B (1 mg/kg/d) or fluconazole (400 mg/d). Preemptive antifungal therapy was started in patients with persistent candidal colonization and was defined as the use of fluconazole before the onset of candidemia. When antifungal therapy was started for a fungal infection before the onset of candidemia, it was considered preemptive for candidemia. Days of preemptive therapy were not included in the calculation of the length of therapy for candidemia. Candidemia that developed during preemptive therapy was defined as breakthrough candidemia. Delay in the start of antifungal treatment was calculated from the day of onset of candidemia.

Patients were considered non-neutropenic when their neutrophil count was >500/mm^3. Acute respiratory failure was defined as ventilator dependence, acute renal failure as dialysis dependence, and hemodynamic instability as the need for vasopressors or inotropic agents during the ICU stay.

In-hospital mortality was defined as death within the same hospital admission (ICU and general wards). Mortality attributable to candidemia was estimated by subtracting the crude mortality of the control patients from that of the patients with candidemia (19).

Statistical Analysis

Continuous variables are described as mean ± SD or median (interquartile range). Univariate analyses used the Mann-Whitney *U* test or chi-squared test, as appropriate. We estimated 95% confidence intervals (CI) for attributable mortality rate and the differences between expected and observed mortality. Kaplan-Meier survival curves were compared using the log-rank test. A multivariate Cox proportional hazards model that accounted for the matched design was used to estimate hazard ratios (HR) and 95% confidence intervals. Age was categorized per 10 years and APACHE II score per 5 points. Variables included in the analysis were required to have a plausible relation with mortality as well as a P value <0.1 in univariate analyses. Multivariate survival analysis among patients with candidemia was performed to determine risk factors for death among candidemic ICU patients. Statistical analyses were executed with STATISTICA 4.5 (StatSoft Inc., Tulsa, Oklahoma) and SPSS 9.0 (SPSS Inc., Chicago, Illinois). Statistical significance was defined as P <0.05 (two-sided).

RESULTS

During the study, 73 of the 29,727 ICU admissions were complicated by candidemia (2.5 per 1000 admissions). Fifty-one episodes (70%) were caused by *Candida albicans*, 17 (23%) by *Candida glabrata*, 3 (4%) by *Candida parapsilosis*, 1 (1%) by *Candida tropicalis*, and 1 (1%) by *Candida krusei*. The median duration from ICU admission to the onset of the candidemia was 15 days (interquartile range, 8 to 24 days). Thirty-four (47%) of the patients with candidemia had a surgical admission diagnosis. In 30 patients (41%), the portal of entry of the candidemia was unknown. Other sources of candidemia were contaminated central venous catheters (26% [n = 19]), postsurgical intra-abdominal infections (15% [n = 11]), urinary tract infections (8% [n = 6]), and pneumonia (7% [n = 5]). Three patients had wound infections, 2 had sinusitis, and 1 each had pleuritis and endocarditis. Two sources of infection were detected in 5 patients. Forty-nine patients (67%) had surveillance cultures that were positive for *Candida* before the onset of candidemia. Fourteen patients (20%) received preemptive antifungal therapy and experienced breakthrough candidemia.

Mortality among Patients with Candidemia

Mortality at 14 days after the onset of the candidemia was 26% (n = 19); at 28 days, mortality was 36% (n = 26). Patients in whom antifungal therapy was delayed >48 hours from the onset of candidemia had greater mortality (78% [7/9] vs. 44% [28/64], P = 0.06). Among candi-

Table 1. Characteristics of Intensive Care Unit Patients with Candidemia and Controls

Characteristic	Patients with Candidemia (n = 73)	Controls (n = 146)	*P* Value
	Number (%), or Mean ± SD, Median (Interquartile Range)		
Age (years)	53 ± 18, 58 (41–68)	56 ± 18, 59 (47–69)	0.38
APACHE II score	25 ± 9, 25 (18–29)	25 ± 9, 25 (18–29)	0.99
Acute respiratory failure at ICU admission	69 (95)	126 (86)	0.07
Acute respiratory failure during ICU stay	71 (97)	129 (88)	0.03
Ventilator dependence (days)	29 ± 26, 22 (8–44)	19 ± 19, 16 (5–25)	<0.01
Acute renal failure at ICU admission	5 (7)	10 (7)	0.99
Acute renal failure during ICU stay	20 (27)	40 (27)	0.99
Hemodynamic instability at ICU admission	40 (55)	84 (58)	0.87
Hemodynamic instability during ICU stay	54 (76)	108 (74)	0.99
ICU stay (days)	36 ± 33, 25 (12–49)	25 ± 23, 21 (8–30)	0.02
Hospital stay (days)	77 ± 81, 54 (29–91)	64 ± 69, 38 (18–83)	0.04
Antifungal therapy (n = 69)*			
Patients with preemptive therapy	14 (20)	—	—
Length of preemptive therapy (days)	7 ± 5, 7 (1–11)	—	—
Patients with appropriate therapy	60 (87)	—	—
Length of therapy (days)	16 ± 16, 11 (5–23)	—	—
Delay in start of therapy (days)	2 ± 3, 1 (0–2)	—	—

