Candidemia in Cancer Patients: A Prospective, Multicenter Surveillance Study by the Invasive Fungal Infection Group (IFIG) of the European Organization for Research and Treatment of Cancer (EORTC)

C. Viscoli, C. Girmenia, A. Marinus, L. Collette, P. Martino, B. Vandercam, C. Doyen, B. Lebeau, D. Spence, V. Krcmery, B. De Pauw, F. Meunier, and the Invasive Fungal Infection Group of the EORTC*

In a surveillance study of candidemia in cancer patients that was conducted by the European Organization for Research and Treatment of Cancer, 249 episodes were noted; *Candida albicans* was isolated in 70% (63) of the 90 cases involving patients with solid tumors (tumor patients) and in 36% (58) of the 159 involving those with hematologic disease (hematology patients). Neutropenia in tumor patients and acute leukemia and antifungal prophylaxis in hematology patients were significantly associated with non-*albicans* candidemia in a multivariate analysis. Overall 30-day mortality was 39% (97 of 249). In a univariate analysis, *Candida glabrata* was associated with the highest mortality rate (odds ratio, 2.66). Two multivariate analyses showed that mortality was associated with older age and severity of the underlying disease. Among hematology patients, additional factors associated with mortality were allogeneic bone marrow transplantation, septic shock, and lack of antifungal prophylaxis.

In the past decade, the role of fungal organisms as a cause of nosocomial infections in hospitalized patients has increased substantially. Data from American hospitals belonging to the National Nosocomial Infections Surveillance System showed that the incidence of nosocomial fungal infections increased from 2.0 to 3.8 infections/1,000 discharges from 1980 to 1990, with the incidence of nosocomial candidemia increasing from 1.0 to 4.9 infections/1,000 discharges. *Candida albicans* accounted for about 60% of the isolated pathogens, followed by other *Candida* species (19%) and other fungi (21%) [1, 2].

In recent years, an increasing incidence of non-*albicans* candidal infections has been reported, although *C. albicans* still causes ~60% of the cases [3, 4]. To the best of our knowledge, no multicenter surveillance study of nosocomial candidemia has previously been performed in Europe, because of the lack of a centralized surveillance system. However, there are several reports from individual centers that have witnessed a progressive increase in the rates of nosocomial candidemias, both in the global population of hospitalized patients [5–7] and in the subgroup of cancer patients [8, 9].

In 1992 the Invasive Fungal Infection Group of the European Organization for Research and Treatment of Cancer (EORTC) implemented a surveillance study of candidemia in cancer patients at centers participating in the group’s activities. In a 2-year period, 270 episodes were noted, of which 249 (92%) were candidemias and 21 (8%) were other fungemias. In the present article we analyze the episodes of candidemia with the aim of (1) establishing a clinical description of candidemia in cancer patients, (2) understanding factors associated with the emergence of non-*albicans* species of *Candida*, and (3) understanding factors associated with deaths occurring within 30 days following the onset of candidemia.

Materials and Methods

The surveillance study lasted from 1 November 1992 to 31 October 1994 and was conducted in 30 tertiary care or university medical centers located in Europe (n = 28) and in the Middle East (n = 2). A form was sent to every participating investigator on a monthly basis, asking him or her to report how many cases of candidemia were seen at each institution during the previous month. For every case of candidemia, the participating investigator was required to fill out a clinical report form on the basis of inpatient or outpatient hospital records and laboratory data. Handling of the clinical report forms was centralized at the EORTC Data Center, in Brussels. Every form was first reviewed by the group’s data manager (A.M.) and then by the data review committee (C.V., C.G., and A.M.). All patients were followed until day 30 after diagnosis of candidemia (day of first positive blood culture) or until death.

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* Participating investigators are listed at the end of text.

Reprints or correspondence: Dr. Claudio Viscoli, Immunocompromised Host Disease Unit, Istituto Nazionale per la Ricerca sul Cancro, L.go R. Benzi, 10–16132 Genoa, Italy (viscolic@unige.it).

