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Candidaemia Observed at a University Hospital in Milan (Northern Italy) and Review of Published Studies from 2010 to 2014

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Abstract
Background *Candida* species represent the fourth leading cause of nosocomial bloodstream infections (BSI) worldwide. However, candidaemia rates and species involved vary geographically.
Objectives To evaluate the epidemiological pattern, risk factors for mortality and antifungal therapy of *Candida* BSI over a 5-year period (2008–2012) in a university hospital in northern Italy together with a review of the recent literature concerning candidaemia.
Methods A retrospective cohort study cross-linked with microbiology database was performed.
Results A total of 89 *Candida* BSI were identified in 42 males (47 %) and 47 females (52.8 %). The median age was 69 years (interquartile range 55–78) with 61.8 % of patients being older than 65 years. Considering all hospitalized patients, the overall incidence rate of candidaemia increased significantly from 2008 to 2012 (from 0.4 to 1.68 episodes per 10,000 patient/days) ($p = 0.0001$) with a mean linear increase in 5 new cases per year. *Candida albicans* was the predominant species isolated (64 %) followed by *C. glabrata* (19.1 %). The latter species was observed with significantly higher frequency in Internal Medicine and Intensive Care Units (ICU). In-hospital crude mortality was 41.6 %.
Conclusions Candidaemia is an increasing BSI in our university hospital, in accordance with that observed in northern Italy, and it is still associated with high in-hospital crude mortality.

Keywords Candidaemia · Fungal infections · *C. albicans* · *C. glabrata* · *C. parapsilosis* · Intensive care unit

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Introduction

Candida species represent the most common cause of invasive fungal infections (IFIs) and the fourth most frequent cause of bloodstream infection among hospitalized patients [1, 2]. The incidence of candidaemia

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has increased over last decades due to the substantial increase in the hospital population at risk of this infection [2–4], ranging from 4 to 26/100,000 hospital admission, depending on geographic region [5, 6]. The expansion of elderly population worldwide and the widespread use of immunosuppressive therapy, broad-spectrum antibiotics, intravascular catheters as well as of invasive procedures have had a leading role in the changing epidemiology of invasive candidiasis [7]. Candidaemia is associated with significant mortality, with in-hospital crude mortality rate ranging between 40 and 70 % [3, 8, 9]. Furthermore, a change in *Candida* spp. distribution with a shift towards non-*albicans* species, particularly *C. glabrata*, *C. krusei* and *C. parapsilosis*, has been reported in Europe and USA [10–13].

The aim of this retrospective study was to analyse epidemiology, underlying clinical conditions, risk factors for mortality and impact of antifungal therapy on episodes of candidaemia, in a single-centre cohort of patients observed in a tertiary care hospital in Milan, Italy, during the period 2008–2012. Moreover, we performed a systematic review of studies on candidaemia to summarize the evidence regarding distribution of *Candida* spp. isolated from blood in different geographic region and to evaluate crude mortality of this infection.

Methods

A retrospective chart review of all consecutive cases of candidaemia was conducted at Luigi Sacco Hospital, a 550-bed university hospital in Milan. The study was approved by the Hospital Institutional Review Board. All records from the year 2008–2012 were searched in the in-hospital database using discharge diagnosis according to the International Classification of Diseases, Ninth Revision (ICD-9). All patients hospitalized from January 2008 to December 2012 and diagnosed with candidaemia, defined by at least one positive blood culture for *Candida* spp., were enrolled. For each patient, only the first episode was recorded and the ward of hospitalization registered after being grouped as follows: medical wards (internal medicine wards, oncology, gastroenterology, rheumatology, pneumology and low-care unit); surgical wards (general surgery wards, cardiosurgery and urology); intensive care units and infectious diseases wards. Twenty-two out of 111 records retrieved were excluded from the analysis: seven patients had been improperly registered with a diagnosis of candidaemia and 15 patients had incomplete data.

The variables analysed were sex, age, length of hospital stay preceding the first positive blood culture, any hospitalization or healthcare-associated invasive procedure, including surgery, within 30 days before the diagnosis of candidaemia. Episodes occurring >48 h after hospital admission were defined as hospital-acquired.

The principal comorbidities were registered and estimated by the McCabe classification: class 0 for no underlying disease, class 1 for non-fatal underlying disease, class 2 for ultimately fatal disease (death expected within a 4-year period) and class 3 for rapidly fatal disease (death expected within 1 year) [14].

Among risk factors, mechanical ventilation, central venous catheterization (CVC), total parenteral nutrition, use of corticosteroids (>20 mg/day of prednisone for more than 20 days before the onset of candidaemia), broad-spectrum antibiotics or immunosuppressive therapies were considered.

Microorganism Identification

Candida species were isolated from blood using BACTEC 9240 system (Beckton Dickinson, INC, Sparks, MD), and viable yeasts were subcultured on Sabouraud dextrose agar. Species identification was obtained using the VITEK 2 automated system (bioMérieux Inc., Durham, NC).

Statistical Analysis

Continuous data were analysed using Wilcoxon's nonparametric test, whereas categorical variables by chi-square or Fisher exact tests. Tests were two-sided and a p value <0.05 was considered statistically significant.

Incidence of candidaemia was calculated considering all hospitalized patients from 2008 to 2012, and Cochran–Armitage trend test was performed. Incidence data were expressed as number of episodes per 10,000 patient/days, while the incidence of candidaemia observed in each ward was calculated as number of episodes per 1,000 patient/days.

Multiple logistic model and linear regression analysis were performed by GENMOD procedure to

identify independent predictors of in-hospital mortality and of days of hospital stay.

Variables with a p value <0.20 at univariate analyses were entered in the final model. Analyses were performed using SAS® 9.2 (SAS Institute, Cary, NC, USA).

