Epidemiology of Candida blood stream infections in patients with hematological malignancies or solid tumors

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Invasive Candida infections are associated with high morbidity and mortality. Due to an increased incidence in patients with hematological or oncological malignancies, fluconazole prophylaxis became a common practice in many centers in the late 1990s. Until recently, there was insufficient data on the effect of the use of azoles on the incidence of Candida blood stream infections and species distribution. Here we present a single center retrospective study of the epidemiology of Candida blood stream infections in hospitalized patients at a German university medical center from 2003–2009. Twenty-one Candida species were isolated in culture from blood specimens of 20 patients. The annual rate of candidemia approached 1.1 per thousand hospitalizations, during the first 5 years of the survey, but showed a significant increase after 2007. Candida albicans, although still the dominant species, was recovered as the responsible pathogen from only 28.6% of the cases. A high rate of fatal outcomes was noted at 30 days (56%) and 100 days (67%) after the first positive finding of Candida in blood culture. These results underline the clinical significance of this infectious complication, and the need for continuous monitoring for Candida blood stream infections in order to improve the clinical and therapeutic management of this specific patient population.

Keywords epidemiology, Candida, hematology, oncology, blood stream infection

Introduction

Candida blood stream infections (BSI) can be life threatening, especially in immunocompromised patients and those hospitalized with serious underlying diseases such as hematopoietic malignancies [1–3]. As a complication of cancer and its treatment, these infections are associated with an increased mortality rate of between 30% and 50%, prolonged hospitalization, and rising healthcare costs [4–10].

Immunosuppression due to metabolic dysfunction, mucosal or cutaneous barrier disruption, extreme age, defects in the number and function of neutrophils or in cell-mediated immunity, are well known risk factors for fungal infections. These and other causes including the use of broad-spectrum antibiotics, cytotoxic chemotherapies, and transplantation, increase the risk of systemic yeast infections and associated mortality in patients with hematological or other malignancies [1,11].

Occurrences of Candida blood stream infections are most often associated with intensive care and surgical treatment. According to a European survey, 40.2% and 48.2% of all candidemias were found in these departments, respectively [2]. Up to 35.0% of candidemias were noted in patients with hematological malignancies or solid tumors as the underlying diseases. Due to the increased risk and incidence of candidemia, fluconazole is often used to prevent invasive yeast infections in this patient population and since its introduction during the 1990s, it has also been recommended as a treatment option of Candida BSIs [12]. Probably this widespread use of azole prophylaxis has had an impact on the incidence of candidemia [13], and changes in the distribution of the etiologic agents.
In Europe, *Candida albicans* is the dominant isolate, accounting for 50–60% of BSIs in general, but as a result of azole prophylaxis, the rate of its recovery is lower in hematological patients [9,13,14]. In the European study, Tortorano and colleagues identified a rate of 35% of *C. albicans* BSIs and a shift in epidemiology towards non-*C. albicans Candida* spp. in hematological patients [3]. *Candida krusei* and *C. glabrata* represented 22% of the isolates in this study, and constituted a relevant segment of the yeast population associated with infections.

In recent studies a similar shift to higher recovery rates of *C. krusei* and *C. glabrata* has been noted in the US [15] and has been described in other reports [9,13,16]. This change in species distribution is of clinical importance relative to the choice of antifungal therapy, as these two species are often innately resistant to fluconazole [12,17]. In an Australian population-based survey of 1,095 candidemia cases, 288 of which were in adult cancer patients, poorer outcomes were observed when the patients were treated inappropriately and in those cases in which the etiologic agent proved to be fluconazole resistant [18].