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**Definitions and Classifications**

Candidemia was defined by a *Candida* species-positive culture of blood from a patient with cancer (e.g., leukemia, lymphoma, multiple myeloma, or solid tumor) who presented with fever. Episodes involving afebrile patients were included in the analysis only if they were accompanied by hypotension and other signs of septic shock. Duration of candidemia was defined as the time interval (days) between the first and last positive blood cultures (yielding the same pathogen). Persistent candidemia was defined as the persistence of positive blood cultures for >2 days, from the time of the first positive blood culture. Fever was defined as an axillary temperature of >37°C.

Since the standard of care was not the same in all centers participating in the study, we were forced to use a nonstandard definition of catheter-related candidemia. Indeed, quantification of the catheter tip culture was performed only occasionally. Candidemia was considered to be correlated to the intravenous catheter if the catheter was removed and its culture yielded the same yeast that had been previously isolated in the blood culture, regardless of the colony count. In all other cases the correlation of the infection with the catheter was considered unknown. No guidelines were given about criteria for catheter removal, and the decision was left to the discretion of the participating investigator. Similarly, each participating center was allowed to use its standard microbiological methods for isolation and identification. These included at least the germ-tube test to differentiate *albicans* from non- *albicans Candida* strains and a variety of manual or semiautomatic methods for species identification.

Neutropenia was defined as an absolute neutrophil count lower than $1 \times 10^9/L$. Severe neutropenia was defined as an absolute neutrophil count lower than $0.1 \times 10^9/L$. Breakthrough candidemia was defined as candidemia in a patient receiving either an orally absorbable agent or an intravenous antifungal agent given for prophylaxis or therapy, regardless of the in vitro susceptibility of the isolated strain. Organ involvement in candidemic patients was defined by positive blood cultures along with histologic and/or cultural documentation of infection in internal organs. Endophthalmitis and embolic skin lesions were considered to be signs of organ involvement. Concomitant bloodstream infection was defined as the isolation of another microorganism from the blood within a 24-hour period before or after the first isolation of *Candida* in blood culture. The term advanced disease was used with reference to the stage of the underlying neoplasm. Patients with advanced disease were those with a hematologic disease in relapse or with a solid tumor with multiple localizations.

Candidemia was considered to be the primary cause of death of patients who died within 48 hours following a positive blood culture, when no other cause (including the primary disease, other infections, and hemorrhage) was identified. Candidemia was considered to be an associated cause of death when, although it was still present at time of death (as indicated by fever, with or without positive cultures), another complication (e.g., hemorrhage or a secondary nonfungal infection) or an uncontrolled underlying disease was also present. Death was considered to be due to another cause when candidemia was cleared at time of death (as indicated by the lack of fever or positive cultures) and there was another likely cause (usually the underlying disease).

**Methods of Analysis**

In light of the existence of major prestudy and poststudy differences in clinical status, predisposing factors, and etiology between patients with solid tumors (tumor patients) and patients with hematologic malignancy (hematology patients), we decided to analyze the two groups separately. In addition to a descriptive clinical analysis, two multivariate analyses were performed with the aim of identifying factors associated with etiology (*albicans* vs. non-*albicans* Candida) and outcome in both groups of patients.

A univariate logistic regression model, modeling the probability of having infection with non-*albicans* Candida over that with *C. albicans* [10], was used to assess the association of all variables with the frequency of the etiology of candidemia. The variables that were significant at the 0.10 level were then evaluated in a multivariate logistic regression model. Variables that did not reach the 0.05 significance level were then removed one by one from the model, starting with the least significant variable. At the end of this backward selection procedure, the final multivariate logistic regression model was estimated with use of all the available information. The odds ratios were computed as the odds for a patient having *C. non-albicans* candidemia, divided by the odds for a patient having that due to *C. albicans*. The univariate logistic model was preferred over the $\chi^2$ test for the sake of homogeneity of the statistical methods used in the univariate and multivariate models.

