European Review for Medical and Pharmacological Sciences 2014; 18: 661-674

Candidemia in intensive care unit: a nationwide prospective observational survey (GISIA-3 study) and review of the European literature from 2000 through 2013

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Abstract. – BACKGROUND: ***Candida*** **bloodstream infections (BSI) represent an important problem in Intensive Care Units (ICUs). The epidemiology of candidemia is changing with an increase in the proportion of *Candida* (C.) non-*albicans*.**

OBJECTIVES: An Italian 2-year observational survey on ICU was conducted to evaluate the species distribution and possible differences between BSI caused by *C. albicans* and *C.* non-*albicans.* For comparative purposes, we performed a European literature-based review to evaluate distribution and frequency of *Candida* spp. causing ICU candidemia, during the period 2000-2013.

MATERIALS AND METHODS: This laboratory-based survey involved 15 microbiology centers (GISIA-3 study). All candidemia episodes in adult patients were considered. Data were prospectively collected from 2007 to 2008. PubMed was searched for peer-reviewed articles.

RESULTS: In total, 462 candidemia episodes were collected. *C. albicans* accounted for 49.4% of the isolates, followed by *C. parapsilosis* (26.2%) and *C. glabrata* (10.4%). Mortality was higher in patients with *C.* non-*albicans* than *C. albicans* (47.3% vs. 32.4 %, $p > 0.05$). Among risk factors, parenteral nutrition was more common ($p = 0.02$) in non-*albicans* candidemia, while surgery was more frequent ($p = 0.02$) in *C. albicans* candidemia. Twenty-four relevant articles were identified. *C. albicans* was the predominant species in almost all studies (range 37.9% -76.3%). *C. glabrata* was commonly isolated in the German-speaking countries, France, UK and North Europe; *C. parapsilosis* in Turkey, Greece and Spain.

CONCLUSIONS: Although *C.* non-*albicans* BSI is increasing, our study shows that *C. albicans* is still the predominant species in ICU candidemia. There are differences in the epidemiology of *Candida* BSI among European countries, with a prevalence of *C. glabrata* and *C. parapsilosis* in Northern and Southern countries, respectively.

Key Words:
Yeast infections, Candidemia, Intensive Care Unit, Literature review, *Candida* spp.

Introduction

Candida bloodstream infections (BSI) represent an important problem in critically ill patients hospitalized in Intensive Care Units (ICUs). *Can-*

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dida BSI is often a consequence of the use of complex surgical procedures, invasive medical devices, and/or long term broad spectrum antibiotic therapy[1]. The Extended Prevalence of Infection in Intensive Care (EPIC II) survey, which included 14,414 patients from 1265 ICUs across 75 countries, provided an up-to date picture of the prevalence, treatment, and outcomes of ICU infections[2-3]. A subgroup analysis of the BSI data, recorded a prevalence of 6.9 candidemia cases/1000 patients, and showed that candidemia was associated with the highest mortality rate (43%) of all BSIs[2]. Invasive *Candida* infections are associated with prolonged hospital stays and increased costs of medical care[4]. Although *C. albicans* (CA) is still the most common species[2,5], recent epidemiological studies have demonstrated an increasing incidence of *C.* non-*albicans* (CnA) candidemia among critically ill patients[6]. Generally, *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. krusei* represent about one half of all cases of candidemia, with *C. glabrata* ranked as second in the USA, Northern Europe and Australia[7-9], while *C. parapsilosis* is the most relevant non-*albicans* species in Latin America and Southern Europe[10-12].

In Italy, national epidemiological data on *Candida* BSI in critically ill patients are lacking[13]: recent epidemiological studies are limited to selected hospitals or a specific region[14-16]. Therefore, we conducted a 2-year large observational Italian survey on candidemia in ICU to evaluate the species distribution and to identify possible differences between BSI due to CA and CnA. For comparative purposes, we performed a literature based review of European studies concerning the distribution and the frequency of *Candida* spp. causing BSI in adult ICU patients, during the period 2000 to 2013.

Materials and methods

Design of the study

This study was performed in the context of the GISIA-3 study, designed as a prospective, observational nationwide laboratory-based survey from January 2007 to December 2008. This investigation involved 15 Microbiology Centers distributed all over Italy and representative of the country. The primary aim of GISIA-3 was to characterize the freshly isolated yeast strains in terms of their *in vitro* susceptibility to systemic antifungal drugs available in Italy at the time of the study[17].

