ORIGINAL ARTICLE

SUSCEPTIBILITY PROFILE TO ANTIFUNGALS OF *CANDIDA* SPP. ISOLATED FROM INFANTS AND CHILDREN

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Highlights: (1) Most cases of candidiasis and candidemia occurred in the age group of 1 to 3 months. (2) *C. albicans* was the most prevalent species found in children (34.92%), followed by *C. parapsilosis* (29.82%) and *C. tropicalis* (22%). (3) *C. albicans* was predominant in the bloodstream, midstream urine and tracheal secretion ($p<0.001$). (4) The greatest diversity of pathogenic *Candida* species was found in pediatric wards and ICUs. (5) *C. albicans* population showed resistance to amphotericin B and fluconazole, *C. parapsilosis* and *C. tropicalis* showed resistance to fluconazole, amphotericin B and caposfungin.

http://dx.doi.org/10.21527/2176-7114.2025.50.15426

How to cite:

Schneider GC, Marques SG, Lima IN de SB, Furtado HLA, Luz RL, do Carmo MS. Susceptibility profile to antifungals of candida spp. Isolated from infants and children. Rev. Contexto & Saúde, 2025;25(50): e15426

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SUSCEPTIBILITY PROFILE TO ANTIFUNGALS OF *CANDIDA* SPP. ISOLATED FROM INFANTS AND CHILDREN

ABSTRACT

Pediatric candidiasis and candidemia are important causes of morbidity and mortality worldwide. This study aimed to analyze the incidence and antifungal susceptibility profile of *Candida* spp. isolated from infants and children in maternity wards and public hospitals. This is a retrospective, analytical-cross-sectional observational study carried out through the analysis of data from medical records and the antifungigram of patients diagnosed with candidiasis or candidemia admitted from January 2015 to December 2021 in the city of São Luís-MA, Brazil. A total of 627 episodes of *Candida* infection were observed (45.3% female and 54.7% male). The highest incidence occurred within the age groups of 1-3 months (41.63%) and 1-3 years (22.65%) and the main isolated species were *C. albicans (*34.92%), *C. parapsilosis* (29.82%) and *C. tropicalis* (22%). The highest variability of pathogenic *Candida* was detected in blood, mid-stream urine, and tracheal secretions ($p<0.001$) recovered mainly from patients hospitalized in the pediatric ward and ICU. The species *C. glabrata*, *C. haemulonii* and *C. tropicalis* exhibited resistance to 2-3 differents antifungals (amphotericin B, caspofungin, fluconazole and voriconazole). Our study indicates the urgency of implementing more rigorous control measures in maternity wards and pediatric hospitals and serves as a guide to conduct health professionals in selecting the most appropriate antifungal therapy.

Keywords: Candidiasis; Candidemia; Antifungal resistance.

PERFIL DE SUSCEPTIBILIDADE AOS ANTIFÚNGICOS DE *CANDIDA* SPP. ISOLADAS DE LACTENTES E CRIANÇAS

RESUMO

A candidíase e a candidemia pediátrica constituem importante causa de morbidade e mortalidade em todo o mundo. Este estudo teve como objetivo analisar a incidência e o perfil de susceptibilidade antifúngica de *Candida* spp. isolados de lactentes e crianças internadas em maternidades e hospitais públicos. Trata-se de um estudo observacional retrospectivo, analítico-transversal realizado através da análise de dados de prontuários e do antifungigrama de pacientes com diagnóstico de candidíase ou candidemia admitidos no período de janeiro de 2015 a dezembro de 2021 na cidade de São Luís-MA. Foram detectados 627 episódios de infecção por *Candida* (45,3% sexo feminino e 54,7% sexo masculino). A maior incidência

ocorreu nas faixas etárias de 1 a 3 meses (41,63%) e de 1 a 3 anos (22,65%) e as principais espécies isoladas foram *C. albicans*, *C. parapsilosis* e *C. tropicalis*. A maior diversidade de *Candida* patogênica foi detectada no sangue, urina jato médio e secreção traqueal (p<0,001) recuperadas principalmente de pacientes hospitalizados na enfermaria e UTI pediátrica. As espécies *C. glabrata*, *C. haemulonii* e *C. tropicalis* apresentaram resistência a 2-3 diferentes antifúngicos (anfotericina B, caspofungina, fluconazol e voriconazol). Este estudo indica a urgência de implementação de medidas de controle mais rigorosas nas maternidades e hospitais pediátricos e serve como guia para orientação dos profissionais de saúde na seleção da terapia antifúngica mais adequada.

