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ORIGINAL



The risk and clinical outcome of candidemia depending on underlying malignancy

Olivier Lortholary^{1,2*}, Charlotte Renaudat¹, Karine Sitbon¹, Marie Desnos-Ollivier¹, Stéphane Bretagne^{1,3}, Françoise Dromer¹ and The French Mycoses Study Group

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Abstract

Purpose: To assess the risk factors and outcomes associated with fungemia caused by the six most commonly occurring *Candida* species in patients with and without malignancies.

Methods: Analysis of the episodes of fungemia due to common *Candida* species in adults, based on an active hospital-based surveillance program (Paris area, France, 2002 to 2014).

Results: Of the 3417 patients (3666 isolates), 1164 (34.1%) had a solid tumor (45.7% digestive tract) and 586 (17.1%) a hematological malignancy (41.8% lymphoma, 33.5% acute leukemia). The hematology patients were significantly younger, more often pre-exposed to antifungals, more often infected by *C. tropicalis*, *C. krusei*, or *C. kefyr*, and more often treated in the first instance with an echinocandin. Compared with inpatients who were not in ICU at the time of fungemia, those in ICU were less frequently infected by *C. parapsilosis* ($p < 0.02$), had more recent surgery ($p < 0.03$), and died more frequently before day 8 and day 30 ($p < 0.0001$). An increase in crude mortality over time in ICU was observed only in oncology patients ($p < 0.04$). For all patients, lack of prescription of antifungals despite knowledge of positive blood culture increased the risk of death. The odds of being infected by a given *Candida* species compared with *C. albicans* were uneven regarding age, gender, type of malignancy, hospitalization in ICU, central venous catheter, HIV status, intravenous drug addiction, and previous exposure to antifungal drugs. Compared with *C. albicans*, *C. glabrata* (OR = 0.69 [0.54–0.89]) and *C. parapsilosis* (OR = 0.49 [0.35–0.67]) were associated with a decreased risk of death by day 8 and day 30.

Conclusion: The clinical context of underlying malignancy and hospitalization in ICU may be relevant to the initial management of candidemia.

Keywords: *Candida*, Echinocandins, Fluconazole, Hematological malignancy, Cancer, ICU, Non-*albicans* species

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Take-home message: The type of underlying malignancy (solid vs hematological) and hospitalization in vs outside ICU impact differentially on fungemia by different species of *Candida*.

Introduction

Candidemia currently represent up to 10% of nosocomial bloodstream infections [1–3] with associated mortality, increased length of stay and cost [4]. It is therefore a public health concern everywhere [5]. Among the risk factors, hematological malignancies and solid tumors represent a large proportion [6, 7]. Many changes have occurred over the last decade with the increased incidence of fungemia due to *Candida glabrata* at least in some settings [8, 9], the availability of echinocandins

[10–12] and new broad-spectrum triazoles prophylaxis in hematology, the implementation of management guidelines [13, 14], and better suspicion/awareness of clinicians. Whether or not all these changes impact the characteristics and outcome of candidemia among adults with malignancy needs to be further investigated. Several retrospective monocentric studies described the local epidemiology of candidemia among patients with malignancy [15–17] and only two recent prospective studies concerned cancer patients [18, 19]. No study has ever analyzed the characteristics and outcome of infection in patients with solid tumor or hematological malignancy developing candidemia and the impact of their hospitalization in intensive care unit (ICU) [20].

We launched in 2002 a large prospective hospital-based surveillance program on patients developing candidemia in the Paris area and recently reported the characteristics of patients hospitalized in ICU [9] and of those who developed fungemia due to rare yeasts [21]. The goal of the present study was to characterize over more than a decade *Candida* spp. distribution and prognostic factors according to underlying malignancy and ICU hospitalization. We also determined if the context associated with non-*albicans* candidemia was suggestive enough to help the clinician with the first therapeutic choice.

Materials and methods

Population studied and isolates characterization

A sustainable active surveillance program on yeast fungemia (YEASTS program) was implemented with participation of 26 short-stay university hospitals in the Paris area. All blood cultures positive with yeasts were notified, with data completed on a standardized form, on a secured website. All isolates were sent to the French National Reference Center for Invasive Mycoses and Antifungals (NRCMA). There, purity and identification were assessed [22] and in vitro susceptibility testing performed according to the EUCAST procedure [23]. The current analysis concerns the incident episodes of candidemia recorded in patients aged at least 15 years old between October 2002 and December 2014, and due to *C. albicans*, *C. glabrata*, *C. tropicalis*, *C. parapsilosis* complex that includes *C. metapsilosis* and *C. orthopsilosis* (hereafter named *C. parapsilosis*), *C. krusei* (current name *Pichia kudriavzevii*), and *C. kefyr* (current name *Kluyveromyces marxianus*). Single and mixed (>1 species) infections were considered.