In this study, we considered only patients older than 18 years who developed candidemia, either on admission or during their stay in the ICU. For patients with multiple candidemic episodes, only the first episode was included. Detection and species identification of *Candida* isolates were performed in the notifying laboratories according to standard protocols in use in each laboratory. A common dataset was used to collect data about age, gender, reasons for ICU admission (medical, surgical or trauma), predisposing risk factors for *Candida* BSI [*i.e.* vascular lines (for > 3 days), treatment with broad spectrum antibiotics (for > 5 days)] and outcome at 30 days after diagnosis]. At the time of study, informed consent was not required because of the observational nature of the surveillance.

Case identification

An episode of candidemia was defined as isolation of *Candida* spp. from blood culture in a patient with temporally related clinical signs and symptoms. Subsequent positive cultures from the same patient were defined as a new episode only if there was an interval of ≥4 weeks between the two episodes. According to diagnoses at the time of ICU admission, patients were classified as surgical, trauma, or medical. Surgical patients were those admitted in ICU for the postoperative control of an elective procedure, trauma patients were those with trauma-related acute lesions, and medical patients were those admitted for any other critical illness. A case was defined as likely to be catheter related when (1) semi-quantitative culture of the catheter tip yielded more than 15 CFU of a *Candida* species or (2) simultaneous quantitative cultures of blood samples showed a ratio of 5:1 in CFU of blood samples obtained through the catheter and a peripheral vein.

Statistical Analysis

SAS system version 9.2 was used for statistical analysis. Categorical variables were given as number and percentages. The Chi-square test was used to evaluate the difference in prevalence between CA and CnA. Kaplan-Meier survival curves and log-rank test results were performed for survival comparisons between CA and CnA candidemia groups. A p-value <0.05 was considered significant.

Literature Review Criteria

A review of full-text articles published in English from January 2000 to February 2013 was

performed. Four of the authors (MTM, GM, GL, EB) independently performed the literature search to judge the contents of the articles separately; disagreement in opinion about evaluations was solved by discussion.

The MEDLINE database was used for the bibliographic research, using the following key words: "candidemia", "Candida epidemiology", "candidemia intensive care unit", "*Candida* intensive care unit" and "fungemia". In addition, the bibliographies of the selected articles were reviewed for relevant publications. The exclusion criteria were: studies carried out prior to year 2000, letters and randomized controlled trials, and studies reporting a total number of *Candida* spp. isolates less than ten. From each selected study, the following data were collected: geographic location, year of publication, study period, type of study, total number of isolated *Candida* spp., and relative proportion of each *Candida* spp. In addition, if data were available, the risk factors for CA and CnA candidemia in the ICU were analyzed.

Results

Prospective Analysis of Cases in Italy

The surveillance identified 462 cases of candidemia. CA was isolated with the highest frequency (49.4%); *C. parapsilosis* ranked second (26.2%), followed by *C. glabrata* (10.4%), *C. tropicalis* (6.5%), *C. krusei* (2.8%), *C. guilliermondii* (1.5%), *C. lusitaniae* (1.3%), *C. lipolytica* (0.6%) and *C. famata*, *C. sake*, *C. utilis* (0.4%, each one). Sixty-one percent of the patients were men and the highest frequency of candidemia occurred in patients aged >51 years (56.3%). A total of 412 patients had central lines in *situ* at the onset of candidemia. Catheters were studied for the source of infection in 249 cases: 196 (78.7%) were likely catheter associated. Most patients had undergone a surgical procedure (45.5%). In this group, gastrointestinal surgery was predominant (53.8%), followed by cardiac surgery (23.3%). Surgical patients were more likely to develop CA than CnA candidemia (50.9 % vs. 40.2%, $p = 0.02$). Parenteral nutrition was significantly more frequent when candidemia was due to CnA than when it was due to CA (60.2% vs. 49.6%, $p = 0.02$) (Table I).

Data on outcome was available for 201 patients: 79 (39.3%) died within 1 month after onset of candidemia. Figure 1 presents the Kaplan-Meier survival curves of patients with CA and CnA candidemia: the *p*-value of the log-rank test was 0.492.