Only a limited number of studies in the last few decades have investigated the incidence of candidemia in relation to hospitalized patients and data on actual epidemiology remain scarce. The last multicenter international European study was conducted from September 1997 through December 1999 by six national societies and demonstrated an incidence of 0.2 to 0.38 cases of candidemia per 1,000 admissions. In other European surveys, involving 5 to 71 hospitals, rates ranging from 0.28–1.09 per 1,000 admissions were detected [2,3] and similar rates were found in multicenter studies in the United States. Here, a surveillance study from 1995–2002 revealed an average rate of 0.42 infections per 1,000 hospital admissions [15]. Most of these surveys were not restricted to a specific patient population.

In this report we present data on the incidence, species distribution, resistance patterns and clinical outcome of *Candida* BSIs in relation to hospitalization of hematological patients in a 7-year single center evaluation in a tertiary care unit of a university hospital in Germany.

### Materials and methods

#### Study design and data collection

From 1 January 2003 to 31 December 2009 we retrospectively analyzed the information pertaining to *Candida* BSIs of patients hospitalized in the hematological department, including a stem cell unit (since May 2005) at the University of Würzburg Medical Center, a public teaching hospital. Patients with acute leukemia, lymphomas and other hemat-oncological malignancies were hospitalized in these departments. Since May 2005, 228 allogeneic stem-cell transplantations were performed. All adults selected for further analyses had at least one positive blood culture of *Candida* spp. as identified by searching the microbiological database of the Institute of Microbiology and Hygiene. The study was approved by the local university ethics commission.

Age, gender, underlying disease, treatment of underlying disease and previous stem cell transplantation, neutropenia, use of prophylactic and antifungal therapeutics within 4 weeks before and after the onset of candidemia, as well as patient survival 30 and 100 days after the first positive *Candida* blood culture, were analyzed from the hospital database and patient charts.

#### Microbiological methods

Information about the *Candida* species recovered and the isolates in vitro susceptibility to fluconazole were obtained from the electronic archive of the microbiological institute. The data bank investigations included the search terms ‘Candida’ and ‘yeast’, each in combination with ‘blood culture’. Blood cultures were processed by an automated system (BacT/ALERT 3D, bioMérieux, Marcy l’Etoile, France) and fungal isolates were sub-cultured on sheep blood agar (bioMérieux), Sabouraud dextrose agar (in-house preparation) and Chromagar Candida (Becton Dickinson, Heidelberg, Germany). *Candida* spp. were differentiated using standard phenotypic methods, such as colony color and morphology on CHROMagar Candida (for *C. albicans* only), microscopic morphology on rice-tween agar, and assimilation patterns with the ID 32 C strip (bioMérieux).

In vitro susceptibility assays were performed with the Sensititre Yeast One Colorimetric Antifungal Panel (TREK Diagnostic Systems, East Grinstead, England, UK) according to the manufacturer’s instructions. Data obtained with this method have shown 98% agreement with that determined for fluconazole, itraconazole and 5-fluorocytosine found with the Clinical and Laboratory Standards Institute (CLSI) reference method in M27-A2 for *Candida* spp. [19]. CLSI M27-A3/S3 azole breakpoints, including voriconazole, were used in this study. As no breakpoints have thus far been established for amphotericin B, a strain was considered susceptible if it had an MIC ≤1 µg/ml and resistant with an MIC >1 µg/ml according to the Yeast One Sensititre procedure. Microbiological methods remained unchanged throughout the study period.

#### Definitions

Candidemia was defined according to published guidelines [20] as any blood culture with the growth of a yeast
identified as Candida species. Exclusive isolation of Candida species from central venous line, any other foreign body or a normally sterile site was not taken into account. Repeat positive Candida blood cultures from a single patient were considered distinct only if they were separated by at least a 30-day period, during which no other blood cultures were positive for Candida spp. Neutropenia was defined as an absolute neutrophil count < 500/µl and/or a leukocyte count below 1000/µl.

