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# HAS THE EPIDEMIOLOGY OF NOSOCOMIAL CANDIDEMIA CHANGED?

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## ABSTRACT

**OBJECTIVE:** To assess changes in the epidemiology of nosocomial candidemia in the post-fluconazole era among hospitalized patients using a case–control study design.

**DESIGN:** Candidemia case-patients were matched 1:1 on diagnosis, age, and length of stay with control-patients. Conditional logistic regression was used to determine predictors and outcomes of candidemia. Treatment regimens and compliance with national practice guidelines were compared among case-patients.

**SETTING:** Barnes–Jewish Hospital, a 1,278-bed, tertiary-care center affiliated with Washington University School of Medicine, St. Louis, Missouri.

**PARTICIPANTS:** Patients admitted from January 1 to December 31, 2000. Case-patients were identified through the hospital microbiological surveillance system and matched with control-patients.

**RESULTS:** Predictors of candidemia included Hickman catheters (odds ratio [OR], 9.53; 95% confidence interval [$CI_{95}$], 1.34 to 68.01), gastric acid suppressants (OR, 6.38; $CI_{95}$, 2.33 to 17.43), nasogastric tubes (OR, 3.69; $CI_{95}$, 1.27 to 10.78), antibiotics (OR, 1.46; $CI_{95}$, 1.15 to 1.86), and admission to the intensive care unit (OR, 6.40; $CI_{95}$, 2.12 to 19.31). The crude case-fatality rate was 40%. Seventeen (15%) of the case-patients received the recommended treatment regimen according to recently published practice guidelines.

**CONCLUSIONS:** The epidemiology of candidemia has changed little at our hospital during the past decade and remains a significant cause of mortality. Further studies on the benefits of preventive therapy will be essential to improve the outcome of this infection (*Infect Control Hosp Epidemiol* 2004;25:628-633).


Since early reports documenting the importance of yeast as a cause of nosocomial infections, the role of fungal organisms as a cause of infections among hospitalized patients has increased substantially. Data from the National Nosocomial Infections Surveillance System for the 10-year period from 1980 to 1990 documented an increase in the incidence of all nosocomial fungal infections from 2.0 to 3.8 infections per 1,000 patients discharged, with the incidence of nosocomial fungemia increasing from 1.0 to 4.9 infections per 10,000 discharges.[1] *Candida* species accounted for approximately 85% of the nosocomial fungal infections.[1] Recent data from the Surveillance and Control of Pathogens of Epidemiologic Importance (SCOPE) project showed that *Candida* species were the fourth most common cause of nosocomial bloodstream infections, accounting for approximately 8% of the total.[2] *C. albicans* has historically been the most frequently isolated species, accounting for approximately 60% to 70% of the infections; however, recent studies have documented an increase in the proportion of infections due to non-*albicans* species.[1-11] Previous studies have suggested several risk factors for the acquisition of a nosocomial candidal bloodstream infection.[2] These data are somewhat limited by the fact that many of the epidemiologic studies focused on specific patient populations, were observational in nature, and were conducted prior to the era of increased use of azoles.[2,12-18]

A retrospective case series of 106 patients with candidemia performed at our institution from September 1, 1988, to September 1, 1989, documented similar risk factors.[19] Although much is known about the epidemiology of candidemia, few recent case–control studies have been performed among a general hospitalized patient population. To assess changes in the epidemiology of candidemia since azoles have become widely used, a case–control study was performed among all hospitalized patients with candidemia during 2000.

## METHODS

### *Participants*

Barnes–Jewish Hospital is a 1,287-bed, tertiary-care center affiliated with Washington University School of Medicine, St. Louis, Missouri. All patients admitted to Barnes–Jewish Hospital between January 1 and December 31, 2000, with at least one blood culture positive for

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*Candida* species were included in the study. We defined a patient with nosocomial candidemia as any patient with at least one blood culture positive for *Candida* species that was performed at least 48 hours after admission. Case-patients were identified through our microbiological surveillance mechanism. Control-patients were selected from all admissions to Barnes–Jewish Hospital during this same period. This study was approved by the Human Studies Committee at Washington University School of Medicine.