Palavras-chave: Candidíase; Candidemia; Lactentes; Crianças; Resistência antifúngica.

INTRODUCTION

Candidiasis is an opportunistic infection caused by *Candida* spp., which primarily colonize the oral cavity, vagina and gastrointestinal tract. It occurs as a secondary infection in individuals immunocompromised or when the host has or is exposed to other risk factors that facilitate infection such as broad-spectrum antibiotics, immunosuppressive agents/chemotherapy, prematurity, intravascular medical devices, extended ICU stay and invasive procedures[1,2].

Besides, candidemia consists of the presence of *Candida* spp. in the hematogenous pathway. It is the main cause of invasive fungal infections in hospitalized infants and children and the third most common type of nosocomial bloodstream infection worldwide, preceded by bacteremias caused by coagulase-negative *Staphylococcus*, *S. aureus* and *Enterococcus* spp.[3].

Managing invasive fungal infections presents numerous challenges in infants and childrens, most of them are related to: fungal epidemiology, limited pharmacokinetic data and inconsistency of dose recommendation. The excessive use of antifungals is also problematic because selects for strains that are resistant or refractory to treatment[4,5].

Although *C. albicans* is the most prevalent etiological agent, a significant increase in non-albicans species (NAC) can be observed recently. Knowledge about NAC species is important for epidemiological monitoring of fungal infections, assessment of virulence/pathogenicity and better understanding of the drug response to commercially

available antifungals. Therefore, the goal of this study was to draw up a clinical-epidemiological panel of candidiasis and candidemia in infants and children in maternity wards and public hospitals in the city of São Luís-MA, Brazil.

METHODS

Type of study and ethical issues

This is a retrospective, analytical-cross-sectional observational study that was carried out by collecting microbiological data from patients diagnosed with candidiasis and candidemia. All samples originated from maternity wards and public pediatric hospitals in the city of São Luís- MA.

According with the standards that govern research with human beings in Resolution nº 466/12, of the National Health Council, this research was approved by the Ethics and Research Committee (CEP) of CEUMA University under nº. 3.893.916. All information collected was protected, maintaining ethics and confidentiality regarding the identity of the participants. After analyzing the data obtained, the results were disseminated to the clinical team of the participating institutions.

Location, study period and data collection

We collected antifungigram data from medical records infants and children admitted to Maternidade de Alta Complexidade do Maranhão (MAC), Maternidade Benedito Leite and Hospital Pediátrico Juvêncio Matos from January 2015 to December 2021. The antifungigram was analyzed data regarding pathogens and their respective susceptibility profile to antifungals with Minimum Inhibitory Concentration (MIC). The microorganisms were identified by the Mald Tof-Bruker® method and susceptibility to antifungals (amphotericin B, caspofungin, fluconazole, 5-fluorocytosine or Flucytosine, ketoconazole, micafungin and voriconazole) were determined by Vitek II – Biomèrieux®. The microbiological data were made available by Laboratório Cedro.

Population and sampling

The study included infants and children hospitalized at the Maternidade de Alta Complexidade do Maranhão (MAC), Maternidade Benedito Leite and Hospital Pediátrico Juvêncio Matos. The patients were composed by infants (1-12 months) and children (1-10 years) with a confirmed clinical diagnosis of candidiasis and candidemia. Patients with inconclusive cultures, incomplete antimicrobial susceptibility profile and with no description of the Minimum Inhibitory Concentration (MIC) were excluded.

Statistical analysis

For statistical analysis, the GraphPad Prism® software version 9.5 was used. The crossing of the classification variables was analyzed using the Chi-square test of independence ($\chi 2$) and the contingency coefficient C. The level of significance adopted in all tests was 5%, that is, statistically significant when $p<0.05$.