The following variables were analyzed: geographic location of the center (northern vs. southern/eastern Europe); patient’s age (≤16 years, 17–59 years, >59 years); gender; stage of disease (onset/chronic, remission, progressive-resistant [for hematologic malignancies], advanced/nonadvanced [for solid tumors]); type of underlying disease (acute leukemia: yes/no [only for hematologic diseases]); days from hospital admission to onset of fungemia (0, <15, 15–30, >30); chemotherapy administered in the 30 days prior to onset of candidemia (for solid tumors: yes/no; for hematologic diseases: none, induction, consolidation/maintenance, second-line chemotherapy, allogeneic bone marrow transplantation [BMT], autologous BMT, and other); administration of steroids (yes/no); total parenteral nutrition administered in the 30 previous days (yes/no); administration of antibacterial prophylaxis (yes/no); administration of antifungal prophylaxis (for solid tumors: yes/no, since patients who received absorbable and nonabsorbable antifungals were lumped together because of small numbers; for hematologic diseases: none, nonabsorbable drugs, or absorbable
drugs); breakthrough fungemia (yes/no); catheter correlation (yes/no); patients with unknown correlation were excluded from the analysis; granulocyte count (cells × 10⁹/L) at onset (for solid tumors: ≤1/≥1; for hematologic diseases: <0.1, 0.1–1, >1); occurrence of neutropenia in the previous 30 days (yes/no); body temperature (°C) at onset (≤37.9, 38–38.5, >38.5); presence of shock (yes/no); and presence of organ involvement (yes/no).

Multivariate models for survival were derived in a similar way. All variables were scanned for their prognostic effect on duration of survival in a univariate Cox proportional hazards regression model [11, 12]. Patients still alive at day 30 were censored at that point. All variables that were significant at the 0.10 level in the univariate analysis were selected for inclusion in a multivariate Cox model. A backward selection procedure was then applied with 0.05 as the significance level for staying in the model. The final multivariate model was then estimated with use of all available information.

The odds ratio and its 95% confidence interval were computed for each variable. The variables considered were the same as for the previous analysis, with the addition of the following: months from diagnosis of the underlying disease to onset of fungemia (<1, 1–6, 7–12, >12 [only for hematologic disease]), type of pathogen (C. albicans/C. non-albicans); and number of pathogens involved (single-agent/mixed infection or polymicrobial infection). All the analyses were performed with use of Statistical Analysis Software (SAS Institute, Cary, NC) [13, 14].

Results

A total of 249 episodes of candidemia involving 245 patients were prospectively recorded. A single fungal strain was isolated in 223 episodes (89%), whereas in 7 episodes (3%), 2 different fungal strains were isolated (polymicrobial infections). The remaining 19 episodes (8%) were due to mixed infections (with a fungus plus a bacterium). The median number of episodes reported by each center was 5.5 (range, 1–36), with 11 centers reporting >10 episodes each.

Patient’s Characteristics and Histories

Of 249 candidemias, 90 occurred in patients with solid tumors and 159 in patients with hematologic malignancies. The median age was 41 years (range, 2–81 years) among patients with solid tumors and 56 years (range, 1–90 years) among patients with hematologic malignancies. The overall male/female ratio was 132/117. Most patients with hematologic malignancies had acute leukemia (110 of 159; 69%), but there were also patients with lymphoma (30 cases; 19%), multiple myeloma (14 cases; 9%), and chronic leukemia (5 cases; 3%). Solid tumors were mainly located in the genitourinary tract (26 cases; 29%) and the gastrointestinal tract (26 cases; 29%). There were also 15 cases (17%) involving patients with head and neck tumors and 23 cases (25%) involving patients with other types of tumors.

About half of the cases of candidemia involved patients without an advanced or relapsing/resistant underlying disease (50% of those with solid tumors and 55% of those with hematologic diseases). A total of 225 of the 249 episodes of candidemia (90%) involved hospitalized patients. For these patients, the median time from hospitalization to onset of infection was 14 days among those with solid tumors and 20 days among those with hematologic malignancies. Almost all hematology patients and 60% of tumor patients had received antineoplastic chemotherapy in the month prior to onset of candidemia. Conversely, major surgery (excluding placement of intravenous catheters) was much more common among patients with solid tumors (41 of 90; 45%) than among those with hematologic diseases (5 of 159; 3%).