Literature Review

For the purpose of systematic review, we performed searches in the PubMed and Scopus databases (in the period between January 2010 and May 2014) using the following keywords: 'Candida', 'candidaemia', 'Candida bloodstream infection', 'Candida epidemiology', 'Candida species distribution' and 'ICU candidaemia'. The time-span chosen was dictated by the fact that the period from 1996 to 2009 has been covered by a recent systematic review [10].

Only studies describing 70 or more cases of candidaemia and written in English language were considered. We also excluded studies performed only in selected populations (i.e. paediatric or onco-haematological patients), as well as studies focused on a single *Candida* species. To enhance the populations homogeneity, we separately evaluated studies performed in hospitals and those conducted in ICUs. From all the studies retrieved, we evaluated: the geographic distribution, the study design (prospective and retrospective), the study period, gender distribution and age of the studied population, and crude mortality. We also reported the relative frequency of *C. albicans* and non-*albicans* species, and the most frequently isolated *non-albicans* strain for each published casistic.

Results

Eighty-nine patients with candidaemia were identified during the study period, with an overall incidence of 1.15 episodes per 10,000 patient/days. The median age of patients was 69 years [IQR (interquartile range) 55–78], with a 61.8 % being ≥65 years old, and 52.8 % (47) were females. The main characteristics of the patients are summarized in Table 1.

The incidence rate significantly increased from 2008 to 2012 (from 0.4 to 1.68 episodes per 10,000 patient/days; $p = 0.0001$), with a mean linear increase in 5 new cases per year (R^2 0.91; $p = 0.012$) (Fig. 1).

Table 1 Characteristics of 89 patients with candidaemia

Variable	Number (%) of patients
Demographic characteristics	
Female gender	47 (52.8 %)
Age (years), median (IQR)	69 (55–78)
Age ≥ 65 years	55 (61.8)
Ward	
ICU	18 (20.2)
Medicine	19 (21.4)
Surgery	18 (20.2)
Infectious diseases	34 (38.2)
Hospital stay duration (days), median (IQR)	35 (19–60)
Time to infection (days), median (IQR)[a]	21 (11.5–32)
Comorbidity	
Diabetes mellitus	20 (22.5)
Solid malignancy	27 (30.3)
Haematological malignancy	4 (4.5)
HIV infection	13 (14.6)
IVDU	9 (10.1)
McCabe classification	
Score 0	10 (11.2)
Score 1	34 (38.2)
Score 2	40 (45)
Score 3	5 (5.6)
Charlson comorbidity score, median (IQR)	2 (0–5)
Concomitant risk factors	
Broad-spectrum antimicrobial therapy[b]	84 (94.4)
Bloodstream bacterial infection	24 (27)
Central venous catheter	74 (83.2)
Corticosteroid therapy[b]	18 (20.2)
Immunosuppressive therapy[b]	17 (19.1)
Total parenteral nutrition	61 (68.5)
Mechanical ventilation	26 (29.2)
Recent surgery[b]	22 (24.7)
Non-surgical invasive procedure[b]	53 (59.6)
Neutrophil count ≤500/μL	4 (4.7)

IQR interquartile range; *ICU* intensive care unit; *IVDU* intravenous drug user

[a] Time from admission to the date of the first positive blood culture, for the nosocomial-acquired infection only

[b] Within 30 days prior to diagnosis of candidaemia

No statistically significant difference in the crude distribution among wards was observed (Table 1). However, when incidence data were analysed, the highest incidence was registered in ICUs (1.95 per

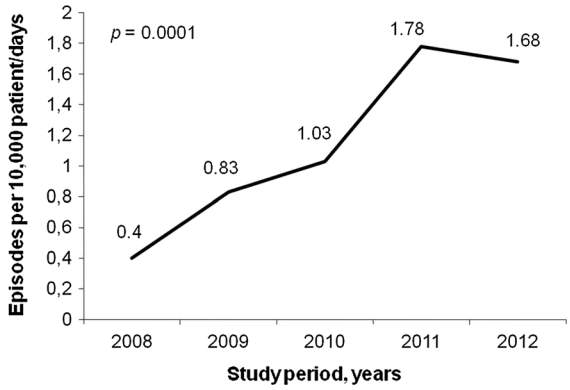

Fig. 1 Incident cases of candidaemia observed at L. Sacco Hospital in the period 2008–2012: $p = 0.0001$ according to the Cochran–Armitage trend test

1,000 patient/days vs 0.28, 0.20 and 0.085 per 1,000 patient/days in Infectious Diseases Department, surgical and medical wards, respectively) with a significant difference between ICUs and the other wards considered together (1.95 vs 0.17 per 1,000 patient/days; $p = 0.0001$). Furthermore, when the 34 patients hospitalized in the infectious diseases wards were compared with those admitted in the other wards, they were found to be younger, more frequently HIV-infected and had received mechanical ventilation or total parenteral nutrition to a lesser extent (Table 2).

A hospital-acquired infection was revealed in 81/89 patients (91 %). The median time between hospital admission and the diagnosis of candidaemia was 16 days (IQR 6.25–27). Seven of the 8 patients with a diagnosis of candidaemia within 48 h from hospital admission had a hospital or chronic-care facilities admission during the last 30 days, whereas a community-acquired infection occurred in one intravenous drug user.

In 27 % (24) of the study cohort, a bloodstream bacterial infection was reported during hospitalization, either as candidaemia concomitant infection or independent occurrence. The most frequently isolated microorganisms were as follows: *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Acinetobacter* spp., *Enterococcus* spp. and multibacterial infection.