Literature Review

A literature search to identify *Candida* species responsible of candidemia was performed. Comparison of data among studies should be compromised by differences in case definitions and data collection methods. The studies cited in this review were, therefore, chosen to provide only a

Table I. Characteristics of ICU patients with candidemia, Italy 2007-2008.

Characteristics[#]	Total n. 462	*C. albicans* n. 228 (49.4)[§]	*C.* non-*albicans* n. 234 (50.6)[§]
Age			
18-50	202 (43.7)	110 (48.2)	92 (39.3)
51-99	260 (56.3)	118 (51.8)	142 (60.7)
Male	281 (60.8)	139 (61.0)	142 (60.7)
Admission service			
Medical	191 (41.3)	87 (38.2)	104 (44.4)
Surgery*	210 (45.5)	116 (50.9)	94 (40.2)
Trauma	61 (13.2)	25 (11.0)	36 (15.4)
Central venous catheterization	412 (89.2)	209 (91.7)	203 (86.7)
Antibacterial therapy	282 (61.0)	145 (63.6)	137 (58.5)
Total parenteral nutrition*	254 (55.0)	113 (49.6)	141 (60.2)
Diabetes mellitus	44 (9.5)	26 (11.4)	18 (7.7)
Solid neoplastic tumor	28 (6.1)	10 (4.4)	18 (7.7)
Corticotherapy	26 (5.6)	9 (3.9)	17 (7.3)
Burns	21 (4.5)	9 (3.9)	12 (5.1)
Hematological malignancy	19 (4.1)	5 (2.2)	14 (6.0)

[#]More than one factor may be present in a single case; [*]Statistically significant *p*-value (< 0.05); [§]Numbers in parentheses, percent.

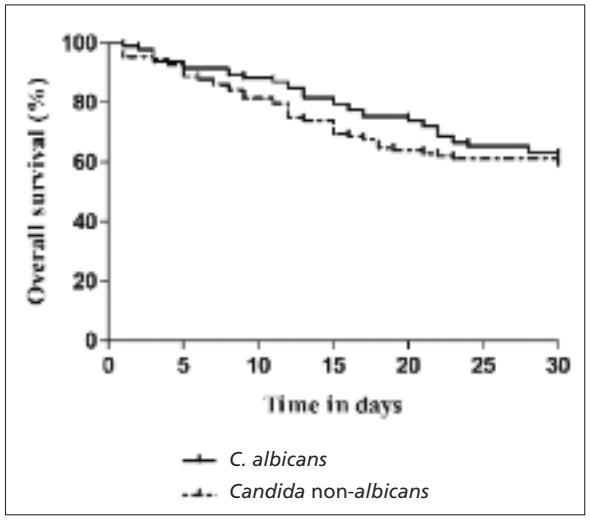

Figure 1. Kaplan Meier curves for survival time in ICU patients with *Candida albicans* (solid line) and *Candida* non-*albicans* candidemia (dash line); Log rank test, $p = 0.4922$.

broad overview of the European epidemiology of candidemia.

We selected a total of 24 articles (Table II). In 21 studies, CA was the most common species: in 17 articles it accounted for 51.3% to 76.3% of all *Candida* infections[13,18-33], and in four studies from southern European countries, the proportion of CA was between 37.9% and 49%[14,16,34-35]. In the remaining three studies, the proportion of CA was extremely low. In two studies conducted in Turkey[10,36], CA strains accounted for 18.6% and 22.9% of all *Candida* infections. In a survey from Greece[12], CA and *C. parapsilosis* were almost equally distributed (33.3% and 36.4%, respectively).

Regarding CnA, the three most prevalent species were *C. glabrata*, *C. parapsilosis* and *C. tropicalis*.

Candida glabrata was prevalent in studies from German-speaking countries, France, UK, and North Europe, reaching proportions of 13.2-31.2%[19,21-23,26-28,30-31,33]. *Candida parapsilosis* emerged as an important opportunistic fungal pathogen in the Mediterranean area: Turkey (77.1%), Italy (37%), Greece (36.4%) and Spain (28.8%)[12,16,35-36]. In contrast, *C. parapsilosis* was a less common cause of candidemia in recent surveys from France[30] and Denmark[19] (0% and 2.6%, respectively).

Candida tropicalis was, in general, less prevalent. It was the fourth most common species of *Candida* in German-speaking countries, France, Italy and Polish[13,20-22,27-29,31], and the second in Portugal[34] and in Turkey[10,25], accounting for 21.2% and 12.7% of all *Candida* BSIs, respectively.

