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Original Research

Infections due to *Candida* spp in a Brazilian Tertiary Hospital: Species and Susceptibility to Antifungals

Infecções por Candida spp em um Hospital Terciário Brasileiro: Espécies e Suscetibilidade aos Antifúngicos

Infecciones por Candida spp en Hospital de Tercer Nivel Brasileño: Especies y Susceptibilidad a los Antifúngicos

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Abstract

Introduction: Infections caused by *Candida* spp are a major public health concern, due to the high mortality rate and the limited therapeutic arsenal. Objectives: To assess the prevalence of *Candida* spp infections and susceptibility to antifungal agents in a general hospital. Methods: Descriptive, cross-sectional study with collection of epidemiological and laboratory data on *Candida* spp cultures (2014 to 2019), at a large tertiary and philanthropic hospital in the city of Piracicaba, São Paulo state, Brazil. Results: A total of 63 episodes of *Candida* spp infection were eligible, being more prevalent in adults (88.9%) aged ≥ 70 years (41.3%), causing 40 deaths (63.5%). The *C. albicans* species represented 41.3% of the infections, with a mortality rate of 37.5%, while non-*albicans* species accounted for 58.7%, highlighting *C. tropicalis* (25.4%) and *C. glabrata* (23.8%), with a mortality rate of 27.5% for both species. Regarding the susceptibility profile, most were sensitive to echinocandins and azoles over the years. *C. glabrata* presented one case of resistance and dose-dependent sensitivity to caspofungin and micafungin and fluconazole, which was expected due to the decreased sensitivity to azoles, while the results for echinocandins were in agreement with previous studies showing increased resistance to this group of drugs. Conclusion: Given the high prevalence of hospital fungal infections and the associated mortality rate, determining the local epidemiological profile and susceptibility to drugs is an important strategy for guiding antifungal therapy.

Descriptors: Candida; Hospital Infections; Microbial Sensitivity, Tests; Antifungals Agents.

Resumo

Introdução: As infecções causadas por *Candida* spp constituem uma grande preocupação de saúde pública frente a elevada taxa de mortalidade e o limitado arsenal terapêutico. Objetivos: Avaliar a prevalência das infecções por *Candida* spp e suscetibilidade aos antifúngicos em um hospital geral. Métodos: Estudo descritivo, com delineamento transversal e coleta de dados epidemiológicos e laboratoriais de culturas de *Candida* spp (2014 a 2019), em um hospital terciário e filantrópico de grande porte do município de Piracicaba, São Paulo, Brasil. Resultados: Foram elegíveis 63 episódios de infecção por *Candida* spp, sendo mais prevalente em adultos (88,9%) com idade ≥ 70 anos (41,3%), causando 40 óbitos (63,5%). A *C. albicans* representou 41,3% das infecções, com taxa de mortalidade de 37,5%, já, as espécies não-*albicans* causaram 58,7%, destacando *C. tropicalis* (25,4%) e *C. glabrata* (23,8%), com taxa de mortalidade de 27,5% para ambas as espécies. Em relação ao perfil de suscetibilidade, a maioria foi sensível às equinocandinas e aos azóis ao longo dos anos. *C. glabrata* apresentou um caso de resistência e sensibilidade dose dependente para caspofungina e micafungina e fluconazol, o que era esperado pela sensibilidade diminuída aos azóis, e quanto às equinocandinas, reforça alguns achados mostrando o aumento da resistência para este grupo de fármacos. Conclusão: Frente a alta prevalência de infecções fúngicas hospitalares e do índice de mortalidade, traçar o perfil epidemiológico local e de suscetibilidade aos fármacos é de grande valia para direcionar a terapia antifúngica.

Descritores: Candida; Infecção Hospitalar; Testes de Sensibilidade Microbiana; Antifúngicos.

