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Candidemia in Intensive Care Unit Patients: Risk Factors for Mortality

Summary: Aim of this study was to evaluate whether risk factors which predict the development of candidemia may also predict death in ICU patients with candidemia. During an 8-year-period all ICU patients whose blood cultures yielded *Candida* species (n = 40) were retrospectively evaluated in a case-control fashion. The average incidence of *Candida* bloodstream infections was 5.5 per 10,000 patient days, ranging from 2.4 in 1990 to 7.4 in 1994. *C. albicans* was the most common pathogen in candidemic patients, but the proportion of non-*C. albicans* strains showed an increasing trend during 1989–1993, with a major shift towards non-*C. albicans* species in 1994. The overall mortality of patients with candidemia was 58%. Mortality was highest in the group of patients with multi-organ dysfunction syndrome, especially among those in need of hemodialysis. Risk factors for the development of candidemia, such as age, malignancy, steroid use, i.v. catheterization, and the use of broad-spectrum antibiotics were not correlated with mortality in the ICU patients studied.

Introduction

ICU patients account for only a small part of the hospital population, but contribute considerably (about one-fourth) to the overall rate of endemic and epidemic nosocomial infections [1, 2]. Development of hospital-acquired infections is a major determinant of morbidity and mortality in these patients.

Candidemia occurs most frequently in immunocompromised patients with an underlying malignancy or hematological disorder as well as surgical and neonatal intensive care unit patients [3–6]. In recent years the incidence of *Candida* bloodstream infections increased dramatically with *Candida* becoming the third to fourth most common pathogen causing bloodstream infections [7–10]. In general, critically ill patients who develop nosocomial bloodstream infection are at greater risk to die than patients with comparable severity of underlying disease without this complication [10]. Patients with fungal bloodstream infections such as those due to *Candida*, where shown to have the shortest survival prospects of any blood-borne infection [11]. *Wey* et al. [12] reported in a well-matched case-control study a crude and attributable mortality of 57% and 38%, respectively.

Various risk factors for the development of systemic *Candida* infections have been reported, among which the severity of underlying illness (assessed by APACHE II), number and extent of prior antibiotic therapy, concomitant isolation of *Candida* species from other sites, the presence of central venous catheters, and prior hemodialysis were proven in multiple logistic regression models, or were unanimously identified by all investigators [12–14].

The purpose of this paper was to evaluate whether risk factors for the development of candidemia may be used to identify ICU patients at risk of dying from *Candida* bloodstream infections. Improved stratification of the risk of candidemia would help to identify ICU patients in whom preemptive treatment with toxic and/or expensive (new) antifungal agents would be reasonable. Furthermore, we examined whether an increased incidence of candidemia and mortality is attributable to the emergence of non-*C. albicans* species.

Patients and Methods

The University Hospital Nijmegen is a 980-bed tertiary care teaching hospital with several intensive care facilities. The central ICU encompasses 37 beds, primarily for patients recovering from thoracic and abdominal surgery. Results of all blood cultures from patients admitted to the ICU between January 1st, 1987 and December 31st, 1994 were screened for *Candida* species. All patients with at least one blood culture positive for a *Candida* species were subjected to a retrospective chart review and analyzed in a case-control fashion. Candidemic patients who died during their ICU stay (non-survivors) were considered as cases; those surviving candidemia and being discharged from the ICU served as controls (survivors).

Census data of the department of intensive care were used to calculate incidence of candidemia, which was expressed as cases per 10,000 patient days. Furthermore, the distribution between the incidence of *Candida albicans* versus non-*C. albicans* strains was determined. Medical records of all selected cases were reviewed for patient demographics, severity of underlying diseases (SAPS II score [15]), the time on ventilator, the time with indwelling intravascular catheters, colonization with *Candida* species, the length of stay in the ICU before development of candidemia and antimicrobial/fungal therapy. Multi-organ dysfunction syndrome (MODS) was classified according to the following criteria: respiratory failure, acute respiratory distress syndrome (ARDS), hypotension, renal failure requiring acute hemodialysis, and hepatic dysfunction with coagulation system disorders or gastrointestinal dysfunction.

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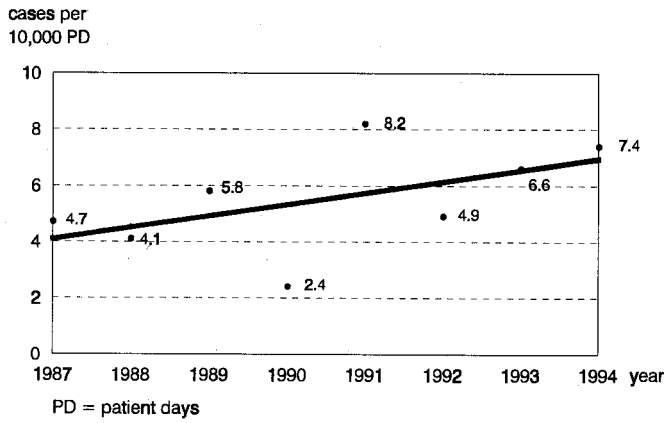

Figure 1: Incidence of *Candida* bloodstream infections 1987–1994.