Definitions

The date of candidemia was that of blood sampling (day 0). Patients were assigned to one of three groups: hematological malignancy, solid tumor (“oncology”), or “no malignancy”. Surgery and antifungal preexposure

(whatever dosage and duration) occurring within 30 days prior to candidemia were recorded. First-line antifungal therapy was analyzed only for patients for whom the positivity of the blood culture was known before death and was categorized into four groups: “fluconazole”, “echinocandins”, “other treatments” (all other antifungals and drug combinations), and “no antifungals”. Antifungal drug resistance was defined as minimum inhibitory concentration (MIC) ≥ 8 mg/L [24] for fluconazole and MIC >0.25 mg/L for caspofungin [25].

Statistical analysis

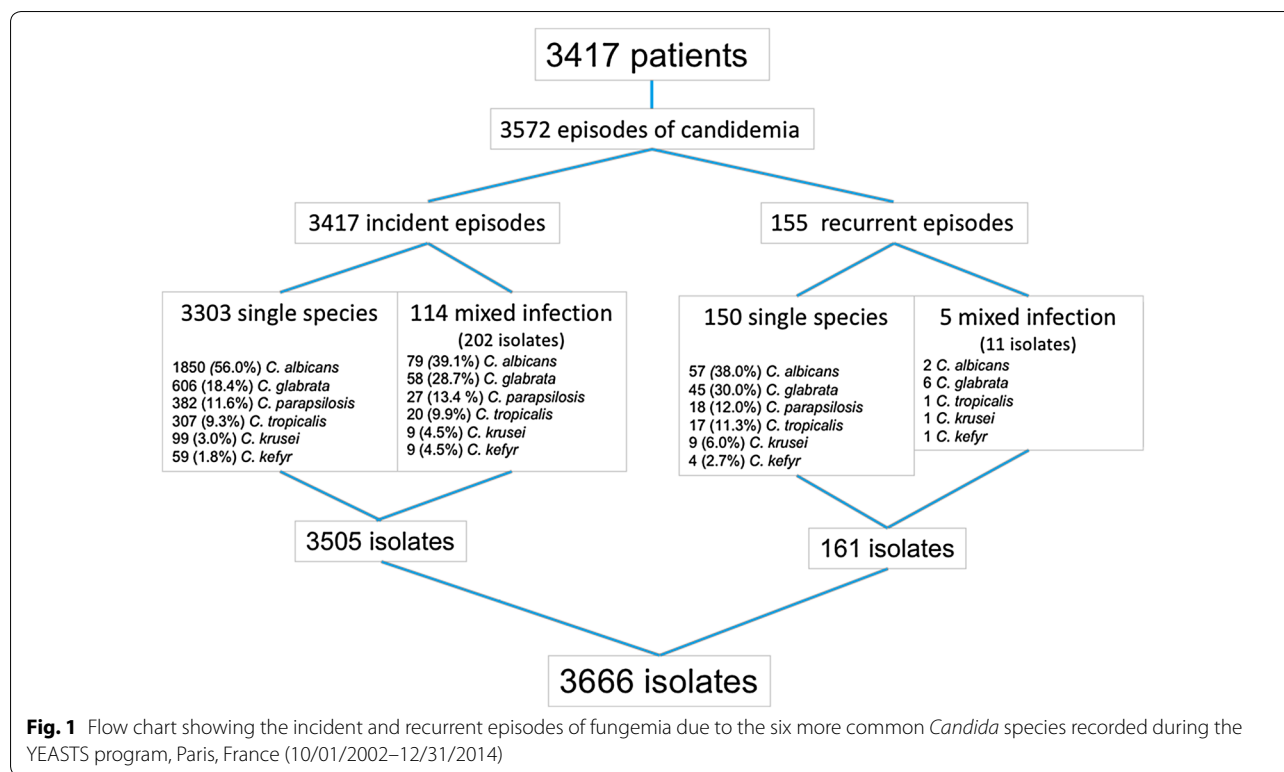
Univariate analysis was based on Chi2 or Fisher’s exact test when needed for discrete variables. Kruskal–Wallis test was used to compare means for groups with unequal variances. Chi2 test for trends was used to determine trends over time. In order to identify risks factors for fungemia due to non-*albicans Candida* species, a multinomial regression analysis was performed that analyzed parameters suggesting infection by a given species or by multiple species based on information available at the time of the positive blood culture. The most common species, i.e., *C. albicans*, was used as reference to avoid blurring the picture by changing the reference for each species. All baseline variables representing pre-existing conditions before fungemia were first included in a full model and only risk factors significantly associated ($p < 0.05$) with at least one species were kept in the final model adjusted on the year of fungemia.

To identify risk factors associated with death (crude death rate at day 30 or day 8), backward stepwise logistic regression models adjusted for the hospital and the year of inclusion were used for all patients and the three groups. First, non-colinear covariates with a p value under 0.25 in the univariate analysis were simultaneously entered into the models and then removed one by one until all of the covariates remaining in the reduced models had a p value under 0.05. Survivals were compared by the logrank test. Data were analyzed using Stata Statistical Software (version 12.0; College Station, TX).

