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Epidemiology, Species Distribution, Antifungal Susceptibility, and Outcome of Candidemia across Five Sites in Italy and Spain

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Candidemia has become an important bloodstream infection that is frequently associated with high rates of mortality and morbidity, and its growing incidence is related to complex medical and surgical procedures. We conducted a multicenter study in five tertiary care teaching hospitals in Italy and Spain and evaluated the epidemiology, species distribution, antifungal susceptibilities, and outcomes of candidemia episodes. In the period of 2008 to 2010, 995 episodes of candidemia were identified in these hospitals. The overall incidence of candidemia was 1.55 cases per 1,000 admissions and remained stable during the 3-year analysis. *Candida albicans* was the leading agent of infection (58.4%), followed by *Candida parapsilosis* complex (19.5%), *Candida tropicalis* (9.3%), and *Candida glabrata* (8.3%). The majority of the candidemia episodes were found in the internal medicine department (49.6%), followed by the surgical ward, the intensive care unit (ICU), and the hemato-oncology ward. Out of 955 patients who were eligible for evaluation, 381 (39.9%) died within 30 days from the onset of candidemia. Important differences in the 30-day mortality rates were noted between institutions: the lowest mortality rate was in the Barcelona hospital, and the highest rate was in the Udine hospital (33.6% versus 51%, respectively; $P = 0.0005$). Overall, 5.1% of the 955 isolates tested were resistant or susceptible dose dependent (SDD) to fluconazole, with minor differences between the hospitals in Italy and Spain (5.7% versus 3.5%, respectively; $P = 0.2$). Higher MICs for caspofungin were found, especially with *C. parapsilosis* complex (MIC_{90}, 1 μg/ml). Amphotericin B had the lowest MICs. This report shows that candidemia is a significant source of morbidity in Europe, causing a substantial burden of disease and mortality.

Candida is an important cause of bloodstream infections (BSIs), leading to significant mortality and morbidity in health care settings. The incidence of candidemia is growing with the increasing complexity of surgical procedures, the existence of patient populations who are at higher risk of infection, and changes in patient demographics. The global incidence of candidemia increased 5-fold in the past 10 years, and *Candida* spp. are currently between the fourth and the sixth most common nosocomial bloodstream isolates found in studies done in the United States and Europe (1, 2). However, candidemia rates vary geographically. For example, an increasing incidence of candidemia in Iceland was reported for the period between 1980 and 1999 (3) but the same was not observed in Switzerland, where a national surveillance study showed that the incidence of candidemia had remained unchanged between 1991 and 2000 (2). Therefore, it seems that differences do exist in the epidemiology of candidemia between different countries, underscoring the need for continuous surveillance to monitor trends in the incidence, species distribution, and antifungal drug susceptibility profiles. The epidemiology of candidemia has been studied extensively in the United States, Europe, and some countries in South America (4–16).

Candidemia remains associated with high crude and attributable mortality rates and with increased costs of patient care and duration of hospitalization. The attributable mortality rates have been reported to range from 5% to 71%, and crude mortality rates have been reported to be as high as 81% (4–6, 14, 17–19). In terms of species of *Candida*, recently, a shift toward non-*albicans* species was reported by some authors, especially in hematological, transplanted, and intensive care unit (ICU) patients (12, 20, 21).

A reduced antifungal susceptibility in non-*albicans* *Candida* species and a correlation with routine fluconazole prophylactic use has been suggested (15). Intrinsic and emerging resistance to azoles represents a major challenge for empirical therapeutic and prophylactic strategies (5).

This study was performed to evaluate the contemporary epidemiology, species distribution, antifungal susceptibilities, and outcomes of candidemia episodes in five big teaching hospitals in Italy and Spain.

MATERIALS AND METHODS

The study was conducted in five tertiary care teaching hospitals in Italy and Spain: (i) Trieste University Hospital (700 beds) in Trieste, Italy, (ii) Santa Maria Misericordia University Hospital (1,200 beds) in Udine, Italy, (iii) Policlinico Gemelli (1,500 beds) in Rome, Italy, (iv) Val d'Hebron

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TABLE 1 Characteristics of 955 episodes of candidemia stratified by hospital

