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Invasive Candidiasis in Brescia, Italy: Analysis of Species Distribution and Antifungal Susceptibilities During Seven Years

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Abstract The aims of this study were to evaluate the epidemiology of nosocomial candidemia in a large teaching hospital in Brescia, Italy, and the in vitro antifungal susceptibility of isolates. We analyzed 196 isolates causing fungemia in patients admitted in our hospital, between January 2009 and December 2015. Strains were identified by VITEK 2 and MALDI-TOF MS. MICs were determined by Sensititre Yeast One$_{TM}$. The resistance was defined by using the revised CLSI breakpoints/epidemiological cutoff values to assign susceptibility or wild type to systemic antifungal agents. Most infections were caused by *Candida albicans* (60%), *Candida parapsilosis* (15%), *Candida glabrata* (12%) and *Candida tropicalis* (6%). The susceptibility rate for fluconazole was 96.5%. Non-*Candida* species isolates exhibited full susceptibilities to echinocandins according to CLSI breakpoints. Amphotericin B demonstrated excellent activity against all *Candida* species. Local epidemiological and antifungal susceptibility studies are necessary in order to improve empirical treatment guidelines.

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Introduction

Invasive candidiasis (IC) is an important cause of nosocomial infections, related to different risk factors such as previous antimicrobial therapy, immunodeficiency, parenteral nutrition, presence of catheters and intensive care unit permanence. [1, 2]. Although *Candida albicans* is still the main pathogen, non-albicans *Candida* species are increasing in IC patients [3]. This change has been attributed to the more frequent use of azole antifungals and invasive procedures [3]. In addition, there are geographical differences in the epidemiology of *Candida* infection [4]. In fact, *Candida glabrata* is the species more frequent after *C. albicans* in North America [5]. On the contrary, *Candida parapsilosis* or *Candida tropicalis* is relatively more common in Europe, Australia, Latin America and Asia [6–8]. In India, *C. tropicalis* causes are seen in more cases of candidemia than *C. albicans* [9]. Furthermore, different species such as *Candida guilliermondii* and *Candida rugosa* are diffusing [10, 11].

Compared to other bloodstream infections, IC appears to be associated with a particularly high rate of mortality, due to mainly, in the form of a delay in diagnosis or even failure of the antifungal therapy.

Different papers have shown that the rate of resistance to fluconazole ranges from 2.5 to 9% in

Candida spp. isolated from blood [12, 13]. Most *Candida* species are considered good targets for the three echinocandins (anidulafungin, caspofungin and micafungin) that are used as first-line agents for the treatment of fungemia; however, what has been found is the increasing use of these drugs determines the emergence of resistance in *Candida* and non-*Candida* species [14].

An effective infection control is required due to higher incidence of IC, increased mortality and the growing prevalence of resistance to fluconazole.

The aim of this study was to conduct a seven-year retrospective analysis in order to analyze the incidence and species distribution in patients with fungemia in a large hospital located in Brescia, Italy. The rates of antifungal resistance were determined according to the newly revised CLSI clinical breakpoints (CBPs) or, in the absence of CBPs, according to epidemiological cutoff values (ECVs) for nine antifungal agents [15].

Materials and Methods

Collection of Isolates

We conducted this study in a large university hospital, Spedali Civili, in Brescia, North of Italy. We collected isolates from patients with candidemia from January 2009 to December 2015. An episode of candidemia was defined as *Candida* infection involving at least one blood culture. Only the first episode of fungemia was reported per patient with recurrent or subsequent episodes of infection. Patients whose cultures grew >1 documented species of *Candida* were excluded from the analysis. The study did not require the approval by the Institutional ethics committee due to the descriptive nature.

Yeast Identification

Yeasts were isolated from patient blood cultures collected during normal routine and processed by the BACTEC (BD Diagnostic Systems, Sparks, MD) system. Identification of all species was performed using VITEK 2 YST cards from bioMérieux (Marcy, l' Etoile, France) or since 2012, by matrix-assisted laser desorption ionization–time-of-flight mass spectrometry (MALDI-TOF).