### *Design*

A 1:1 matched case–control study design was used to determine the risk factors associated with *Candida* bloodstream infections. A control-patient could not have any evidence of *Candida* infection during the hospitalization period studied. Matching of case-patients and control-patients was based on the following criteria: the principal diagnosis of the case as identified by the International Classification of Diseases, 9th revision, Clinical Modification code; age within 10 years; and length of hospitalization. The length of stay in the hospital was calculated from the date of hospital admission until the date of discharge for control-patients and from the date of hospital admission until the date of the first blood culture positive for *Candida* for case-patients. If a control-patient could not be found to match the case-patient on principal diagnosis, secondary diagnoses were considered. The secondary diagnoses were used only if the primary diagnosis was extremely rare and the secondary diagnoses were clinically similar to the principal diagnosis.

Control-patients meeting the matching criteria were identified from hospital admissions from January 1 to December 31, 2000. Matching control-patients were randomly selected for case-patients using the random digit generator (Rand Corp., Santa Monica, CA).

### *Risk Factors*

Data for case-patients and control-patients were abstracted from electronic hospital records, the medical informatics system, and medical chart review. Demographic data included age, race (white, black, or other), and gender. Data were collected regarding the patient's hospital stay including length of stay, intensive care unit (ICU) admission, unit of admission, and previous admissions.

Severity of illness was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score.[20] APACHE II scores were calculated for case-patients using the worst values obtained 24 hours prior to the identification of a culture positive for *Candida*. APACHE II scores were calculated for control-patients using the worst values obtained within the first 48 hours of hospital admission. If a patient had missing APACHE values, the mean value from the cases was used for case-patients and the mean value from the controls was used for control-patients.

Various underlying medical illnesses were assessed as dichotomous variables including diabetes mellitus, insulin dependence, chronic obstructive pulmonary disease, solid organ tumor, hematologic malignancy, coronary artery disease, congestive heart failure, asthma, end-stage liver disease, cirrhosis and pancreatitis, human immunodeficiency virus, acquired immunodeficiency syndrome, and cytomegalovirus. In addition, data were collected regarding the receipt of a bone marrow or stem cell transplant including the type of transplant, receipt of total body irradiation, receipt of cyclophosphamide, and prophylaxis for veno-occlusive disease of the liver. Data regarding previous surgeries within a 6-month period of hospital admission were collected including type of surgery, surgical complications, and returns to surgery.

Nosocomial manipulations included type of central venous catheter (eg, Hohn, Hickman, Quentin [Kendall, Mansfield, MA], peripherally inserted central catheters, or Swan-Ganz), nasogastric feeding tube, gastrostomy tube, nasogastric tube, endotracheal tube, tracheostomy, Foley catheter, chest tube, and surgical drains. Dichotomous variables were created regarding hemodialysis and the receipt of a transfusion of red blood cells, whole blood, or platelets. Pharmacologic data were collected including the receipt and duration of antibiotics, adrenocortical steroids, immunosuppressants, chemotherapy, and gastric acid suppressants. Compliance with the practice guidelines of the Infectious Diseases Society of America for the treatment of candidemia was assessed among the case-patients.

The cost of hospitalization for each patient was obtained from the cost accounting database of Barnes–Jewish Hospital. Mean costs of hospitalization and ranges were compared between case-patients and control-patients.

### *Statistical Analyses*

Demographics, nosocomial exposures, severity of illness, and underlying medical illness variables were compared for case-patients and matched control-patients using the chi-square test for categorical variables and the *t* test for continuous variables. Conditional logistic regression for matched data was performed for multivariate analyses with SPSS software (version 10.0; SPSS, Inc., Chicago, IL). Significant risk factors ($P < .05$) were considered in the multivariate analyses. Interactions between all main effects were assessed in each model. Regression diagnostics were used to determine any outlying or influential cases. Log-likelihood was used to assess the fit of the model.

