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Worrisome trends in incidence and mortality of candidemia in intensive care units (Paris area, 2002–2010)

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The group's members are listed in the Appendix.

Take-home message: Neither the availability of new antifungals nor the publication of numerous guidelines prevented an increase of *C. albicans* candidemia and death in ICU patients between 2002 and 2010 in the Paris area.

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Abstract *Purpose:* To analyze trends in incidence and mortality of candidemia in intensive care units (ICUs) vs. non-ICU hospitalized patients and to determine risk factors for infection by specific species and for death. *Methods:* Active hospital-based surveillance program of incident episodes of candidemia due to common species in 24 tertiary care hospitals in the Paris area, France between October 2002 and September 2010. *Results:* Among 2,507 adult cases included, 2,571 *Candida* isolates were collected and species were *C. albicans* (56 %), *C. glabrata* (18.6 %), *C. parapsilosis* (11.5 %), *C. tropicalis* (9.3 %), *C. krusei* (2.9 %), and *C. kefyr* (1.8 %). Candidemia occurred in ICU in 1,206 patients (48.1 %). When comparing ICU vs. non-ICU patients, the former had significantly more frequent surgery during the past 30 days, were more often preexposed to fluconazole and treated with echinocandin, and were less frequently infected with *C. parapsilosis*. Risk factors and age remained unchanged during the study period. A significant increased incidence in the overall population and ICU was found. The odds of being infected with a given species in ICU was influenced by risk factors and preexposure to fluconazole and caspofungin. Echinocandins initial therapy increased over time in ICU (4.6 % first year of study, to 48.5 % last year of study, $p < 0.0001$). ICU patients had a higher day-30 death rate than non-ICU patients (odds ratio [OR] 2.12; 95 % confidence interval [CI] 1.66–2.72; $p < 0.0001$). The day-30 and early (<day 8) death rates increased over time in ICU (from 41.5 % the first to 56.9 % the last year of study ($p = 0.001$) and 28.7–38.8 % ($p = 0.0292$), respectively). Independent risk factors for day-30 death in ICU were age, arterial catheter, *Candida* species, preexposure to caspofungin, and lack of antifungal therapy at the time of blood cultures results ($p < 0.05$). *Conclusions:* The availability of new antifungals and the publication of numerous guidelines did not

prevent an increase of candidemia and death in ICU patients in the Paris area.

Keywords Candida · Echinocandins · Fluconazole · Hematological malignancy · Intensive care unit · Epidemiology · Risk factors · Non-*albicans* species

Introduction

Candidemia currently represents up to 5.6–10 % of nosocomial bloodstream infections [1–3] with associated mortality and increased length of stay and cost [4]. It is therefore a public health concern everywhere [5]. Intensive care units (ICU) are increasingly involved, with more empiric or preemptive antifungal strategies being implemented in patients deemed at risk [6–8]. Many changes have occurred over the last decade with the availability of echinocandins, the implementation of management guidelines [9, 10], and, at least in some centers, the extended availability of new tools with improved diagnostic performances. Therefore, it is of utmost importance to analyze whether all these (expensive) changes impacted the incidence of candidemia and its associated death.

The analysis of epidemiological trends mainly relies on hospital registers which are often focused on a specific population [11, 12], based on a single center [13], limited to a short period of time [14], or restricted to microbiological data with limited clinical documentation [1]. We launched in 2002 a large prospective hospital-based surveillance program for patients developing candidemia in the Paris area (France). Our expectation was that a large population of patients over a long period of time without selection bias related to the cause of hospitalization cause could unravel some epidemiological shifts, in particular by comparing populations of patients with different underlying diseases. The goals of the study were to describe adult patients with candidemia, to analyze trends in incidence and mortality of candidemia in ICU versus non-ICU hospitalized patients, and to determine risk factors for infection by specific species and risk factors for death.

Materials and methods

Population studied and isolates characterization

A sustainable active surveillance program on yeast fungemia (YEASTS program) was implemented in October 2002 with participation of 24 short-stay university hospitals in the Paris area. All blood cultures positive with yeasts were reported by the participants, with clinical and epidemiological data (age, recent surgery within 30 days, cancer, hematological malignancy, transplantation, HIV serostatus, immunosuppressive therapy, intravenous drug addiction, invasive procedures, and recent administration of antifungals 30 days prior to candidemia), filled on a standardized form, on a secured website and all isolates were sent to the French National Reference Center for Invasive Mycoses and Antifungals (NRCMA). There, isolates were checked for purity and identified to the species level using carbon assimilation profiles (ID32C, bioMérieux) or nucleotide sequencing as needed [15]. Because of their low proportion, *C. orthopsilosis* and *C. metapsilosis* were included with *C. parapsilosis* in a "*C. parapsilosis*" complex. The current analysis concerns the incident episodes of candidemia due to common species (i.e., those accounting for at least 1.5 % of all *Candida* spp.) recorded in adults patients (at least 15 years old) between October 2002 and September 2010.

