Predictors of adverse outcome from candidal infection in a tertiary care hospital

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Summary Objectives. To retrospectively delineate predictors of adverse outcome by looking at the demographic features, therapy and outcome of systemic candida infection in a large tertiary care university-affiliated medical center.

Methods. We reviewed the clinical data on 186 inpatients with candidemia over a 6-year period. The major reason for their hospital admission was an underlying malignancy or an infection other than candidemia.

Results. Candida albicans, tropicalis, parapsilosis, glabrata and krusei caused 54, 22, 13, 8 and 3\% of the candidemia episodes, respectively. The overall mortality was 42\% and it was highest in patients suffering from candidemia of the glabrata species (73\%). Forty-eight (63\%) of the 76 patients who received no anti-fungal treatment died compared to 38 (34\%) of 110 patients who were treated (P < 0.05). Predictors of adverse outcome were intensive care unit stay, renal failure, thrombocytopenia and the need for mechanical ventilation or inotropic support.

Conclusions. We identified four predictors of mortality from candidemia infection. Their validity should be further assessed and the specific candida strains and their susceptibility need to be methodically identified. Our data support immediate initiation of therapy at first identification of infection.

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Introduction

Fungal infections are prominent among the causes of nosocomial infection.\textsuperscript{1,2} Great vessel cannulation, prolonged endotracheal intubation, the administration of wide spectrum antibiotic therapy and the use of total parenteral nutrition are recognized risk factors for the development of invasive fungal infections.\textsuperscript{3,4} In addition, the use of modern regimes of chemotherapy and bone marrow or organ transplantation techniques have caused a substantial increase in immunocompromised patients who
are highly susceptible to disseminated fungal infections which have often proved to be lethal.\textsuperscript{5,6} Candida species were reportedly responsible for up to 15\% of all hospital-acquired bloodstream infections,\textsuperscript{7} with Candida albicans constituting more than half of fungal isolates\textsuperscript{2} and bearing a mortality rate of greater than 50\%.\textsuperscript{8} Although it is the one most frequently isolated, the proportion of infections caused by other species is increasing\textsuperscript{9} as well as by strains resistant to amphotericin B-the 'golden standard' of anti-fungal chemotherapeutic agent.\textsuperscript{1,10}

The purpose of this study is to search for predictors of mortality from candida infections by examining data on the demographic features, therapy and outcome of systemic candida infection in a large tertiary care university-affiliated hospital that were accumulated during a 6-year period. Based on these findings, we support the administration of anti-fungals at first identification of infection.

**Material and methods**

The Chaim Sheba Medical Center is a 1200-beds multidisciplinary, one of the six major tertiary medical centers in Israel. The medical records and case notes from January 1992 to January 1998 of its inpatients suffering from candidemia were reviewed by the authors. Blood culture identification method used the Bactec BD, CA, USA. The presence of the condition was defined by at least one blood culture being positive for each on of the candida species, which was identified from the microbiological test logs.\textsuperscript{11} The retrieved information included data on demographics, basic disease/condition, cause of current admission, and the service in which the patient was hospitalized, duration of hospital stay, clinical course, the presence of infective complications and outcome. Candidemic patients were routinely screened for candida endophthalmitis and infective endocarditis. Candidemia was considered as being a direct cause of death when it occurred within 1 week from patient demise.\textsuperscript{7} Emphasis was placed on the identification of data pertaining to the presence of risk factors for systemic fungal infections in the 30 days before the detection of a positive cultures, i.e. the placement of central catheters, hyperalimentation, immunosuppression, chemotherapy, neutropenia (lowest absolute neutrophile count <1000/mm\textsuperscript{3}), thrombocytopenia (<100 000/mm\textsuperscript{3}), renal failure (creatinine >2 mg/dl).

Statistical evaluation of the data was done using the BMDP statistical software.\textsuperscript{12} The analysis of variance (ANOVA) and Pearson chi-square tests were used to compare clinical data to patient outcome, and stepwise logistic regression was used to quantitatively identify the relationship between the clinical parameters and outcome. Statistical significance was assigned at a P value less than 0.05. Data are presented as mean \pm standard deviation.

**Results**

**Patient demographics**

Demographic, risk factors and clinical data on a cohort of 186 patients with a M/F ratio of 60%/40\% and mean age of 48 years (range 5 days-91 years) with candidemia are presented in Table 1.

**Mortality**

The overall mortality of our series was 79 (42\%), with a similar distribution being noted throughout the study period. The direct reasons for death included candidemia or its complications (meningitis, endocarditis, hepatitis) in 14 (17.5\%), septic shock in 51 (65\%) (of which 35 (70\%) was caused by polymicrobial infection), cardiogenic shock in 5 (6.3\%), complication of malignancy in 5 (6.3\%), prematurity in 1 (1.3\%) and other reasons 3 (3.6\%).

**Risk factors**

Duration of neutropenia was 9 days \pm 8.4 (range 1-43). No differences were found between the prevalence of the following risk factors for fungemia (e.g., steroids, immunosuppression, broad-spectrum antibiotics and hyperalimentation) throughout the studied years and as a function of the different medical services (i.e., medical, surgical and paediatric).