Resumen

Introducción: Las infecciones causadas por *Candida* spp constituyen un importante problema de salud pública dada la alta tasa de mortalidad y el limitado arsenal terapéutico. Objetivos: Evaluar la prevalencia de infecciones por *Candida* spp y susceptibilidad a los antifúngicos en un hospital general. Métodos: Estudio descriptivo, transversal y recolección de datos epidemiológicos y de laboratorio sobre cultivos de *Candida* spp (2014 a 2019), en un gran hospital terciario y filantrópico de la ciudad de Piracicaba, São Paulo, Brasil. Resultados: Fueron elegibles 63 episodios de infección por *Candida* spp, siendo más prevalentes en adultos (88,9%) con edad ≥ 70 años (41,3%), causando 40 muertes (63,5%). *C. albicans* representó el 41,3% de las infecciones, con una mortalidad del 37,5%, mientras que las especies no albicans causaron el 58,7%, destacando *C. tropicalis* (25,4%) y *C. glabrata* (23,8%), con una mortalidad del 27,5% para ambas especies. En cuanto al perfil de susceptibilidad, la mayoría fue sensible a equinocandinas y azoles a lo largo de los años. *C. glabrata* presentó un caso de resistencia y sensibilidad dependiente de la dosis a caspofungina y micafungina y fluconazol, lo que era de esperarse por la disminución de la sensibilidad a los azoles, y en cuanto a las equinocandinas, refuerza algunos hallazgos que muestran una mayor resistencia para este grupo de fármacos. Conclusión: En vista de la alta prevalencia de infecciones fúngicas nosocomiales y la tasa de mortalidad, rastrear el perfil epidemiológico local y la susceptibilidad a los medicamentos es de gran valor para la terapia antifúngica directa.

Descriptores: Candida; Infección Hospitalaria; Pruebas de Sensibilidad Microbiana; Antifúngicos.

INTRODUCTION

Despite the existence of a range of diagnostic and therapeutic strategies, recent decades have seen a substantial increase in nosocomial fungal infections worldwide[1-3]. These infections can vary from superficial and mild to

invasive and systemic, with the potential to progress to sepsis and death[1,4]. Invasive systemic fungal infections are a major concern due to a high mortality rate, affecting up to 50% of hospitalized patients[4], a limited range of antifungal agents, compared to antibacterials[5], and increasing resistance of these microorganisms[6].

Although the opportunistic pathogens causing fungal infections may be commensal in healthy individuals, these organisms can take advantage of poor health conditions, such as in cases of immunosuppression, due to microbial dysbiosis. The outcome of the human-pathogen interaction is mainly determined by factors related to the host, rather than to the virulence of the fungus[1,4,7].

Among the pathogenic fungi, *Candida* spp can be highlighted due to the impacts of these microorganisms on patient morbidity and mortality[1,3]. The genus *Candida*, which includes around 500 species, is considered the yeast genus of greatest medical significance, causing a broad spectrum of diseases in both adults and children[8-10].

In the United States, candidemia is the fourth most common cause of nosocomial systemic infections, causing 10% of bloodstream infections and 25% of urinary tract infections in intensive care units (ICUs), presenting a challenge to medical teams due to the difficulties associated with diagnosis and treatment[3,9,11-13].

The most prevalent species is *Candida albicans*, responsible for 50-70% of the cases of invasive systemic candidiasis, constituting a public health problem in the hospital environment, especially in ICUs, where the patient often presents comorbidities, requiring the use of various invasive devices and an extended period in hospital, which can favor translocation of the commensal agent into the bloodstream[9,14].

Infections by *Candida* spp other than *C. albicans* are increasingly reported worldwide, with impacts including increased resistance to antifungals and a high mortality rate of around 30-50%, further exacerbating health problems caused by fungal infections[15]. Among these species can be highlighted *Candida glabrata*, *Candida tropicalis*, *Candida parapsilosis*, *Candida dubliniensis*, *Candida guilliermondii*, *Candida krusei*, and *Candida kefyr*[15].

There are geographic differences between species in terms of prevalence and epidemiology, the reasons for which are not fully understood, although one of the factors cited is previous exposure to polyenes (nystatin, natamycin, and amphotericin B) and azoles (itraconazole and fluconazole). Therefore, it is essential to be able to monitor the trends for the different species, since they differ in terms of the production of virulence factors and sensitivity to antifungals[14-16].

The difficulty in developing new and safe broad-spectrum drugs is accentuated by the similarity between human and fungal cells, since both are eukaryotic organisms, which limits the number of molecular targets that can be used without risk of toxicity[17].

Knowledge of the epidemiological profile of patients with candidemia, as well as the *Candida* species that are most prevalent in nosocomial infections, and their susceptibility to antifungals, could assist in the provision of more effective treatment that reduces the rates of mortality and morbidity in hospital patients[18]. Therefore, the objective of this study was to evaluate the prevalence of *Candida* spp infections and the susceptibility of the microorganisms to antifungals, in a hospital environment.