Definitions

The date of candidemia was the day of blood sampling (day 0). An incident case corresponded to the first episode of positive blood culture. A recurrent episode was considered in case of isolation of the same species at least 10 days after the initial isolation or of a new species with no time limit. To avoid autocorrelation, only incident episodes were considered in the subsequent analysis. Both single (one *Candida* species) and mixed (more than one *Candida* species) infections were considered. ICU patients were those hospitalized in ICU at the time of sampling and we individualized candidemia episodes occurring within 48 h of ICU stay vs. those not. 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" (aggregating all three drugs available), "other treatments" (all other antifungal drugs and drug combinations), and "no treatment" (no antifungal therapy).

Statistical analysis

Incidence rates were calculated per 10,000 hospitalization days using annual hospital activity data available since 2004 (SAE administrative data, Ministry of Health, DREES). Univariate analysis was based on χ^2 or Fisher's exact test when needed for discrete variables. χ^2 test for trends was used to determine trends over time in crude mortality and treatments rates, and incidences of candidemia. In order to identify risks factors for fungemia due

to non-*albicans Candida* species, a multivariate multinomial regression analysis was performed using *C. albicans* as reference. The year of inclusion and all baseline variables representing preexisting conditions of patients before fungemia were introduced into the model. To identify risk factors associated with death in ICU during fungemia (crude death rate), a mixed logistic regression model was used, to account for dependency of measurement within hospitals and adjusted on the basis of the year of inclusion. Three models were built for the three outcomes evaluated, i.e., overall death (at day 30), early death (before day 8), and delayed death (between day 8 and day 30). All covariates associated with the outcome in univariate analysis with a p value less than 0.25 were introduced into the multivariate model to identify covariates significantly associated with the outcome ($p < 0.05$) using a backward stepwise procedure. Survivals were compared by the logrank test. Data were analyzed using Stata Statistical Software (version 12.0; College Station, TX).

Results

Characteristics of the population

During the study period, 2,507 patients had candidemia including 95 who developed 122 recurrences. A total of 2,571 isolates were recovered during the incident episodes related mainly to single species (2,424/2,571, 94.3 %). Candidemia occurred in ICU in 48.1 % of the cases and major characteristics of ICU hospitalized patients are provided in Table 1. Briefly, the majority were male (62 %), with 518/1,206 (43.0 %) patients aged at least 65 years. Surgery within the past 30 days was found in 48.1 % of the patients with digestive tract and cardiovascular surgery representing 45.2 % and 20.7 % of surgical procedures, respectively. *C. albicans* was involved in 57.1 % of the cases. In ICU, 19.8 % (96/484) of patients developed candidemia within 48 h following admission. Their characteristics did not differ from those developing candidemia later on in terms of age, sex, allogeneic HSCT, transplantation, hematological malignancy, arterial catheter, prior exposure to antifungals, species, and outcome.

When comparing ICU vs. non-ICU patients, the former had more frequent recent surgery and central venous and arterial catheters, were more often preexposed to fluconazole and treated with echinocandin, and were less frequently infected with *C. parapsilosis*.

Outcome in patients with single species candidemia

ICU patients had a higher overall death rate (51 %) than non-ICU patients (30.7 %) ($p < 0.001$) and this was also true when considering early deaths (before day 8) (Table 1). In ICU, the survival rate of patients infected with *C. parapsilosis* was higher (logrank test $p = 0.0005$) and that of patients infected with *C. krusei* (logrank test $p = 0.0148$) or *C. kefyr* (logrank test $p = 0.0267$) lower compared to patients infected by *C. albicans* (Fig. 1a). Outside ICU, the survival rate of patients infected with *C. parapsilosis* was also higher (logrank test $p = 0.0018$) and that of patients infected with *C. krusei* (logrank test $p = 0.0267$) also lower compared to patients infected by *C. albicans* (Fig. 1b). All first-line antifungal treatments (fluconazole, echinocandins, or others) were associated with a similar survival (data not shown). The odds of death in ICU was then analyzed according to its timing in patients with single infections using logistic regression analysis (Table 2). Independent risk factors for death at 30 days were age, presence of arterial catheter, infection by *C. kefyr*, preexposure to caspofungin, and lack of antifungal therapy given in those for whom the positivity of the blood culture was known before death and/or for whom the information about treatment was recorded ($p < 0.05$). In contrast, recent surgery and infection caused by *C. parapsilosis* or *C. glabrata* were protective. The factor associated with the highest odds of death (11.04) was lack of initial antifungal treatment when considering early death before day 8.