Results

Characteristics of patients with candidemia according to the presence of malignancy and/or hospitalization in ICU

A total of 3417 adults were diagnosed with candidemia, for a total of 3572 episodes (Fig. 1). Almost half (47.2%) were hospitalized in ICU (Table 1). The 586 hematological malignancies consisted mainly of lymphoma (41.8%) and acute leukemia (AL, 33.5%). Allogeneic hematopoietic cell transplantation (HSCT, 10.9%) and graft versus host disease (5.1%) were recorded in hematology. The 1164 solid tumors involved the digestive (45.7%),



genital (12.3%), or urinary (8.9%) tract, or the ear, nose, and throat area (11.0%). Almost half (46.5%) of the 1667 patients with no malignancy had recent surgery involving the digestive tract (364/775, 46.9%) or cardiovascular invasive procedures (200/775, 25.8%), and the majority had a central venous catheter (64.6%). Hospitalization in ICU was significantly more frequent in patients with no malignancy (1080/1667, 64.8%) compared to oncology (335/1164, 28.8%) or hematology (199/586, 34.0%) patients ($p < 0.0001$). Recent surgery was overall significantly more frequently recorded in ICU vs. outside ICU (Tables 1, S1), especially for patients with lymphoma (Table S2) and those with digestive tumors (Table S3).

The most frequent first-line treatment was fluconazole (51.2%) or echinocandin (29.7%) with major differences according to the underlying disease and stay in ICU (Tables 1, S1–S3). Prescriptions were similar in vs. outside ICU for hematology patients but not in others. The proportion of patients who received no antifungal drug was similar in the three groups whether in or outside ICU.

Species distribution and impact of ICU hospitalization and underlying disease

Of the 3666 isolates recovered, 737 (20.1%) were considered resistant to fluconazole. The vast majority (89%) was composed of *C. glabrata* (76.1% of them) and

C. krusei (all), and a few isolates of *C. parapsilosis* (7.5%), *C. tropicalis* (8.4%), and *C. albicans* (0.8%). A caspofungin MIC >0.25 $\mu\text{g/mL}$ concerned 211 (6.5%) isolates including 41.5% of the *C. parapsilosis*, and few *C. albicans* and *C. tropicalis* (0.7% each), *C. glabrata* (2.5%), *C. krusei* (2.6%), and *C. kefyr* (1.7%). The proportion of patients preexposed to antifungals was significantly higher in hematology (Table 1), especially those with AL (Table S2), with no impact of ICU hospitalization. In oncology, the proportion of breakthrough infections was low and similar to that recorded in patients with no malignancy. However, oncology patients had twice as many breakthrough infections when in ICU compared to outside ICU, whereas the figures did not change for patients with no malignancy (Table S1).

Mixed infection accounted for 3.3% of all episodes, less frequently in hematology patients (Table 1). Species involved differed significantly ($p < 0.001$) between single and mixed infection, the latter involving predominantly *C. albicans* and *C. glabrata* (Fig. 1). The interval between sampling and blood culture positivity varied significantly with almost 40% of the cultures recovered after more than 3 days for *C. glabrata* compared to more than 40% of the cultures positive in less than 24 h for *C. krusei*, *C. kefyr*, and *C. tropicalis* ($p < 0.0001$, Fig. 3).

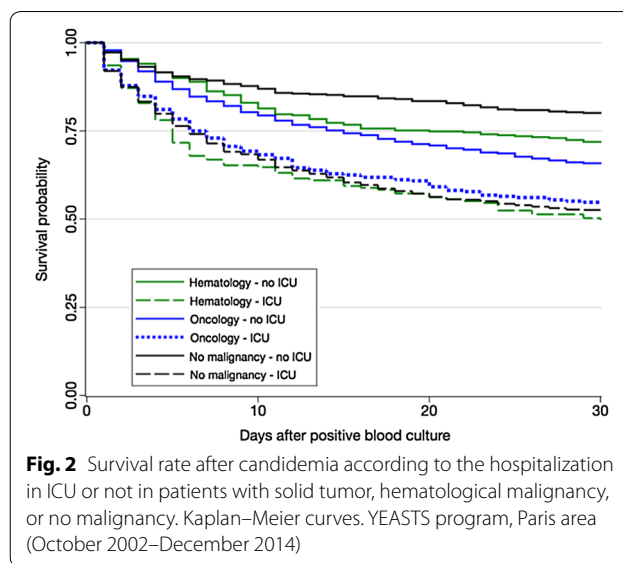
For single infections, species distribution varied significantly with the underlying condition and stay in

ICU (Tables 1, S1–S3). *C. albicans* was the predominant species in all settings, but its proportion was significantly lower in hematology patients compared to those with solid tumor or no malignancy. This decrease was observed specifically in patients with AL, especially in ICU where *C. albicans* accounted for only 29.4% of the species compared to more than 50% in patients with other hematological malignancies including lymphoma. *Candida tropicalis* was almost as frequent as *C. albicans* in ICU patients with AL, and almost twice as much as in the other hematology patients outside ICU. ICU patients with lymphoma had very few *C. parapsilosis* infections compared to those outside ICU, or to AL patients (Table S2), as did ICU patients with non-digestive tumors compared to those with digestive tumors, or to all oncology patients outside ICU (Table S3). Overall, *C. parapsilosis* was less frequent in ICU than outside ICU in both hematology and oncology patients (Table 1). *Candida glabrata* was more frequent in oncology than in hematology patients and those with no malignancy, and even more in ICU. The proportion of *C. glabrata* was significantly higher outside ICU in oncology patients with digestive tumor than in those without, whereas it was similar in ICU. Finally, *C. kefyr* was more frequent in hematology patients, whether in ICU or not (Table 1).