Table III lists the association of CA and CnA candidemia with risk factors as reported in five out of the 24 studies of candidemia considered for analysis. Four studies did not find any difference when examining central venous catheter (CVC) placement or glucocorticosteroid therapy[14,24,26,28]: in only one study[24] was CnA candidemia independently associated with CVC and significantly associated with glucocorticosteroid therapy on multivariate analysis. In addition, Holley et al[26] found the duration of CVC placement to be predictive for a CnA BSI. Four studies examined surgery[14,16,26,28] and diabetes mellitus[16,24,26,28]; in only one study[16], diabetes was associated with a four-fold increased risk of developing CA BSI and abdominal surgery two-fold, compared to CnA BSI.

The issue of antifungal prophylaxis is addressed by all five studies. In this Italian study[16], previous exposure to azole drugs reduced the risk of CA infection. In another Italian surveillance report[14], an increase in the proportion of CnA was associated with increasing use of fluconazole prophylaxis (from 21% to 76% between 2000 and 2003). In one of the studies[24], the difference in mortality between CnA and CA was statistically significant using multivariate analysis, showing an odds ratio of 6.7 for lethal outcome in ICU patients with CnA, compared with CA candidemia. A number of other risk factors (neutropenia, parenteral nutrition, solid tumor and duration of mechanical ventilation) were significantly associated with the occurrence of CnA infections, but only on univariate analysis.

Discussion

Invasive candidiasis is the most frequent life-threatening fungal disease in ICU patients[3], and candidemia represents more than two thirds of all invasive cases[8]. *Candida albicans* is the dominant species causing BSIs[2], and in most series it remains close to 50%[37-38].

In our data, CA was the leading fungal pathogen, accounting for 49% of *Candida* BSIs; this figure is in agreement with frequencies reported from other European countries[34-35]. Over the last two decades, an increase in the proportion of CnA bloodstream isolates has been re-

Table II. Distribution of *Candida* spp. from bloodstream infections in ICU patients, Europe 2000-2013.

Author		Presterl et al. 2007[31]	Lagrou et al. 2007[27]	Holley et al. 2009[26f]	Arendrup et al. 2011[19]	Dimopoulos et al. 2008[24]	Holley et al. 2009[26f]
Country/Period of design observation		**Austria** 2001-2006	**Belgium** 2001-2005	**Belgium** 2001-2006	**Denmark** 2006	**Greece** 2001-2005	**Greece** 2001-2006
Study design/setting		Retrospective observational study/single university hospital - medical, surgical ICU and wards	Retrospective hospital-based study/single university hospital - medical-surgical ICU and wards	Retrospective cohort study/single university hospital - multidisciplinary ICU	Prospective semi-national surveillance/10 university hospitals, 20 district hospitals - mixed, surgical, medical ICUs	Prospective observational study/single tertiary hospital - medical-surgical ICU[c]	Retrospective cohort study/single university hospital multidisciplinary ICU
% of isolates	No. Isolates[a]	104	140	55	155	56[d]	49
	C. albicans	69.2	63.0	52.7	60.0	64.3	63.3
	C. parapsilosis	7.7	6.2	7.3	2.6	5.4	12.2
	C. glabrata	14.4	22.6	29.1	20.6	14.3	12.2
	C. tropicalis	5.8	4.1	7.3	3.9	10.7	6.1
	C. krusei	—	—	7.3	7.1	1.8	6.1
	C. kefyr	—	—	—	—	—	—
	C. dubliniensis	—	—	—	1.9	1.8	—
	C. famata	—	—	—	—	—	—
	C. guilliermondii	—	—	—	—	—	—
	C. intermedia	—	—	—	—	—	—
	C. lipolytica	—	—	—	—	—	—
	C. lusitaniae	1.0	—	—	—	1.8	—
	C. norvegensis	—	—	—	—	—	—
	C. sake	—		—	—	—	—
	C. utilis	1.0		—	—	—	—
	Candida spp.[b]	1.0	4.1	—	3.9	—	—

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Table II. Distribution of *Candida* spp. from bloodstream infections in ICU patients, Europe 2000-2013.