Over the same period of time prior to candidemia, 141 hematology patients (89%) and 36 tumor patients (40%) had an episode of neutropenia, lasting a median of 11 days (range, 1–66 days). A total of 212 of 249 patients (85%) had received antibacterial drugs either for prophylaxis or for therapy, and 124 of 249 patients (50%) had received absorbable or nonabsorbable antifungal drugs. Of these 124 patients, 60 (50%) had received an orally absorbable or intravenous antifungal drug (34, fluconazole; 15, itraconazole; 11, other). The proportion of patients who had received antifungals was much higher among hematology patients (106 of 159; 67%) than among tumor patients (18 of 90; 20%).

Clinical Presentations

The proportions of patients who were neutropenic on the first day of candidemia (day of the first positive blood culture) were 20% of those with solid tumors (18 of 90) and 69% of hematology patients (109 of 159). The proportions of those who were severely neutropenic were 12% (11 of 90) and 53% (85 of 159), respectively. In addition, 47% and 35% of hematology patients and 27% and 28% of tumor patients were receiving steroid treatment and total parenteral nutrition, respectively. Unfortunately, we cannot provide information about the duration of steroid therapy and parenteral nutrition before fungemia or about the dosage of steroids.

Fever was a very common initial sign of infection, as it was present in 99% of the episodes. The only two patients who had no fever at presentation had hypotension and signs suggestive of septic shock. Twenty-three of 247 patients (9%) presented with low-grade fever (<38°C). In the majority of patients (220 of 249; 88%), fever remained the only sign of infection. Clinically or microbiologically/histologically documented organ involvement was present in only 24 patients (10%). There were 10 patients with skin embolic lesions; 4 with pneumonia; 3 with peritonitis; 2 each with esophagitis, hepatosplenic disease, and endophthalmitis; and 1 with endocarditis. In 10% of the cases (25 of 249), candidemia presented with septic shock.
On the first day of candidemia, 242 patients (97%) were fitted with an intravenous line (31 peripheral lines, 168 central catheters, 42 Port-a-caths [Pharmacia, North Ryde, Australia], and 1 combination). The intravenous line was removed and cultured in 130 cases (54%), and a correlation with the catheter was demonstrated in 40 cases (31%). Although the numbers are small, a statistically significant difference ($P = .002$) was found in the rate of catheter removal among the seven centers that reported more than 10 episodes. This rate varied from 12% (2 of 16) in Strasbourg, France, to 81% (13 of 16) in Riyadh, Saudi Arabia.

A total of 210 of 249 patients (84%) were receiving broad-spectrum antibacterials for prophylaxis or therapy on the day of the first positive blood culture. A smaller proportion (77 of 249; 31%) was receiving absorbable antifungal drugs. These episodes were defined as breakthrough candidemias. Of the 77 breakthrough candidemias, 42 developed in patients receiving empirical antifungal therapy and 35 in patients receiving systemic prophylaxis (33 patients, fluconazole; 21, amphotericin B [3, lipid formulations]; 12, itraconazole; 6, other antifungals; and 5, various combinations). The proportion of patients with breakthrough candidemia was 40% among hematology patients and 16% among tumor patients ($P < .001$).

### Etiology

Table 1 shows the distribution of the various species of _Candida_ identified in the two patient populations. Overall, _C. albicans_ accounted for about half of the episodes of candidemia, and _Candida glabrata, Candida tropicalis, Candida krusei_, and _Candida parapsilosis_ each caused 10% of the remaining cases. The other 26 episodes (10%) were caused by a miscellaneous group of non-_albicans Candida_ species, including _C. guilliermondii_ (11 cases); _C. lusitaniae_ (4); _C. famata, C. lypolitica_, and _C. kefyr_ (2 each); and _C. inconspicua, C. norvegiensis, C. zeylanoides_, and _C. stellatoidea_ (1 each).