MATERIAL AND METHOD

- *Study design*

This was a retrospective, descriptive, and cross-sectional study, with data collection by analysis of documented laboratory tests of cultures positive for *Candida* spp, from 2014 to 2019, at a large philanthropic tertiary hospital in the city of Piracicaba, state of São Paulo, Brazil. The hospital had 319 beds, with over 70% of them allocated for use by the national health service (SUS), while also providing private health care, accepting referrals from a further 25 municipalities in the Piracicaba region.

This research was approved by the Research Ethics Committee of the Methodist University of Piracicaba (UNIMEP) (CAAE: 20786619.4.0000.5507), as well as by the hospital.

- *Sample*

The patients analyzed were identified by the Hospital Infection Control Service (SCIH), based on the documented results of cultures performed by the clinical analysis laboratory of the institution, together with the presence of clinical signs and symptoms indicative of infection.

A record of each patient was kept, documenting demographic data (age, gender, and place of internment at the time of infection), clinical conditions (use of total parenteral nutrition, presence of central venous catheter,

ICU admission, abdominal surgery, and neoplasm, as well as the duration of internment and the average between the days of hospitalization and the dates of collection of the exam and the clinical outcome, whether discharge or death), and laboratory analysis data (*Candida* species identification, type of sample collected, and antifungigram results).

- *Inclusion criteria*

The patients included in the study were those who remained in hospital for longer than 24 h. *Candida* infection was considered to occur when the patient presented clinical signs and symptoms of infection, together with laboratory analysis showing the isolation of any species of the genus *Candida*. An episode of *Candida* infection was considered as being within a period of 30 days after the date of collection of the first positive culture. If another positive culture occurred during this period, involving either the same or a different species, this culture was recorded as part of the same episode of infection. However, if another positive culture was obtained for a patient after 30 days following the initial culture, this was counted as a fresh episode, so a new record was made. The study excluded outpatients and individuals lacking antifungigram results.

- *Microbial susceptibility*

Among the types of clinical samples analyzed, there was a predominance of blood and urine samples. Processing of the cultures employed the automated BactAlert system (bioMérieux, France), with those showing positive being seeded on blood agar, chocolate agar, or CLED agar, depending on the origin of the sample. The antifungal sensitivity profile was obtained using the automated Vitek method (bioMérieux, France). The criteria used to interpret the antifungigram followed the recommendations of the Clinical and Laboratory Standards Institute (CLSI, standard M27 S4, December 2012), considering the species *C. albicans*, *C. tropicalis*, *C. glabrata*, *C. parapsilosis*, *C. krusei*, *C. intermedia*, *C. dubliniensis*, and *C. lusitaniae*. For the last three species, the CLSI did not provide criteria for interpreting the MIC.

- *Statistical analysis*

The statistical procedures were performed using Microsoft Excel and SigmaPlot 14.0 for Windows. In the case of the categorical variables, the chi-squared test and Fisher's exact test were used. Data normality was evaluated using the Shapiro-Wilk test and the continuous variables were analyzed using the Kruskal-Wallis and Mann-Whitney tests, together with Dunn's post-hoc test. Statistical significance was considered for $p < 0.05$.

RESULTS

There were 81 cases of infection by *Candida* species identified during the study period. Of these, 18 (22.2%) were excluded because they did not meet the eligibility criteria, resulting in 63 episodes being included.

Infection by *Candida* species was more prevalent in adult patients (88.9%), predominantly those aged over 70 years (41.3%; median = 68 years), with 50.8% being male and 49.2% female. Seven cases of infection were observed in pediatric patients. The patients were usually in ICUs when samples were collected for laboratory tests (Table 1), with a median stay of 32 days. No statistically significant differences were found between the numbers of days of hospitalization associated with different *Candida* species (Kruskal-Wallis and Mann-Whitney tests, $p > 0.05$), or between the species associated with the different genders (chi-squared test, $p > 0.05$).

Table 1. Demographic data and risk factors for patients interned at the general hospital in Piracicaba (São Paulo state, Brazil), considering the period from 2014 to 2019.