Author		Vardakas, et al. 2009[32]	Pratikaki et al. 2011[12]	Ylipalosaari et al. 2012[33]	Bougnoux et al. 2008[21]	Cohen et al. 2010[22]	Leroy et al. 2010[28]
Country/Period of design observation		**Greece** 2001-2007	**Greece** 2004-2006	**Finland** 2000-2009	**France** 2001-2002	**France** 2003-2006	**France** 2005-2006
Study design/setting		Retrospective case-control study/single hospital - medical, surgical ICU	Prospective mached case-control study/single teaching hospital - medical-surgical ICU[c]	Retrospective cohort study/single university hospital - medical-surgical ICU	Prospective observational study/14 university hospitals - surgical medical, hematology unit and burn ICUs	Prospective cohort study/five university affiliated-tertiary care hospitals - ? ICUs[c e]	Prospective national observational study/? hospitals-medical-surgical, medical and surgical ICUs
% of isolates	No. Isolates[a]	46[d]	33[d]	38[d]	57[d]	154	141
	C. albicans	67.4	33.3	76.3	54.2	59.1	55.3
	C. parapsilosis	4.3	36.4	7.9	13.5	1.3	8.5
	C. glabrata	4.3	15.2	13.2	17.0	31.2	17.7
	C. tropicalis	10.9	6.1	—	8.5	7.8	6.4
	C. krusei	2.2	—	—	3.5	0.6	4.3
	C. kefyr	—	—	—	—	—	2.8
	C. dubliniensis	—	—	—	—	—	—
	C. famata	6.5	6.1	—	—	—	—
	C. guilliermondii	4.3	—	—	—	—	—
	C. intermedia	—	—	—	—	—	—
	C. lipolytica	—	—	—	—	—	—
	C. lusitaniae	—	3.0	—	—	—	—
	C. norvegensis	—	—	—	—	—	—
	C. sake	—	—	—	—	—	—
	C. utilis	—	—	—	—	—	—
	Candida spp.[b]	13.0	—	2.6	3.3	—	5.0

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Table II. Distribution of *Candida* spp. from bloodstream infections in ICU patients, Europe 2000-2013.

Author		Parmeland et al. 2013[30]	Bassetti et al. 2006[14]	Tortorano et al. 2012[13]	Montagna et al. 2013[16]	Bassetti et al. 2011[20]	Montagna et al. present study
Country/Period of design observation		**France** 2009-2010	**Italy** 2000-2003 (original period 1999-2003)	**Italy** 2006-2008	**Italy** 2007-2008	**Italy** 2008-2010	**Italy** 2007-2008
Study design/setting		Prospective laboratory based study/single institutional hospital - ? ICU and works	Retrospective laboratory based study/single university hospital - medical-surgical ICU and wards	Prospective observational study/27 hospital medical-surgical ICUs	Prospective observational study/16 hospitals - medical, surgical ICUs	Prospective laboratory - based study/single university hospital - ? ICUs	Prospective laboratory based study/15 hospitals- medical-surgical, ICUs
% of isolates	No. Isolates[a]	56	161[d]	239	92	68	462
	C. albicans	58.9	37.9	60.7	40.2	66.2	49.4
	C. parapsilosis	—	24.8	15.9	37.0	19.1	26.2
	C. glabrata	21.4	16.8	13.0	9.8	8.8	10.4
	C. tropicalis	7.1	7.5	5.9	9.8	–	6.5
	C. krusei	7.1	—	1.7	—	2.9	2.8
	C. kefyr	—	—	—	—	—	—
	C. dubliniensis	—	—	—	—	—	—
	C. famata	—	—	—	—	—	0,4
	C. guilliermondii	—	—	0.8	1.1	—	1.5
	C. intermedia	—	—	0.4	1.1	—	—
	C. lipolytica	—	—	0.4	—	—	0.6
	C. lusitaniae	—	—	1.3	—	—	1.3
	C. norvegensis	—	—	—	1.1	—	—
	C. sake	—	—	—	1.1	—	0.4
	C. utilis	—	—	—	—	—	0.4
	Candida spp.[b]	5.4	13.0	—	—	2.9	—

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Table II. Distribution of *Candida* spp. from bloodstream infections in ICU patients, Europe 2000-2013.