In one case, the species was not identified. The etiologic distribution was different according to the underlying disease. _C. albicans_ accounted for 70% of cases among patients with solid tumors (63 of 90) but for only 36% among those with hematologic diseases (58 of 159). _C. glabrata, C. tropicalis, C. parapsilosis, C. krusei_, and other non-_albicans Candida_ species accounted for 12%–14% each of the cases among patients with hematologic malignancies and for 2%–9% of those among patients with solid tumors.

Persistent candidemia was demonstrated in 116 of 249 cases (47%) and was more frequent among hematology patients (73%) than among tumor patients (26%). There was no difference in the incidence of persistent candidemia according to the type of _Candida_ involved. Similarly, there were no major differences in age, duration of hospitalization before onset of candidemia, presence of a central venous line, previous use of parenteral nutrition, steroid administration, administration of antibacterial and antifungal agents, presence of neutropenia, stage of disease, and prior administration of chemotherapy, as related to the different strains of _Candida_. However, the respective numbers of cases of candidemia due to various species were too small to allow definitive conclusions. Concomitant infections were documented in 26 cases (10%) and were due to another fungal organism in 7 cases and to a bacterium in 19 cases.

### Analysis of factors associated with _C. albicans_ or non-_albicans_ candidemia

In a univariate logistic regression analysis, the variables that were significant at the 0.10 level were breakthrough candidemia and absolute neutrophil count at onset (for patients with solid tumors) and type of disease, antifungal prophylaxis, and antibacterial prophylaxis (for those with hematologic malignancies). The results of the multivariate analyses are reported in table 2. For tumor patients, after the backward selection, the only variable retained was absolute neutrophil count at onset, showing a higher risk of non-_albicans_ candidemia among neutropenic patients. Among patients with hematologic malignancies, type of disease and antifungal prophylaxis were retained in the multivariate model, showing the risk of non-_albicans_ candidemia to be higher in patients with leukemia than in those with other malignancies, as well as in patients receiving antifungal prophylaxis, especially with absorbable drugs, than in those receiving no prophylaxis.

### Mortality

Out of 249 patients, 97 (39%) died within 30 days from the onset of candidemia. The overall crude mortality rate did not differ in the two populations of tumor and hematology patients. Death was considered to be directly attributable to candidemia in 21 (8%) of 249 patients. In 40 additional patients the fungal infection was considered to be an associated cause of death, the primary one being the underlying disease (29 patients), a concomitant nonfungal infection (8 patients) or a hemorrhage (3 patients). Therefore, candidemia appeared to have played
Table 2. Multivariate logistic regression model for factors associated with etiology of candidemia (C. albicans vs. non-albicans Candida species) in patients with solid tumors and hematologic malignancies.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>( P ) value (Wald test)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solid tumors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absolute neutrophil count at onset</td>
<td>( &gt;1 ) vs. (&lt;1^* )</td>
<td>0.002</td>
<td>0.18 (0.06–0.55)</td>
</tr>
<tr>
<td>(cells ( \times 10^9/L ))</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hematologic malignancies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type of disease</td>
<td>Leukemia vs. other*</td>
<td>0.031</td>
<td>2.18 (1.07–4.42)</td>
</tr>
<tr>
<td>Antifungal prophylaxis</td>
<td>None* vs. nonabsorbable drugs vs. absorbable drugs</td>
<td>0.041²</td>
<td>1.56 (1.02–2.40)</td>
</tr>
</tbody>
</table>

* Reference category for the computation of the odds ratio (C. non-albicans/C. albicans).
² Test for linear trend.

either a primary or a secondary role in about two-thirds of deaths (61 of 97), with a candidemia-associated mortality rate of 24%.

**Analysis of factors associated with mortality.** In a univariate logistic regression analysis, the variables that were significant at the 0.10 level were age, stage of disease, antibacterial prophylaxis, and catheter correlation (among patients with solid tumors) and geographic location of the center, age, type of disease, time from diagnosis of underlying disease to onset of candidemia, stage of disease, type of chemotherapy, corticosteroid treatment, antifungal prophylaxis, and shock (among those with hematologic malignancies). The results of the multivariate analyses are reported in table 3. In tumor patients, after the backward selection, only age and stage of disease were retained in the final model. Younger age and nonadvanced disease were associated with a lower risk of death than older age and advanced disease. Among patients with hematologic malignancies, age, stage of disease, last chemotherapy, antifungal prophylaxis, and shock remained in the final model as prognostic factors. This model showed that advanced age, progressive or resistant underlying disease, the absence of previous antifungal prophylaxis, bone marrow transplantation as last treatment, and development of shock were all independently associated with a high risk of death.