Age (years)	Number	Frequency (%)
≤9	7	11.1
10-19	0	0
20-29	1	1.6
30-39	2	3.2
40-49	9	14.3
50-59	10	15.9
60-69	8	12.7
70-79	15	23.8
≥80	11	17.5
Sex		
Male	32	50.8
Female	31	49.2
Age group		
Adult	56	88.9
Child (<14 years)	7	11.1
Internment location		
ICU	40	63.5
Nursing ward (surgical section)	8	12.7
Nursing ward (clinical section)	8	12.7
Neonatal/pediatric ICU	4	6.3
Pediatric ward	3	4.8
Risk factors		
Central venous catheter	59	93.7
Antifungal use	53	84.1
Internment in ICU	51	81.0
Digestive system surgery	32	50.8
Total parenteral nutrition	31	49.2
Neoplasm	13	20,6

Among the risk factors presented by the patients (Table 1), the most frequent were the presence of a central venous catheter (93.7%), followed by ICU admission (81%), abdominal surgery (50.8%), and total parenteral nutrition (49.2%). There were no statistically significant differences in these risk factors between the *C. albicans* and non-*C.albicans* groups (chi-squared and Fisher's exact tests, $p > 0.05$).

Fungal infections in adults by *Candida* spp other than *C. albicans* have been steadily increasing over the years. In the present work,

these accounted for 58.7% (n = 37) of all the infectious episodes, while *C. albicans* accounted for 41.3% of the infections (n = 26). However, no statistically significant differences were found between these groups (chi-squared test, p > 0.05). Among the non-*C. albicans* species, the most prevalent was *C. tropicalis* (25.4%), followed by *C. glabrata* (23.8%) and *C. parapsilosis* (4.8%). The species *C. intermedia*, *C. krusei*, and *C. dubliniensis* each presented prevalence of only 1.6% (Table 2).

Table 2. Frequencies of *Candida* species isolated in the laboratory tests.

Species	2014	2015	2016	2017	2018	2019	Total
C. albicans	4	4	5	3	5	5	**26**
C. tropicalis	1	4	1	3	2	5	**16**
C. glabrata	1	3	2	1	3	5	**15**
C. parapsilosis	0	1	0	1	1	0	**3**
C. intermedia	0	0	0	1	0	0	1
C. krusei	0	0	0	0	1	0	1
C. dubliniensis	0	0	0	0	1	0	1
Total non-*C. albicans*	**2**	**8**	**3**	**6**	**8**	**10**	**37**
Total per year	**6**	**12**	**8**	**9**	**13**	**15**	**63**

For the pediatric population, the species *C. tropicalis* and *C. albicans* were equally distributed, with each accounting for 42.9% of cases, while one isolated case of *C. intermedia* was identified (14.2%). Most of the isolates (98%) were obtained from blood samples.

Tests of the susceptibility of the *Candida* species to the different antifungal agents revealed that most of the isolates were sensitive to echinocandins (caspofungin and micafungin) and to azoles (fluconazole), with the exception of *C. glabrata*, which showed resistance (n = 1) to these drug classes and dose-dependent sensitivities to fluconazole (n = 11) and caspofungin (n = 12). Resistance to azoles occurred for only 4.8% (n = 3) of the isolates. There was no significant difference between the species, in terms of susceptibility to the antifungals (Kruskal-Wallis test, p > 0.05).

Despite not being statistically significant, among the patients in 2017, the MIC values for *C. albicans* revealed an isolate with resistance to fluconazole (MIC ≥ 64 µg/mL) and voriconazole (MIC ≥ 8 µg/mL) mL). For *C. glabrata*, during the period studied, there were dose-dependent/intermediate sensitivities to caspofungin (MIC ≤ 0.25 µg/mL) and fluconazole (MIC = 2-4 µg/mL), while in 2018 and 2019, strains appeared that were resistant to these two antifungals (MIC ≥ 64 µg/mL for fluconazole and MIC = 0.5 µg/mL for the echinocandins), as well as to micafungin, which until then had been the antifungal with the highest sensitivity profile (Table 3). The MIC values for the different *Candida* spp isolates are shown in Table 4.