Author		Nawrot et al. 2013[29]	Costa-de-Oliveira et al. 2008[34]	Almirante et al. 2005[18]	Pemàn et al. 2012[35]	Gürcüoglu et al. 2010[25]
Country/Period of design observation		**Polish** 2006-2007	**Portugal** 2004	**Spain** 2002-2003	**Spain** 2009-2010	**Turkey** 2002-2007 (original period 1996-2007)
Study design/setting		Retrospective laboratory based study/20 hospital - ? ICU and wards	Prospective observational study/single university hospital - ? ICU and wards	Prospective population-based study/14 hospital - ? ICU and wards	Prospective population-based study/44 tertiary hospital - ? ICU and wards	Retrospective observational study/single tertiary-care hospital-multidisciplinary ICU
% of isolates	No. Isolates[a]	98	33	115	469	76
	C. albicans	61.2	48.5	51.3	49.0	55.3
	C. parapsilosis	15.3	18.2	27.0	28.8	23.7
	C. glabrata	12.2	9.1	6.1	9.6	2.6
	C. tropicalis	3.1	21.2	8.7	8.7	10.5
	C. krusei	1.0	—	3.5	1.3	2.6
	C. kefyr	—	—	—	—	2.6
	C. dubliniensis	—	—	—	—	—
	C. famata	—	—	—	—	—
	C. guilliermondii	—	—	—	—	—
	C. intermedia	—	—	—	—	—
	C. lipolytica	—	—	—	—	—
	C. lusitaniae	—	—	—	—	—
	C. norvegensis	—	—	—	—	—
	C. sake	—	—	—	—	—
	C. utilis	—	—	—	—	—
	Candida spp.[b]	7.1	3.0	3.5	2.8	2.6

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Table II. Distribution of *Candida* spp. from bloodstream infections in ICU patients, Europe 2000-2013.

Author		Horasan et al. 2010	Dizbay et al. 2010[36]	Das et al. 2011[23]
Country/Period of design observation		**Turkey** 2004-2009	**Turkey** 2007	**UK** 2005-2008
Study design/setting		Retrospective cohort study/single university hospital - medical-surgical, ICU	Prospective laboratory-based study/single tertiary hospital – surgical, anesthesiology, internal, medicine, neurology ICU[c]	Prospective observational study/single tertiary hospital - ? ICU and wards
% of isolates	No. Isolates[a]	118[d]	35	55
	C. albicans	18.6	22.9	52.7
	C. parapsilosis	66.1	77.1	16.4
	C. glabrata	2.5	—	21.8
	C. tropicalis	12.7	—	—
	C. krusei	—	—	—
	C. kefyr	—	—	—
	C. dubliniensis	—	—	—
	C. famata	—	—	—
	C. guilliermondii	—	—	—
	C. intermedia	—	—	—
	C. lipolytica	—	—	—
	C. lusitaniae	—	—	—
	C. norvegensis	—	—	—
	C. sake	—	—	—
	C. utilis	—	—	—
	Candida spp.[b]	—	—	9.1

[a]Refers to the total number of *Candida* isolates from blood (or to the total number of candidemia episodes where the former was not available from the original study). [b]Includes *Candida* spp. not depicted in the table and *Candida* spp. not identified to species level. [c]Non-neutropenic critically ill patients. [d]Patients staying 48 h or more after ICU admission. [e]No fungal colonization. [f]The results for this study cover two countries. [?]Data were not available.

ported in critically ill adults, and in some ICUs it has been higher than 50%[37-38]. Similarly, we also found a slightly higher percentage of CnA (51%) than CA. The reason for this increase in CnA is not yet completely understood. It is possible that prophylaxis with fluconazole plays an important role[7,9,14] . However, a recent study of ICU patients shows that prophylaxis with fluconazole did not increase the proportion of invasive candidiasis caused by CnA[39]. On the other hand, the increase in CnA, may, at least in part, reflect a more accurate identification of yeast isolates at the species level. Yet, we cannot exclude the possibility that an ever-increasing number of previously non-pathogenic species are now emerging as opportunistic pathogens related to the increased number of immunocompromised subjects[40].

In our work, as well as those selected from literature, *C. parapsilosis*, *C. glabrata* and *C. tropicalis* account for around 80% of all CnA candidemia. In addition, a variation in the distribution of these three *Candida* species results throughout the Europe, with a north-south drift. *Candida glabrata* was the second most common species recovered in German-speaking countries, France, UK, and North Europe[19,21-23,26-28,30-31,33] while in Greece, Italy, Polish and Spain it ranked number 3[12-14,20,24,29,32,35]. *Candida parapsilosis* has emerged as an important opportunistic fungal pathogen in Turkey accounting for 66.1% to 77.1% of all *Candida* BSIs[10,36]. The lowest proportion was reported in France[30] and Denmark[19]. The proportion of *C. tropicalis* was generally low in all geographic region except in Portugal[34] and Turkey[10,25] where it ranked second. In addition to the difference across countries, there are also variations within the same country. Proportions of *C. parapsilosis* candidemia in Greek hospitals ranged from 36.4% to 5.4%[12,24] .