Antifungal Susceptibility Testing

The in vitro susceptibility to antifungal drugs was performed by using Sensititre Yeast One (YO-08 from 2009 to 2012 and YO-10 from 2013 to 2015) in accordance with the manufacturer's instructions. Because the ranges of amphotericin B, flucytosine, fluconazole and itraconazole were different from those of the previous version (YO-08), MIC values of 0.008–0.12 μg/mL for amphotericin B and of 0.03–0.12 μg/mL for fluconazole were reported as ≤0.12 g/mL; MIC values of 0.03–0.06 μg/mL for flucytosine were reported as ≤0.06 g/mL; and MIC values of 0.008–0.015 μg/mL for itraconazole were reported as ≤0.015 μg/mL.

Data Analysis

MIC values determined by the Sensititre Yeast One YO-08 and YO-10 were interpreted according to current CLSI species specific CBPs [15]; if no CBPs were defined, ECVs were used.

The CLSI resistance breakpoint for fluconazole was defined as an MIC of >4 g/mL against *C. albicans*, *C. parapsilosis* and *C. tropicalis*, and of >32 μg/mL against *C. glabrata*; for voriconazole, as an MIC of >0.5 μg/mL against *C. albicans*, *C. parapsilosis*, and *C. tropicalis*, and of >1 μg/mL against *C. krusei*. The CLSI resistance breakpoint for echinocandins was indicated as an MIC of >0.5 μg/mL against *C. albicans* and *C. tropicalis* and of 4 g/mL against *C. parapsilosis*; for both anidulafungin and caspofungin, an MIC of >0.25 μg/mL was defined against *C. glabrata* and an MIC of >0.12 μg/mL for micafungin. The ECV of >0.5 μg/mL was used to identify non-WT isolates of *C. glabrata* to voriconazole; ECVs of >0.06, >0.25, >0.12, and >2 μg/mL were used to identify non-WT isolates of *C. albicans*, *C. parapsilosis*, *C. tropicalis* and *C. glabrata*, respectively, to posaconazole [16]. ECVs were also used to identify non-WT isolates of *C. albicans*, *C. parapsilosis*, *C. tropicalis* and *C. glabrata* to amphotericin B (>2 μg/mL for all) and flucytosine (>0.5 μg/mL for all) [16].

Results and Discussion

A total of 196 distinct episodes of candidemia (192 adults and 4 adolescents <18 years of age) were

identified during the study period. Of these, 113 cases (58%) comprised of males and 83 (42%) where females. The median age of patients was 81 years (ranging from 17 to 96 years).

The average incidence of candidemia was 0.365 per 1000 admissions, which is comparable to that reported for centers in Denmark (0.41 case per 1000 admissions) [17], but lower than that of Israel [18], China [19], Brazil [20], Portugal [21] and even from that of different Italian regions [22, 23]. These differences in candidemia rates may depend on various factors such as differences in demographic characteristics, variations in health care practice, long antibacterial therapies and on the local resistance epidemiology. During the years analyzed, this incidence rate varied, increasing from 0.23 cases per 1000 admissions in the year 2009 to 0.55 cases per 1000 admissions in 2015 (Fig. 1). This might be due to an increased exposure to different risk factors such as prolonged antibiotic therapy, the use of urinary catheters, parenteral nutrition and central venous catheters.

The four most prevalent species were *Candida albicans* (60%), *Candida parapsilosis* (15%), *Candida glabrata* (12%), and *Candida tropicalis* (6%), while other species were relatively rare: *Candida famata* (1.5%), *Candida lusitaniae* (1.5%), *Candida lipolytica* (1%), *Candida ciferrii* (0.5%), *Candida dubliniensis* (0.5%) and *Candida guilliermondii* (0.5%). The most affected age group was 61-80 years and these where mostly isolated from intensive care units, medical and surgical wards (Table 1). This result is not surprising, due to the fact that most of the patients admitted to these wards are in immunosuppressive conditions, and are often submitted to antibiotic therapies, predisposing them to an increasing rate of fungal infections.