Statistical analysis

The number of all hospitalized patients in the hematological department was obtained from the hospital’s database. Rate of infection was calculated for the number of patients and for hospitalizations per year. To avoid multiple counts of patients, each patient was related to the first ward admittance in the facility. Transfers among departments or wards were not considered. All calculations were performed with SPSS software version 18.0. Comparisons of proportions were from the Pearson’s chi-square test and Fisher’s exact test. A P-value below 0.05 was considered to be significant. For analysis of mortality, patients lost to follow up were excluded.

Results

Incidence

Between January 2003 and December 2009, 21 Candida isolates were recovered from BSIs of 20 patients (Fig. 1). C. albicans and C. glabrata were simultaneously isolated from one of these patients. There were between zero and eight Candida BSIs per year, with an average rate of three candidemias per year. Within the first 5 years, a maximum of two Candida BSIs were detected, but in the last 2 years, this increased to six and eight cases. Median patient age of those with candidemia was 60.2 years. Eight of the 20 patients were male. Five developed a breakthrough infection, three of which while they were receiving fluconazole, one during posaconazole prophylaxis and one while on voriconazole treatment of suspected pulmonary aspergillosis.

There were 13,911 patients hospitalized in the 7-year study period in the hematological department and the adult stem cell unit. The number of hospitalizations ranged between 1,749 and 2,497, resulting in an average of 1,987 patients hospitalized per year. The relative candidemia rate was between 0 and 0.32% per 1,000 hospitalizations per year, with an average rate of 1.4 per 1,000 hospitalizations (Table 1). Between 2003 and 2007, this annual rate did not exceed 1.1 Candida BSIs per 1,000 hospitalizations, with a mean of 0.7 Candida BSIs over 5 years. More recently, during 2008 and 2009 there was a significant increase in the annual incidence of candidemias with 2.9 per 1,000 hospitalizations for both years (P < 0.01, 95%-confidence interval 0.13–0.45).

Underlying disease

In nearly one third of the patients with candidemia, the underlying disease was acute myeloid leukemia. Four patients were treated for multiple myeloma, three for gastric tumors, three for other solid tumors, two for acute lymphatic leukemia, one for hairy cell leukemia and one for follicular lymphoma. In total, 70% of patients had hematological underlying diseases, while two patients had a history of autologous stem cell transplantation,
Table 1  Number of patients with Candida BSI and rate of infection per annual hospitalization.

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of candidemias</th>
<th>Hospitalizations per year</th>
<th>Candidemia per hospitalization</th>
</tr>
</thead>
<tbody>
<tr>
<td>2003</td>
<td>2</td>
<td>2140</td>
<td>0.09%</td>
</tr>
<tr>
<td>2004</td>
<td>1</td>
<td>1817</td>
<td>0.06%</td>
</tr>
<tr>
<td>2005</td>
<td>0</td>
<td>1876</td>
<td>0%</td>
</tr>
<tr>
<td>2006</td>
<td>2</td>
<td>1862</td>
<td>0.11%</td>
</tr>
<tr>
<td>2007</td>
<td>2</td>
<td>1749</td>
<td>0.11%</td>
</tr>
<tr>
<td>2008</td>
<td>5</td>
<td>1970</td>
<td>0.25%</td>
</tr>
<tr>
<td>2009</td>
<td>8</td>
<td>2497</td>
<td>0.32%</td>
</tr>
</tbody>
</table>

4 years and 2 weeks prior to infection, and one was receiving autologous stem cells 9 days after Candida BSI.

Candidemia was detected in two patients, one each in 2008 and 2009, while they were receiving conditioning chemotherapy. Allogeneic stem cell transplantation was performed 7 days after the drawing of blood for culture which was subsequently found to be positive for Candida. Nine patients were neutropenic at the time of the first isolation of Candida spp. in culture from blood and an additional five patients were neutropenic within 5 days before or after diagnosis of Candida BSIs.