The multinomial analysis uncovered independent factors that were associated with a given species (Table 2). Relative to patients infected by *C. albicans*, those infected by *C. glabrata* were older, had more frequent digestive tumors, and were less likely to have HIV infection. Those infected by *C. krusei* had more frequent non-digestive tumors, AL, or lymphoma, and less frequent surgery. Those infected by *C. parapsilosis* were more often younger and male, had a central venous catheter, and were less likely to be hospitalized in ICU or to have HIV infection. Those with *C. tropicalis* were more often male, more likely suffering from AL or other hematological malignancies. Those with *C. kefyr* were more likely to have AL and be 65–79 years old. Multiple species infection were more likely in the context of intravenous drug addiction, with a trend to be more likely in patients with central venous catheter and non-digestive solid tumors. Finally, preexposure to fluconazole was independently associated with infection by *C. glabrata* and *C. krusei* while preexposure to caspofungin predisposed to infection by *C. glabrata*, *C. krusei*, and *C. parapsilosis*.

Outcome

Survival was significantly decreased in ICU (Fig. 2, logrank test $p < 0.0001$). The crude death rate at day 30 was overall increased in ICU and this was related to an increased rate in patients with no malignancy (Tables 1, S1). The crude day 30 death rate was similar when



hospitalized in ICU and not influenced by the underlying malignancy (Tables S2–S3). The crude death rate at day 30 outside ICU was significantly increased in oncology patients compared to others, and this was related to a significantly increase in delayed death rate (Table 1).

We then analyzed the independent risk factors for death following fungemia due to single species according to its timing and to the groups (Tables 3, S4). For the entire population and each group, the lack of antifungal drug prescription and hospitalization in ICU (the latter not for early death in hematology and oncology patients) were identified as risk factors for death. The odds of death at day 30 was increased in oncology patients compared to patients with no malignancy. Compared to *C. albicans*, *C. glabrata* and *C. parapsilosis* were associated with a decreased risk of day 8 and day 30 deaths (all patients, oncology patients), while only *C. parapsilosis* was in patients with no malignancy (day 8 and day 30). Of note, the risk of early death was 3.07 ($p = 0.052$) for *C. kefyr* infection in oncology patients. The species had no influence on the risk of death for hematology patients. Recent surgery was associated with a decreased risk of day 8 (all patients) and day 30 death (all patients, oncology, no malignancy), while preexposure to echinocandins was associated with an increased risk of death in patients with no malignancy.

Trends over a decade

There was no significant trend over time for the major characteristics of the patients, including the proportion of older patients, lymphoma, and HSCT among the hematological malignancies, or of digestive origin among the solid tumors. Preexposure to antifungals did

Table 1 Comparison of major characteristics according to hospitalization outside ($n = 1803$) or in ($n = 1614$) intensive care unit (ICU) in three major populations (hematological malignancy, solid tumor, or no malignancy) of adult patients with incident candidemia due to common species (YEASTS program, Paris area, Oct 2002–Dec 2014)