Tables 2 and 3 show all the data for susceptibility testing using CLSI guidelines.

All isolates studied showed a WT phenotype to amphotericin B. The MIC_{50} and MIC_{90} values of amphotericin B for all the species were either 0.25 or 0.5 mg/L (Table 2). All isolates were inhibited at drug concentrations of 0.5 mg/L.

This full susceptibility to amphotericin B is important because, although this agent is not a first-line drug for the treatment of invasive candidiasis and candidemia in most clinical approaches [14], it may be used as alternative therapeutic option or where the isolates exhibit a resistance against azoles or echinocandins.

When we looked at the susceptibility to flucytosine, 10 isolates across *C. albicans* (2/116 isolates; 1.7%), *C. parapsilosis* (3/28 isolates; 10.7%), *C. glabrata* (2/22 isolates; 9%) and *C. tropicalis* (2/12 isolates; 25%) were found to be not WT to flucytosine.

The most frequently used antifungals systematically and locally are the azoles. Of the azoles used systematically, fluconazole is the most frequently used one in the yeasts.

Among the group of azoles, *C. parapsilosis* species was susceptible to all four azoles tested. With regard to

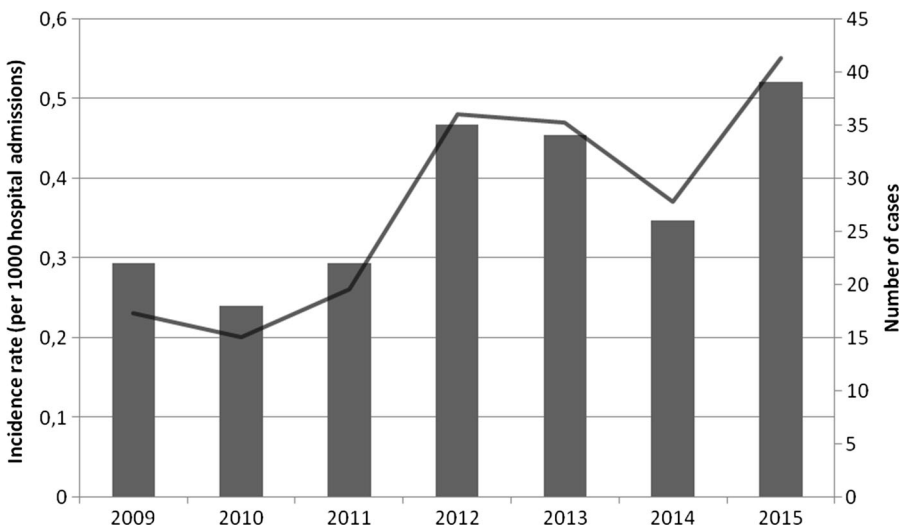

Fig. 1 Patients with Candida bloodstream infections (*bars*) and incidence rate (*line*) observed during a seven years period

Table 1 Distribution and characteristics of patients with bloodstream yeast infections

	No. of isolates (%)					
	C. albicans	*C. parapsilosis*	*C. glabrata*	*C. tropicalis*	Other species	Overall
Gender						
Male	70 (59)	16 (53)	15 (62)	4 (33)	8 (67)	113 (58)
Female	48 (41)	14 (47)	9 (38)	8 (67)	4 (33)	83 (42)
Total	118 (60)	30 (15)	24 (12)	12 (6)	12 (6)	196 (100)
Age group (years)						
<18	4 (4)	–	–	–	1 (8)	5 (3)
19–40	12 (10)	3 (10)	1 (4)	2 (16)	2 (17)	20 (10)
41–60	24 (20)	5 (17)	7 (29)	2 (16)	3 (25)	41 (21)
61–80	52 (44)	17 (56)	11 (46)	4 (34)	5 (42)	89 (45)
>80	26 (22)	5 (17)	5 (21)	4 (34)	1 (8)	41 (21)
Hospital departments						
ICU	22 (18)	3 (10)	6 (25)	1 (8.5)	3 (25)	35 (18)
Surgical wards	22 (18)	6 (20)	5 (20.5)	4 (33)	2 (17)	39 (20)
Medical wards	30 (26)	6 (20)	4 (17)	4 (33)	3 (25)	47 (24)
Hematology	3 (3)	3 (10)	–	1 (8.5)	–	7 (3)
Digestive medicine	7 (6)	1 (3)	3 (12.5)	–	1 (8)	12 (6)
Infectious diseases	13 (11)	1 (3)	3 (12.5)	2 (17)	–	19 (10)
Other wards[a]	21 (18)	10 (34)	3 (12.5)	–	3 (25)	37 (19)