Patient characteristic	Data by hospital (*n*)[a]					
	U (126)	T (140)	R (456)	B (131)	S (102)	Total (955)
Age (mean [±SD]) (yr)	64.4 (21.4)	75.9 (16.1)	65 (15)	61 (19)	59.1 (14)	66.2 (13)
Male sex (*n* [%])	79 (63)	73 (52)	252 (55.2)	82 (62.6)	54 (52.9)	486 (57)
Underlying disease/history (*n* [%])						
Surgery	54 (43)	27 (38)	242 (53.2)	68 (52)	50 (49)	441 (46)
Solid organ transplantation	4 (3.2)	0	19 (4.2)	6 (4.5)	4 (3.9)	33 (3.4)
Hematologic malignancy	12 (10)	3 (4)	24 (5.2)	9 (6.9)	12 (11.8)	60 (6.3)
HIV	3 (2.49)	1 (1)	1 (1.1)	8 (6.1)	6 (5.9)	19 (2)
Solid tumor	47 (37.3)	39 (55)	153 (33.5)	11 (11.5)	35 (34.3)	285 (30)
Cardiovascular disease	72 (57)	12 (17)	143 (31.3)	30 (31)	18 (17.6)	275 (28.8)
Diabetes mellitus	27 (21.5)	26 (36)	100 (21.9)	68 (71.2)	21 (20.6)	242 (25.3)
Distribution of different *Candida* species (*n* [%/rank])						
C. albicans	79 (63/1)	77 (55/1)	274 (60.1/1)	78 (59.5/1)	50 (48.1/1)	558 (58.4/1)
C. parapsilosis complex	22 (17.4/2)	34 (24/2)	87 (19.1/2)	20 (15.3/2)	23 (22.1/2)	186 (19.5/2)
C. glabrata	11 (8.7/3)	14 (10/3)	33 (7.2/4)	14 (10.7/4)	7 (6.7/4)	79 (8.3/4)
C. tropicalis	9 (7.1/4)	6 (4/4)	38 (8.3/3)	15 (11.4/3)	21 (20.2/3)	89 (9.3/3)
Non-*albicans Candida* spp.	5 (2.4/5)	9 (7/5)	24 (5.2/5)	4 (3.11/5)	3 (2.9/5)	45 (4.7/5)

[a] U, Udine; T, Trieste; R, Rome; S, Seville; B, Barcelona.

Hospital (1,150 beds) in Barcelona, Spain, and (v) Virgen Del Rocio University Hospital (851 beds) in Seville, Spain. All patients admitted to these five hospitals who developed candidemia in the period of January 2008 to December 2010 were included in the study and prospectively followed. Patients with at least one positive blood culture for *Candida* spp. and a compatible clinical illness were identified through the microbiological laboratory database, and all information was recorded in an electronic database. For each patient, only the first episode of candidemia was recorded. Patients whose cultures grew >1 species of *Candida* were excluded from the analysis. Patients with candidemia were followed prospectively for 30 days or until their discharge from the hospital. Outcomes were recorded only for patients with ≥30 days of follow-up after the initial episode of candidemia.

During the study period, there were no changes in microbiological laboratory techniques in the five hospitals. *Candida* species were isolated from blood samples using the Bactec 860 system (Becton, Dickinson, Inc., Sparks, MD). The species were identified using the API ID 32C system (bioMérieux, Marcy l'Etoile, France) or the Vitek 2 system (bioMérieux). In the cases of inconclusive results obtained by both systems, isolates were definitively identified using supplemental tests, e.g., by the presence or absence of well-formed pseudohyphae on cornmeal-Tween 80 agar and growth at 42 to 45°C. The last test was also required to differentiate isolates of *C. albicans* from those of *Candida dubliniensis*. Antifungal susceptibility testing to amphotericin B, caspofungin, fluconazole, itraconazole, and voriconazole was performed using the Sensititre YeastOne colorimetric plate (Trek Diagnostic Systems, Cleveland, OH). MIC results were interpreted according to species-specific clinical breakpoints as established by the Clinical and Laboratory Standards Institute (CLSI) for amphotericin B, caspofungin, fluconazole, itraconazole (only with *C. albicans*), and voriconazole (22, 23).

The chi-square test or Fisher's exact test was used to compare categorical variables. Differences between the groups were considered to be significant for variables yielding a P value of <0.05.

This study was approved by the local institutional review boards, and written patient consent was not required because of the observational nature of this study.