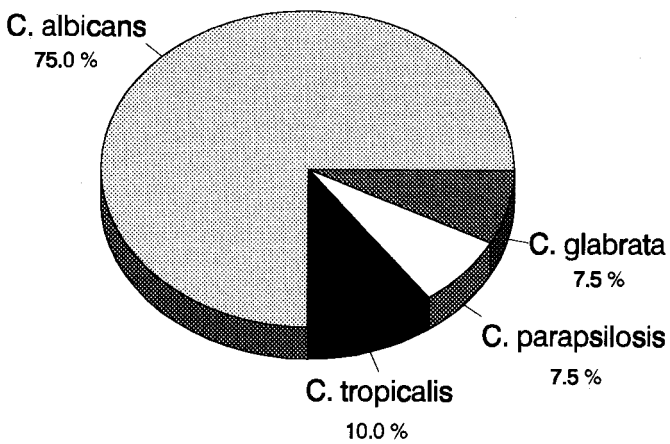

Figure 2: *Candida* species causing bloodstream infections 1987–1994.

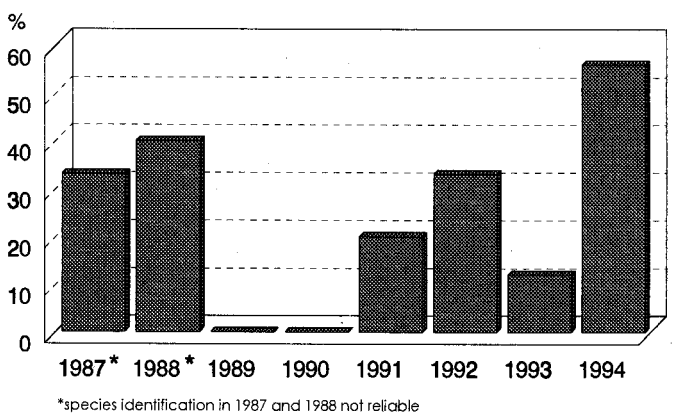

Figure 3: Proportion of non-*Candida albicans* species causing bloodstream infections 1987–1994.

Table 1: Patient demographics.

	Survivors (n = 17)	Non-survivors (n = 23)
Male/female ratio	10/7	12/11
Age	54 ± 5 yr	48 ± 5yr
ICU duration	46 ± 9 days	29 ± 8 days
Days in ICU until first isolation of *Candida* spp.	14 ± 3 days	14 ± 4 days

To analyze risk factors for mortality in cases of candidemia, differences between the groups were evaluated by crosstabs and multiple regression analysis (SPSS for MS windows, version 6.1). The dependent variable was survival, independent variables were risk factors for candidemia.

Results

A total of 40 patients with positive blood cultures for *Candida* and available medical records were identified. Demographic features of the patients are depicted in Table 1. The male/female ratio was similar in survivors (n = 17) and non-survivors (n = 23). The mean age of non-survivors was slightly lower (48 years as compared to 54 years in survivors) but not significantly different. The mean length of stay before development of candidemia was 14 days in cases and controls.

The incidence of candidemia is shown in Figure 1. The average rate of candidemia was 5.5 per 10,000 patient days per year, ranging from 2.4 in 1990 to 8.2 in 1991. During the 8-year-period (1987–1994) *C. albicans* accounted for 75% of all blood culture isolates (Figure 2). Other *Candida* found were *Candida tropicalis* (10%), *Candida parapsilosis* (8%) and *Candida glabrata* (8%). *C. albicans* remained the most prominent pathogen until 1994. In 1994 the proportion of non-*C. albicans* species among the *Candida* isolates from blood cultures rose to 56% (Figure 3).

Antifungal treatment (mostly fluconazole, rarely amphotericin B) was started in 31 of the 40 patients (77.5%); 82% of the survivors versus 74% of the non-survivors. Nine out of 40 patients, of whom six died, had no antifungal treatment. None of the patients received prophylactic antifungal treatment.

Table 2 depicts the underlying diseases and co-morbidity by survival group. All patients were on mechanical ventilation, had intravascular devices, and were undergoing concomitant broad-spectrum antibiotic treatment throughout their ICU stay. All possible determinants for mortality were equally distributed among survivors and non-survivors, except acute hemodialysis, ARDS, and systemic inflammatory response syndrome with MODS. The mortality among patients with MODS was 91%. Within the group of non-survivors 22 patients died due to intractable septic shock, ARDS or MODS. One patient died due to an intracerebral hemorrhage. The crude mortality of all ICU patients with candidemia was 58%.

In the stepwise multiple regression analysis only ARDS and MODS remained significant. The mean (SD) severity illness score determined by SAPS II at admission to the ICU was 47.4 (15.6) and 38.7 (11.0) in survivors and non-survivors, respectively. The corresponding risk of hospital death in survivors and non-survivors was 55% and 30%, respectively. The overall SAPS II score of all study patients was 42, corresponding with an 38% chance of hospital death. Given a crude mortality of 58%, and a predicted mortality of 38%, the attributable mortality in patients with candidemia was 20%.