[a] Other wards included nephrology, cardiology, urology and otorhinolaryngology

C. albicans, 3 isolates were resistant to fluconazole and posaconazole (2.8 and 2.6%, respectively). Three isolates (2.5%) were resistant to voriconazole, while two isolates (1.7%) were resistant to itraconazole. With regard to *C. glabrata*, one isolate (4.5%) was resistant to fluconazole, 2 isolates (8.3%) were resistant to itraconazole, and four isolates (16.6%) were resistant to voriconazole. All isolates were of the WT phenotype for posaconazole. With regard to *C. tropicalis*, 1 isolate (10%) was resistant to fluconazole and 2 isolates (18%) were resistant to posaconazole. All isolates were of the WT phenotype for itraconazole.

Overall, the frequency of fluconazole resistance in our isolates was 3.5%. The MIC values for fluconazole were between 0.25 and 32 mg/L for the 175 *Candida* strains analyzed.

Our findings show a low resistance to fluconazole by *C. glabrata* isolates (4.5%), a percentage comparable to that reported in other Italian studies [23, 24]. Furthermore, we found some isolates of *C. glabrata* susceptible to fluconazole and resistant to voriconazole, a phenotype already described [25].

Echinocandins are in general active against various *Candida* and *Aspergillus* spp. and this explains their large use in clinical practice. In fact, recent European guidelines are recommending echinocandins as the first-line treatment in severe or neutropenic patients, or when there is prior use of azoles or suspected resistance to azoles [26].

In our study, all *Candida*–non-albicans species were full susceptible to echinocandins. Echinocandin resistance in *Candida albicans* was low (1/54, 1.8%) for all the three echinocandins and was similar to that reported in Spain [27], however, different from other countries such as the USA where echinocandin resistance is emerging [28].

Table 4 shows the trend in the resistance rate over the period of the study. We observed a stable trend for azole resistance during the study period with the exception of the year 2014 where there was a decline in the rate of resistance.

This study has several limitations, i.e., the data associated with underlying diseases, risk factors, mortality and previous antifungal therapy were unknown, and therefore, this information could not

Table 2 Activities of nine antifungal agents against the yeast isolates by Sensititre Yeast One method