* In 4 patients, no data on antifungal therapy were available.
APACHE = Acute Physiology and Chronic Health Evaluation; ICU = intensive care unit.

demic patients, older age (HR = 1.25 per 10 years; 95% CI: 1.04 to 1.49; $P = 0.05$) and a delay of antifungal therapy of >48 hours (HR = 2.1; 95% CI: 1.0 to 4.4; $P = 0.05$) were independently associated with in-hospital mortality in a model that also adjusted for APACHE score. Source of the candidemia (primary, catheter-related, intra-abdominal infection) and breakthrough candidemia were not associated with mortality.

Comparison with Matched Controls

Matching on APACHE II score and diagnostic category was successful for all subjects (Tables 1 and 2). Of the 146 control subjects, 4 did not meet the criterion of length of ICU stay greater than or equal to the interval from ICU admission to candidemia in their matched patient with candidemia. In comparison with the control group, candidemic patients developed more acute respiratory failure during their ICU stay, they were mechanically ventilated for a longer period, and they had longer stays in the ICU as well as in the hospital (Table 1). The survival curves of both groups did not differ significantly (Figure, $P = 0.28$). The in-hospital mortality was 48% (35/73) among patients with candidemia compared with 43% (62/146) among the control subjects (Table 3, $P = 0.44$), a difference (attributable mortality) of 5% (95% CI: −8% to 19%). Observed mortality did not differ significantly from the expected mortality based on APACHE II scores (Table 3).

In a multivariate analysis, older age (HR = 1.13 per 10 years; 95% CI: 1.04 to 1.23; $P = 0.004$), acute renal failure (HR = 1.4; 95% CI: 1.1 to 2.0; $P = 0.02$), and APACHE II score (HR = 1.10 per 5-point increase; 95% CI: 1.00 to 1.20; $P = 0.05$) were independent predictors of mortality. In a model that adjusted for these factors, candidemia was not associated with mortality (HR = 0.9; 95% CI: 0.7 to 1.2; $P = 0.53$).

DISCUSSION

In this retrospective analysis, we found no difference in mortality between patients with candidemia and a matched control group. Although the observed mortality (48%) was similar to the results of previous studies, the mortality attributable to candidemia was only 5% (with a 95% confidence interval from −8% to 19%). This candidemia contrasts with the current opinion about this bloodstream infection, for which attributable mortality above 20% have been reported in ICU settings (7–9). In these studies, however, attributable mortality was assessed on clinical findings. Because of the grim prognosis in patients with candidemia, it is difficult to distinguish attributable mortality from death caused by underlying disease (5). Therefore, matched cohort studies are recommended to determine attributable mortality among patients with high expected mortality (19).

A previous study (6) in candidemic patients noted a 38% attributable mortality in patients with candidemia (57% vs. 19%). That study was hospital-wide, compared with the ICU setting in our study. Perhaps candidemia

Table 2. Number of Patients (and Deaths) by Principal Intensive Care Unit Admission Diagnosis

Diagnostic Category	Patients with Candidemia (n = 73)	Controls (n = 146)
	Number of Patients (Number Who Died)	
Surgical patients		
Multiple trauma	12 (2)	24 (3)
Head trauma	5 (1)	10 (5)
General abdominal surgery	5 (3)	10 (6)
Gastrointestinal surgery for neoplasm	2 (1)	4 (1)
General cardiovascular surgery	3 (2)	6 (4)
General thoracic surgery	2 (1)	4 (2)
Peripheral vascular surgery	1 (1)	2 (1)
Surgery for renal neoplasm	1 (0)	2 (0)
Craniotomy for intracranial hemorrhage	1 (1)	2 (0)
Craniotomy for neoplasm	2 (1)	4 (1)
Nonsurgical patients		
Cardiovascular failure due to sepsis	9 (6)	18 (7)
Cardiovascular failure due to shock	9 (6)	18 (13)
Cardiovascular failure due to cardiac arrest	3 (2)	6 (1)
Respiratory failure due to infection	7 (5)	14 (9)
Respiratory failure (general)	1 (0)	2 (1)
Intoxication	3 (0)	6 (2)
Neurologic impairment	2 (1)	4 (0)
Metabolic/renal dysfunction	5 (2)	10 (7)

has a higher attributable mortality in general medical and surgical wards, in which diagnosis and initiation of therapy is probably slower than in ICUs.