Species distribution

The 21 Candida isolates were identified as follows; six C. albicans, four C. parapsilosis, four C. tropicalis, three C. krusei, two C. guilliermondii, and two C. glabrata. In only 28.6% of candidemias was C. albicans detected as the responsible pathogen, while 23.8% of systemic Candida infections were caused by C. krusei and C. glabrata. In all three cases of C. krusei BSIs, the patients were receiving fluconazole prophylaxis prior to infection.

Resistance

The minimal inhibitory concentrations (MICs) to fluconazole were determined for 20 Candida isolates obtained in culture. Sixteen were fluconazole-susceptible, one was susceptible-dose dependent, and three were resistant. The average MIC for fluconazole was 0.5 mg/l for C. albicans, 9.0 mg/l (2 and 16) for C. glabrata, 1.7 mg/l for C. tropicalis and 1.0 mg/l for C. parapsilosis strains. The resistant strains were all C. krusei with a mean MIC of 53 mg/l. The in vitro susceptibility of 12 strains, including all three C. krusei isolates, was shown against voriconazole and amphotericin B and all showed susceptibility to voriconazole and low MICs to amphotericin B.

Treatment and outcome

The most common treatment for proven candidemia included echinocandins. Six patients were first treated with an echinocandin (five with anidulafungin and one with caspofungin), five with fluconazole, three with voriconazole, two with liposomal amphotericin B, three patients did not receive any treatment, and there was no data available for one patient. Treatments were performed as monotherapies in five of the candidemia cases. In 11 patients, treatment was changed, on average, after 6 days of therapy to liposomal amphotericin B (three cases), anidulafungin (two cases), fluconazole (three cases), voriconazole (two cases) or caspofungin (one case). In three cases, initial monotherapy was changed to combination therapy.

Two patients were lost from long-term follow up. Of the remaining 18 patients, overall mortality was 56% (10/18) on day 30 and 67 % (12/18) on day 100 after the diagnosis of Candida BSIs. Five of six patients with acute myeloid leukemia and both allogeneic stem cell recipients died within 30 days. The mortality of patients who were neutropenic at the time of diagnosis of Candida BSIs, was significantly higher compared to patients without any neutropenia or all others on first follow up at day 30. The difference was not significant for other groups or time points. Eight of nine patients who were found to be neutropenic on day 0 died before day 30 but one of them was alive on day 100. From five patients with neutropenia within 5 days before or after positive Candida blood culture, one patient died within the first 30 days and two more within 100 days, but only in one case out of six without neutropenia was a fatal outcome documented.

Discussion

Here we describe the incidence of Candida BSIs, specifically for patients with hematological malignancies or solid tumors, in a German tertiary care medical center. A rate of 1.4 candidemias per 1,000 admissions was detected over a 7-year time period. This rate remained stable during the first 5 years, but a significant increase was observed beginning in 2008. The high rate of non-C. albicans Candida species and of fatal outcomes in Candida BSIs emphasize the relevance of this fungal infection and the need for current epidemiological data for this specific patient population.

The incidence of 1.4 per 1,000 hospitalizations is higher than the rate of 0.20–0.38 per 1,000 admissions obtained from a study performed from 1997–1999 in six European countries [2]. The latter reflects the isolation in culture of Candida species from blood samples, in a general hospital population, independent of underlying diseases and their risk factors. In contrast, the rate of Candida BSIs in the present investigation seems low compared to other infectious complications, epidemiological data before introduction of fluconazole prophylaxis and specific hematological observations.
The SEIFEM-2004 study reported an incidence of 1.6% invasive yeast infections, related to all enrolled patients. But this may include several episodes of chemotherapy and hospitalization for each subject [21]. Altogether, 11,802 hematological patients admitted to 18 wards in Italian facilities between 1999 and 2003 were evaluated. The incidence had a broad range between 0.1% for patients with chronic lymphatic leukemia to 4.4% for those with acute myeloid leukemia. Patient populations might be similar to some degree, as acute leukemia followed by multiple myeloma and non-Hodgkin’s lymphoma, are the dominant malignancies for patients hospitalized on wards included in this survey.