Results and discussion

A total of 627 microbiological test results from Laboratório Cedro positive for *Candida* spp. were analyzed, covering the period from January 1, 2015 to December 31, 2021. Of this total, 54.70% of patients were male and 45.30% to the female gender (Table 1). The age ranged from 1 month - 10 years, with a higher prevalence of cases of candidiasis and candidemia at the age of 1 - 3 months (41.63%), followed by 1 - 3 years (22.65%) and 4 - 6 months (14.51%), a fact explained by the immaturity of the immune system associated with non-integrity of the skin and mucous membranes[6-9].

Table 1. Distribution of clinical samples according to gender and age group

Variables	No.	%
Gender		
Woman	284	45.30
Man	343	54.70
Age range (m/y*)		
1 - 3 m	261	41.63
4 - 6 m	91	14.51
7 – 9 m	37	5.90
10 – 12 m	30	4.78
1- 3 a	142	22.65
4 - 6 a	38	6.06
7 - 10 a	28	4.46

* Subtitle: m=months; a=years

C. albicans was the most prevalent species found in children (34.92%), followed by *C. parapsilosis* (29.82%) and *C. tropicalis* (22%) (Table 2). Recent studies demonstrated a higher prevalence of *C. albicans* and the predominance of *C. parapsilosis* within non-albicans species, as the main etiological agents related to the development of invasive candidiasis and pediatric candidemia[10,11].

Table 2. Frequency of *Candida* spp. isolated from infants and children in public maternities and pediatric hospitals in São Luís-MA (2015-2021).

Isolated	No.	%
C. albicans	219	34.92
C. parapsilosis	187	29.82
C. tropicalis	138	22.0
C. orthopsilosis	29	4.62
C. guilliermondii	17	2.71
C. glabrata	10	1.59
C. pelliculosa	7	1.11
C. haemulonii	4	0.64
C. intermedia	3	0.48
C. krusei	3	0.48
C. rugosa	3	0.48
C. africana	2	0.32
C. pseudohaemulonii	2	0.32
C. duobushaemulonii	1	0.17
C. fabianni	1	0.17
C. metapsilosis	1	0.17
Σ	627	100

Regarding the abundance of *Candida* spp. by gender, it was observed that *C. albicans* presented a similar distribution in females (35.91%) and males (34.11%), with no statistically significant difference (p= 0.95); the same happened in relation to the species *C. parapsilosis*, which presented a relative abundance of 28.87% in the female gender and 30.61% in the male gender, *C. tropicalis* which presented a relative abundance of 23.23% in the female gender and 20,99% male. The remaining species represented less than 15% in both genera. It is worth mentioning that the species *C. krusei* and *C. intermedia* and *C. africana* were found exclusively in the male gender and the species *C. metapsilosis*, *C. fabiannii*, *C. duobushaemulonii*, *C. pseudohaemulonii* and *C. pelliculosa* only in the female gender (Figure 1).