**Mortality according to Candida species.** Figures 1 and 2 present the Kaplan-Meier survival curves according to the type of pathogen, with both solid tumors and hematologic malignancies grouped together. Figure 1 shows the overall survival curve (all deaths), while figure 2 shows the specific survival curve (i.e., only candidemia-associated deaths). The \( P \) value of the overall log-rank test comparing the survival according to the pathogen is 0.011 for overall survival and 0.008 for specific survival. The comparisons remained significant when the models were stratified for those variables that were shown to affect survival and that were not evenly balanced for all the etiologies (type of underlying disease, stage/severity of the underlying disease, or type of prophylaxis)。

Table 3. Multivariate logistic regression model for factors associated with 30-day mortality among patients with solid tumors and hematologic malignancies.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Level</th>
<th>( P ) value (Wald test)</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Solid tumors</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>(&lt;16^* ) vs. 16–59 vs. ( \geq 60 ) (as a trend)</td>
<td>0.0397</td>
<td>1.74 (1.03–2.93)</td>
</tr>
<tr>
<td>Stage of disease</td>
<td>Advanced vs. nonadvanced*</td>
<td>0.0017</td>
<td>3.07 (1.52–6.20)</td>
</tr>
<tr>
<td><strong>Hematologic malignancies</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (y)</td>
<td>(&lt;16^* ) vs. 16–59 vs. ( \geq 60 ) (as a trend)</td>
<td>0.0013</td>
<td>2.24 (1.37–3.67)</td>
</tr>
<tr>
<td>Stage of disease</td>
<td>Remission* vs. onset/chronic vs. progressive/resistant (as a trend)</td>
<td>0.0002¹</td>
<td>2.22 (1.45–3.39)</td>
</tr>
<tr>
<td>Last chemotherapy</td>
<td>Second-line vs. no second-line*; BMT (allo or auto) vs. no BMT*</td>
<td>0.0065¹</td>
<td>2.44 (1.16–5.13)</td>
</tr>
<tr>
<td>Antifungal prophylaxis</td>
<td>None* vs. nonabsorbable drugs vs. absorbable drugs (as a trend)</td>
<td>0.0022¹</td>
<td>0.58 (0.41–0.82)</td>
</tr>
<tr>
<td>Shock</td>
<td>Shock vs. no shock*</td>
<td>0.0001</td>
<td>4.93 (2.47–9.84)</td>
</tr>
</tbody>
</table>

NOTE. Allo = allogeneic; auto = autologous; BMT = bone marrow transplantation.
º The reference category for computation of the odds ratio.
¹ Test for linear trend.
² Per \( \chi^2 \) test with 2 degrees of freedom.
disease, use and type of antifungal prophylaxis, and age), with $P$ values of 0.015 for overall survival and 0.025 for specific survival. With respect to $C. albicans$ (1-reference), the adjusted hazard ratios for overall survival were 2.66 (95% CI, 1.24–5.73) for $C. glabrata$, 1.99 (95% CI, 0.98–4.03) for $C. tropicalis$, 0.58 (95% CI, 0.21–1.58) for $C. parapsilosis$, 1.67 (95% CI, 0.68–4.10) for $C. krusei$, and 0.53 (95% CI, 0.17–1.62) for other Candida strains. $C. glabrata$ was therefore associated with a significantly poorer survival rate than that with the other strains.

**Discussion**

This is the first multicenter international surveillance study of candidemia in Europe, and, to our knowledge, the largest prospective study of cancer patients with candidemia ever reported. This study provides information about the clinical presentation of candidemia in cancer patients in Europe, as well as about the emergence of non-$albicans$ Candida strains and about candidemia-associated mortality. The study was not designed to provide information about the relative incidence of

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**Figure 1.** Kaplan-Meier estimates of overall survival (%), according to pathogen causing candidemia ($O =$ no. of deaths; $N =$ no. of patients).