Data on multivariate analysis are presented in Table 2. Stay in the intensive care unit (ICU), thrombocytopenia, creatinine, and the need for mechanical ventilation or inotropic support were found as predictors of mortality in candidemic patients.

Data on patients' distribution on the hospital wards as a function of the years and medical services are presented in Table 3. In the latter years of the study, fewer patients were hospitalized in the ICU and a larger percentage of the patients were cared for in the hemato-oncology departments.
Treatment

Of the 76 patients who received no anti-fungal treatment, 48 (63%) died compared to 38 (34%) of 110 patients who were treated ($P < 0.05$). No statistically significant correlation was found between time of blood sampling, treatment initiation and duration and mortality.

A retrospective review of the medical charts revealed no reason for failing to administer anti-fungal therapy. The policy for giving anti-fungal therapy was found to vary significantly between wards: the majority of the patients with candidemia (73%) received no anti-fungal therapy in the internal medicine service, while amphotericin B was used more frequently in the ICU ($P < 0.05$); and fluconazole was used more frequently in the hemato-oncology service including its prophylactic administration ($P < 0.05$). Because of the failure of the initial anti-fungal therapy, additional drugs were given to 17 patients (amphotericin B to 3 patients, fluconazole to 10 and 5-flucytosine to 4). Intravascular catheters were removed in 100/125 (80%) patients.

Data on cause of admission and the distribution of mortality are presented in Table 4. The relative distribution over time of candida in the hospital at large showed a trend toward a lower rate of candida isolation in the medical and surgical wards as well as in the ICUs, with the exception of the hemato-oncology department where an increased rate of candida isolation was observed over the years (Table 3). In addition, there was a steady rise in the frequency of bone marrow transplantation among patients with candidemia.

Microbiology

The candida species isolated from patients with candidemia and the related mortality are presented in Table 5. The frequency of candida due to non-albicans candida species increased significantly throughout the study period (Fig. 1). Non-albicans candida species were identified in the blood cultures of 33 (41%) of the non-survivors. Whereas fungemia due to C. albicans was present in 61% of the patients in the first 2 years of the study period,
its relative frequency dropped to 43% during the last 2 years and there was a parallel increase in the rate of infection with *C. tropicalis* (from 14% to 40%). This trend was well demonstrated among the hematologic-oncology patients where 33% of the infections were caused by *C. tropicalis*. Multiple candida species were identified in the blood cultures of four patients (2.1%), all of whom survived after being treated with amphotericin B. The additional candidal species were *C. tropicalis*—2, and *parapsilosis*—2. Ninety patients (48%) had polymicrobial sepsis (positive blood cultures for candida and another microbial agent). These included Gram-positive cocci (*Staphylococcus aureus, epidermidis* and *Streptococcus*) in 49 cases (54.5%) and aerobic Gram-negative bacilli (*Klebsiella pneumoniae, Pseudomonas aeruginosa* and *Escherichia coli*) in 41 cases (45.5%).

### Discussion

Our data support previous publications on the rising trend of candidal bloodstream infection among severely ill patients. Indeed, hematologic-oncology malignancies or infections were the leading causes of patients’ admission in our series. These patients were inevitably exposed to multiple risk factors for fungemia, such as steroids, immunosuppression, broad-spectrum antibiotics and hyperalimentation.

Our crude mortality rate from candidemia (42%) is similar to that of other reports. Sepsis from unknown sources was the most frequent cause of death (65%), whereas candidemia was found to be a primary cause of mortality in only 17.5% of the cases. These results support the fact that candidemia is sometimes only a marker of disease severity in critically ill patients. In fact, superinfection with candida was reported to occur in as many as 12% of blood samplings in critically ill patients.

The higher mortality among the untreated patients’ group as compared to the treated ones is similar to what had already been reported on the lethality of candidemia. An expectant approach, i.e. removal of a central catheter, following the finding of positive blood culture for candida, without the immediate initiation of anti-fungal therapy was the common treatment policy in our institution. The anti-fungal therapy was initiated only after repeated positive blood cultures confirmed the presence of candida. This practice was recently changed according to the international consensus on practice guidelines for the treatment of candidiasis which recommended both immediate empirical start of anti-fungals and removal of central venous access.

Our current data point to a high mortality rate associated with positive blood cultures for candida, thus establishing a strong case to establish a policy of immediately initiating anti-fungal therapy when positive blood cultures of candidemia are identified for the first time. This is further supported by the facts that it is difficult both to predict which patient will develop serious consequences of the infection and to differentiate between transient or sustained...
candidemia. In addition, delays in microbiological diagnosis sometimes occur because none of the non-culture methods (serological assays) are adequately sensitive or specific.\(^1^8\) The mean number of days (2.9) from the onset of candidemia until the initiation of therapy in our investigation was similar to the figures reported by Viudes et al.\(^1^7\) However, while they found increased mortality among patients whose candidemia lasted longer than 2 days, we did not find that a delay of a few days in initiating treatment to be related to increased mortality.