We matched subjects based on severity of illness and the main diagnostic category at the time of ICU admission, because these are the most important prognostic

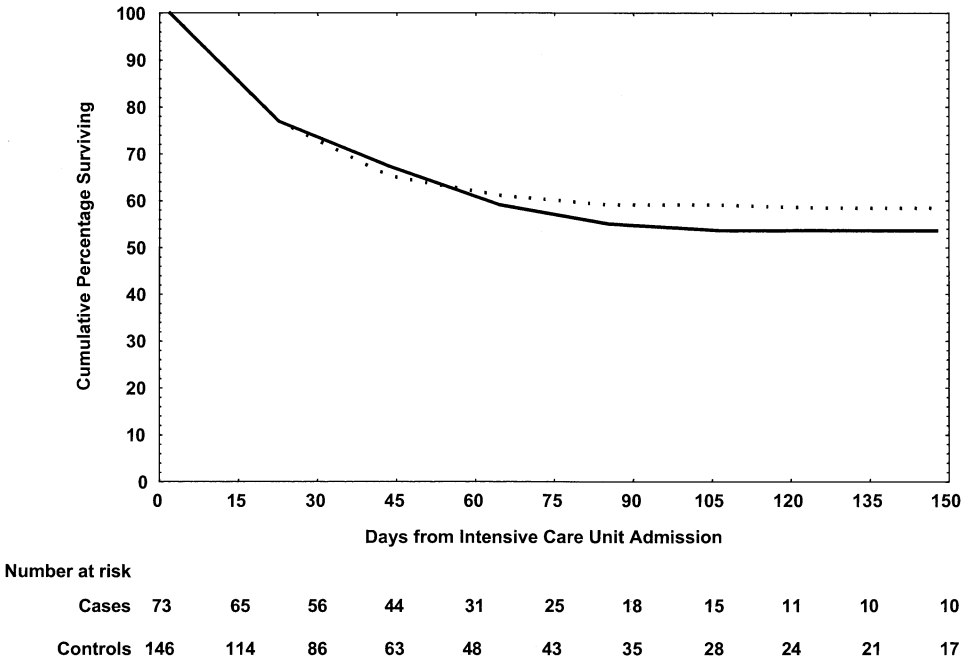

Figure. Kaplan-Meier survival curves for patients in the intensive care unit with candidemia and controls. The solid line represents the cumulative survival for the 73 patients with candidemia, and the dashed line represents the cumulative survival for the 146 control patients ($P = 0.28$).

Table 3. Observed and Expected Mortality for Patients with Candidemia and Controls

	Patients with Candidemia (n = 73)	Controls (n = 146)	*P* Value
Observed in-hospital mortality	35 (48%)	62 (43%)	0.44
Expected in-hospital mortality (95% confidence interval)*	45% (36%–59%)	44% (34%–50%)	0.85

* Based on the Acute Physiology and Chronic Health Evaluation II system (14).

indicators in ICU patients and in patients with candidemia or bacteremia (11,14,15,18,20,21). An advantage of this matching procedure is that the validity of the control group can be judged by comparing the observed and expected mortality rates, which were nearly equal in our study. Matching at the time of ICU admission rather than at the time of onset of candidemia may have affected our results (20); length of hospitalization before the onset of infection might confound the effects of nosocomial bloodstream infections. DiGiovine et al. (20) found that candidemic ICU patients had a substantial increase in severity of illness between the day of ICU admission and the days preceding candidemia. This observation is not supported by our data, because expected mortality, which was estimated from characteristics obtained on the first day of ICU admission, correlated well with observed mortality in the candidemic patients.

Favorable developments in supportive treatment and anti-infective management are most likely responsible for the low attributable mortality from candidemia. Another explanation might be our intensive screening policy, in which site-specific surveillance cultures were obtained three times a week. In our study, two thirds of the episodes of candidemia were preceded by candidal colonization; in those who also had fever of unexplained origin, preemptive therapy was started. Surveillance sampling likely contributed to the short delay in the start of treatment (median of 1 day), which is of major importance in the therapy of candidemia (22–24). In addition, we found that most patients (87%) were treated appropriately. Delay >48 hours in the initiation of antifungal therapy was associated with worse outcome. This observation, together with the facts that blood cultures have a low sensitivity (at most 50%) for detecting infections with *Candida* and that processing blood cultures takes almost 2 days, confirms the importance of preemptive therapy in case of persistent, multisite candidal colonization (22,25). Moreover, approximately 20% of patients with candidemia do not have fever, and 50% do not have leukocytosis, which are major factors in decisions about obtaining blood cultures (24).

Catheter replacement in patients with fever of unexplained origin, which is common practice in our ICU, might also have contributed to our results (26–28). Together with obtaining blood cultures, catheter replacement is the first step in the algorithm for managing patients with fever without an apparent focus. In our study, the contaminated catheter was removed within 1 day of the onset of candidemia in 17 of the 19 patients with catheter-related candidemia.

In conclusion, we found that candidemia occurs in severely ill ICU patients. Despite its correlation with longer ICU and hospital stays, and with ventilator dependence, candidemia did not increase mortality, which was mainly attributable to the severity of underlying disease and acute illness. Our results may be due to our policy of prompt catheter removal, as well as to a high rate of appropriate antifungal therapy and a short delay in starting treatment.

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