Factors associated with infection by non-*albicans Candida* species or by multiple species

Since infections due to some non-*albicans* species are associated with specific management recommendations, we analyzed by multinomial regression analysis the odds of being infected with a given species in comparison with that of being infected with *C. albicans* in ICU hospitalized patients (Table 3). The odds of infection by *C. glabrata* were increased in older patients and in case of recent exposure to fluconazole or caspofungin. The odds of infection by *C. parapsilosis* were increased in patients with recent caspofungin exposure. The odds of being infected by *C. krusei* were reduced in case of recent surgery, and increased in patients with solid tumor or solid organ transplantation, and recent exposure to fluconazole or caspofungin. The odds associated with *C. tropicalis* candidemia were the presence of hematological disorders and recent exposure to fluconazole while the odds were reduced in case of solid tumor. *C. kefyr* was associated with recent exposure to caspofungin. Finally, odds associated with candidemia due to multiple species were caspofungin preexposure and active intravenous drug addiction.

Trends over the last decade

The incidence of candidemia in the overall population and in ICU patients increased overtime ($p = 0.01$ and

Table 1 Comparison of major characteristics according to hospitalization in intensive care unit (ICU) or not for adult patients with incident candidemia due to common species (YEASTS program, Paris area, October 2002 to September 2010)

Conditions	Hospitalization wards, *n* (%)			
	ICU ($N = 1{,}206$)	Outside ICU ($N = 1{,}301$)	p	
Male gender	748 (62.0 %)	763 (58.7 %)	0.0844	
Age categories				
<45 years	219 (18.2 %)	241 (18.5 %)		0.9320
45–64 years	469 (38.9 %)	499 (38.4 %)		
65–79 years	384 (31.8 %)	407 (31.3 %)		
≥80 years	134 (11.1 %)	154 (11.9 %)		
Age mean ± SD	60 ± 17	60 ± 17	0.7482	
Central venous catheter	936 (77.6 %)	919 (70.6 %)	<0.0001	
Arterial catheter	401 (33.3 %)	40 (3.1 %)	<0.0001	
Surgery within 30 days	580 (48.1 %)	389 (29.9 %)	<0.0001	
Digestive tract[a]	262/580 (45.2 %)	190/389 (48.8 %)		<0.0001
Cardiovascular	120/580 (20.7 %)	20/389 (5.1 %)		
Orthopedic	45/580 (7.8 %)	56/389 (14.4 %)		
Urinary tract	23/580 (3.4 %)	46/389 (11.8 %)		
Gynecologic	7/580 (1.2 %)	12/389 (3.1 %)		
Neurosurgery	13/580 (2.4 %)	5/389 (1.3 %)		
Unspecified/other sites	71/580 (12.2 %)	40/389 (10.3 %)		
Multiple sites[b]	39/580 (6.7 %)	20/389 (5.1 %)		
Malignancy				
No malignancy	828 (68.7 %)	418 (32.1 %)		<0.0001
Hematological malignancy	137 (11.4 %)	285 (21.9 %)		
Solid tumor	241 (20.0 %)	598 (46.0 %)		
Solid organ transplantation	127 (10.5 %)	35 (2.7 %)	<0.0001	
HIV infection	51 (4.3 %)	47 (3.8 %)	0.4372	
Allo HSCT/BMT	18 (1.5 %)	28 (2.2 %)	0.2189	
Intravenous drug addiction	9 (0.75 %)	17 (1.3 %)	0.1664	
Previous antifungal treatment				
All	128 (10.6 %)	109 (8.4 %)	0.0559	
Fluconazole	79 (6.6 %)	56 (4.3 %)	0.0127	
Caspofungin	25 (2.1 %)	28 (2.2 %)	0.8904	
Type of infection				
Single pathogen				
C. albicans	668/1169 (57.1 %)	689/1255 (54.9 %)	0.2664	0.0167
C. glabrata	234/1,169 (20.0 %)	216/1,255 (17.2 %)	0.0758	
C. parapsilosis	106/1,169 (9.1 %)	173/1,255 (13.8 %)	0.0003	
C. tropicalis	106/1,169 (9.1 %)	119/1,255 (9.5 %)	0.7253	
C. krusei	35/1,169 (3.0 %)	35/1,255 (2.8 %)	0.7631	
C. kefyr	20/1,169 (1.7 %)	23/1,255 (1.8 %)	0.8204	
Multiple pathogens	37 (3.1 %)	46 (3.5 %)	0.5131	
First-line treatment after diagnosis[b]				
Fluconazole	506/914 (55.4 %)	665/1,111 (59.9 %)	0.0415	0.0013
Echinocandins	239/914 (26.2 %)	212/1,111 (19.1 %)	0.0001	
Others (including combination)	115/914 (12.6 %)	148/1,111 (13.3 %)	0.6224	
No treatment	54/914 (5.9 %)	86/1,111 (7.7 %)	0.1057	
Death rate				
Overall death at day 30	591/1,158 (51.0 %)	371/1,210 (30.7 %)	<0.0001	
Before day 8	367/1,151 (31.9 %)	182/1,204 (15.1 %)	<0.0001	
Proportional mortality day 8/day 30	367/584 (62.8 %)	182/365 (49.9 %)	<0.0001	
Between days 8 and 30	217/1,151 (18.9 %)	183/1,204 (15.2 %)	0.0183	
Proportional mortality day 8–30/day 30	217/584 (37.2 %)	183/365 (50.1 %)	<0.0001	