Candida albicans was the predominant species (64 %) isolated, followed by *C. glabrata* (17; 19.1 %), *C. tropicalis* (6; 6.74 %) and *C. parapsilosis* (4; 4.5 %). *C. dubliniensis* was isolated in three of the remaining 5 episodes, while *C. famata* and *C. lusitaniae* were responsible for one episode each. The distribution of the most frequently isolated *Candida* species according to the hospital ward is shown in Fig. 2. Although no significant difference emerged in the overall distribution of the *Candida* isolates, the proportion of *C. albicans* (range 47.3–66.7 %) and *C. glabrata* (range 5.5–36.8 %) isolates varied considerably among the hospital wards. Particularly, the distribution of *C. glabrata* resulted significantly higher in medical wards and ICUs (36.8 and 27.8 %, respectively) compared with surgical and infectious diseases wards (5.5 and 11.8 %, respectively; $p = 0.012$).

With respect to species distribution, no statistically significant increase in the number of *C. glabrata* infections was observed throughout the study period.

Nineteen patients (21.4 %) did not receive antifungals either because they died or were discharged from the hospital for hospice-care units (6; 6.7 %) and were lost to follow-up before the notification of microbiological diagnosis (13; 14.6 %). Overall, 56 (63 %) were treated within 48 h of the diagnosis, and fluconazole was most frequently used as initial treatment (in 65.2 % of patients), without significant differences among different wards. The echinocandins caspofungin and anidulafungin were administered in 5.6 % and 3.4 %, respectively. Echinocandins were more frequently used in the Infectious Diseases Department ($p = 0.01$), while liposomal amphotericin B and voriconazole were administered to 2 patients each. In 22.47 % (20) of patients, the initial antifungal regimen was subsequently modified: from fluconazole to echinocandins in 15 patients, from echinocandins to fluconazole in 3 and from liposomal amphotericin B to echinocandins in 2.

In-hospital crude mortality was 41.6 % (37/89 patients), with no differences among hospital wards. Mortality rates did not differ significantly by species. No significant change emerged by the analysis of the crude mortality rate trend during the study period.

Univariate analysis of the factors significantly associated with in-hospital mortality among 89 patients with candidaemia (52 survivors and 37 non-survivors) is reported in Table 3. Multiple logistic model showed older age (OR 1.064, IC 95 % 1.016–1.115; $p = 0.0087$) and higher McCabe classification score (OR 2.412, IC 95 % 1.047–5.556; $p = 0.0386$) to be the only independent risk factors for in-hospital mortality. Although the antifungal

Table 2 Characteristics of patients with candidaemia hospitalized in the Infectious Diseases Department

Variable	Infectious Diseases Department (*n* 34) Number (%) of patients	Other wards (*n* 55) Number (%) of patients	*P* value
Demographic characteristics			
Female gender	16 (47)	31 (56.4)	0.51
Age (years), median (IQR)	59.5 (47–74)	62 (64–80)	**0.0031**
Hospital stay duration (days), median (IQR)	22.5 (13–49)	40 (22–68)	**0.032**
Comorbidity			
Diabetes mellitus	8 (23.5)	12 (21.8)	1
Solid malignancy	9 (26.5)	18 (32.7)	0.63
Haematological malignancy	3 (8.8)	1 (1.8)	0.15
HIV infection	11 (32.4)	2 (3.6)	**<0.001**
IVDU	9 (26.5)	–	**<0.001**
Concomitant risk factors			
Broad-spectrum antimicrobial therapy[a]	32 (94)	52 (94.5)	1
Bacterial infection	23 (67.6)	41 (74.5)	0.76
Central venous catheter	25 (73.5)	49 (89.1)	0.8
Corticosteroid therapy[a]	6 (17.7)	12 (21.8)	0.78
Immunosuppressive therapy[a]	8 (23.5)	9 (16.4)	0.42
Total parenteral nutrition	14 (41.2)	47 (85.5)	**<0.001**
Mechanical ventilation	3 (8.8)	23 (41.8)	**<0.001**
Previous ICU recovery[b]	5 (14.7)	28 (59.9)	**<0.001**
Recent surgery[a]	5(14.7)	17 (30.9)	0.12
Non-surgical invasive procedure[a]	21 (61.8)	32 (58.2)	0.82
Neutrophil count ≤500/μL	3 (9.1)	1 (1.9)	0.15
In-hospital mortality	13 (38.2)	24 (43.6)	0.66

Bold value indicates significant of p values

IQR interquartile range, *ICU* intensive care unit, *IVDU* intravenous drug user

[a] Within 30 days prior to diagnosis of candidaemia

[b] Within 15 days prior to diagnosis o candidaemia

treatment was significantly associated with survival, neither the antifungal drug used, nor its early introduction was found to be protective.

At multiple regression analysis, the presence of CVC (*b-coefficient* 0.654, SE 0.212; $p = 0.0028$) and ICU stay (*b-coefficient* 0.426, SE 0.195; $p = 0.032$) was independently associated with longer hospitalization. In-hospital death was associated with shorter hospital stay ($p = 0.019$).

Literature Review

We retrieved 1,197 documents, 225 of which were excluded because they were review of literature, 65 were published as 'letters to the Editor' and 25 as notes. Of the 817 remaining papers, after excluding those performed only in children or onco-haematological patients, as well as those involving a single *Candida* species, duplicated publications or those unrelated to candidaemia, 50 original articles were selected [3, 6, 15–62]. Forty-one articles [3, 6, 15–22, 24–54] reported data from single hospitals or were multicentre or nationwide studies (Table 4), and nine were conducted in ICUs (Table 5) [23, 55–62]. Seventeen (34 %) were prospective studies [3, 6, 15–17, 19, 21, 25, 27, 28, 30, 31, 34, 35, 41, 42, 52, 58, 61, 62].