## RESULTS

### *Case-Patients*

During the study period, 113 patients with candidemia were identified. *C. albicans* was the most common isolate and accounted for 64 (56%) of the infections. *C. parapsilosis* (18; 16%), *C. glabrata* (17; 15%), *C. tropicalis* (14; 12%), and *C. krusei* (2; 2%) were identified among the remainder of case-patients.

Twenty-six (23%) of the patients with a blood culture positive for *Candida* on admission were excluded from the matched case–control analysis of patients with nosocomial candidemia. There were 57 patients with can-

**TABLE 1**
RISK FACTORS FOR CANDIDEMIA

| Factor | All Species | | | |
|---|---|---|---|---|
| | No. of Case-Patients (%)* | No. of Control-Patients (%)* | OR | $CI_{95}$ |
| Previous admission | 35 (46.7) | 31 (41.3) | 1.24 | 0.65–2.37 |
| APACHE II score | | | | |
| 0% to 25% mortality | 37 (49.3) | 59 (78.7) | 1.00 | |
| 26% to 55% mortality | 21 (28.0) | 14 (18.7) | 2.08 | 0.92–4.66 |
| ⩾ 56% mortality | 7 (9.3) | 2 (2.7) | 3.73 | 0.72–19.27 |
| Concomitant bloodstream infection | 35 (46.7) | 31 (41.3) | 1.24 | 0.65–2.37 |
| Medical condition | | | | |
| Diabetes mellitus | 15 (20.0) | 21 (28.0) | 0.64 | 0.30–1.37 |
| Insulin dependent | 7 (9.3) | 17 (22.7) | 0.35 | 0.14–0.91 |
| COPD | 8 (10.7) | 8 (10.7) | 1.00 | 0.36–2.82 |
| Asthma | 3 (4.0) | 3 (4.0) | 1.00 | 0.20–5.12 |
| ESLD | 3 (4.0) | 1 (1.3) | 3.08 | 0.31–30.34 |
| Cirrhosis | 1 (1.3) | 4 (5.3) | 0.24 | 0.03–2.20 |
| Pancreatitis | 4 (5.3) | 3 (4.0) | 1.35 | 0.29–6.26 |
| CAD | 21 (28.0) | 8 (10.7) | 3.26 | 1.34–7.93† |
| CHF | 19 (25.3) | 8 (10.7) | 2.84 | 1.16–6.98† |
| Hematologic malignancy | 14 (18.7) | 14 (18.7) | 1.00 | 0.44–2.27 |
| Nosocomial manipulation | | | | |
| ICU admission | 41 (54.7) | 8 (10.7) | 10.10 | 4.26–23.93† |
| Neutropenia | 6 (8.0) | 4 (5.3) | 1.54 | 0.42–5.7 |
| Central venous catheter | 55 (73.3) | 34 (45.3) | 3.32 | 1.67–6.58† |
| Hohn | 28 (37.3) | 22 (29.3) | 1.44 | 0.73–2.84 |
| Hickman | 13 (17.3) | 2 (2.7) | 7.65 | 1.66–35.23† |
| Quentin‡ | 4 (5.3) | 3 (4.0) | 1.35 | 0.29–6.26 |
| PICC | 3 (4.0) | 8 (10.7) | 0.35 | 0.09–1.37 |
| Swan-Ganz | 14 (18.7) | 6 (8.0) | 2.64 | 0.96–7.29 |
| Feeding tube | 34 (45.3) | 14 (18.7) | 3.61 | 1.73–7.56† |
| Nasogastric tube | 43 (57.3) | 12 (16.0) | 7.06 | 3.27–15.21† |
| Gastrostomy | 10 (13.3) | 11 (14.7) | 0.90 | 0.36–2.25 |
| Endotracheal tube | 43 (57.3) | 17 (22.7) | 4.56 | 2.26–9.31† |
| Foley catheter | 55 (73.3) | 35 (46.7) | 3.14 | 1.59–6.23† |
| RBC transfusion | 42 (56.0) | 38 (50.7) | 1.24 | 0.65–2.36 |
| Platelet transfusion | 20 (26.7) | 9 (12.0) | 2.67 | 1.12–6.33† |
| Drug therapy | | | | |
| Adrenal corticosteroids | 37 (49.3) | 11 (14.7) | 5.67 | 2.59–12.40† |
| Antibiotics | | | | |
| None | 5 (6.7) | 30 (40.0) | 1.00 | |
| 1 to 3 | 29 (38.7) | 30 (40.0) | 5.80 | 1.98–16.99† |
| 4 or more | 41 (54.7) | 15 (20.0) | 6.81 | 3.06–15.14† |
| Immunosuppressants | 17 (22.7) | 8 (10.7) | 2.46 | 0.99–6.10 |
| Gastric suppressants | 37 (49.3) | 13 (17.3) | 4.64 | 2.19–9.83† |
| Surgery | | | | |
| Previous surgery | 40 (53.3) | 32 (42.7) | 1.54 | 0.81–2.93 |
| Neurosurgery | 2 (2.7) | 0 | 1.54 | 0.60–3.98 |
| Cardiac | 10 (13.3) | 6 (8.0) | 1.77 | 0.61–5.15 |
| Thoracic | 10 (13.3) | 5 (6.7) | 2.15 | 0.70–6.64 |
| Gastrointestinal | 11 (14.7) | 7 (9.3) | 1.67 | 0.61–4.57 |
| Obstetrics/gynecology | 3 (4.0) | 4 (5.3) | 0.74 | 0.16–3.42 |
| Urology | 3 (4.0) | 0 | | |
| Orthopedic | 4 (5.3) | 8 (10.7) | 0.47 | 0.14–1.64 |
| ENT | 1 (1.3) | 2 (2.7) | 0.49 | 0.04–5.56 |