This variability may reflect differences in health care practices among different countries, as well as the study design adopted by different

Table III. Risk factors for *Candida albicans* and *C.* non-*albicans*, Europe 2000-2013.

Risk factor	Study	Univariate analysis OR (95% CI)	*p*-value	Multivariate analysis OR (95% CI)	*p*-value	Comment
Abdominal surgery	Montagna et al, 2013[16]	NS	< 0.05	2.3 (1.9 to 3.2)	< 0.05	Independent risk for *C. albicans*
Age	Bassetti et al, 2006[14]	…	< 0.05	NC		Older in *C.* non-*albicans*
Antifungal prophylaxis	Montagna et al, 2013[16]	NS	< 0.05	0.2 (0.04 to 0.9)	< 0.05	Reduced risk for *C. albicans*
Candiduria	Dimopoulos et al, 2008[24]	NS	< 0.001	16.5 (1.6 to 173.9)	0.02	Independent risk for *C.* non-*albicans*
CVC	Dimopoulos et al, 2008[24]	NS	0.02	26.2 (2.1 to 334.8)	0.01	Independent risk for *C.* non-*albicans*
CVC days	Holley et al, 2009[26]	…	0.004	1.2 (1.05 to 1.3)	0.005	Independent risk for *C.* non-*albicans*
Diabetes mellitus	Montagna et al, 2013[16]	NS	< 0.05	4.9 (1.02 to 9.3)	< 0.05	Independent risk for *C. albicans*
Female gender	Holley et al, 2009[26]	2.1 (1.2 to 3.9)	0.010	2.1 (1.1 to 3.9)	0.018	Independent risk for *C.* non-*albicans*
Glucocorticosteroids	Dimopoulos et al, 2008[24]	NS	0.005	45.1(3 to 669.9)	0.005	Independent risk for *C.* non-*albicans*
LOS	Montagna et al, 2013[16]	…	< 0.05	–		Shorter in *C. albicans*
	Leroy et al, 2010[28]	…	0.03	NC		Shorter in *C. albicans*
Neutropenia	Leroy et al, 2010[28]	NS	0.04	NC		Associated with *C.* non-*albicans*
Parenteral nutrition	Montagna et al, 2013[16]	NS	< 0.05	–		Associated with *C.* non-*albicans*
	Holley et al, 2009[26]	2.4 (1.0 to 5.8)	0.048	–		Increased likelihood of *C.* non-*albicans*
	Dimopoulos et al, 2008[24]	NS	0.03	–		Associated with *C.* non-*albicans*
	Montagna et al, present study	NS	0.02	NC		Associated with *C.* non-*albicans*
SAPS II	Leroy et al, 2010[28]	…	0.015	NC		Higher in *C. albicans*
SOFA	Leroy et al, 2010[28]	…	0.03	NC		Higher in *C. albicans*
Solid tumor surgery	Bassetti et al, 2006[14]	NS	< 0.05	NC		Associated with *C.* non-*albicans*
	Montagna et al, present study	NS	0.02	NC		Associated with *C. albicans*
Trauma	Holley et al, 2009[26]	8.9 (1.1 to 71.3)	0.014	–		Increased likelihood of *C. albicans*
Ventilator days	Holley et al, 2009[26]	…	0.024	–		Longer in *C.* non-*albicans*
Mortality rate	Dimopoulos et al, 2008[24]	NS	0.005	6.7 (1.2 to 37.7)	0.03	Higher in patients with *C.* non-*albicans*

OR = odds ratio; CI = confidence interval; CVC = central venous catheter; LOS = length of stay; NC = not calculated; NS = not specified; SAPS = simplified acute physiology score; SOFA = sepsis-related organ failure assessment.

authors, including differences in the examined population and the case definition. In our experience, *C. parapsilosis* was the second most common species, responsible for roughly a quarter of all candidemia episodes, according to data from studies carried out in South Europe[16,24-25,35]. However, differences were observed when we considered the Italian regions; the proportions of *C. parapsilosis* and *C. glabrata* varied from North to South, but only *C. glabrata* isolation showed a statistically significant difference ($p < 0.001$)[17] .