	Outside ICU				In ICU			
	Hematology ($n = 387$)	Oncology ($n = 829$)	No malignancy ($n = 587$)	p	Hematology ($n = 199$)	Oncology (335)	No malignancy ($n = 1080$)	p
Age (mean \pm SD)	54 \pm 18	63 \pm 14	60 \pm 21	0.0001	57 \pm 16	64 \pm 13	59 \pm 17	0.0001
Male gender	217 (56.1%)	496 (59.8%)	347 (59.1%)	0.455	133 (56.8%)	209 (62.4%)	652 (60.4%)	0.214
Recent surgery (<30 days)	20 (5.2%)	295 (35.6%)	246 (41.9%)	<0.0001	20 (10.1%)	194 (57.9%)	529 (49.0%)	<0.0001
Central venous catheter	329 (85.0%)	657 (79.3%)	269 (45.8%)	<0.0001	165 (82.9%)	268 (80.0%)	808 (74.8%)	0.014
Previous antifungal treatment	72 (18.6%)	39 (4.7%)	41 (7.0%)	<0.0001	49 (24.6%)	32 (9.6%)	96 (8.9%)	<0.0001
Fluconazole	22 (5.7%)	30 (3.6%)	25 (4.3%)	0.252	19 (9.6%)	20 (6.0%)	58 (5.4%)	0.075
Echinocandins	30 (7.8%)	6 (0.7%)	8 (1.4%)	<0.0001	17 (8.5%)	7 (2.1%)	22 (2.0%)	<0.0001
Type of infection								
Single pathogen	($n = 382$)	($n = 789$)	($n = 568$)		($n = 195$)	($n = 321$)	($n = 1048$)	
<i>C. albicans</i>	187 (49.0%)	444 (56.3%)	339 (59.7%)	0.005	97 (49.7%)	179 (55.8%)	604 (57.6%)	0.122
<i>C. glabrata</i>	42 (11.0%)	156 (19.8%)	97 (17.1%)	0.001	32 (16.4%)	79 (24.6%)	200 (19.1%)	0.041
<i>C. parapsilosis</i>	64 (16.8%)	91 (11.5%)	78 (13.7%)	0.047	14 (7.2%)	22 (6.9%)	113 (10.8%)	0.054
<i>C. tropicalis</i>	54 (14.1%)	62 (7.9%)	44 (7.8%)	0.001	34 (17.4%)	20 (6.2%)	93 (8.9%)	<0.0001
<i>C. krusei</i>	20 (5.2%)	24 (3.0%)	7 (1.2%)	0.002	10 (5.1%)	14 (4.4%)	24 (2.3%)	0.035
<i>C. kefyr</i>	15 (9.9%)	12 (1.5%)	3 (0.5%)	<0.0001	8 (4.1%)	7 (2.2%)	14 (1.3%)	0.028
Multiple pathogens	5 (1.3%)	40 (4.8%)	19 (3.2%)	0.007	4 (2.0%)	14 (4.2%)	32 (3.0%)	0.341
First-line treatment after diagnosis	($n = 348$)	($n = 709$)	($n = 275$)		($n = 111$)	($n = 265$)	($n = 809$)	
Fluconazole	104 (29.9%)	460 (64.9%)	275 (58.9%)	<0.0001	45 (28.5%)	121 (49.6%)	411 (50.8%)	<0.0001
Echinocandins	144 (41.4%)	135 (19.0%)	107 (22.9%)	<0.0001	67 (42.4%)	86 (35.3%)	273 (33.8%)	0.114
Others (including combination)	74 (21.3%)	52 (7.3%)	53 (11.4%)	<0.0001	36 (22.8%)	27 (11.1%)	75 (9.3%)	<0.0001
No treatment	26 (4.5%)	62 (8.7%)	32 (6.9%)	0.475	10 (6.3%)	10 (4.1%)	50 (6.2%)	0.451
Death rate ^a								
Overall death at day 30	111/377(29.4%)	265/760 (34.9%)	119/529 (22.5%)	<0.0001	98/191 (51.3%)	150/312 (48.1%)	524/1036 (50.6%)	0.699
Early death ($<$ day 8) ^b	57/376 (15.2%)	130/757 (17.2%)	68/525 (13.0%)	0.119	65/190 (34.2%)	94/310 (30.3%)	334/1030 (32.4%)	0.645
Late death (between days 8–30)	53/376 (14.1%)	132/757 (17.4%)	47/525 (9.0%)	<0.0001	32/190 (16.8%)	54/310 (17.4%)	184/1030 (17.9%)	0.937

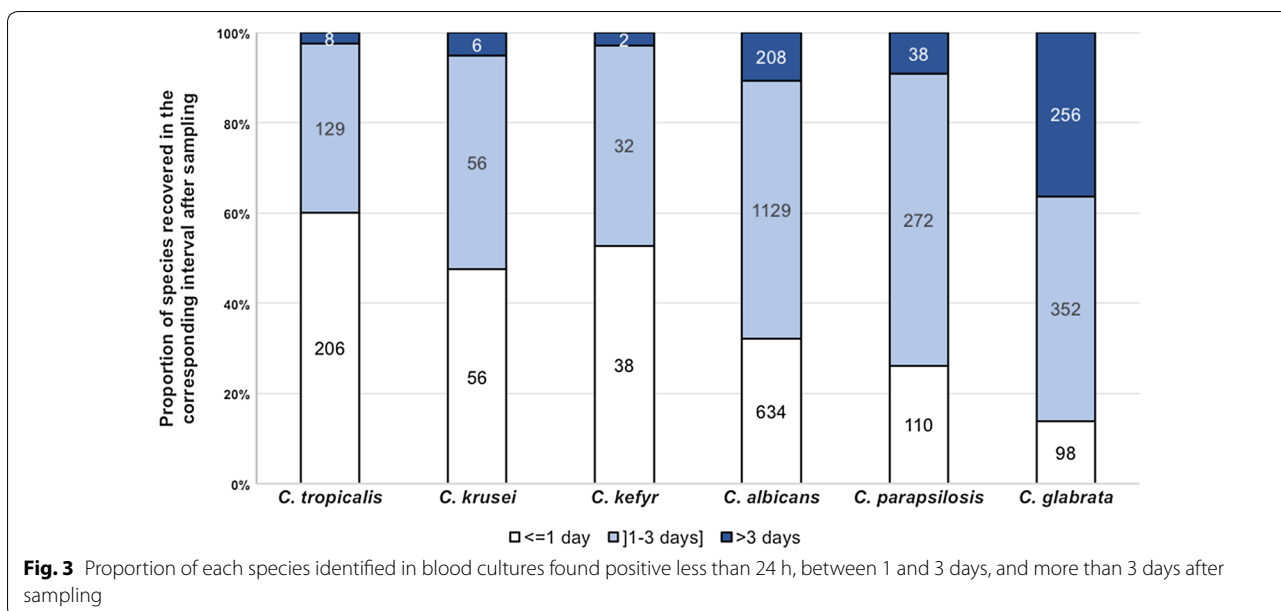
Data are mean \pm SD or n/N (%)—denominator is specified when data are missing