Analysis of our data revealed that fluconazole was the favored first-line anti-fungal agent outside the intensive care facilities. Its good bioavailability when given orally and ease of administration compared to amphotericin B are advantages for planning anti-fungal therapy in the set-up of the general ward. Amphotericin is still regarded as the gold standard anti-fungal agent despite its widely known serious allergic side effects and renal toxicity. Although there are data pointing to equal utility of fluconazole in non-high risk patients,\(^1^9\) it must be kept in mind that some *candida* species, such as *glabrata* or *krusei*, may be intrinsically resistant to fluconazole.\(^2^0\) Thus, careful identification of the specific strains and their susceptibility should be undertaken in the laboratory. In these cases, prompt institution of amphotericin B treatment is life-saving, especially in high-risk patients for whom another fungal infection such as *Aspergillus* spp., which is not sensitive to fluconazole can be present.\(^6,^2^1\)

The highest mortality was observed in patients suffering from the *glabrata* species of candidemia, as had been described by Nguyen et al.\(^1^0\) The species distribution in our patients and the shift in time towards *non-albicans* species probably result from a combination of the effects of the nosocomial flora of our hospital and the increase in the number of immunocompromised hosts or the use of prophylactic anti-fungal agents (i.e., fluconazole) in the various hospital wards especially the hematology-oncology service. Similar trend toward fewer

| Table 5  |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|---------------------------------|-----------------|-----------|-----|-----|-----|-----|-----|-----|
| Total no. of candidemic episodes | 190 (100%)      | 79 (42%)  | 22  | 29  | 36  | 39  | 31  | 28  |
| Albicans                        | 103 (54%)       | 46 (45%)  | 15  | 16  | 20  | 26  | 14  | 12  |
| Tropicalis                      | 41 (22%)        | 15 (37%)  | 3   | 6   | 7   | 5   | 9   | 11  |
| Parapsilosis                    | 25 (13%)        | 5 (20%)   | 3   | 5   | 6   | 4   | 5   | 2   |
| Glabrata                        | 15 (8%)         | 11 (73%)  | 2   | 3   | 4   | 1   | 3   | 2   |
| Krusei                          | 6 (3%)          | 2 (33%)   | 1   | 1   | 0   | 3   | 0   | 1   |

\(^a\) *P* < 0.05

Figure 1  Distribution of *candida* strains throughout the study period. Y-axis, percentage of patients with candidemia, X-axis, years of the study.

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fungemic episodes due to *C. albicans* and more due to *non-albicans* species was recently reported by others. For example, Malani et al. in their survey of yeast causing fungemia over a 12-year period at a large tertiary medical center. In their report on a total of 966 unique episodes of fungaemia, the trend toward increased isolation of *non-albicans* species was attributed to increase use of fluconazole. Clearly, further comparative research is needed to better define *candida* species flora in view of the associated high mortality and complication rate.

Candidal infection can cause disseminating disease. The small number of patients who suffered from systemic spread of the infection is probably an underestimation since no post-mortem examination was done. It is reasonable to assume that some of the patients who probably had developed systemic complicating *candida* had died before these were clinically manifested thus, preventing an accurate diagnosis to be made ante-mortem. Indeed, the report by Prescott et al. stressed the importance of necropsy in the clinicopathological audit of deaths in this group of patients. In addition, systemic complications following candidemia-like endophthalmitis or osteomyelitis resulting from hematogenous spread of the fungus can appear up to 2 years following the first identification of candidemia. In our study, the failure to conduct long-term surveillance probably led to these cases being missed in our data bank.

One-third of our studied population was hospitalized in one of the ICUs. ICU hospitalization was identified as a risk factor for mortality from candidemia, together with thrombocytopenia and impaired renal function, all pointing to patient disease complexity, which mandates invasive therapeutic interventions. Indeed, mechanical ventilation and inotropic support were also identified as predictors of mortality. The increased awareness of the medical team and better patient monitoring in the ICU have undoubtedly contributed to higher detection rates of candidemia in this patient group. When ICU admission rates were analysed as a function of time, a trend towards a decrease rate of ICU hospitalization in favor of the hemato-oncology wards was revealed. We hypothesized that this trend was due to improved rationing and cost-containment considerations on the part of the medical team.

The establishment of clinical predictors for outcome that would be capable of differentiating between survivors and non-survivors among candidemic patients would facilitate the selection of proper therapies without additional morbidity potential.

Several limitations of the current study need to be considered. The main limitation of our analysis is that, due to the retrospective nature of the study, relatively limited clinical information was collected during the course of hospitalization, preventing us from analysing our data according to the denominator of ‘per 1000 hospital admission’. Furthermore, we were unable to evaluate the role of specific treatment factors in patient outcome, such as changes in drug therapy. Although a fairly large population was examined, the non-randomization of innovative techniques makes it difficult to evaluate their role in patient survival.

**Conclusion**

*Non-albicans* candidemia carries high mortality, especially if not treated. The validity of the predictors of mortality identified from our data should be further assessed, focusing upon their ability to predict outcome from *non-albicans* candidemia in view of the growing frequency of infections caused by these species. This will help to establish a better plan of species-targeted therapy for minimizing systemic complications and multi-organ involvement and for improving prognosis.

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**References**


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