Seventeen hospital-studies were conducted in Europe [3, 6, 15, 17, 20, 21, 24–34], seven in South

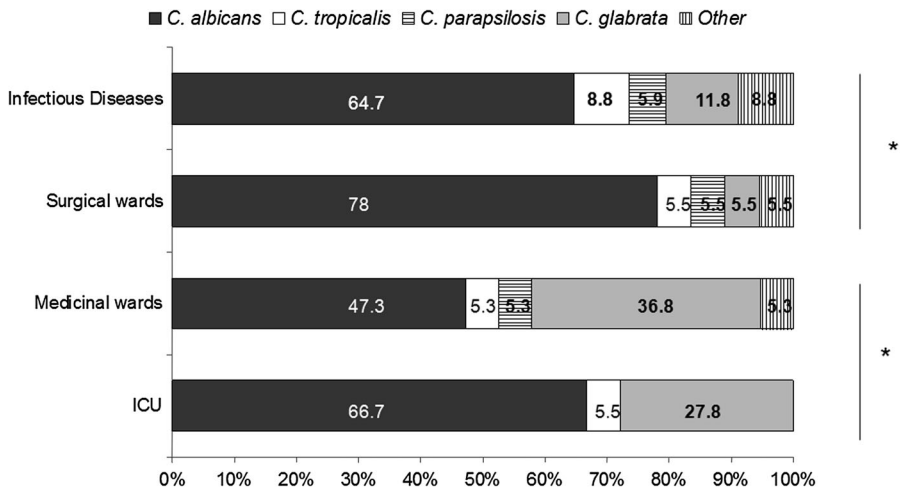

Fig. 2 Distribution of *Candida* species by hospital service. Other species include *C. dubliniensis*, *C. lusitaniae* and *C. famata.* *The distribution of *C. glabrata* resulted significantly higher in medical wards and ICUs compared with surgical and infectious diseases wards ($p = 0.0123$)

Table 3 Univariate and multivariate analyses of factors associated with in-hospital mortality among patients with candidaemia

Variable	Univariate			Multivariate		
	OR	IC (95 %)	*P* value	OR	IC (95 %)	*P* value
Female gender	1.584	0.675–3.715	0.290			
Age	1.031	1.001–1.062	**0.044**	1.035	1.001–1.069	**0.041**
Solid malignancy	0.763	0.301–1.930	0.567			
Haematological malignancy	4.500	0.449–45.082	0.200			
HIV infection	1.198	0.337–4.264	0.780			
Diabetes mellitus	0.700	0.249–1.970	0.499			
McCabe classification	7.714	0.932–63,845	**0.058**	14.239	1.476–137.3	**0.021**
Charlson index	1.047	0.894–1,226	0.570			
Corticosteroid therapy	1.159	0.408–3.288	0.782			
Immunosuppressive therapy	0.980	0.335–2,867	0.970			
Central venous catheter	0.779	0.255–2.377	0.661			
Total parenteral nutrition	1.791	0.700–4.583	0.224			
Mechanical ventilation	1.625	0.646–4.085	0.301			
ICU recovery	1.288	0.539–3.074	0.568			
Recent surgery	1.235	0.468–3.260	0.670			
Neutrophil count $\leq$500/μL	1.343	0.180–10.004	0.773			
C. albicans vs non-*albicans* spp.	0.870	0.362–2.089	0.806			
Early treatment[a]	0.899	0.381–2.122	0.807			
Antifungal therapy	0.246	0.083–0.730	**0.011**	0.186	0.053–0.652	**0.008**
Azoles vs echinocandins	2.238	0.042–1.327	0.101			

Bold value indicates significant of p values

[a] Within 48 h of the diagnosis

Table 4 Major review studies of candidaemia

Reference/Country	Study design/observation time period/number of participating institutions	Total number of cases	Male sex, *n* (%)	Age (mean or median ± SD or range)	*C. albicans*/ non-*albicans* cases, *n* (%)	Principal non-*albicans* isolates, *n* (%)	Crude mortality, *n* (%)
Europe							
Gurcuoglu et al. [24]/ Turkey	Retrospective/1996–2007/single centre	743	NA	286 children	343 (45)/417 (55)	*C. parapsilosis*, 95 (27.1)	NA
Spiliopoulou et al [25]/ Greece	Prospective/1998–2008/single centre	255	NA	61 newborns	163 (67)/92 (33)	*C. parapsilosis*, 35 (13.7)	NA
Poikonen et al. [26]/ Finland	Prospective/2004–2007/nationwide	603	337 (56)	64 (0–94)	406 (67)/193 (32) 4 (1) unknown	*C. glabrata*, 115 (19)	208/598 (35)
Bassetti et al. [3]/Italy	Prospective/2008–2010/single centre	348	185 (53.3)	68.7 ± 15.95	170 (49)/178 (51)	*C. parapsilosis,* 99 (28.4)	141/324 (43.5)
Ortega et al. [27]/Spain	Prospective/1991–2008/single centre	529	260 (49)	57 ± 19	252 (48)/277 (52)	*C. parapsilosis,* 95 (18)	168 (32)
Das et al. [28]/UK	Prospective/2005–2008/single centre	107 (102 patients)	52 (49)	55 (median) (17–95)	46 (43)/61 (57)	*C. glabrata*, 33 (30,8)	40 (37)
Chalmers et al. [29]/UK	Retrospective/2008/multicentre (5 institutions)	93	43 (48)	64 (median) (4–97)	50 (54)/43 (46)	*C. glabrata*, 24 (25.8)	36/89 (40.4)
Fortun et al. [30]/Spain	Prospective/2000–2009/single centre	419	234 (55.8)	58.7 ± 21	177 (42.2)/242 (57.9)	*C. parapsilosis*, 144 (34.4)	157 (37.5)
Ericsson et al. [31]/ Sweden	Prospective/2005–2006/nationwide	403	206 (51)	<1 year: 21 (5) 1–20 years: 18 (4.5) 21–40 years: 23 (5.7) 41–60 years: 97 (24) 61–80 years: 180 (44.6) ≥81 years: 63 (15.6)	245 (61)/158 (39)	*C. glabrata*, 81 (20.1)	NA
Luzzati et al. [32]/Italy	Case–control study/2008–2011/single centre	145 (140 patients)	73 (52.1)	75.3 ± 15.4	80 (55)/65 (45)	*C. parapsilosis,* 35 (24.1)	62 (45)
Tortorano et al. [15]/Italy	Prospective/2009/multicentre (34 institutions)	467	275 (58.8)	NA	50.4 %/45.6 %	*C. glabrata*, (20.3)	99/328 (30.2)
De Rosa et al. [20]/Italy	Retrospective/2004–2008/multicentre (2 institutions)	779	443 (56.8)	68 (median) (IQR 56–77)	447 (57.4)/332 (42.6)	*C. glabrata*, 86 (11)	354 (45.4)
Nawrot et al. [33]/Poland	Retrospective/2006–2007/multicentre (20 institutions)	302 (294 patients)	150 (51)	NA	159 (51)/143 (49)	*C. glabrata,* 44 (14.1)	NA
Bassetti et al. [17]/Italy and Spain	Prospective/2008–2010/multicentre (5 institutions)	995	486 (57)	66.2 ± 13	558 (58.4)/399 (41.8)	*C. parapsilosis*, 186 (19.5)	398 (40)
Garnacho-Montero et al. [34]/Spain	Prospective/2004–2009/single centre	188	114 (60.6)	58 (median) (IQR, 28)	87 (46.3)/101 (53.7)	*C. parapsilosis*, 37 (19.7)	67 (in-hospital, 35.6)