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

HSCT hematopoietic stem cell transplant, *BMT* bone marrow transplantation

[a] Digestive tract surgery includes gastroesophageal, hepatobiliary, colorectal, and pancreatic surgical procedures

[b] 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

$p = 0.0001$, respectively) (Fig. 2). In the overall population, *C. albicans* and *C. glabrata* were responsible for this increase (from 0.55 in 2004 to 0.64 episodes/10,000 days of hospitalization in 2009 ($p = 0.02$) and from 0.16 in 2004 to 0.22 episodes/10,000 days of hospitalization in 2009 ($p = 0.01$), respectively) while the

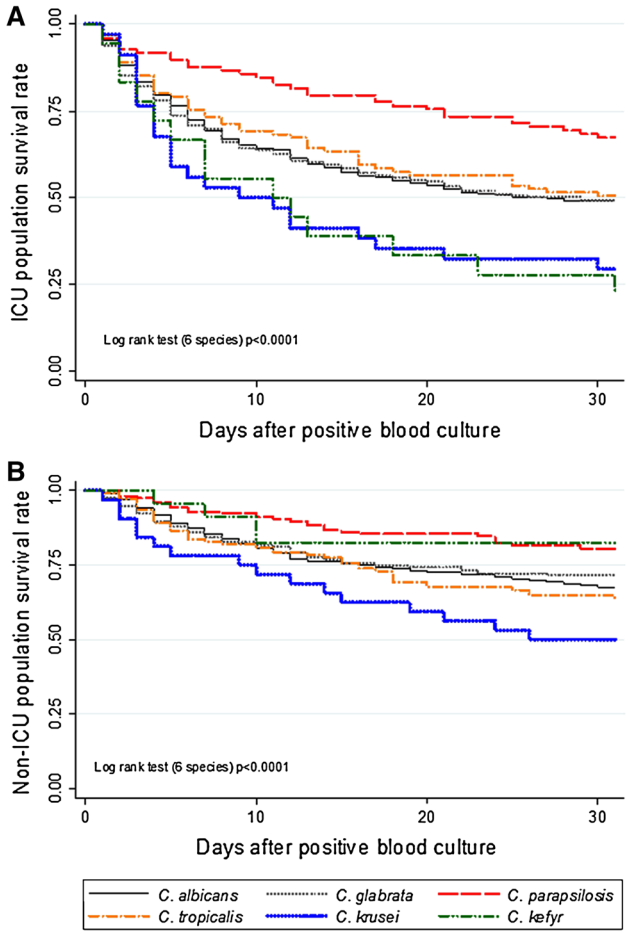

Fig. 1 Kaplan–Meier curves illustrating survival rate after candidemia according to the species involved in case of single infection in ICU **a** and outside ICU **b**. YEASTS program, Paris area (October 2002 to September 2010)

incidence of candidemia due to other species remained unchanged during the study period. In ICU patients only *C. albicans* incidence increased from 4.72 in 2004 to 6.31 episodes/10,000 days of hospitalization in 2009 ($p = 0.005$).

The major characteristics of the patients, including the proportion of older patients, did not change between 2002 and 2010 (data not shown). Preexposure to fluconazole did not change over time, while that of caspofungin increased in ICU patients ($p = 0.0004$, data not shown). In ICU, prescription of fluconazole decreased over time (from 64.8 to 38.8 % in the first and last year of study, respectively, $p < 0.0001$), while that of echinocandins increased over time (from 4.6 to 48.5 % in the first and last year of study, respectively, $p < 0.0001$).

Finally, the overall death rate increased over time in ICU from 42.7 % in 2003 to 53.9 % in 2009 ($p < 0.003$) but remained unchanged in the overall population (Fig. 2).