Figure 1. Distribution of *Candida* species by patient gender

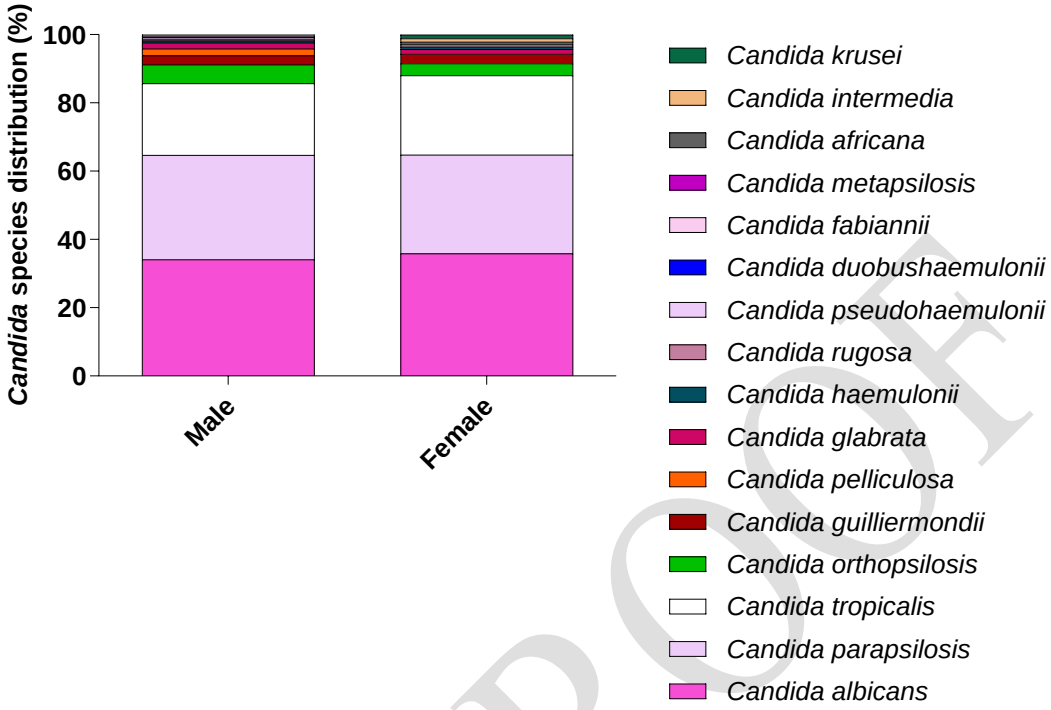
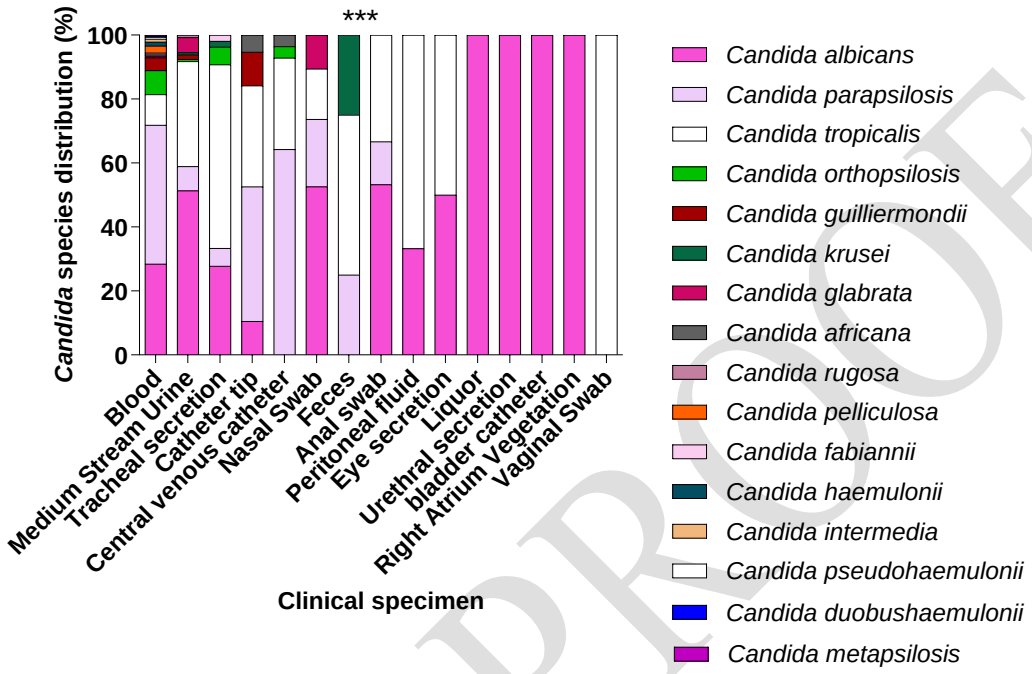