^a Denominator represents the number of patients for whom the positivity of the blood culture was known before death and/or for whom the information about treatment was recorded

^b Precise date of death was missing, preventing definition of “early death” or “late death” in the corresponding patients

not vary for fluconazole, whereas preexposure to echinocandins significantly increased in the global population, and in the three groups, but only in ICU (chi² for trends, $p = 0.015$ for hematology, $p = 0.022$ for oncology, and $p = 0.0395$ for no malignancy). The proportion of *C. parapsilosis* significantly decreased in patients with solid tumor (from 15.4% to 5.6%, $p = 0.026$). There was no increase in the proportion of resistant isolates

among those of species intrinsically susceptible to fluconazole or caspofungin. After candidemia diagnosis, fluconazole first-line prescription decreased (from 59.8% to 29.8%, $p < 0.0001$), while echinocandin first-line therapy increased (from 4.9% to 57.6%, $p < 0.0001$), with the same trends observed when analyzing specifically the three groups. Finally, there was no trend in crude mortality among hematology patients in or outside ICU. There



was a significant trend towards an increase in day 30 (from 18.2% to 58.3%, $p = 0.0321$) and day 8 (from 9.1% to 41.7%, $p = 0.0047$) deaths among oncology patients in ICU, but not outside ICU, and no trend observed among patients with no malignancy.

Discussion

We used a prospective multicentric hospital-based surveillance program to analyze whether fungemia due to common *Candida* species differed depending on the underlying disease and what the impact of ICU hospitalization was. Malignancies currently represent approximately 35% of underlying diseases during candidemia [7, 26] lower than what we found (50.5%). Candidemia represents approximately 30% of invasive fungal infections in hematology patients [27], mostly in those with AL [28, 29], whereas a predominance of lymphoma was observed here. The incidence of fungemia (90% candidemia) is reported at 0.23%/145,030 admissions in 13 European cancer centers [19] and at 0.14% in nine hematology centers in Greece [18]. In France, an incidence of 2.5/100,000 population/year was reported with significant increase in the hematology and oncology populations [30].

Overall, a higher proportion of *C. tropicalis* and *C. krusei* [7, 31–34], *C. kefyr* [35], and sometimes *C. glabrata* [32] fungemia is found in hematology, and multi-species episodes are more frequent in oncology [36]. We and others evidenced the impact of preexposure to antifungals on the distribution of *Candida* species [22, 37, 38], and that duration of fluconazole exposure influences the risk of *C. krusei* fungemia in hematology [6, 39]. We observed less *C. albicans* in hematology, that being related to AL

patients. Less *C. parapsilosis* was observed in ICU, which may reflect more drastic hygiene procedures there. These observations were reinforced by those of the multinomial analysis demonstrating independent factors of being infected by a given *Candida* species.

Crude mortality at day 30 in hematology patients was comparable to former series [18, 40]. It was higher for oncology patients than for the other two groups outside ICU, and hospitalization in ICU increased mortality. One may speculate that the better early outcome found in patients with AL outside ICU may be related to early empiric antifungal therapy administered during prolonged febrile neutropenia. However, crude mortality in ICU was not influenced by underlying disease, which suggests that organ failure(s) was (were) probably the major determinant(s) of outcome. The worrisome trend in the evolution of candidemia mortality that we reported in ICU [9] is explained by the outcome in oncology patients, suggesting that specific actions should now be focused on this currently rising population. One can hypothesize that the oncology patients sent to ICU now have more severe illnesses. Using the multivariate analysis, we showed that the independent risk factors for death varied depending on the underlying disease. In hematology patients, the species recovered from blood culture did not influence death nor did the type of hematological malignancy, while the age and hospitalization in ICU did. In oncology patients and in patients with no malignancy, other factors influenced survival.