Discussion

On the basis of our analysis of a population whose characteristics are similar to those found in a recent multicenter study of septic shocks attributable to *Candida* spp. [16], a significant increasing incidence of candidemia was observed together with an increasing mortality rate in ICU. This was observed through a large prospective multicentric hospital-based surveillance program implemented over almost a decade in the Paris area. Even if we are fully aware that the epidemiology of candidemia is highly variable in Europe and elsewhere, these trends are worrisome in the context of expanded antifungal armamentarium, published management guidelines, and better diagnostic tools available at least in large tertiary care centers such as those involved in the present study [17, 18].

Of importance, similar incidence trends for candidemia and even other invasive fungal infections were observed recently using national registries in Europe [14, 19]. Indeed, the epidemiology of candidemia that we described here did not differ drastically from recently published data even if some differences can be noted. The global proportion of *C. albicans* was higher than in two recent North American studies (56 vs. 38–42.1 %) [20, 21]. That of *C. glabrata* was lower here (13.6 %) than in several recent studies reporting at least 20 % of *C. glabrata* among isolates causing fungemia [6, 20, 21]. *C. parapsilosis* ranked second in Spain, Brazil, and Italy and third here [13, 22, 23]. Of note, relative to ICU patients infected with *C. albicans*, those with *C. parapsilosis* were less likely to be hospitalized in ICU, those with *C. tropicalis* were more likely to have hematological disorders and less likely solid tumor, and those with *C. krusei* were more likely to have a solid tumor and solid organ transplantation but less recent surgery.

The increased incidence found here concerned two species (*C. albicans* and *C. glabrata*) at least in the overall population and only *C. albicans* in ICU. A specific increase in *C. glabrata* fungemia was recently reported in the USA, Europe, and Brazil [20, 24, 25]. We have no explanation for the increased incidence of *C. albicans*. We know that species involved can largely be influenced by ecosystems and local management of the patients at risk. In a recent study, 15 % of the patients were preexposed to antifungal, including fluconazole in 64 % and echinocandins in 15 % [7], while in another one, preexposure concerned up to 43.4 % of the patients [21] especially (more than 67 % of the cases) those with breakthrough episodes [12]. Here, preexposure concerned 10.6 % of patients hospitalized in ICU. Preexposure to fluconazole did not change over time, while that of caspofungin increased in ICU. We and others have previously evidenced the impact of prolonged prior fluconazole exposure on the distribution of *Candida* species [15, 24, 26]. Interestingly, in the current multinomial analysis performed in ICU patients with *C. albicans* as the reference, preexposure to fluconazole was an independent factor of infection

Table 2 Risk factors for death in adult patients hospitalized in intensive care unit (ICU) with incident candidemia due to a single isolate (logistic regression), YEASTS program, Paris area, October 2002 to September 2010

	Death before day 30			Death before day 8			Death between day 8 and day 30		
	Adj. OR	95 % CI	*p*	Adj. OR	95 % CI	*p*	Adj. OR	95 % CI	*p*
Male gender							0.71	0.51–0.99	0.043
Age categories									
<45 years	1		0.0001				1		0.0003
45–64 years	1.66	1.09–2.53					2.32	1.38–3.89	
65–79 years	2.49	1.60–3.56					3.19	1.88–5.43	
≥80 years	3.09	1.73–5.49					2.91	1.45–5.83	
Arterial catheter	1.39	1.01–1.92	0.0430				1.47	1.02–2.11	0.0371
Surgery within 30 days	0.62	0.46–0.84	0.0017				0.54	0.39–0.76	0.0004
Species									
C. albicans	1		0.0013	1		0.0031			
C. grabrata	0.65	0.43–0.98		0.58	0.34–1.02				
C. parapsilosis	0.43	0.25–0.76		0.18	0.06–0.52				
C. tropicalis	0.99	0.61–1.63		1.00	0.53–1.86				
C. krusei	1.78	0.71–4.47		1.55	0.57–4.23				
C. kefyr	3.88	1.14–13.26		2.79	0.84–9.21				
Preexposure to caspofungin	3.83	1.29–11.35	0.0153	3.54	1.09–11.53	0.0357			
First-line treatment									
Fluconazole	1		0.0003	1		<0.0001			
Echinocandin	1.23	0.85–1.80		0.98	0.59–1.61				
Other treatment	1.11	0.69–1.79		0.81	0.42–1.56				
No treatment	4.34	2.23–8.45		11.04	5.72–21.30				

Variables included in full model (with $p < 0.25$ in univariate analysis of death): male gender, age, arterial catheter, surgery within 30 days, malignancy, transplantation, preexposure to caspofungin, species, first-line treatment