Figure 2 illustrates the distribution of *Candida* spp. by anatomical collection site. *C. albicans* was predominant in the bloodstream, midstream urine and tracheal secretion ($p<0.001$). This prevalence is due to its ability to colonize different human sites, which is one of the main reasons why this species is the most common in infections of this type. Although these sites show different microbiota with different physicochemical characteristics, the ability of *C. albicans* to adapt to inhospitable conditions of colonization sites is noted[12,13]. In other sites (nasal swab, feces, catheter tip, anal swab, peritoneal fluid, cerebrospinal fluid, wound secretion, urinary catheter secretion, urethral secretion, right atrium vegetation, vaginal swab, ocular secretion, central catheter) there was a predominance of *C. tropicalis*, *C. parapsilosis* and *C. albicans.*

Figure 2. Relative abundance of *Candida* spp per clinical specimen. The contingency test C was applied to evaluate the statistical difference in the abundance of *Candida* spp. between groups of clinical specimens (p<0.001).



Candida infections are increasing considerably worldwide. Blood is rich in electrolytes, amino acids, glucose, lipids and vitamins, which can be used in the metabolism of aerobic and anaerobic microorganisms, leading to proliferation. Several studies have observed that *C. parapsilosis* and *C. tropicalis* are emerging as the most frequent pathogens of bloodstream infections, as found in this study[14- 18].

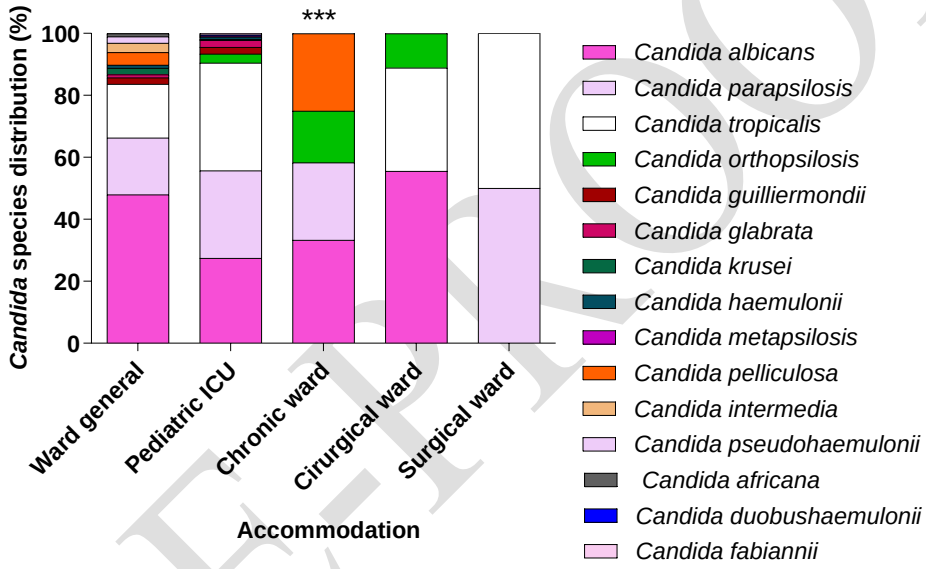
The detection of *Candida* spp. in tracheal secretion is an important predictor of fungal pneumonia. The access of yeast to the lower respiratory tract is a sign of contamination due to manipulation by healthcare professionals, especially during the process of aspiration of secretions from the tracheostomy, a factor that may explain the findings of this study[19].

The presence of *Candida species* in urine (canduria) is a common clinical finding and can serve as a marker of candidemia. Fungal infections of the urinary tract can be caused either by hematogenous spread to kidneys (anterograde infection) or by the ascending route through

the urethra and bladder (retrograde infection)[20]. Risk factors for candiduria in children include use of a bladder catheter and recent use of antimicrobials[21].

The distribution of *Candida* spp. according to the hospital accommodation sector can be seen in Figure 3. We found the higher diversity of pathogenic *Candida* in ward and pediatric ICU ($p<0.001$). In general, the most prevalent species were *C. albicans* and *C. parapsilosis.*

Figure 3. Relative abundance of *Candida* spp. for hospital accommodation. The contingency test C was applied to evaluate the statistical difference in the abundance of *Candida* spp. between hospital accommodation groups ($p<0.001$).