**Figure 2.** Kaplan-Meier estimates of specific survival (%), according to pathogen causing candidemia ($O =$ no. of deaths; $N =$ no. of patients).
candidemia among cancer patients or about the role of fungal organisms among all pathogens causing infection in cancer patients or the role of central intravenous catheters in affecting the risk of candidemia and its outcome. In addition, owing to the short period of surveillance (2 years), this study could not assess changes in etiology or clinical presentation of candidemias over time.

For many years candidal infection was commonly considered a rare event, mainly occurring in patients who were dying as a result of their underlying disease. The present study shows that this is not completely true. Indeed, ~50% of patients with candidemia had a nonadvanced disease (i.e., neither a relapsing hematologic disease nor a disseminated tumor). In addition, candidemia developed relatively shortly after the diagnosis of the underlying disease (in <6 months in half of the patients with solid tumors and about one-third of those with hematologic malignancies).

Candidemia is definitely a nosocomial infection. In our study, only 10% of the episodes occurred outside of the hospital. The clinical presentation included fever in the majority of patients, although there were cases with only low-grade fever. In 10% of the episodes, candidemia presented with septic shock, thus showing that this event is not merely a complication of bacterial infections. Finally, in a relatively small proportion of patients (10%), there was some evidence of deep-seated infection at diagnosis. However, this proportion might be underestimated, since the study was not designed to provide information about the incidence of deep-seated candidal infections, including retinitis, in candidemic patients.

Breakthrough candidemias accounted for 31% of the episodes (ranging from 16% in cases of solid tumors to 40% in cases of leukemia), probably because patients with acute leukemia were more often receiving prophylaxis than were those with solid tumors. This incidence seems to be higher than the one reported by others, probably because of differences in the patients’ underlying diseases. Indeed, Nguyen and co-workers reported an incidence of 13%, but no information was given about the patients’ predisposing conditions [15]. Nucci et al. found that 25% of their fungemic episodes (10 of 43) were breakthrough candidemias, but only three of their patients had acute leukemia, while the others presumably had lymphoma [16]. Non-albicans strains of Candida were isolated in 65% of the cases of breakthrough candidemia (50 of 77) and in 45% of those of nonbreakthrough candidemia (78 of 172) \( (P = .007) \). Moreover, 67% of the C. tropicalis and 50% of the C. krusei strains were isolated in breakthrough episodes. Many factors may account for the occurrence of breakthrough candidemias, including resistance to the allocated antifungal drug, pharmacokinetic problems, and insufficient dosage. Unfortunately, we cannot give more insight on this issue. However, it should be noted that breakthrough candidemias occurred not only in patients receiving triazole drugs but also in patients receiving amphotericin B, including three receiving lipid compounds.

In recent years, a shift has occurred in the etiology of candidemia. Although in most studies C. albicans was still the most frequent cause of candidemia, there was an increase in the isolation of non-albicans Candida strains, such as C. parapsilosis, C. krusei, C. tropicalis, and C. glabrata [3, 4, 15–22]. In the present study, non-albicans Candida strains accounted for 51% of the cases, but as already reported [21], this incidence varied significantly according to the underlying disease. C. albicans occurred significantly more frequently among patients with solid tumors than among those with hematologic malignancies (70% vs. 36%; \( P < .0001 \)). By contrast, non-albicans strains of Candida were prevalent among patients with hematologic disorders. C. krusei and C. glabrata infections accounted for \( >25\% \) of the episodes involving patients with hematologic malignancies and only 6% of those involving patients with solid tumors.

The multivariate analysis for factors associated with the emergence of non-albicans candidal infections yielded different results in the two populations of patients (with solid tumors or hematologic malignancies). In tumor patients the only factor significantly associated with non-albicans candidemia was being neutropenic at the time the infection was diagnosed. In hematology patients, both antifungal prophylaxis (especially with absorbable drugs) and acute leukemia as the underlying disease were significantly associated with a higher incidence of non-albicans candidemia.