Adj. OR adjusted odds ratio for hospital and year, *95 % CI* odds ratio 95 % confidence interval, *HSCT* hematopoietic stem cell transplant, *BMT* bone marrow transplantation

with *C. krusei*, *C. tropicalis*, or *C. glabrata*, whereas preexposure to caspofungin was an independent factor of infection with *C. parapsilosis*, *C. krusei, C. kefyr, C. glabrata*, and mixed infections, thereby emphasizing the broader than expected ecological impact of echinocandin exposure [15, 27, 28]. It should also be remembered that in addition to the emergence of potentially more virulent *Candida* species induced by echinocandin exposure such as *C. krusei* and *C. kefyr* found here, the emergence of echinocandin resistance among usually susceptible *Candida* species is also worrisome [29, 30].

Our large database allowed us to focus on trends in death and look for explanations of the increased death rate over time in the overall population and in ICU. The first explanation could be the species involved. Here and in other studies [3, 13, 21, 31], *C. parapsilosis* and *C. krusei*/*C. kefyr* were associated with the lowest and highest death rates, respectively, while others found an increased death rate among patients with *C. tropicalis* or *C. glabrata* fungemia [32, 33]. However, the mortality trends cannot be explained by the evolving distribution of *C. parapsilosis* or *C. krusei/C. kefyr*. Another explanation might have been an increased proportion of elderly patients over time in ICU. However, it remained stable yet high (31.8 and 11.1 % of episodes occurred in patients aged at least 65 years and at least 80 years, respectively) as already noted by others with the highest incidence rates of candidemia in adults over 65 [7]. The death rate is also known to depend on underlying diseases or settings, as found here in ICU patients (51 %) and as already reported [14]. However, although mortality remained stable for the overall population, the most worrying finding is its increase in ICU. Several recent studies reported changes in the case-mix of critically ill patients. Nationwide trends of severe sepsis in the USA showed that from 2000 to 2007, more patients had at least three organ system failures [34]. In an Australian tertiary ICU, there was a significant increase in severity of illness and Charlson comorbidity index of the patients over a 16-year study period [35]. Finally, although we did not capture this information during our large prospective surveillance program, unpublished data from ICUs which participated in the present study indicate that the simplified acute physiology score II score and the percentage of mechanically ventilated patients increased from 37, 42 to 44, and from 41, 49, to 60 % in 2000, 2005, and 2010, respectively [CubRea Network ("Collège des Utilisateurs des Bases de Données en Réanimation"), Ile de France; Biostatistique et Informatique Médicale, Hôpital Ambroise Paré, Boulogne, France]. However, a recent study showed an average annual increase in the incidence of severe sepsis of 13 % between 2004 and 2009 while in-hospital death decreased from 35 to 25.6 % across the 6-year period [36]. In addition, a recent meta-analysis of 36 multicenter severe sepsis trials, with a total of 14,418 participants, found a decreasing mortality of 3.0 % annually (95 % CI, 0.8–5.0 %; $p = 0.009$), decreasing from 46.9 % during years 1991–1995 to 29 % during years 2006–2009 [37]. Thus, it can be speculated that more ICU

Table 3 Risk factors for fungemia in intensive care unit ($N = 1{,}206$) due to *C. glabrata, C. parapsilosis, C. tropicalis, C. krusei, C. kefyr,* or multiple species in reference to fungemia due to *C. albicans*