Table 4 continued

Reference/country	Study design/observation time period/number of participating institutions	Total number of cases	Male sex, *n* (%)	Age (mean or median ± SD or range)	*C. albicans*/non-*albicans* cases, *n* (%)	Principal non-*albicans* isolates, *n* (%)	Crude mortality, *n* (%)
Arendrup et al. [6]/ Denmak	Prospective/2010–2011/nationwide	1,028	612 (59.5)	66 (median) (0–105)	536 (52)/462 (45) 30 (multiple species, 2.9 %)	*C. glabrata*, 288 (28)	NA
Asmundsdottir et al. [21]/Iceland	Prospective/2000–2011/nationwide	208 (199 patients)	113 (57)	64 (median) (17–92)	124 (55.9 % of 222 isolates)/87 (39.4 %); 12 (multiple species, 5.8 %)	*C. glabrata*, 36 (16)	56/189 (29.6)
North–South America							
Camargo et al. [35]/ Brazil	Prospective/1997–2007/single centre	151 (147 patients)	86 (57)	60 ± 24.9	67 (44)/84 (56)	*C. parapsilosis,* 34 (22)	65/151 (43)
Motta et al. [36]/Brazil	Retrospective/2006/single centre	136 (132 patients)	77 (59.9)	40 (median) (0–87)	71 (52.2)/65 (47.8)	*C. parapsilosis*, 30 (22.1)	NA
Shah et al. [37]/USA	Retrospective/2006–2009/single centre	161	87 (54)	59 ± 16	80 (50)/81 (50)	*C. glabrata*, 31 (19)	NA
Guimaraes et al. [22]/ Brazil	Retrospective/1994–2004/ multicentre (14 institutions)	987	569 (57.6)	NA	396 (39)/591 (61)	*C. tropicalis,* 240 (24)	562 (57)
Bonfietti et al. [38]/ Brazil	Retrospective/1998–2007/single centre	100	46 (46)	48.5	44 (44)/56 (56)	*C. parapsilosis*, 34 (34)	55 (55)
Mondelli et al. [39]/ Brazil	Retrospective/2000–2006/single centre	98	NA	< 1 year: 44 (45) 1–10 years: 11 (11) 11–18 years: 3 (3) 19–59 years: 22 (22) ≥ 60: 18 (18)	33 (33.6)/65 (66.3)	*C. parapsilosis,* 37 (37.7)	52 (53.1)
Wille et al. [40]/Brazil	Retrospective/1994–2004/single centre	388	234 (60.3)	32.4 (0–99)	165 (42.4)/223 (57.6)	*C. tropicalis,* 106 (27.3)	215 (55.4)
Pfaller et al. [16]/USA and Canada	Prospective/2004–2008/multicentre (25 institutions)	4,067 (3,640 patients)	1,934 (53)	52.3 (0–96)	1,711 (42.1)/2,356 (57.9)	*C. glabrata*, 903 (22.2)	1,574 (38.7)
Diekema et al. [18]/ USA	Retrospective/2004–2007/single centre	108	53 (49)	44	51 (47)/57 (53)	*C. glabrata*, 31 (29)	36 (33)
Nucci et al. [19]/Latin America	Prospective/2008–2010/multicentre (21 institutions)	672	396 (58.9)	26 (median) (0–98)	253 (37.6)/419 (62.4)	*C. parapsilosis*, 178 (26.5)	237/583 (40.7)
Matsumoto et al. [41]/ USA	Prospective/2011–2012/multicentre (14 institutions)	163	74 (45)	56 (median) (0–94)	69 (42)/94 (58)	*C. glabrata*, 36 (22)	33 (20)
Australia							
Playford et al. [42]/ Australia	Prospective/1999–2008/multicentre (14 institutions)	1,137	591 (52)	50.1 ± 24.7	516 (45.4)/621 (54.6)	*C. parapsilosis*, 306 (26.9)	NA