Nosocomial fungal infections can have endogenous and exogenous origins. In infection of endogenous origin, microorganisms come from the individual's microbiota, which induce infection due to some predisposing factor in the host or fungus. The infection can also show exogenous form, in which the fungi reach the patient from external sources, such as the hands of healthcare professionals, probes, catheters and even the hospital's air conditioning system[22], which result in an increase in nosocomial infections.

In Brazil, nosocomial infections caused by *Candida* represent 80% of all fungal infections, including blood, surgical site and urinary tract infections[23]. Studies show that healthcare-related infections pose a high risk to patients hospitalized in ICUs and wards, representing an increase of more than 50%[23]. The main species found are: *C. albicans, C. tropicalis, C. parapsilosis, C. glabrata and C. krusei*. In recent years, an increase in the

frequency of systemic infections caused by non-*Candida* species has been observed[24,25], which corroborates this research, in which the main species found were *C. albicans*, *C. parapsilosis* and *C. tropicalis.*

In this scenario, biofilms play an important role. The biofilms are associated with resistance against most antimicrobials and the persistence of the microorganism in the infectious process[26]. *C. albicans* has a greater potential to form biofilms on different invasive medical devices, while *C. tropicalis* is more commonly reported on catheter surfaces[26-30].

Due to high contamination probability and multi-resistant features of *Candida* spp the admission of patients to the intensive care unit (ICU) may be dangerous. The main risk factors related to the development of candidemia in neonatal and pediatric patients are central venous catheters (CVC), prolonged use of broad-spectrum antibiotics, parenteral nutrition and immunocompromise[4,31,32].

The Table 3 show the susceptibility panel to antifungal drugs with the minimum inhibitory concentration (MIC) (µg/mL), including the sensitivity profile, which defines the efficiency of the antifungal; the resistance profile, which determines the action of the microorganism against the antifungal; and intermediate resistance, in which the drug's effectiveness may not have the expected effect.

Susceptibility testing to antifungal drugs has become increasingly important in clinical routine due to the increase in new antifungal agents on the market and the recovery of clinical isolates that present inherent or developed resistance to antifungals[33]. In this study, the susceptibility profile of all yeast isolates was tested against seven drugs, namely amphotericin B, caspofungin, fluconazole, fluorocytosine or flucytosine, ketoconazole, micafungin and voriconazole.

The susceptibility test revealed antimicrobial resistance in three *Candida* species. *C. albicans* population showed resistance to amphotericin B (0.46%) and fluconazole (0.91%). *C. parapsilosis* and *C. tropicalis* showed resistance to fluconazole (3.74% and 2.90% respectively), amphotericin B (0.72%) and caposfungin (0.72%). These data corroborate with Khan *et al.* (2019)[33-34], which reported an increase in fluconazole resistance rates in recent years. Castanheira *et al.* (2016) also reported that *C. albicans and C. tropicalis* showed resistance to fluconazole (0.4% and 11.6%, respectively).

Candida species also showed resistance to fluconazole, *C. glabatra* (MIC= ≤1 – 4 μg/mL), *C. guilliermondii* (MIC= 2 – 4 μg/mL), *C. haemulonii* (MIC = 2 – 256 μg/mL), *C. pelliculosa* (MIC= 2 – 4 μg/mL) and *C. krusei* with 100% of resistant isolates (MIC= 8 – 64 μg/mL). Fluconazole is one of the most prescribed antifungals for *Candida* infections which is the main cause of resistance[36].

The species *C. glabrata* showed intermediate sensitivity to capsofungin (10%) and 20% of the isolates demonstrated resistance to the antifungal agent (MIC= ≤0, 12 – 0.5 μg/mL). Furthermore, 50% of isolates showed resistance to fluconazole (MIC= ≤1 – 4 μg/mL). Previous studies reported that *C. glabrata* has high rates of resistance to azoles due to the upregulation of drug transporters and target modification[37,38]

Table 3. Antifungal susceptibility pattern of *Candida* spp. isolated from infants and children in public maternities and pediatric hospitals in São Luís-MA (2015-2021).