	C. glabrata			*C. parapsilosis*			*C. tropicalis*		
	Adj. OR[a]	95 % IC[b]	*p*	Adj. OR[a]	95 % IC[b]	*p*	Adj. OR[a]	95 % IC[b]	*p*
Male gender	1.07	0.78–1.48	0.660	1.10	0.71–1.69	0.683	1.27	0.81–1.99	0.294
Age less than 45 years	**1**			**1**			**1**		
Between 45–64 years	1.60	0.96–2.67	0.074	0.77	0.45–1.32	0.340	1.09	0.59–2.02	0.788
Between 65–79 years	2.02	1.19–3.43	0.009	0.55	0.30–1.01	0.055	1.54	0.81–2.90	0.187
80 years and more	2.68	1.43–5.01	0.002	0.73	0.33–1.60	0.428	0.95	0.38–2.38	0.916
Central venous catheter	1.00	0.69–1.45	0.988	1.36	0.79–2.32	0.263	1.25	0.73–2.14	0.413
Arterial catheter	0.90	0.64–1.27	0.545	0.96	0.60–1.53	0.856	0.91	0.56–1.49	0.710
Surgery within 30 days	1.09	0.79–1.52	0.596	1.27	0.82–1.98	0.291	1.01	0.64–1.61	0.957
No malignancy	**1**			**1**			**1**		
Hematological malignancy	1.08	0.63–1.86	0.771	0.57	0.25–2.29	0.179	2.22	1.24–3.99	0.007
Solid tumor	1.09	0.74–1.60	0.658	0.59	0.32–1.10	0.096	0.49	0.25–0.97	0.042
Solid organ transplantation	0.74	0.42–1.31	0.305	0.76	0.38–1.51	0.428	0.75	0.35–1.62	0.469
HIV infection	0.51	0.19–1.39	0.188	1.08	0.39–3.03	0.879	0.92	0.34–2.45	0.861
Intravenous drug addiction	2.01	0.34–11.90	0.444	NC			NC		
Caspofungin pre-exposure	16.63	3.51–78.76	<0.001	17.86	3.27–97.46	0.001	3.42	0.29–39.68	0.326
Fluconazole pre-exposure	4.09	2.26–7.41	<0.001	1.02	0.33–3.09	0.976	3.48	1.63–7.46	0.001
	C. krusei			*C. kefyr*			"Mixed" infections		
	Adj. OR[a]	95 % IC[b]	*p*	Adj. OR[a]	95 % IC[b]	*p*	Adj. OR[a]	95 % IC[b]	*p*
Male gender	1.65	0.74–3.71	0.222	0.74	0.29–1.88	0.532	1.06	0.52–2.19	0.865
Age less than 45 years	**1**			**1**			**1**		
Between 45–64 years	0.73	0.28–1.90	0.513	1.90	0.39–9.38	0.429	1.27	0.39–4.07	0.691
Between 65–79 years	0.88	0.30–2.60	0.811	2.97	0.59–14.86	0.184	1.46	0.43–5.00	0.543
80 years and more	1.43	0.33–6.23	0.632	1.02	0.09–11.91	0.990	4.19	1.15–15.31	0.030
Central venous catheter	0.92	0.39–2.16	0.849	0.80	0.27–2.33	0.677	1.47	0.58–3.70	0.412
Arterial catheter	0.51	0.21–1.24	0.136	1.45	0.52–4.01	0.480	0.92	0.44–1.95	0.832
Surgery within 30 days	0.40	0.17–0.92	0.032	0.58	0.21–1.59	0.291	1.28	0.60–2.71	0.528
No malignancy	**1**			**1**			**1**		
Hematological malignancy	2.07	0.72–5.93	0.177	2.06	0.57–7.40	0.270	1.23	0.33–4.58	0.757
Solid tumor	3.11	1.29–7.49	0.012	1.42	0.47–4.29	0.536	1.68	0.74–3.83	0.215
Solid organ transplantation	3.06	1.13–8.31	0.028	0.54	0.07–4.45	0.569	1.45	0.45–4.64	0.530
HIV infection	1.72	0.42–7.04	0.452	NC			1.19	0.21–6.84	0.848
Intravenous drug addiction	NC			NC			13.71	1.77–106.28	0.012
Caspofungin pre-exposure	51.86	8.44–318.52	<0.001	16.93	1.29–221.63	0.031	12.51	1.05–149.70	0.046
Fluconazole pre-exposure	6.43	2.32–17.83	<0.001	4.33	0.88–21.24	0.071	0.77	0.10–6.02	0.800

Multivariate multinomial regression analysis, YEASTS program, Paris area, October 2002 to September 2010

Adj. OR adjusted odds ratio for year, *95 % CI* odds ratio 95 % confidence interval