**TABLE 1 (*cont'd*)**
RISK FACTORS FOR CANDIDEMIA

| Factor | All Species: No. of Case-Patients (%) | All Species: No. of Control-Patients (%) | All Species: OR | All Species: $CI_{95}$ |
|---|---|---|---|---|
| Outcome | | | | |
| Mortality | 29 (38.7) | 3 (4.0) | 15.8 | 4.55–55.02† |

OR = odds ratio; $CI_{95}$ = 95% confidence interval; APACHE = Acute Physiology and Chronic Health Evaluation; COPD = chronic obstructive pulmonary disease; ESLD = end-stage liver disease; CAD = coronary artery disease; CHF = congestive heart failure; ICU = intensive care unit; PICC = peripherally inserted central catheter; RBC = red blood cell; ENT = ear, nose, and throat.
*Number of case-patients = 75; number of control-patients = 75.
†Significant at $P < .05$.
‡Kendall, Mansfield, MA.

didemia (66%) who had another site positive for a *Candida* species or yeast (not further identified).

### *Control-Patients*

There was a match on principal or secondary diagnosis, age, and length of stay for 75 (86%) of 87 case-patients. Control-patients were randomly matched on all criteria (principal diagnosis, age, and length of stay) with 64 (74%) of 87 case-patients. The secondary diagnosis was used for patients who had disseminated candidemia as a principal diagnosis or whose principal diagnoses were rare.

### *Analysis: Match Criteria = Principal Diagnosis + Age + Length of Stay*

Demographic characteristics were not significantly different between case-patients and control-patients. However, there were slight differences in underlying medical histories between case-patients and control-patients. Case-patients were more likely than control-patients to have coronary artery disease (21 [28.0%] vs 8 [10.7%], respectively; $P < .01$) and congestive heart failure (19 [25.3%] vs 8 [10.7%], respectively; $P < .01$). Surgical histories within the past 6 months were not significantly different between case-patients and control-patients. Case-patients had more severe illness using the APACHE II score compared with control-patients (19.28 vs 15.60; $P < .01$) and the percentage of case-patients with ICU admissions was significantly higher than the percentage of control-patients (41 [54.7%] vs 8 [10.7%]; $P < .01$). There were 29 (38.7%) deaths among case-patients compared with 3 (4.0%) deaths among control-patients ($P < .01$) (Table 1). The average cost of hospitalization for case-patients was $77,434 compared with $33,383 for control-patients (range, $2,212 to $197,184; $P < .01$).