Several reports have focused attention on the increasing rate of colonization with and infection due to the natively resistant Candida species (C. krusei and C. glabrata) in patients receiving fluconazole [23–25]. However, this phenomenon has not been confirmed in large prospective studies [26–29]. In our study, antifungal prophylaxis (not only with fluconazole) was associated with an increased risk of non-albicans candidemia in patients with hematologic malignancies.

Whether the shifting from C. albicans to non-albicans Candida species as the cause of candidemia is an undesirable event is questionable. In our study, the multivariate analysis for survival showed that candidemia due to a non-albicans Candida species or to C. albicans was not a factor associated with a higher mortality rate. Unfortunately, it was impossible to investigate the association between each Candida species and the mortality rate in a multivariate fashion, because of an insufficient number of cases. However, a Kaplan-Meier curve examining the role of different species of Candida in the survival rate showed a significantly better survival rate for other Candida species and C. parapsilosis than for C. albicans, while C. glabrata, C. tropicalis, and to a lesser extent C. krusei were associated with worse survival rates than for C. albicans. This difference remained significant even after adjustment for those variables significantly affecting mortality. Indeed, animal and human studies have shown that C. tropicalis is intrinsically more virulent than C. albicans [30, 31], while C. parapsilosis is usually considered a nonvirulent strain [17, 21]. Conversely, C. glabrata is not usually
considered an aggressive pathogen [21], while in our study this strain was associated with the highest mortality rate. We found one other study that has suggested that C. glabrata may be more virulent than C. albicans [32].

The overall mortality rate that we found in this study was similar to the one observed in other studies. For example, Meunier et al. [8] reported a 42% crude mortality rate in a single-center study of candidemia. Similarly, we observed a 1-month crude mortality rate of 39%, but the candidemia-associated mortality rate was 24%. In this study the risk of death seemed to be mainly correlated with host-related factors. Indeed, aging and an advanced underlying disease were predictive of poor survival, both in tumor patients and hematologic patients.

In addition, among hematology patients, the risk of death was higher for those with progressive or resistant disease than for those with new onset or chronic disease (the risk of death in this last group was higher than that for patients in remission) and higher for recipients of bone marrow transplants (or in patients treated with second-line chemotherapy) than for patients who had induction, consolidation, or maintenance treatment. Finally, the risk of death was higher in patients with septic shock and in those who did not receive any type of antifungal prophylactic treatment than in those who did not have shock and had received both nonabsorbable and (to a greater extent) absorbable antifungals.

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Participating Investigators in the EORTC Study

Pietro Martino, Università La Sapienza, Rome, Italy; Bernadette Lebeau, Hôpital Michallon, Grenoble, France; Vladimir Krmery, Department of Clinical Oncology, Bratislava, Slovak Republic; David Spence, King Faisal Hospital, Riyadh, Saudi Arabia; Bernard Vander- cam, Chantal Doyen Université Catholique de Louvain, Louvain, Belgium; Raoul Herbrecht, Hôpital Universitaire Hautepierre, Stras- bourg, France; Jacques Troncy, Hôpital É. Herriot, Lyon, France; Michel Aoun, Institut J. Bordet, Brussels, Belgium; Damir Nemet, Hospital Rebro, Zagreb, Croatia; Maria Anna Viviani, Università di Bari, Bari, Italy; Jean-Christophe Cordonnier, Lille, France; Simon de Marie, Universitair Ziekenhuis Antwerpen, Antwerp, Belgium; Ben De Pauw, St. Radboud, Nijmegen, the Netherlands; Philippe Moreau, Centre Hospitalier Universitair Nantes, France; Giuseppe Todeschini, Università di Verona, Verona, Italy; Fritz Offner, Universitair Ziekenhuis Gent, Gent, Belgium; Michèle Tjean, Hôpital Verviers, Verviers, Belgium; Anna Gregor, Withington Hospital, Edinburg, Scotland; and Raffaella Giacchino, Gaslini Children’s Hospital, Genoa, Italy.

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