Species	Antifungal drug	MIC (µg/mL)	% of sensitive isolates	% of intermediate isolates	% of resistant isolates
***C. africana* (2)**	ANF-B	0.5 – 1	100	-	-
	CPF	≤0.12	100	-	-
	FLZ	≤0.5 – 0.5	100	-	-
	5-CF	≤1	100	-	-
	KET	NT	100	-	-
	MCF	≤0.06	100	-	-
	VCZ	≤0.12	100	-	-
***C. albicans* (219)**	ANF-B	≤ 0.12 - ≥16	99.54	-	0.46
	CPF	≤0.12 - ≤1	100	-	-
	FLZ	≤0.5 - ≤64	99.09	-	0.91
	5-CF	≤1	100	-	-
	KET	NT	100	-	-
	MCF	≤0.06 – 2	100	-	-
	VCZ	≤0.12 – 4	100	-	-
***C. duobushaemulonii* (1)**	ANF-B	NT	100	-	-
	CPF	NT	-	-	-
	FLZ	NT	100	-	-
	5-CF	NT	-	-	-
	KET	NT	100	-	-
	MCF	NT	-	-	-
	VCZ	NT	-	-	-
***C.fabianni* (1)**	ANF-B	0.5	100	-	-
	CPF	0.25	100	-	-
	FLZ	≤ 0.5	100	-	-
	5-CF	≤1	100	-	-
	KET	NT	-	-	-
	MCF	0.12	100	-	-
	VCZ	≤0.12	100	-	-
***C. glabrata* (10)**	ANF-B	≤ 0.25 – 1	100	-	-
	CPF	≤0.12 – 0.5	70	10	20
	FLZ	≤1 – 4	50	-	50
	5-CF	≤1	100	-	-
	KET	NT	-	-	-
	MCF	≤0.06	100	-	-
	VCZ	≤0.12 – 0.25	100	-	-

***C. guilliermondii* (17)**	ANF-B	≤0.25 – 1	100	-	-
	CPF	≤0.12 – 1	100	-	-
	FLZ	2 – 4	41.18	-	58.82
	5-CF	≤1	100	-	-
	KET	NT	100	-	-
	MCF	≤ 0.06 – 0.5	100	-	-
	VCZ	≤0.12	100	-	-
***C. haemulonii* (4)**	ANF-B	1- ≤ 32	25	-	75
	CPF	≤0.6	100	-	-
	FLZ	2 – 256	25	-	75
	5-CF	≤1	100	-	-
	KET	NT	100	-	-
	MCF	0.12 – 1	100	-	-
	VCZ	≤0.5 – 4	75	-	25
***C. intermedia* (3)**	ANF-B	≤0.25 – 0.5	100	-	-
	CPF	≤0.25 – 0.25	100	-	-
	FLZ	two	100	-	-
	5-CF	≤1	100	-	-
	KET	NT	100	-	-
	MCF	0.12	100	-	-
	VCZ	≤0.12	100	-	-
***C. krusei* (3)**	ANF-B	0.5	100	-	-
	CPF	≤0.25	100	-	-
	FLZ	8 – 64	-	-	100
	5-CF	NT	-	-	-
	KET	NT	-	-	-
	MCF	<0.19	100	-	-
	VCZ	≤0.12 – 1	100	-	-
***C. metapsilosis* (1)**	ANF-B	NT	100	-	-
	CPF	NT	-	-	-
	FLZ	NT	100	-	-
	5-CF	NT	-	-	-
	KET	NT	100	-	-
	MCF	NT	-	-	-
	VCZ	NT	-	-	-
***C. orthopsilosis* (29)**	ANF-B	≤0.25 – 1	100	-	-
	CPF	≤0.25 – 0.5	82.76	17.24	-
	FLZ	≤0.5 - ≤ 4	100	-	-
	5-CF	≤1 - ≥64	82.21	-	13.79
	KET	NT	-	-	-
	MCF	≤0.06 – 0.5	100	-	-
	VCZ	≤0.12	100	-	-