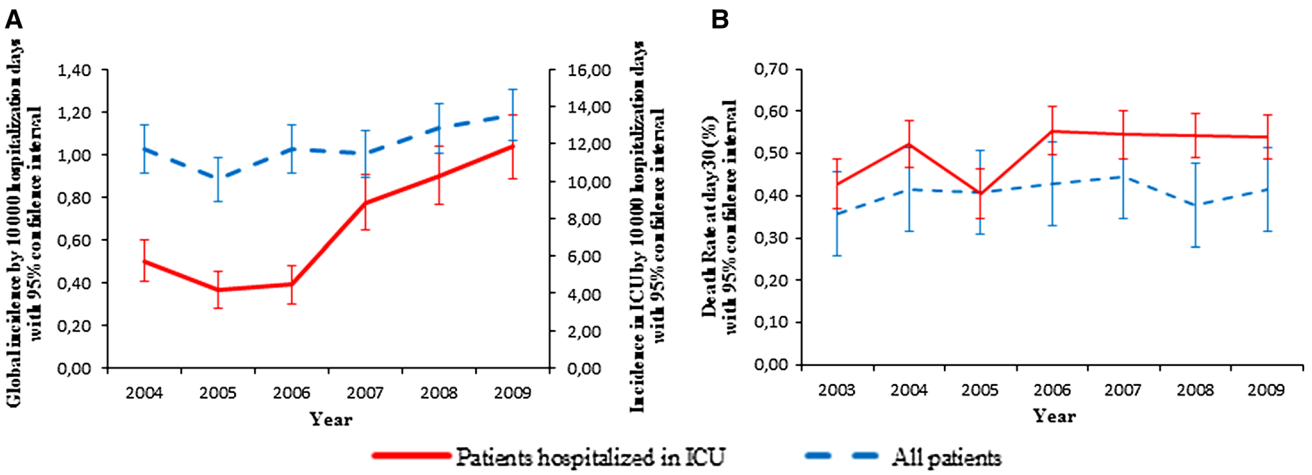

Fig. 2 Trends in the incidence of candidemia (**a**) and in death rate at day 30 (**b**). YEASTS program, Paris area, France. The parameters are analyzed for all patients (*blue line*) and patients hospitalized in ICU (*red line*)

patients now survive from bacterial sepsis and could be further exposed to life-threatening ICU-acquired candidemia.

The lack of overall diminution and a fortiori the increased death rate found in ICU patients are shocking knowing that new antifungals became available and that several guidelines for the management of candidemia were published during the same period. Among ICU patients, 55.4 % were treated with fluconazole and 26.2 % with an echinocandin, a percentage close to what was reported recently in the USA [7] even if more echinocandins were prescribed in one study [31]. Other studies found that receiving an antifungal was an independent factor decreasing both early and late death [22] and that echinocandins as first-line therapy reduced the death rate [38]. In the present study, outcome did not change according to initial antifungal therapy, and only lack of initial antifungal therapy impacted both overall and early deaths. Moreover, preexposure to caspofungin had a negative impact on the outcome. Although numerous other factors not captured here may have influenced the outcome, such as the delayed initiation of adequate antifungal therapy [8, 39, 40], although controversial [16], lack of consideration of antifungal dosing issues [40–42], and inadequate source control as recently emphasized [16], both the strong ecological impact and potentially its deleterious effect on outcome emphasize the need for not only triazole but also echinocandin stewardship in our hospitals.

In conclusion we observed an increase in the incidence of candidemia and its death rate in ICU. The causes of these worrisome trends merit further studies.

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Conflicts of interest OL and MW: member of speaker's bureau Merck, Pfizer, Astellas, Gilead. SB: member of speaker's bureau Gilead. FD, CR, LD, KS, and AF: none

Ethical standards 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 "Commission Nationale de l'Informatique et des Libertés" was obtained, ensuring that the patients' data were kept anonymous according to French regulations.

Appendix

The following investigators participated in the YEASTS program of the French Mycosis Study Group: collection of data in each participating center: C. Bouges-Michel (hôpital Avicenne, Bobigny), I. Poilane (hôpital Jean Verdier, Bondy), J. Dunan (hôpital Ambroise Paré, Boulogne), G. Galeazzi (hôpital Louis Mourier, Colombes), A. Alanio, F. Foulet (hôpital Henri Mondor, Créteil), N. Fauchet (Centre Intercommunal, Créteil), E. Forget (hôpital Beaujon, Clichy), C. Lawrence (hôpital Raymond Poincaré, Garches), A. Angoulvant, C. Bonnal, C. Hennequin, F. Botterel (hôpital du Kremlin Bicêtre, Kremlin-Bicêtre), O. Eloy (Centre Hospitalier, Le Chesnay), M.-F. David, N. Khassis, L. Milhaila (hôpital Paul Brousse, Villejuif), E. Chachaty (Institut Gustave Roussy, Villejuif), and in Paris: C. Chochillon (hôpital Bichat), F. Lesle, A. Paugam, M.-T. Baixench (hôpital Cochin), M.-C. Escande (Institut Curie), M. Cornet (Hôtel Dieu), M.-E. Bougnoux, Y. Sterckers, S. Challier (hôpital Necker), E. Dannaoui, V. Lavarde (hôpital Européen Georges Pompidou), A. Datry, B. L. Mimouni, S. Brun, A. Fekkar (hôpital de la Pitié-Salpétrière), J. Guitard, J.-L. Poirot (hôpital Saint Antoine), C. Lacroix (hôpital Saint Louis, Fernand Widal et Lariboisière), D. Moissenet (hôpital Trousseau), M. Develoux (hôpital Tenon), P. Mariani, S. Bonacorsi (hôpital Robert Debré). Technical analysis of the isolates at the National Reference Center for Invasive Mycoses and Antifungals: Marie Desnos-Ollivier, Dea Garcia-Hermoso, Damien Hoinard, Dorothée Raoux.

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