Being infected by *C. parapsilosis* or *C. glabrata* was independently associated with a more favorable outcome. In the multinomial analysis, we found that, in comparison

Table 2 Risk factors for fungemia due to *C. glabrata*, *C. parapsilosis*, *C. tropicalis*, *C. krusei*, *C. kefyr* or multiple species in reference to fungemia due to *C. albicans* ($n = 1850$), multivariate multinomial regression analysis (YEASTS program, Paris area, October 2002–December 2014)

	<i>C. glabrata</i>			<i>C. krusei</i>			<i>C. parapsilosis</i>		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Male sex	0.86	0.71–1.04	0.116	1.37	0.88–2.14	0.163	1.58	1.24–2.01	<0.0001
Age (years)									
<45	1			1			1		
45–64	1.25	0.92–1.70	0.146	0.86	0.09–1.53	0.615	0.67	0.49–0.90	0.007
65–79	1.34	0.98–1.84	0.064	0.68	0.36–1.29	0.238	0.46	0.33–0.65	<0.0001
≥80	1.77	1.23–2.56	0.002	0.69	0.28–1.74	0.436	0.42	0.26–0.67	<0.0001
ICU	1.22	0.99–1.50	0.060	1.43	0.91–2.27	0.122	0.64	0.49–0.82	0.001
Recent surgery (<30 days)	0.94	0.76–1.14	0.516	0.55	0.33–0.92	0.024	0.89	0.69–1.15	0.387
Underlying disease									
No malignancy	1			1			1		
Digestive tumor	1.62	1.24–2.12	<0.0001	1.48	0.70–3.12	0.304	0.79	0.54–1.14	0.206
Other solid tumor	1.01	0.76–1.33	0.948	2.45	1.35–4.45	0.003	0.75	0.53–1.06	0.101
Acute leukemia	1.11	0.66–1.88	0.682	3.36	1.49–7.55	0.003	1.22	0.74–2.00	0.440
Lymphoma	0.81	0.54–1.24	0.338	2.28	1.09–4.76	0.028	0.66	0.41–1.07	0.095
Other hematological malignancy	0.60	0.34–1.06	0.079	1.48	0.53–4.15	0.456	0.78	0.43–1.39	0.394
Central venous catheter	0.88	0.71–1.09	0.244	1.30	0.75–2.26	0.344	1.44	1.08–1.92	0.012
HIV infection	0.55	0.31–0.99	0.046	0.36	0.10–1.27	0.114	0.50	0.27–0.94	0.032
Intravenous drug addiction	1.04	0.34–3.21	0.941	NC			0.36	0.08–1.62	0.183
Preexposure to antifungal drugs									
Fluconazole	2.42	1.63–3.59	<0.0001	6.17	3.44–11.07	<0.0001	1.03	0.58–1.85	0.919
Echinocandins	3.45	1.88–6.33	<0.0001	3.70	1.40–9.80	0.009	5.79	3.22–10.43	<0.0001
	<i>C. tropicalis</i>			<i>C. kefyr</i>			Multiple species		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Male sex	1.51	1.16–1.97	0.002	0.90	0.52–1.55	0.706	0.95	0.64–1.42	0.812
Age (years)									
<45	1			1			1		
45–64	1.32	0.91–1.93	0.143	1.84	0.72–4.73	0.201	1.01	0.54–1.89	0.963
65–79	1.14	0.95–2.10	0.085	3.18	1.24–8.16	0.016	1.11	0.58–2.12	0.754
≥80	0.99	0.58–1.71	0.982	0.77	0.15–4.07	0.762	1.51	0.70–3.24	0.289
ICU	1.08	0.82–1.41	0.594	1.56	0.88–2.78	0.132	0.96	0.62–1.48	0.839
Recent surgery (<30 days)	0.83	0.62–1.10	0.200	0.83	0.43–1.58	0.567	0.96	0.63–1.47	0.867
Underlying disease									
No malignancy	1			1			1		
Digestive tumor	0.73	0.47–1.14	0.169	1.93	0.82–4.58	0.134	1.52	0.85–2.69	0.155
Other solid tumor	0.98	0.68–1.43	0.936	1.63	0.71–3.76	0.248	1.70	1.00–2.90	0.051
Acute leukemia	4.16	2.58–6.70	<0.0001	12.36	5.15–29.64	<0.0001	0.82	0.24–2.83	0.753
Lymphoma	1.28	0.79–2.07	0.318	2.55	0.93–7.00	0.069	0.14	0.02–1.04	0.055
Other hematological malignancy	1.71	1.01–3.06	0.044	1.31	0.28–6.04	0.732	1.25	0.46–3.36	0.663
Central venous catheter	1.03	0.77–1.39	0.822	0.75	0.40–1.41	0.373	1.66	1.00–2.76	0.052
HIV infection	0.95	0.51–1.75	0.857	0.46	0.59–3.61	0.461	0.82	0.27–2.50	0.730
Intravenous drug addiction	1.74	0.56–5.41	0.341	NC			8.31	2.82–24.49	<0.0001
Preexposure to antifungal drugs									
Fluconazole	1.14	0.63–2.08	0.668	1.95	0.67–5.76	0.223	0.50	0.12–2.08	0.340
Echinocandins	0.33	0.08–1.43	0.137	2.74	0.75–10.09	0.129	1.59	0.35–7.22	0.551

OR adjusted odd ratio for year, 95% CI odd ratio 95% confidence interval, NC non-calculable