RESULTS

A total of 995 episodes of candidemia were identified during the study period (January 2008 to December 2010). The median patient age was 66.2 years old and 57% were males. The demographic and clinical characteristics of the patients are summarized in Table 1. The majority of patients (93.1%) had one or more comorbidities at the time of candidemia diagnosis. Four hundred forty-one patients (46%) had undergone a surgical intervention, 285 (30%) had a solid tumor, 275 (28.8%) had cardiovascular diseases, 242 (25.3%) were diabetic, 60 (6.3%) had hematological malignancies, 33 (3.4%) received a solid organ transplantation, and 19 (2%) had human immunodeficiency virus (HIV) infection. The overall incidence of candidemia was 1.55 cases per 1,000 admissions and remained stable during the 3-year analysis. As shown in Table 2, the incidences differed across hospitals, with the highest incidence in Rome (2.53 cases per 1,000 admissions), and the lowest in Udine (0.8 per 1,000 admissions).

C. albicans was the leading cause of infection (58.4%), followed by *C. parapsilosis* complex (19.5%), *C. tropicalis* (9.3%), and *C. glabrata* (8.3%). *C. albicans* accounted for >50% of infections in all 3 Italian hospitals and in the hospital in Barcelona, Spain; only in Seville did non-*albicans Candida* species represent >50% of the isolates. The distribution of *C. albicans* and non-*albicans Candida* strains differed according to the patient population and risk factors, as shown in Fig. 1. In hemato-oncology patients, *C. albicans* was isolated in 41.8% of the cases, *C. tropicalis* in 20%, and *C.*

TABLE 2 Incidence of candidemia in the study period

Hospital	Mean incidence (no. of episodes/1,000 admissions) by period:			
	2008	2009	2010	2008–2010
Udine, Italy	0.73	0.79	0.84	0.8
Trieste, Italy	2.11	1.73	1.4	1.74
Rome, Italy	2.35	2.53	2.71	2.53
Barcelona, Spain	1.6	1.57	1.54	1.55
Seville, Spain	0.98	1.08	1.25	1.12
Overall	1.55	1.54	1.71	1.55

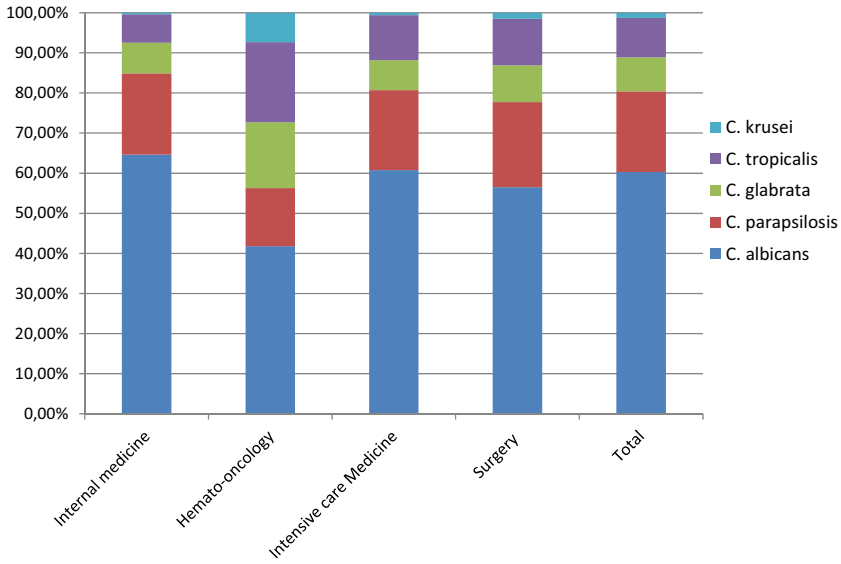

FIG 1 Distribution (%) of *Candida* species according to underlying pathology or medical care.

glabrata in 16.4%; in the internal medicine ward, the ICU, and the surgery ward, *C. albicans* accounted for around 60% of the cases.

The majority of the candidemia episodes were found in the internal medicine department (49.6%), followed by the surgery, ICU, and hemato-oncology wards (Table 3).

Crude mortality rates stratified by hospital and ward are reported in Table 3. Out of 955 evaluable patients, 381 (39.9%) died within 30 days from the onset of candidemia. Important differences in the 30-day mortality rates were noted between institutions: the lowest mortality rate was in the hospital in Barcelona, and the highest rate was in the hospital in Udine (33.6% and 51%, respectively; $P = 0.0005$).