Patients receiving chemotherapy for solid tumor were not excluded but are a minority as this kind of treatment most often is provided in an outpatient department. In contrast to the SEIFEM study [21], we calculated the rate of infection per hospitalization. This may provided information about patients’ risks at time of admission. The low rate of Candida BSIs at our center probably resulted from a general antifungal prophylaxis with fluconazole for all patients receiving chemotherapy.

Reasons for the observed significant increase in 2008 and 2009 cannot be specifically determined. Allogeneic hematopoietic stem cell transplantation, with an annually increasing number beginning in 2005, as well as more intense chemotherapy may have contributed to the rise in number of BSIs. This hypothesis may be supported by the two allogeneic transplant recipients with systemic Candida infections while receiving conditioning therapy during these 2 years. In addition, decreased adherence to recommended fluconazole prophylaxis over time cannot be ruled out, as only five patients were receiving systemic antifungal agents at the time of Candida BSIs.

Data from the Prospective Antifungal Therapy Alliance Registry indicated a predominance of non-C. albicans Candida species in 54.4% of 2,019 patients with candidemia [22]. In 2010, an Australian study showed a predominance of 67% of non-C. albicans Candida spp. in hemato-oncological patients [18]. The species distribution also depended on geographic regions [10,23] of the country. The European survey in 2003 already detected C. albicans in only 35% and C. krusei in 12% of the cases [2]. This trend is confirmed by our study results, as only in 28.6% of BSIs were caused by C. albicans. In 71% of cases, five different non-C. albicans Candida species were isolated. Candida krusei, which is innately resistant and C. glabrata, which is associated with an increase in its resistance to fluconazole, were responsible for 23.8% of Candida BSIs. The recommended intensive use of fluconazole for antifungal prophylaxis may explain the broad range of different Candida species and trend towards non-C. albicans Candida species as the etiologic agents of BSIs.

The severity of candidemia is confirmed by the high associated and overall mortality. In recent phase III trials of echinocandins, the rate of death from all causes was between 23 and 31% [24,25]. But here, patients with all kinds of underlying disease were enrolled.

The European survey detected a mortality rate of 45% in hemato-oncological patients [2]. Analyses from Finland and Barcelona confirm this trend with mortality rates of 35% and 44% [26,27,28], respectively. In our retrospective study, mortality was even higher at 56% within 30 days and 67% within 100 days after diagnosis of Candida BSIs. This high mortality might be explained by a low rate of C. albicans isolates as the etiologic agents, severity of underlying disease, but even more importantly, by cellular immunosuppression.

Only one of nine patients with neutropenia at the time of the first positive Candida blood culture survived. This risk factor is excluded [24] or insufficiently addressed [25] in the previously mentioned phase III trials on candidemia. Thus, therapy of patients with low neutrophil count remains a challenge and needs further investigation.

Similar to other retrospective surveys and multicenter non-interventional trials, antifungal treatment varied in our study and the low number of candidemias does not allow an analysis of antifungal efficacy. In addition, it must be mentioned that patients diagnosed on wards including intensive care units of other departments would have been missed as the primary analysis focused on Candida infection in patients hospitalized in the hematological and oncological departments.

Nevertheless, the epidemiological data presented here include a very low rate of C. albicans BSIs. This should be taken into account while treating suspected or proven yeast infections in cancer patients. Differentiation of Candida species and resistance testing should be recommended at least if fluconazole is used in patient treatment. Further prospective epidemiological evaluations and even more interventional trials to optimize therapy for patients with neutropenia are warranted.

Declaration of interest: J. Zirkel, H. Klinker, A. Kuhn, M. Abele-Horn, D. Tappe, D. Turnwald, and H. Einsele: none. W. J. Heinz has received honoraria from Essex/Schering-Plough, Gilead, MSD, Pfizer and served as an advisor for Essex/Schering-Plough and MSD.

References

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