Table 3 Independent factors associated with death before day 8 or before day 30 in all adult patients with incident episode of fungemia due to single isolate of common *Candida* species (YEATS program, Paris area, 2002–2014)

	Death before day 8 ^a			Death before day 30 ^b			
	OR ^c	95% CI	<i>p</i>	OR ^c	95% CI	<i>p</i>	
Age category (years)							
<45	1			1			
45–64	1.39	0.94–2.05	0.101	0.0073	1.59	1.20–2.09	0.001
65–79	1.76	1.18–2.62	0.005		2.13	1.60–2.84	<0.0001
≥80	2.11	1.30–3.41	0.002		2.92	2.05–4.15	<0.0001
Hospitalization in ICU	2.39	1.84–3.12	<0.0001		2.47	2.03–3.01	<0.0001
Recent surgery (≤30 days)	0.75	0.57–0.97	0.031		0.66	0.54–0.80	<0.0001
Underlying disease							
No malignancy					1		
Digestive tumor					1.42	1.08–1.85	0.012
Non-digestive tumor					1.42	1.10–1.84	0.007
Acute leukemia					1.06	0.70–1.62	0.773
Lymphoma					1.25	0.88–1.78	0.214
Other hematological malignancy					0.99	0.64–1.56	0.982
Species recovered from blood culture							
<i>C. albicans</i>					1		
<i>C. glabrata</i>	0.61	0.43–0.89	0.009		0.69	0.54–0.89	0.004
<i>C. parapsilosis</i>	0.30	0.17–0.52	<0.0001	<0.0001	0.49	0.35–0.67	<0.0001
<i>C. tropicalis</i>	1.00	0.67–1.49	0.999		1.00	0.74–1.34	0.987
<i>C. krusei</i>	1.24	0.62–2.44	0.544		1.52	0.91–2.54	0.106
<i>C. kefyr</i>	1.79	0.84–3.80	0.132		1.36	0.74–2.53	0.325
Initial antifungal treatment							
Fluconazole alone					1		
Echinocandin alone	1.02	0.74–1.41	0.909	<0.0001	1.08	0.86–1.36	0.517
Other treatments	0.75	0.46–1.21	0.234		0.84	0.62–1.15	0.283
No antifungal drug	10.96	7.60–15.81	<0.0001		4.94	3.51–6.95	<0.0001

^a Other variables included in full model (with *p* < 0.25 in univariate analysis of early death) not conserved because not significant: allo-BMT, male gender, and type of underlying disease

^b Male gender included in the model but not conserved because not significant

^c OR adjusted for hospital and year (introduced in the model as dummy variable)

to those infected by *C. albicans*, patients with *C. glabrata* infections were more often very old, more often had digestive tumors, and were more often preexposed to echinocandins or fluconazole. These factors were also independently associated with death at day 30. It is possible that the observation by others [41] that patients infected by *C. glabrata* have a higher crude mortality can be related to specificity of the cohort (249 patients with candidemia, 23 infected by *C. glabrata*) studied in several centers in 1992–1994 and to preexposure to antifungals, reflecting more severe cases as already described in the ICU population [42] rather than to the species itself. Evolution of patients' management may indeed at least partially explain the discrepant results.

Recent studies found that antifungal treatment was an independent factor decreasing both early and late death [31] and that echinocandins as first-line therapy reduced

death rate [43]. As already reported [44] and shown here, a major observation is that a constant risk factor for death was the lack of antifungal prescription despite knowledge of the blood culture positivity, with no influence of the initial antifungal choice. In contrast to what is observed in the USA [7, 45], resistance to antifungals is not yet of concern in our area, with overall less than 1% resistance to caspofungin in isolates not identified as *C. parapsilosis*, less than 2.3% resistance to fluconazole in isolates not identified as *C. krusei* or *C. glabrata*, and no increase in these figures over time. Thus, we would recommend early prescription of antifungals based on the most likely species and the known susceptibility profile of its wild-type isolates rather than waiting for the precise identification and a fortiori for MIC determination. It may later be appropriate to switch to a more adapted treatment as recently validated in ICU [46].

The limitations of our database are the restriction to one city, the lack of information regarding severity of illness, the duration of candidemic period, central venous catheter removal [26], lack of consideration of antifungal dosing issues [47–49], and delayed initiation of adequate antifungal therapy [47, 50, 51], concomitant mold infections, or bacteremia.

Even if we are fully aware that characteristics of candidemia are highly variable, especially in terms of species distribution, we think that our data are relevant for hematologists, oncologists, and ICU physicians practicing in the Western world. Indeed, characteristics and risk factors for death during candidemia differ in patients with hematological malignancies from those with solid tumors. Furthermore, the odds of infection by a given *Candida* species was influenced not only by host underlying disease but also by hospitalization in ICU and preexposure to antifungal drugs.

Electronic supplementary material

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Compliance with ethical standards

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Ethics committee approval

The research described herein was carried out in compliance with French law and the Declaration of Helsinki (as adopted in 2000), and was approved by the Institut Pasteur institutional review board (IRB #2009-34). Approval of the

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