A total of 77.7% (n = 49) of the patients were treated using empirical antifungal monotherapy, while 6.3% (n = 4) received antifungal polytherapy, and 15.9% (n = 10) either received antibiotics or had no treatment. Among the patients treated using antifungal monotherapy, 66% received fluconazole (n = 35), 18.9% micafungin (n = 10), 5.7% anidulafungin (n = 3), and 1.9% amphotericin B (n = 1). For the *C. glabrata* species, 40% of the patients received fluconazole as the primary therapy, with the antifungigrams showing dose-dependent sensitivity, while 20% and 6.7% received echinocandins and polytherapy, respectively. Figure 1 shows the distribution of antifungal use, according to *Candida* species.

The mortality rate was 63.5% (40 deaths), with infections by *C. albicans* accounting for 37.5% of this total, and women being most affected (57.5%). The next highest death rates (27.5%) were caused by *C. glabrata* and *C. tropicalis*. There was only one death among the pediatric patients (2.5%), which was due to *C. albicans*. Among the 23 patients (36.5%) discharged from the hospital, the species most prevalent in infections were *C. albicans* (47.8%), *C. tropicalis* (21.7%), and *C. glabrata* (17.4%), with men accounting for a higher number of cases (60.9%), although the differences were not statistically significant.

Table 3. Profile of sensitivity to antifungal agents for *Candida* species isolates obtained at the general hospital in Piracicaba (São Paulo state, Brazil), considering the period from 2014 to 2019.

		***In vitro* sensitivity profile**		
Species	**Antifungal agent**	**S (n)**	**DDS or IS (n)**	**R (n)**
C. albicans	Fluconazole	24	0	1
	Caspofungin	21	0	0
	Micafungin	21	0	0
	Voriconazole	24	0	1
	Amphotericin	8	0	0
C. tropicalis	Fluconazole	15	0	1
	Caspofungin	11	1	0
	Micafungin	12	0	0
	Voriconazole	15	0	1
	Amphotericin	4	0	0
C. glabrata	Caspofungin	2	10	1
	Fluconazole	-	10	1
	Micafungin	12	0	1
	Amphotericin	3	1	0
C. parapsilosis	Fluconazole	3	0	0
	Caspofungin	2	0	0
	Micafungin	3	0	0
	Voriconazole	2	0	0
	Amphotericin	1	0	0
C. intermedia	Fluconazole	1	0	0
	Caspofungin	1	0	0
	Micafungin	1	0	0
	Voriconazole	1	0	0
C. krusei	Caspofungin	0	1	0
	Micafungin	1	0	0
	Voriconazole	1	0	0
C. dubliniensis	Fluconazole	1	0	0
	Caspofungin	1	0	0
	Micafungin	1	0	0
	Voriconazole	1	0	0

S: Sensitive – high probability of therapeutic success, depending on the site of infection and dosage; **DDS** or **IS**: Dose-dependent or intermediate sensitivity – therapeutic success depending on the site of infection and dosage; **R**: Resistant – avoid use of the antifungal in question, high probability of therapeutic failure.

Table 4. MIC values for the Candida species isolates exposed to the antifungal agents, using an automated broth microdilution method (Vitek, bioMérieux, France), at the general hospital in Piracicaba (São Paulo state, Brazil), considering the period from 2014 to 2019.

		In vitro sensitivity profile		
Species	**Antifungal agent**	**S**	**DDS or IS**	**R**
C. albicans	Amphotericin	0.25 to 1	-	-
	Fluconazole	0.13 to 1	-	≥64
	Caspofungin	≤0.12 to 0.25	-	0
	Micafungin	≤0.06	-	≥8
	Voriconazole	≤0.1	-	0
C. tropicalis	Amphotericin	0.25 to 0.5	-	-
	Fluconazole	0.25 to 2	-	8
	Caspofungin	≤0.12 to 0.25	0.5	-
	Micafungin	≤0.06 to 0.12	-	-
	Voriconazole	≤0.1	-	1
C. glabrata	Fluconazole	0	2 to 4	≥64
	Caspofungin	≤0.12	≤0.25	0.5
	Micafungin	≤0.06	0	0.5
C. parapsilosis	Amphotericin	≤0.25	-	-
	Fluconazole	≤1 to 2	-	-
	Caspofungin	≤0.2 to 1	-	-
	Micafungin	0.5	-	-
	Voriconazole	≤0.1	-	-
C. krusei	Caspofungin	≤0.25	0.5	-
	Micafungin	0.12	-	-
	Voriconazole	≤0.1	-	-
C. dubliniensis	Fluconazole	≤0.5	-	-
	Caspofungin	≤0.12	-	-
	Micafungin	≤0.06	-	-
	Voriconazole	≤0.1	-	-

S: Sensitive – high probability of therapeutic success, depending on the site of infection and dosage; **DDS** or **IS**: Dose-dependent or intermediate sensitivity – therapeutic success depending on the site of infection and dosage; **R**: Resistant – avoid use of the antifungal in question, high probability of therapeutic failure.