Concerning risk factors, the most commonly recognized risk factors were: number of antibiotics received prior to candidemia development; isolation of *Candida* spp. from sites other than blood; previous hemodialysis; prior use of a Hickman catheter; recent extensive gastro-abdominal surgery, and length of ICU stay. Several risk factors were likely to be combined in individual patients. Furthermore, some subsets of ICU patients were at particular risk for candidemia, such as those with peritonitis, acute pancreatitis, neutropenia, or cancer patients exposed to chemotherapy[37,41-43].

Our data from GISIA-3 study are in agreement with above-mentioned studies. In addition, according to other authors[44], 78.7% of analyzed catheters should be considered a source of *Candida* BSI, highlighting the relevance of catheter-related candidemia. Candidemia associated with intravenous lines is problematic since these devices act as substrates for production of biofilm, which shows resistance to immunological effector mechanisms and to the activity of antifungal agents[45].

Few studies are available on the differences in the risk factors between CA and CnA BSIs in ICU patients. Some authors do not identify any differences[46], while our literature review highlights contradictory results. In fact, many potential risk factors for CnA BSI have been found (presence of CVCs, duration of CVC implantation, corticotherapy, female gender, neutropenia, receipt of parenteral nutrition, presence of solid tumor, and duration of mechanical ventilation), but no clinical factors appeared sufficiently pertinent to guide the choice of empirical antifungal therapy.

GISIA-3 data highlights an association between parenteral nutrition and CnA, and the high proportion of *C. parapsilosis* may explain this finding. Parenteral nutrition facilitates *C. parapsilosis* disease, since the yeast possesses a selective growth advantage in hyperalimentation solutions with high concentrations of glucose[47]. Conversely, surgery resulted more frequently in CA infection, although other authors do not consider surgery a particular risk factor for CA candidemia development[9,22].

It is well known that *Candida* BSIs affect the survival of ICU patients. The EPIC II[2] reported that patients with candidemia, compared with patients with Gram-positive and Gram-negative infections, have the greatest crude ICU mortality (42.6%, 25.3%, and 29.1%, respectively). In this study, we had these data available only for 201 patients, the 30-day mortality rate was 39.3%, similar to that reported in previous researches[16,20,29]. Our finding supports that mortality associated with candidemia has not changed substantially in the past two decades, despite the availability of less toxic and more active antifungal agents. Although an increased mortality was reported in patients with CnA BSI[24], this relationship is not documented by other authors[16,26]. In our study, mortality rate was higher in patients with CnA compared with CA BSIs (47.3% vs. 32.4%, respectively), although the survey analysis was not statistically significant.

As GISIA-3 was an observational laboratory-based survey, our study has some limitations: (1) severity of illness scores was not obtained; (2) we did not have data on the type and duration of antifungal therapy; (3) data on mortality associated with candidemia were not available.

Nevertheless, this study shows that CA remains the predominant species in ICU candidemia and CnA BSI is increasing. In addition, our results reinforce the fact that candidemia plays an important role in ICU patients treated with indwelling devices and that *Candida* BSI is associated with high mortality. Our review reveals a geographic variation among cases of candidemia in different parts of the Europe, with a north-south drift, showing an increasing of *C. glabrata* in northern countries, and of *C. parapsilosis* in southern countries.

Conclusions

These data demonstrate that physicians should base their antifungal choices on local epidemiology. It is, therefore, important periodically to determine the distribution of *Candida* spp. in each institution, especially when empirical therapy is common practice.

Conflict of Interest

The GISIA-3 study was supported by Pfizer Italia, srl. Medical writing assistance was provided by Mary Hines, in Science Communications, Springer Healthcare. This assistance was funded by Pfizer Italia, srl. Maria Teresa Montagna received honoraria from MSD Italia, Pfizer Italia and Gilead. Giulia Morace received honoraria from Astellas Pharma SpA, MSD Italia, Pfizer Italia and Schering Plough Italia, Maria Teresa Montagna has been a speaker for MSD, Gilead and Pfizer. Giulia Morace has been a speaker for Gilead, Astellas and Pfizer.

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