Table 4 continued

Reference/Country	Study design/observation time period/number of participating institutions	Total number of cases	Male sex, *n* (%)	Age (mean or median ± SD or range)	*C. albicans*/ non-*albicans* cases, *n* (%)	Principal non-*albicans* isolates, *n* (%)	Crude mortality, *n* (%)
Africa							
Kreusch et al. [43]/South Africa	Retrospective/1990, 1998–2002, 2005–2007/single centre	268 (266 patients)	101/203 (49.7)	37.6 (median) (14–89)	123 (46)/145 (54)	*C. parapsilosis,* 67 (25)	122 (45)
Asia							
Zhang et al. [44]/China	Retrospective/2000–2009/single centre	270	148 (54.8)	63 (1–92)	97 (35.9)/173 (64.1)	*C. tropicalis,* 59 (21.8)	181/270 (67)
Ma et al. [45]/China	Retrospective/2009–2011/single centre	133	91 (68.4)	1–14 years: 3 (2.3) 15–49 years: 29 (21.8) 50–65 years: 40 (30.1) > 65 years: 61 (45.9)	31 (23.3)/102 (76.7)	*C. tropicalis,* 38 (28.6)	34/133 (26)
Yang et al. [46]/China	Retrospective/2008–2012/single centre	121	87 (71.9)	57.3 ± 19.9	45 (37.2)/76 (62.8)	*C. parapsilosis,* 24 (19.8)	34/121 (28.1)
Wu et al. [47]/China	Retrospective/2009–2011/single centre	238	142 (59.7)	44 (1–88)	71 (29.8)/167 (70.2)	*C. parapsilosis,* 66 (27.7)	49/238 (20.6)
Chen et al. [48]/Taiwan	Retrospective/2000–2008/single centre	871	580 (66.6)	64 ± 22	541 (62.1)/330 (37.9)	*C. tropicalis,* (15.4)	321 (36.9)
Chen et al. [49]/Taiwan	Retrospective/2006–2009/single centre	437	300 (67.1)	68 ± 16	258 (59)/179 (41)	*C. tropicalis,* 67 (15)	215 (48.1)
Chen et al. [50]/Taiwan	Retrospective/2002 and 2010/single centre	504	300 (59.5)	58.5 ± 21.5	273 (54.1)	*C. tropicalis,* 109 (21.6)	227 (45)
Ha et al. [51]/Korea	Retrospective/2008–2009/multicentre (4 institutions)	199	106 (53.3)	68 (27–88)	90 (45.2)/109 (54.8)	*C. tropicalis,* 51 (25.6)	81/169 (47.9)
Singh et al. [52]/India	Prospective/2008–2009/single centre	89	72 (80.9)	35.4 (2–82)	15 (16.85)/74 (83.15)	*C. tropicalis,* 29 (32.6)	45/89 (50.6)
Taj-Aldeen et al. [53]/ Qatar	Retrospective/2004–2010/single centre	201 (187 patients)	123 (65.8)	< 1 year: 78 (38.8) 1–18 years: 15 (7.5) 19–40 years: 18 (9) 41–60 years: 33 (16.4) > 60 years: 57 (28.4)	68 (33.8)/133 (66.2)	*C .glabrata,* 38 (18.9)	105/187 (56.1)
Al Thagafi et al. [54]/ Saudi Arabia	Retrospective/2002–2009/single centre	258 (252 patients)	134 (53.2)	< 1 year: 49 (19.4) 1–5 years: 32 (12.7) 6–14 years: 22 (8.7) 15–59 years: 83 (32.9) > 60 years: 66 (26.2)	86 (34.1)/166 (65.9)	*C. tropicalis,* 39 (15.5)	139/252 (53.9) [12 months]

Table 5 Studies on candidaemia conducted in ICU published between January 2010 and May 2014

Reference/country	Study design/observation time period/number of participating institutions	Total number of cases	Male sex *n* (%)	Age (mean or median ± SD or range)	*C. albicans*/non-*albicans* cases (%)	Principal non-*albicans* isolates, *n* (%)	Crude mortality, *n* (%)
Horasan et al. [55]/Turkey	Retrospective/2004–2009/single centre	118	71 (60)	45 ± 25	22 (18)/96 (81.4)	*C. parapsilosis*, 78 (66)	83 (70)
Zilberberg et al. [23]/USA	Retrospective/2004–2007/single centre	90	46 (51)	56 ± 19	58 (64)/32 (36)	*C. glabrata*, 15 (17)	23 (28.8)
Leroy et al. [56]/France	Prospective/2005–2006/multicentre	136	84 (61.8)	62.1 ± 14.9	78 (57.4)/58 (42.6)	*C. glabrata*, 25 (18.4)	NA
Kett et al. [57]/worldwide (76 countries)	Retrospective/one day 2007/multicentre	99	88 (89)	60.7 (46–71)	70 (70.7)/29 (29.3)	NA	53 (53.3)
Gonzalez de Molina et al. [58]/worldwide	Prospective/2006–2007/multicentre (38 institutions)	38	24 (63.2)	59 ± 17.1	22 (57.9)/16 (42)	*C. parapsilosis*, 9 (23.7)	20 (52.6)
Ylipalosaari et al. [59]/Finland	Retrospective/2000–2009/single centre	82	54 (65.8)	63.5 (45–75)	60 (73.2)/22 (26.8)	*C. glabrata*, 15 (18.3)	22 (26.8)
Bassetti et al. [60]/Italy, Spain	Retrospective/2009–2011/multicentre (5 institutions)	216	126 (58.3)	63.4 ± 18.5	131 (61)/85 (39.3)	*C. parapsilosis*, 35 (16)	116 (53.7)
Puig-Asensio et al. [61]/Spain	Prospective/2010–2011/nationwide (29 institutions)	168 (164 patients)	108 (65.9)	63 (median; IQR 49–74)	90/173 isolates (52)/83 (48)	*C. parapsilosis*, 41 (23.7)	77 (47)
Montagna et al. [62]/Italy	Prospective/2007–2008/nationwide	462	281 (60.8)	NA	228 (49.4)/234 (50.6)	*C. parapsilosis*, 121 (26.2)	79/201 (39.3)