Species	Drug	No. of isolates tested	MIC (mg/L)		
			Range	50%	90%
C. albicans	Anidulafungin	54	≤0.015–8	≤0.015	0.03
	Caspofungin	116	≤0.008–8	0.03	0.125
	Micafungin	54	≤0.008–8	≤0.008	≤0.008
	Fluconazole	106	≤0.12–256	0.25	1
	Itraconazole	118	≤0.015–16	0.03	0.125
	Voriconazole	118	≤0.008–8	0.008	0.008
	Posaconazole	113	≤0.008–8	0.016	0.03
	Amphotericin B	106	≤0.12–8	0.25	0.5
	Flucytosine	116	≤0.06–64	0.06	0.125
C. parapsilosis	Anidulafungin	15	≤0.015–8	0.5	2
	Caspofungin	30	≤0.008–8	0.25	1
	Micafungin	15	≤0.008–8	0.5	2
	Fluconazole	28	≤0.12–256	0.5	1
	Itraconazole	30	≤0.015–16	0.06	0.125
	Voriconazole	30	≤0.008–8	0.008	0.016
	Posaconazole	27	≤0.008–8	0.03	0.125
	Amphotericin B	28	≤0.12–8	0.25	0.5
	Flucytosine	28	≤0.06–64	0.125	1
C. glabrata	Anidulafungin	14	≤0.015–8	0.03	0.03
	Caspofungin	24	≤0.008–8	0.06	0.125
	Micafungin	14	≤0.008–8	0.016	0.016
	Fluconazole	22	≤0.12–256	16	32
	Itraconazole	24	≤0.015–16	0.5	1
	Voriconazole	24	≤0.008–8	0.25	2
	Posaconazole	18	≤0.008–8	1	2
	Amphotericin B	22	≤0.12–8	0.25	0.5
	Flucytosine	22	≤0.06–64	0.06	0.125
C. tropicalis	Anidulafungin	6	≤0.015–8	0.03	0.25
	Caspofungin	12	≤0.008–8	0.06	0.125
	Micafungin	6	≤0.008–8	0.016	0.03
	Fluconazole	10	≤0.12–256	1	2
	Itraconazole	11	≤0.015–16	0.125	0.25
	Voriconazole	12	≤0.008–8	0.03	0.25
	Posaconazole	11	≤0.008–8	0.06	0.25
	Amphotericin B	10	≤0.12–8	0.25	0.5
	Flucytosine	12	≤0.06–64	0.06	64
Other species	Anidulafungin	6	≤0.015–8	0.016	0.5
	Caspofungin	12	≤0.008–8	0.06	0.5
	Micafungin	6	≤0.008–8	0.016	0.5
	Fluconazole	9	≤0.12–256	0.5	32
	Itraconazole	12	≤0.015–16	0.06	0.5
	Voriconazole	12	≤0.008–8	0.008	0.25

Table 2 continued

Species	Drug	No. of isolates tested	MIC (mg/L)		
			Range	50%	90%
	Posaconazole	10	≤0.008–8	0.016	0.5
	Amphotericin B	9	≤0.12–8	0.25	0.5
	Flucytosine	12	≤0.06–64	0.06	8

Table 3 Distribution of MIC values according to the Clinical and Laboratory Standards Institute (CLSI) guidelines

Species (no. of isolates)	Drug	R breakpoint or ECV CLSI	No. (%) of R CLSI
C. albicans	Anidulafungin	>1	1 (1.8%)
	Caspofungin	>0.5	1 (0.8%)
	Micafungin	>1	1 (1.8%)
	Fluconazole	>4	3 (2.8%)
	Itraconazole	>1	2 (1.7%)
	Voriconazole	>0.5	3 (2.5%)
	Posaconazole	>0.06	3 (2.6%)
	Amphotericin B	>1	0
	Flucytosine	>0.5	2 (1.7%)
C. parapsilosis	Anidulafungin	>4	0
	Caspofungin	>4	0
	Micafungin	>4	0
	Fluconazole	>4	0
	Itraconazole	>1	0
	Voriconazole	>0.5	0
	Posaconazole	>0.25	0
	Amphotericin B	>1	0
	Flucytosine	>0.5	3 (10.7%)
C. glabrata	Anidulafungin	>0.25	0
	Caspofungin	>0.25	0
	Micafungin	>0.12	0
	Fluconazole	>32	1 (4.5%)
	Itraconazole	>1	2 (8.3%)
	Voriconazole	>0.5	4 (16.6)
	Posaconazole	>2	0
	Amphotericin B	>1	0
	Flucytosine	>0.5	2 (9%)
C. tropicalis	Anidulafungin	>0.5	0
	Caspofungin	>0.5	0
	Micafungin	>0.5	0
	Fluconazole	>4	1 (10%)
	Itraconazole	>1	0
	Voriconazole	>0.5	0
	Posaconazole	>0.12	2 (18%)
	Amphotericin B	>1	0
	Flucytosine	>0.5	3 (25%)

Table 3 continued

Species (no. of isolates)	Drug	R breakpoint or ECV CLSI	No. (%) of R CLSI
Other species			
	Anidulafungin	>2	0
	Caspofungin	>2	0
	Micafungin	>2	0
	Fluconazole	>64	2 (6.25%)
	Itraconazole	>1	0
	Voriconazole	>4	0
	Posaconazole	>4	0
	Amphotericin B	>1	0
	Flucytosine	>32	0