Among the 40 deaths, 10 cases (25%) were not treated using antifungals or antibiotics. It should be noted that for these cases, positive results for fungi in the blood cultures were only made available close to the date of death (median of 5 days previously), while in one case, the blood culture was performed *post mortem*.

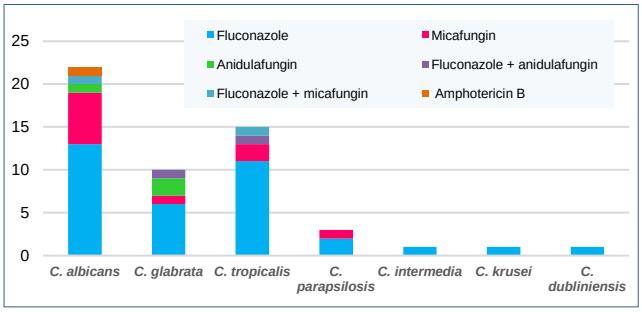

Figure 1: Distribution of antifungal use, according to *Candida* species.

DISCUSSION

Candida species are the commonest causes of fungal infections, varying according to the clinical profile of the patient, geographic location, and the antifungal protocols employed. Among the different species, *C. albicans* is the one most frequently isolated in hospitals worldwide. However, in the last two decades, there have been progressive increases of non-*C. albicans* species, notably *C. glabrata, C. tropicalis, C. parapsilosis, C. dubliniensis, C. guilliermondii*, and *C. krusei*[14,15]. In the present work, *C. albicans* accounted for 41.3% of infectious episodes, while 58.7% were caused by non-*C. albicans* species, of which the most prevalent were *C. tropicalis* (43.2%) and *C. glabrata* (40.5%).

The growth rates of non-*C. albicans* species may be influenced by previous and/or prolonged exposure to antifungals, resulting in increased intestinal fungal colonization, together with additional risk factors such as malignant diseases, use of internal catheters, and age[15].

The studies by Tortorano et al.[19] and Arendrup et al.[20] showed epidemiological features similar to those observed in the present work, with a predominance of male patients and individuals older than 70 years. The most important species identified were *C. albicans*, followed by *C. glabrata*, with the latter tending to become more frequent with increasing age[19].

In Latin America, *C. parapsilosis* and/or *C. tropicalis* have been found more frequently than *C. glabrata* and *C. krusei*[8]. Although *C. glabrata* is less common in Brazil, the present work found similar frequencies (over 20%) for *C. tropicalis* and *C. glabrata*. In Argentina, the study by Tiraboschi et al.[21] also found similar rates for these two species, between around 13.9% and 15.5%. Infection by *C. tropicalis*, in the presence of neoplasm, occurred in only 13% of the cases.

Considering the relation between epidemiology and the clinical conditions presented by the patients, previous studies found that infection by *C. parapsilosis* was associated with nosocomial transmission, targeting neonates, immunosuppressed patients, and those using catheters, probes, other devices, and parenteral nutrition8,16. This species is often found on human hands, so colonization of the hands of health professionals can lead to infection, especially in immunosuppressed patients, with *C. parapsilosis* having been isolated in countries in Europe, Asia, and Latin America[22].

The species *C. tropicalis*, which is associated with cancer and neutropenia[16], is frequently isolated in Asia and South America[15]. *C. krusei* and *C. glabrata* are associated with previous exposure to azoles[16], with *C. glabrata* being more common in individuals aged over 60 years, as well as in those who have received solid organ transplants[8]. These fungi have been reported in northern and central Europe, as well as in the United States[15]. The presence of *C. krusei*, which is the less common of the species, has been found in patients with hematologic neoplasms[8].