America (6 of which in Brazil) [19, 22, 35, 36, 38–40], 4 in North America [16, 18, 37, 41], 9 in Asia [44–52] and 2 in the Middle-East [53, 54]. Finally, one cohort was evaluated in Australia [42] and one in South Africa [43]. Overall, 19,369 patients were studied in 41 studies most of which had a retrospective design (22/41) and 4 were nationwide prospective studies. Male gender was predominant almost everywhere with a frequency ranging from 45 [41] to 81 % [52], and 18 studies included patients younger than 14 years old [6, 16, 19, 24–26, 29, 31, 36, 39, 40, 44, 45, 47, 52–54]. Among the studies conducted in ICUs, 5 were retrospective [23, 55, 57, 59, 60] and 4 prospective [56, 58, 61, 62] and multicentre.

The most frequently isolated *Candida* spp. was *C. albicans* in every Continent studied with a frequency ranging from 42.2 [30] to 67 % [25] in Europe, from 42 [16] to 50 % [37] in North America, from 33.6 [39] to 52 % [36] in South America and from 16.8 [52] to 62 % [48] in Asia. Only one Indian study reported *C. tropicalis* as responsible of the majority of cases of candidaemia (32.6 %) [52]. Among non-*albicans* species, *C. glabrata* was the second most frequently isolated species in all studies from North America [16, 18, 37, 41] and 9 from Europe [6, 15, 20, 21, 26, 28, 29, 31, 33] with a frequency ranging from 11 to 30.8 % [20, 28]; *C. parapsilosis* was the main non-*albicans* isolated species in all the 8 studies from southern Europe (Greece, Italy, Spain and Turkey) [3, 17, 24, 25, 27, 30, 32, 34].

C. parapsilosis predominated in 5 out of 7 studies from South America [19, 35, 36, 38, 39] (with a frequency ranging from 22 to 37.7 %) [35, 39], and *C. tropicalis* was the dominant species in Asia in 7 out of 9 studies [44, 45, 48–52] (ranging from 15 to 32.6 %) [52]. In 8/9 studies performed in ICUs, *C. albicans* was the most frequently isolated (frequency from 49.4 to 73.2 %) [35, 39], and only one study conducted in Turkey reported a higher incidence of *C. parapsilosis* (66 %) [55].

Crude mortality rate ranged from 20 to 38.7 % in data from North America [16, 41], from 29.6 to 45.4 % in Europe [20, 21], from 40.7 to 57 % in South America [19, 22] and from 20.6 to 67 % in Asia [44, 47]. In ICUs casistic, the mortality rate ranged from 26.5 to 70 % [55, 59]. The higher mortality rate observed in South America and Asia in respect of Europe and North America might reflect the relative higher prevalence of *C. parapsilosis* and *C. tropicalis* in the latter geographic setting.

Discussion

This single-centre study confirmed the increasing incidence of candidaemia in the hospitalized population reported by surveys conducted in North America and Europe [5, 6, 63]. We found a mean incidence of candidaemia of 1.15 per 10,000 patient/days, ranging from 0.4 infections per 10,000 patient/days in 2008 to 1.7 per 10,000 patient/days in 2012, similar to what has been observed in North America [5, 63], in Denmark [6] and in Northern Italy [15]. An increased incidence of candidaemia from 2008 to 2010 was reported in another Italian single-centre study, although since they did not consider the variable of time, a comparison of incidence data cannot be done [64].

In accordance with most of the epidemiological data reported [4, 16], the highest incidence of candidaemia among our hospital wards was observed in ICU (1.95 vs 0.17 per 1,000 patient/days in the other wards; $p = 0.0001$). Noteworthy, two recently published studies from Italy and Spain highlighted the problem of candidaemia in Internal Medicine, by comparing the distribution of candidaemia rather than reporting the incidence or prevalence data [17, 64]. This probably overestimated the occurrence of candidaemia in the general internal medicine compared with other wards. We observed 0.085 cases of candidaemia per 1,000 patient/days in general medicine wards, and 0.28 cases in infectious diseases wards, with a frequency 22 and 7 fold lower than in ICU patients, respectively. However, the problem of the 'frail elderly patient' increasingly hospitalized in Internal Medicine wards, some of which share many of the risk factors for candidaemia observed in ICU patients should not be overlooked.

Patients in our cohort were found to be elderly and with high rates of intravascular catheters, total parenteral nutrition, mechanical ventilation, cancer disease, surgery, diabetes and HIV infection. In addition, most of the patients were exposed to broad-spectrum antibiotic therapy, corticosteroids and immunosuppressive agents.

The low prevalence of haematological malignancies and the relative high number of HIV-infected patients result from the lack in our hospital of oncohaematological ward and from the presence of a large Infectious Diseases Department.