Regarding the crude mortality rates in the different units, patients in hemato-oncology wards had the highest mortality rate (56.9%), followed by patients in the ICU (46%) and in the internal medicine wards (45.9%). Patients in general surgery showed the lowest mortality rate of all the centers, with a mean rate of 18.7%.

Table 4 shows the *in vitro* activities of 5 systemically active antifungal agents tested against 955 BSI isolates of *Candida* spp. based on CLSI breakpoints (23). The rates of susceptibility to fluconazole were 98.6% for *C. albicans* and 97.3% for *C. parapsilosis* complex. Decreased susceptibility to fluconazole was mostly seen with *C. glabrata* (54.4%) and *C. tropicalis* (94.9%). Overall, 5.1% of the 955 isolates tested were resistant, intermediate, or susceptible dose dependent (SDD) to fluconazole. Higher MICs for caspofungin were found in *C. albicans*, *C. glabrata*, and especially in *C. parapsilosis* complex (MIC_{90}, 1 μg/ml), which had 5 resistant strains (2.7%). Amphotericin B had the lowest MIC values. Some

TABLE 3 Thirty-day crude mortality rates and distributions of candidemia in hospital wards

Distribution of candidemia episodes/ mortality rate by hospital ward	Data by hospital (*n*)[a]					
	U (126)	T (140)	R (456)	B (131)	S (102)	Total (955)
Overall 30-day mortality rate (*n* [%])	64 (51)[b,c]	63 (45)	178 (39.9)[c]	44 (33.6)[b]	32 (31.4)[b]	381 (39.9)
Internal medicine						
n (%)	72 (57)	95 (67.8)	237 (56.9)	42 (32)	29 (28.4)	475 (49.7)
30-day mortality rate (*n* [%])	42 (52.3)[b,c]	48 (51.5)	108 (45.6)	13 (33.3)[b]	7 (24)[b]	218 (46)
Hemato-oncology						
n (%)	12 (10)	0 (0)	24 (5.3)	11 (8.4)	11 (10.8)	58 (6.1)
30-day mortality rate (*n* [%])	8 (67)[b]	0 (0)	16 (66.6)	4 (36.4)[b]	5 (45.5)	33 (56.9)
Intensive care						
n (%)	20 (16)	22 (15.7)	59 (12.9)	42 (32)	44 (43.1)	187 (19.6)
30-day mortality rate (*n* [%])	10 (50)	9 (41)	29 (49.1)	20 (47.6)	18 (41)	86 (46)
General surgery						
n (%)	22 (17)	23 (16.4)	136 (29.8)	36 (27.5)	18 (17.6)	235 (24.6)
30-day mortality rate (*n* [%])	4 (18)	6 (26)	25 (18.4)	7 (19.4)	2 (11.1)	44 (18.7)

[a] U, Udine; T, Trieste; R, Rome; S, Seville; B, Barcelona.
[b] U versus B and S, $P = 0.0005$.
[c] U versus R, $P = 0.002$.

TABLE 4 Frequency of antifungal resistance in *Candida* bloodstream infections according to CLSI breakpoints and MICs