In 51% of the study patients *Candida* was the first pathogen isolated from blood cultures. Thirty-three percent of the patients initially had suffered from bacteremia due to gram-negative or gram-positive pathogens prior to development of candidemia and in 7% of the patients bacteremia and candidemia occurred simultaneously. In the remaining patients (9%) candidemia was followed by bacteremia.

Table 2: Underlying diseases and co-morbidity by survival group.

	Survivors (n = 17)	Non-survivors (n = 23)	Odds ratio (95% CI)
Abdominal surgery	1	11	3.2 (1.0–10.5)
Acute hemodialysis	1	11	1.8 (1.2–2.7)
Antibacterial use	17	23	
• > 7 days	12	18	1.3 (0.5–3.9)
• > 2 classes	7	11	1.1 (0.7–2.0)
ARDS	0	21	10.8 (2.9–40.9)
COPD	0	1	1.0 (0.9–1.1)
CVC	15	23	0.9 (0.7–1.0)
Diabetes mellitus	0	1	1.0 (0.9–1.1)
Malignancy	5	6	1.0 (0.6–1.4)
MODS	2	21	10.1 (2.7–38.6)
Pneumonia	2	4	1.0 (0.8–1.4)
Splenectomy	3	2	0.9 (0.7–1.2)
Steroid use	4	8	1.2 (0.8–1.7)
TPN	14	20	1.4 (0.3–5.9)

ARDS = acute respiratory distress syndrome; COPD = chronic obstructive pulmonary disease: CVC = central venous catheter; MODS = multi-organ dysfunction syndrome; TPN = total parenteral nutrition; 95% CI = confidence interval.

Discussion

The management of patients with severe diseases and life-threatening conditions routinely involves the use of mechanical ventilation, invasive monitoring, parenteral nutrition, and indwelling catheters. Obviously, these patients are prone to nosocomial infections. The rate of hospital-acquired infection among ICU patients is accordingly five to ten times higher than among general ward patients [1]. Over the past decade the incidence of *Candida* bloodstream infections has been reported to increase markedly in hospitals in the USA [7–9]. A similar, but less striking increase has been shown for most of the Dutch university hospitals [16]. Given the "natural" accumulation of high-risk patients in tertiary care referral hospitals, incidence rates of candidemia are highest in these hospitals and were described to be as high as 8.5 per 10,000 admissions [12]. Mortality in most studies is high, ranging from 38% to 79%. The overall mortality in our patients with candidemia was 58%, which is in accordance with previous reports. In a case-control study performed by *Wey* et al. [12] 57% of all patients with candidemia died, whereas 38% died as a direct result of candidemia (attributable mortality). Our analysis showed a lower attributable mortality (20%), probably reflecting the severity of the already existing underlying disease at the onset of candidemia. The low attributable mortality observed makes it even more difficult to explain the difference between survivors and non-survivors concerning the risk of hospital death at ICU admission (estimated by SAPS II), which was considerably higher in survivors. In order to exclude concomitant bacterial sepsis, which might have contributed to the non-fungal-related mortality, we evaluated the sequential occurrence of pathogens isolated from blood cultures. Eighty-four percent of the patients had primary candidemia, or candidemia following bacteremia. In both cases it might be assumed that the bacteremia did not contribute to the death of the patient, which probably was the case in those patients who suffered from simultaneous bacteremia (7%), or whose candidemia was followed by bacterial sepsis (9%). Risk factors for the development of candidemia were of no further value to predict mortality once candidemia had developed. Other clinical conditions associated with impaired immunity that may facilitate opportunistic infections, such as age, sex, gastrointestinal bleeding, pneumonia, diabetes mellitus, chronic obstructive pulmonary disease, steroid use, or prior alcohol abuse, did not significantly contribute to mortality in patients with candidemia.

In recent years epidemiological changes of *Candida* infections have been documented by several authors indicating a shift toward (less azole-susceptible) non-*C. albicans* species especially in patients with AIDS and cancer [17, 18]. Whether or not these changes are due to the excessive use of fluconazole is debated in the literature, and would expand the spectrum of this discussion [19, 20]. Overall, 75% of all blood culture isolates during the 8-year study period were *C. albicans*. Until 1995, no patient with *C. krusei* candidemia was observed among ICU patients in our hospital

[21], and the proportion of other non-*C. albicans* species remained low. However, we demonstrated on upward trend during 1989 to 1993, and a steep increase of non-*C. albicans* species in 1994, when for the first time less than 50% of the *Candida* blood culture isolates were *C. albicans*.

Frequently, ICU clinicians consider candidemia as an epiphenomenon in already severely ill patients with a past history of bacterial sepsis. On the basis of our results candidemia should be considered as an independent variable for morbidity and mortality. Risk factors that might be helpful to predict the development of candidemia among non-neutropenic critically ill patients had no further value in predicting mortality among ICU patients with candidemia. The SAPS II score taken at ICU admission was insufficient to indicate the actual risk of hospital death, since the clinical outcome was primarily determined by the development of multiple organ dysfunction, reflecting the severity of illness when candidemia occurred.

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