Nosocomial risk factors significantly more common in case-patients are listed in Table 1 and included the presence of a central venous catheter (particularly a Hickman catheter), nasogastric tube, endotracheal tube, and Foley catheter. Other risk factors identified in univariate analysis to be significantly more common among case-patients included receipt of a platelet transfusion, corticosteroids, gastric acid suppressants, and antibiotics. Most (93.4%) of the case-patients received at least one antibiotic compared with 60.0% of the control-patients. Case-patients were also more likely to receive more than 4 antibiotics (54.7%) compared with control-patients (20.0%).

**TABLE 2**
MATCHED (IE, PRINCIPAL DIAGNOSIS, AGE, AND LENGTH OF STAY) CASE–CONTROL MULTIVARIATE ANALYSIS FOR PREDICTORS OF CANDIDEMIA

| Variable | Unit | Adjusted OR | $CI_{95}$ |
|---|---|---|---|
| Hickman catheter | Yes/no | 9.53 | 1.34–68.01 |
| Gastric acid suppressants | Yes/no | 6.38 | 2.33–17.43 |
| ICU admission | Yes/no | 6.40 | 2.12–19.31 |
| Nasogastric tube | Yes/no | 3.69 | 1.27–10.78 |
| No. of antibiotics | Continuous | 1.46 | 1.15–1.86 |

OR = odds ratio; $CI_{95}$ = 95% confidence interval; ICU = intensive care unit.

With the use of multivariate analyses, risk factors identified as predictors of candidemia included presence of a Hickman catheter (adjusted odds ratio, 9.53; 95% confidence interval [$CI_{95}$], 1.34 to 68.01), receipt of a gastric acid suppressant (adjusted OR, 6.38; $CI_{95}$, 2.33 to 17.43), ICU admission (adjusted OR, 6.40; $CI_{95}$, 2.12 to 19.31), presence of a nasogastric tube (adjusted OR, 3.69; $CI_{95}$, 1.27 to 10.78), and the number of antibiotics received (adjusted OR, 1.46; $CI_{95}$, 1.15 to 1.86) (Table 2).

### *Treatment*

Of the 113 patients identified with candidemia, 32 (28%) did not have a follow-up blood culture. Thirteen (28%) of 47 patients surviving 14 days or longer received less than 14 days of antifungal therapy. Of the 34 patients receiving at least 14 days of therapy, only 17 (50%) received 2 weeks of treatment beyond the last positive blood culture. Of those receiving less than 14 days of treatment, approximately half had only 1 positive blood culture. Eight (10%) of the patients with at least 7 days in the hospital received no antifungal treatment.

Amphotericin B was the initial antifungal agent used

in 32 (28%) of the case-patients. This was subsequently switched to fluconazole in 18 (56%) of those patients. Conversely, fluconazole was the initial antifungal in 61 (54%) of the 113 case-patients but was subsequently switched to amphotericin in 24 (39%). Of the patients with *C. albicans*, 8 (13%) received only amphotericin and 4 (50%) of these patients died, whereas 24 (38%) of the patients received only fluconazole and 5 (21%) of these patients died. Of the patients with *C. glabrata*, 2 (12%) received only amphotericin and 1 (50%) patient died, whereas 3 patients (18%) received only fluconazole and 2 (67%) of these patients died.