Species (*n*)	Antifungal agent	No. (%) of isolates resistant, intermediate, or SDD to the antifungal agent in[a]:					Total no. of nonsusceptible strains (% SDD, intermediate, or resistant)	MIC_{50}/MIC_{90} (μg/ml) of isolates in:				
		U	T	B	R	S		U	T	B	R	S
C. albicans (558)	Amphotericin B	NA	NA	NA	NA	NA	NA	0.06/0.125	0.25/0.5	0.19/0.38	0.06/0.25	0.5/1
	Caspofungin	0	0	0	0	0	0	0.06/0.12	<0.06/0.12	0.047/0.125	0.03/0.125	0.03/0.06
	Fluconazole	2 (3.8)	1 (1)	0	5 (1.8)	0	8 (1.4)	0.25/1	<0.12/0.5	0.25/1	0.125/2	0.25/0.5
	Itraconazole	2 (6)	1 (1)	18 (23.1)	5 (1.8)	0	26 (4.7)	0.06/0.25	<0.06/0.12	0.047/0.5	0.06/0.5	0.03/0.0795
	Voriconazole	2 (3.8)	1 (1)	0	4 (1.5)	0	7 (1.2)	0.008/0.06	<0.06/<0.06	0.016/0.064	0.016/0.125	0.008/0.008
C. parapsilosis complex (186)	Amphotericin B	NA	NA	NA	NA	NA	NA	0.06/0.25	0.25/0.5	0.25/0.5	0.03/0.125	0.5/1
	Caspofungin	1 (4.5)	0	2 (10)	2 (2.3)	1 (4.3)	5 (2.7)	0.25/1	0.25/0.5	0.125/0.38	0.25/1	0.25/1
	Fluconazole	1 (4.5)	1 (3)	0	3 (3.4)	0	5 (2.7)	1/4	0.5/1	0.25/1.5	0.25/1	1/1
	Itraconazole	NA	NA	NA	NA	NA	NA	0.06/0.25	0.06/0.25	0.032/0.25	0.06/0.25	0.06/0.125
	Voriconazole	2 (9)	0	0	0	0	2 (1)	0.023/0.125	<0.06/<0.06	0.008/0.047	0.03/0.125	0.008/0.03
C. glabrata (79)	Amphotericin B	NA	NA	NA	NA	NA	NA	0.125/0.25	0.25/1	0.5/1	0.125/0.25	0.5/1
	Caspofungin	0	0	0	0	0	0	0.09/0.125	<0.06/0.12	0.064/0.19	0.016/0.06	0.06/0.86
	Fluconazole	1 (10)	7 (50)	16 (48.5)	9 (27.3)	3 (42.8)	36 (45.6)	4/8	8/16	3/16	4/128	16/128
	Itraconazole	NA	NA	NA	NA	NA	NA	0.25/0.5	0.5/4	1/4	0.06/4	0.5/11.2
	Voriconazole	NA	NA	NA	NA	NA	NA	0.045/0.25	0.5/1	0.094/0.19	0.06/8	0.25/2.8
C. tropicalis (89)	Amphotericin B	NA	NA	NA	NA	NA	NA	0.25/0.5	0.5/1	0.19/0.38	0.125/0.5	1/1
	Caspofungin	0	0	0	0	0	0	0.120/0.125	<0.06/0.12	0.047/0.125	0.06/0.25	0.06/0.125
	Fluconazole	0	0	1 (6.7)	2 (5.3)	1 (4.8)	4 (4.5)	1/2	0.5/4	0.75/2	0.25/2	1/2
	Itraconazole	NA	NA	NA	NA	NA	NA	0.25/0.375	0.25/0.5	0.032/1	0.03/0.25	0.25/0.25
	Voriconazole	0	0	0	1 (2.6)	2 (9.5)	3 (3.4)	0.015/0.06	0.06/0.5	0.047/0.19	0.03/0.5	0.06/0.125

[a] SDD, susceptible dose dependent; U, Udine; T, Trieste; R, Rome; S, Seville; B, Barcelona; NA, species-specific clinical breakpoint not available.

minor differences were found for fluconazole resistance in all *Candida* species between the hospitals in Italy and Spain (5.7% versus 3.5%; $P = 0.2$).

DISCUSSION

Several studies have shown a substantial increase in the incidence of candidemia in the past 2 decades. Our data show that in the 5 hospitals we analyzed, the incidence of candidemia has increased steadily in two of the institutions (Rome Catholic Hospital and Seville Hospital) and has remained stable in the other three. The mean rates are higher than those reported for centers in the Northern Hemisphere, including the United States (0.42 cases per 1,000 admissions) (24), Canada (0.45 per 1,000 admissions) (25), and some European countries (0.20 to 1.09 cases per 1,000 admissions) (26), but they are much higher than those reported in Finland (0.026 to 0.03 cases per 1,000 admissions [27]). The differences in candidemia rates between these countries may reflect differences in the representativeness and age distributions of the study populations, variations in health care practices, blood culture patterns, and antibiotic usage and resistance patterns.