C. albicans is also the main etiological agent of candidiasis among neonatal ICU patients, although the infection epidemiology has been changing in the same way as for adult patients[23,24]. Among the non-*C. albicans* species, *C. parapsilosis* was previously found to be the most prevalent[25]. However, in the present work, the same proportions of cases of *C. tropicalis* and *C. albicans* were found in neonatal ICU patients. The frequent presence of *C. tropicalis* was also reported by Fernandes[26] and Xavier et al.[27].

At the time of the test, most of the patients were in the ICU, where several conditions exist that are associated with the development of candidemia, including serious disease, use of steroids, multiple transfusions, parenteral nutrition, major surgery, hemodialysis, central venous catheter, and pancreatitis, in addition to long hospitalization times and the use of broad-spectrum antibiotics[28]. A central venous catheter was present in 93.7% of the cases, but the characteristics of the study meant that no information was available regarding its removal subsequent to the diagnosis of candidemia. Digestive system surgery affected 50.8% of the patients, representing a risk factor due to the disturbance of colonized gastrointestinal barriers, potentially leading to fungal translocation[8]. In addition, 49.2% of the patients used parenteral nutrition, which could be considered a protective factor, since nutritional care can reduce the rates of morbidity and mortality due to malnutrition[29].

The sensitivity profile showed that the Candida species found at the hospital were sensitive to fluconazole, a traditional antifungal that is less expensive than echinocandins. However, cases of resistance to these antifungals were detected. Echinocandins are usually considered as promising broad-spectrum alternative fungicidal agents, potentially effective as a solution to the resistance mechanisms observed for azoles, since all fungi possess β-(1,3)-glucan synthase in their cell walls[22]. However, Candida species resistant to these drugs have recently emerged in laboratory and clinical environments[22], corroborating the present findings. Therefore, it is essential to develop strategies focusing on reducing the indiscriminate use of antifungals, in order to reduce selective pressure and the emergence of microorganisms resistant to these drugs.

It has been reported that *C. albicans* and *C. parapsilosis* present high levels of resistance to azoles and echinocandins, with *C. parapsilosis* having 5-fold higher resistance to fluconazole, compared to *C. albicans*, as well as an intrinsic resistance to echinocandins, with higher MIC values, compared to other species (2 mg/L and 0.25 mg/L for *C. parapsilosis* and *C. albicans*, respectively)[22]. Lower susceptibility of *C. parapsilosis* to echinocandins can be explained by the natural polymorphisms of the FKS genes[30]. However, only 3 cases involving *C. parapsilosis* infection were found in the present work, with the fungus showing sensitivity to azoles and echinocandins.

The fungi *C. dubliniensis* and *C. glabrata* showed no substantial increases of resistance to these classes of drugs, although the sensitivity profile of *C. glabrata* may be lower for fluconazole, while *C. krusei* appears to be intrinsically resistant to fluconazole[20]. Here, a dose-dependent/intermediate sensitivity of *C. glabrata* to fluconazole was observed, but this was also found for caspofungin, with strains resistant to these two antifungals, as well as to micafungin, appearing towards the end of the period evaluated. Between the years 2001 and 2010, the frequency of resistance to echinocandins increased from 4.9 to 12.3%, which could be explained by the induction of mutations in FKS genes[31].

In the case of *C. tropicalis*, although resistance to fluconazole of around 4-9% has been reported[30], only one case of resistance (to fluconazole and voriconazole) was observed in the present work, suggesting that geographic differences and previous exposure to azoles could influence the profile of sensitivity to antifungals.

Therefore, while national and international monitoring programs are important for identifying epidemiological trends, the success of individual therapeutic approaches is highly dependent on knowledge of local epidemiological factors, as well as the profile of the sensitivity of different strains to antifungal agents, since fungal infections are increasingly present in the hospital environment, associated with high rates of morbidity and mortality. In addition to guiding therapeutic actions, such knowledge enables the establishment of measures designed to control and prevent these infections.

Limitations of this study were that it was retrospective (since the analyzed data were not collected for this specific purpose) and that there was difficulty in accessing information, since the institution did not possess an electronic medical

record. Some of the information related to the clinical conditions of the patients was previously collected by the Hospital Infection Control Service, which excluded information on aspects such as comorbidities, invasive procedures, and the previous use of antimicrobial or antifungal therapies, prior to the diagnosis.

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CONFLICTS OF INTERESTS

The authors declare no conflicts of interests.

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