## DISCUSSION

Over the years, many studies evaluating risk factors for the development of nosocomial candidemia have been conducted; however, most have been in specific patient populations, have been generally retrospective, and have not used a case–control methodology.[12-18] Studies that employed a case–control design were conducted prior to the widespread use of azole antifungal agents. Using a case–control design, we identified several independent risk factors for the development of nosocomial candidemia including the presence of a Hickman catheter, the presence of a nasogastric tube, ICU admission, and receipt of multiple antibiotics. The results of this matched case–control study confirm risk factors cited in other studies, which, despite the widespread use of azole antifungals, have not changed substantially over the years. Interestingly, we also identified the use of gastric acid suppressants as an independent risk factor. To the best of our knowledge, this risk factor has not previously been documented. In critically ill patients, gastric alkalinization has been associated with an increase in gastric bacterial and fungal colonization.[21-23] Several reports have also found a role for gastric acid inhibitors as predisposing factors in the development of *Candida* esophagitis.[24,25] Although gastric alkalinization may increase gastric bacterial and fungal colonization, there are no data to suggest that an increase in gastric colonization would lead to an increase in bloodstream infections. Numerous studies have shown that shock, parenteral nutrition, and antibiotics facilitate the translocation of enteric bacteria.[26-31] Gastric alkalinization, with concomitant bacterial and fungal overgrowth, in critically ill ICU patients receiving multiple antibiotics may facilitate the translocation of *Candida*. Further studies will be necessary to confirm this finding.

Although many studies have documented an increase in the prevalence of non-*albicans Candida* species, particularly *C. glabrata*,[2,5,10,11,32] the number and distribution of *Candida* species recovered were similar to those found in a retrospective case study evaluating predictors of mortality[19] performed at the same institution from 1988 to 1989. A greater percentage of patients had *C. parapsilosis* in 2000 (16%) compared with 1988 to 1989 (6.5%). However, the percentages of patients identified with *C. glabrata* were similar: 15% in 2000 versus 13% (14 of 106) in 1988 to 1989.

In addition, we did not find a statistically significant difference in the percentage of isolates identified as *C. albicans*, *C. tropicalis*, or *C. krusei*.

*C. parapsilosis*, as a cause of fungemia, has been identified most recently in 7% of patients enrolled in both a statewide, longitudinal surveillance study of candidemia and the National Epidemiology of Mycoses Survey (NEMIS) study among surgical ICU patients.[9,32] Other studies including the SCOPE project have identified *C. parapsilosis* in 4% to 11% of patients with fungemia.[2,4] By contrast, *C. parapsilosis* was the etiologic agent of candidemia in 29% of neonatal ICU patients in the NEMIS study.[9] Historically, *C. parapsilosis* has accounted for 3% to 27% of cases of fungemia in large hospital-based studies.[33] During a 12-year period from 1983 to 1994, the frequency of *C. parapsilosis* fungemia increased from 8% to 30% among patients with hematologic malignancies.[34] In studies showing an increase in non-*albicans* candidemia over time, *C. glabrata* accounted for the increase. The increase in *C. parapsilosis* in the current study may be related to geographic variations.

Recent practice guidelines of the Infectious Diseases Society of America for the treatment of candidemia recommend the continuation of therapy for 2 weeks after the last positive blood culture and resolution of signs and symptoms of infection.[35] Given the design of our study, we did not find significant differences in mortality based on the duration of therapy or length of time to documented negative blood cultures. Previous studies have documented unacceptably high mortality rates in untreated patients. However, there remains a small subset of patients who rapidly clear their candidemia (within 24 hours), are less acutely ill, and have shorter hospital stays who survive inadequate antifungal therapy.[19] Treating these carefully selected patients with a short course of amphotericin B has proved successful.[36] The substantial number of patients in our study not receiving adequate therapy based on established guidelines suggests that additional educational efforts regarding therapy should be directed toward physicians caring for these patients. In addition, further prospective studies are needed to determine the appropriate duration of therapy based on risk factors as well as to evaluate the impact on late complications.

Although there may be regional differences in percentages of *Candida* isolates causing disease, the major identified risk factors and crude mortality of candidemia have not significantly changed during the past several decades despite the availability of azoles. This study was performed before the availability of echinocandins that may enhance the effectiveness of candidemia therapy. It is also apparent that many patients do not receive adequate therapy based on current Infectious Diseases Society of America guidelines. Prospective, well-controlled studies among carefully selected patients are needed to evaluate the appropriate duration of therapy. Similarly, given the increased and unchanging mortality of candidemia, studies to evaluate the benefits of preventive therapy are essential if we are to have any impact on the outcome of this infection.

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