Over the past 10 years, some studies have reported a shift in the etiology of candidemia. While *C. albicans* is still considered to be the most common species that causes candidemia, increasing rates of candidemia caused by *C. tropicalis*, *C. parapsilosis* species complex, *C. glabrata*, and *Candida krusei* have been reported worldwide (28–31). The reasons for the emergence of non-*albicans Candida* species are not completely understood, but some medical conditions may consistently impact the risk of developing candidemia due to non-*albicans Candida* species: *C. parapsilosis* complex fungemia has been associated with vascular catheters and parenteral nutrition (28), *C. tropicalis* candidemia is associated with cancer and neutropenia (32), and *C. krusei* and *C. glabrata* fungemias are associated with previous exposure to azoles (15). The findings from our surveillance do not support these reports. We observed a predominance of *C. albicans* (around 60%) in candidemia infections. In our study, *C. parapsilosis* complex surpassed the other non-*albicans Candida* spp. to become the most common species isolated after *C. albicans*. Our series clearly supports the concept that *C. parapsilosis* complex accounts for the large majority of non-*albicans Candida* species in southern Europe. The high incidence of candidemia caused by *C. parapsilosis* complex has been previously reported in South American and Italian hospitals (11, 16). Of note, the frequencies of *C. glabrata* candidemia in these regions are lower than those reported in the Northern Hemisphere (33), and their frequency has been surpassed by that caused by *C. tropicalis*. We did not observe important differences across countries regarding the species distributions in the different departments. *C. albicans* dominated in our study in internal medicine, surgery, and ICU departments, while non-*albicans Candida* spp. occurred frequently among hemato-oncology patients, confirming previous observations (28). On the other hand, *C. tropicalis* candidemia was found more frequently in elderly patients, as reported elsewhere (34).

Interesting differences emerged in the profiles of patients with *Candida* BSIs between our data and those previously described elsewhere. Latin American and European studies have indicated that 56.5% and 44.4% of episodes of nosocomial fungemia cases, respectively, occurred in patients in the ICU(31, 34). In contrast, only 19.6% of episodes in our study occurred in ICU patients; this proportion was only a small amount lower than that which occurred in patients in the surgical units (24.6%). In our study, in contrast with those of other studies, an unusually large proportion (49.7%) of candidemia infections occurred among patients in a general internal medicine department, especially in the Italian

hospitals. We hypothesize that this variety of patterns reflects differences in the organization and resourcing of health care delivery practices in various countries rather than significant differences in the characteristics of the populations studied.

Our proportion of fluconazole-resistant or SDD isolates (5.1%) was similar to the rates observed for European (6.3%) and North American (6.6%) hospital isolates (9, 35). Differences in susceptibilities to fluconazole were observed between Italy and Spain, with a higher proportion occurring in Italy, but the rates were lower than those recently reported in a tertiary-care Italian hospital (12). Voriconazole was the azole that exhibited the best *in vitro* antifungal activity. As reported by others (36), caspofungin demonstrated excellent activity for all the *Candida* species, except for *C. parapsilosis* complex, for which higher MICs were observed. The clinical relevance of these findings is unknown because the correlation between MICs and outcomes is still uncertain.

Retrospective cohort studies involving patients with candidemia and various underlying diseases have revealed worldwide crude and attributable mortality rates of 30% to 81% and 5% to 71%, respectively (10). The severity of candidemia is confirmed by the high crude mortality rate found in the European Confederation of Medical Mycology (ECMM) survey (38%) (37–39), as well as in Finland (35%) (40) and in the Barcelona area (44%) (8). In our series, patients with candidemia had a crude 30-day mortality rate of 39.9%. A major finding of the present study is the high mortality rate for candidemia in patients admitted to hemato-oncology and internal medicine wards compared with other wards (44.4% versus 35.4%; $P = 0.002$). Several factors may have impacted the outcome, e.g., the high APACHE II score, patient age, and the presence of multiple comorbidities. Therefore, it is reasonable to assume that these factors played a major role in the poor outcomes in internal medicine wards compared to other wards. Thus, factors that may lead to intervention should be explored in future studies.

Certainly, the severity of a patient's underlying medical condition greatly influences the crude mortality rate in these patient populations; however, for patients in internal medicine wards, inappropriate therapy (consisting mostly of omission of initial empirical therapy and an inadequate choice of antifungals) might represent an important variable that has been associated with increased mortality rates (41).

Finally, the current study has several limitations that should be kept in mind when interpreting the results. All five sites we analyzed were located in teaching institutions, and our observations may not be generalizable to all patients with candidemia. Important intrahospital differences may also be observed in the larger hospitals. Another limitation of our study is that although 5 centers from 2 European countries participated, the results may not be representative of each country.

This report shows that candidemia is a significant source of morbidity in Italy and Spain, causing substantial burdens of disease, mortality, and likely high costs associated with care. Determining the factors associated with high rates of candidemia may lead to the identification of measures that can help prevent disease.

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