According to most of the Italian and international surveys [15, 16, 18], *C. albicans* was the predominant

species and accounted for 64 % of all the isolates in our series, while *C. glabrata* was the second most frequent species isolated, at variance with a recent Italian report which found *C. parapsilosis* (28.4 %) as the most common species after *C. albicans* [3]. *C. parapsilosis* is a relevant pathogen primarily in South America, where it causes from 19 to 38 % of all episodes of candidaemia [19], and Spain (from 15 to 23 %) [65], but recent Italian studies reported a similar burden ranging from 16.8 to 28.4 % of all bloodstream *Candida* isolates [3, 15, 20]. In our systematic review, we found that *C. parapsilosis* was the leading species isolated after *C. albicans* in 22 studies (44.9 %) [3, 11, 19, 24, 25, 27, 30, 32, 34–36, 38, 39, 42, 43, 46, 47, 55, 58, 60–62] followed by *C. glabrata* in 17 studies (34.6 %) [6, 15, 16, 18, 20, 21, 26, 28, 31, 33, 37, 41, 53] and *C. tropicalis* in the remaining 10 studies (20.4 %) [40, 44, 45, 48–52, 54]. Although the epidemiology of candidaemia may vary also in the same country depending on clinical setting, study design and clinical practice, we were able to identify different geographic-specific patterns regarding the predominant species of *Candida* non-*albicans* isolated. In this regard, with few exceptions emerged that *C. parapsilosis* ranked second in southern Europe and Latin America [3, 17, 24, 25, 27, 30, 32, 34–36, 38, 39, 55, 58, 60–62], whereas in Northern Europe and North America this ranking was hold by *C. glabrata* (after *C. albicans*) [6, 16, 18, 21, 26, 28, 29, 31, 33, 37, 41] and in Asia by *C. tropicalis* [44, 45, 48–52].

We could not confirm in our cohort the increasing rates of candidaemia due to non-*albicans* species, particularly *C. parapsilosis*, reported by some studies worldwide [16, 66]. This difference may derive from the small number of patients studied as well as from the low proportion of onco-haematologic or neutropenic patients [18]. Particularly, we observed a low rate of *C. tropicalis* candidaemia similar to those published in European and North American studies [2, 16, 21, 67]. In addition, no cases of *C. krusei* candidaemia were observed over the study period, confirming its low prevalence in Southern Europe [3, 15, 20, 21, 68].

Interestingly, the distribution of *C. glabrata* isolates varied considerably among our hospital wards, being significantly higher in medical wards (other than Infectious Diseases) and ICUs, with a relative distribution of 36.8 and 27.8 %, respectively, higher than that reported by most surveys [16, 17]. An increase in the proportion of cases caused by *C. glabrata* in elderly patients has been observed in most but not all studies [22, 69–72], and the role of diabetes, frequently observed among old patients admitted to Internal Medicine wards, is controversial as a risk factor for *C. glabrata* candidaemia [73, 74].

In our experience, fluconazole was the most frequently employed initial antifungal agent, followed by echinocandins that were administered as initial therapy only in the Infectious Diseases Department and ICUs. Notably, although an early introduction ($\leq$48 h from diagnosis) of antifungals was observed in 63 % of our series, the timing of therapy was not independently associated with survival, probably reflecting the seriousness of underlying diseases. Moreover, since the ESCMID (European Society for Clinical Microbiology and Infectious Diseases) guidelines were released in 2012 [75], the prevalent use of fluconazole rather than echinocandins as initial antifungal is partially justified by the study period considered. Although there is general agreement that echinocandins should be the initial choice in more severely affected patients (such as those with sepsis or hospitalized in ICU) [76, 77], in a recent analysis conducted on 689 ventilated patients with candidaemia, fluconazole as initial monotherapy was significantly associated with longer survival compared with echinocandins [78], in contrast to recent recommendations which, indeed, are based on limited clinical data. The high prevalence of *C. albicans* isolates with low fluconazole resistance, reported by many authors, as well as the low resistance to azoles observed in our series, may account for these discordant data. Nevertheless, deviations from international guidelines were frequently observed in our series, mainly due to suboptimal dosing of fluconazole and short-term therapy (less than 14 days, data not shown). This is an emerging problem with regard to antifungal therapy asking for implementation of antifungal stewardship programme in every hospital. In addition, of the 22 % of patients whose initial antifungal treatment was changed, 65 % switched from azoles to echinocandins, while only in one patient therapy was de-escalated from echinocandins to fluconazole, according to guidelines, as in the other 2 patients the switch was due to intolerance. Noteworthy, 21 % of patients did not receive any antifungal therapy because of a late diagnosis (they either died or were discharged before

the culture results), highlighting the importance of a strict surveillance of hospitalized at risk patients and the need to implement diagnostic tests, such as serum 1,3-β-D-glucan.

The crude in-hospital mortality rate of candidaemia in the present study was still high (41.6 %) and similar to that reported in the literature (30–61 %) [3, 9, 18], in studies from Italy, Spain, North America, Taiwan and Korea [3, 16, 17, 20, 32, 62]. However, it is worth noting the fact that lower rate (about 20 %) [41, 47] but also much higher rate (up to 60–70 %) [44, 55] has been recently recorded in the literature.

The time to discharge was significantly longer in ICU patients and in CVC carriers, possibly for the higher severity of underlying diseases.

Limitations of the present study are mainly related to its retrospective nature with limited follow-up data; although all data had been collected prospectively, some variables could not be explored because of missing data. Furthermore, the study was conducted in a single centre, characterized by the absence of haematology and transplantation wards, where candidaemia is especially frequent; nevertheless, this limited the differences in clinical practices, often observed in multicentre studies.

In conclusion, this report confirms the increasing rate of candidaemia observed in northern Italy, even in a hospital lacking some of the population hosts considered at highest risk. *Candida glabrata*, a species characterized by frequent dose-dependent susceptibility to fluconazole, emerged as the most frequently isolated yeast after *C. albicans* in Internal Medicine and ICU wards, calling for an initial choice of antifungal therapy with echinocandins pending fungal identification and susceptibility results.

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