ECV epidemiological cutoff value, *NA* not available

Table 4 Trends in resistance according to CLSI breakpoints to the antifungal agents studied for *Candida* and non-*Candida* species during the study period (2009–2015)

Antifungal resistance (no. of resistant isolates/no. of isolates tested) (%)							
Drug and species	2009	2010	2011	2012	2013	2014	2015
C. albicans							
Anidulafungin	NA	NA	NA	NA	1/18 (5.5%)	0	0
Caspofungin	0	0	0	0	1/18 (5.5%)	0	0
Micafungin	NA	NA	NA	NA	1/18 (5.5%)	0	0
Fluconazole	0	0	0	1/23 (4.3%)	1/19 (5.2%)	0	1/24 (4.1%)
Itraconazole	0	0	0	1/23 (4.3%)	0	0	1/24 (4.1%)
Voriconazole	0	0	0	1/23 (4.3%)	1/19 (5.2%)	0	1/24 (4.1%)
Posaconazole	0	0	0	1/23 (4.3%)	1/19 (5.2%)	0	1/24 (4.1%)
Amphotericin B	0	0	0	0	0	0	0
Flucytosine	0	1/12 (8.3%)	0	0	1/19 (5.5%)	0	1/24 (4.1%)
C. parapsilosis							
Anidulafungin	NA	NA	NA	NA	0	0	0
Caspofungin	0	0	0	0	0	0	0
Micafungin	NA	NA	NA	NA	0	0	0
Fluconazole	0	0	0	0	0	0	0
Itraconazole	0	0	0	0	0	0	0
Voriconazole	0	0	0	0	0	0	0
Posaconazole	0	0	0	0	0	0	0
Amphotericin B	0	0	0	0	0	0	0
Flucytosine	0	0	0	1/6 (16.6%)	0	1/2 (50%)	0
C. glabrata							
Anidulafungin	NA	NA	NA	NA	0	0	0
Caspofungin	0	0	0	0	0	0	0
Micafungin	NA	NA	NA	NA	0	0	0
Fluconazole	0	0	0	0	1/6 (16.6%)	0	0

Table 4 continued

Antifungal resistance (no. of resistant isolates/no. of isolates tested) (%)							
Drug and species	2009	2010	2011	2012	2013	2014	2015
Itraconazole	0	0	0	0	1/6 (16.6%)	0	1/5 (20%)
Voriconazole	1/2 (50%)	0	0	0	1/6 (16.6%)	0	2/5 (40%)
Posaconazole	0	0	0	1/1 (100%)	1/6 (16.6%)	1/4 (25%)	1/5 (20%)
Amphotericin B	0	0	0	0	0	0	0
Flucytosine	0	0	0	0	1/5 (20%)	0	1/5 (20%)
C. tropicalis							
Anidulafungin	NA	NA	NA	NA	0	0	0
Caspofungin	0	0	0	0	0	0	0
Micafungin	NA	NA	NA	NA	0	0	0
Fluconazole	0	0	0	0	0	1/3 (33%)	0
Itraconazole	0	0	0	0	0	0	0
Voriconazole	0	0	0	0	0	0	0
Posaconazole	0	0	0	0	0	1/3 (33%)	1/2 (50%)
Amphotericin B	0	0	0	0	0	0	0
Flucytosine	0	0	0	1/2 (50%)	1/1 (100%)	0	1/2 (50%)

NA not available

be analyzed. It is also important to highlight the relatively small size of our samples and underline that more isolates (by extending the period of study) would give more reliable and substantial importance to our results.

Finally, since we included only isolates from a single institution, we may not able to extrapolate them to other hospitals.

However, the rates of fluconazole and echinocandin resistance that we have recorded were similar to those reported from other countries [25–30].

Antifungal susceptibility studies performed locally should be a priority in order to monitor continuously the emergence of *Candida* or non-*Candida* species with intrinsically reduced susceptibility or resistance.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no conflict of interest.

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