***C. parapsilosis* (187)**	ANF-B	≤0.25 – 1	100	-	-
	CPF	≤0.12 – 1	100	-	-
	FLZ	≤0.5 – 16	96.26	-	3.74
	5-CF	≤1	100	-	-
	KET	NT	100	-	-
	MCF	≤0.06 – 2	100	-	-
	VCZ	≤0.12 – 0.25	100	-	-
***C. pelliculosa* (7)**	ANF-B	0.5	100	-	-
	CPF	≤0.25	100	-	-
	FLZ	2 – 4	57.15	-	42.85
	5-CF	≤1	100	-	-
	KET	NT	100	-	-
	MCF	NT	100	-	-
	VCZ	≤0.12	100	-	-
***C. pseudohaemulonii* (2)**	ANF-B	0.5	100	-	-
	CPF	≤0.12	100	-	-
	FLZ	1	100	-	-
	5-CF	NT	-	-	-
	KET	NT	-	-	-
	MCF	≤0.06	100	-	-
	VCZ	≤0.12	100	-	-
***C. rugosa* (3)**	ANF-B	1	100	-	-
	CPF	2	100	-	-
	FLZ	≤0.05	100	-	-
	5-CF	≤1	100	-	-
	KET	NT	100	-	-
	MCF	0.12	100	-	-
	VCZ	≤0.12	100	-	-
***C. tropicalis* (138)**	ANF-B	≤0.25 – 8	99.28	-	0.72
	CPF	≤0.25 - ≥8	99.28	-	0.72
	FLZ	≤0.5 – 8	97.10	-	2.90
	5-CF	≤1	100	-	-
	KET	NT	100	-	-
	MCF	≤0.06	100	-	-
	VCZ	≤0.12	100	-	-

Caption: ANF B=amphotericin B; CPF =caspofungin; FLZ=fluconazole; 5-CF=5-fluorocytosine or Flucytosine; KET=ketoconazole; MCF=micafungin; VCZ=voriconazole; NT = not tested; MIC = minimum inhibitory concentration (µg/mL).

In our studies we also detected predominance of non-albicans species, which also demonstrated resistance profile to fluconazole (50%). *C. glabrata* has been reported as one of the main problems related to infections caused by this genus, since it has a high incidence in adults. Previous studies revelated resistance to fluconazole and higher mortality rates when compared to other species[39].

It was also found that 75% of *C. haemulonii isolates* were resistant to amphotericin B and fluconazole, while 25% were resistant to voriconazole. Similar results were observed in a study developed by Jurado-Martín *et al*. (2020)[40], in which six isolates of *C. haemulonii* demonstrated reduced susceptibility to fluconazole and almost all showed reduced susceptibility to amphotericin B.

C. africana, C. duobushaemulonii, C. fabianni, C. intermedia, C. rugosa, C. metapsilosis and C. pseudohaemulonii were sensitive to the antifungals. We found high variation in the spectrum of action for amphotericin B, being 0.12 – 16 µg/mL for *C. albicans* and 1 – 32 µg/mL for *C. haemulonii*; fluconazole, being 0.5 – 64 µg/mL for *C. albicans*, 0.5 – 16 µg/mL for *C. parapsilosis*, 2 – 256 µg/mL for *C. haemulonii* and 8 – 64 µg/mL for *C. krusei.* The MIC for the other antifungals was within the threshold standards stipulated by the Clinical Laboratory Standards Institute (CLSI). It is important to note that the species *C. haemulonii, C. glabrata* and *tropicalis* were resistant to 2-3 antifungals.

Final considerations

This study provides relevant data on local epidemiology, which is important to better conduct the clinical management of patients and select the best therapy. In São Luís maternity wards and public hospitals *C. albicans* is most common specie causing candidiasis and candidemia in infants and children, but it was possible to observe a significant number of non-albicans *Candida* in patients. The highest rates of resistance to fluconazole were observed in less common species, such as *C. krusei, C. pelliculosa* and *C. haemulonii*, which highlights the need for constant surveillance of antifungal resistance.

Acknowledgments

Fundação de Amparo ao Desenvolvimento Científico e Tecnológico do Maranhão - FAPEMA

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Submitted: December 19, 2023

Accepted: December 11, 2024

Published: July 7, 2025

SUSCEPTIBILITY PROFILE TO ANTIFUNGALS OF *CANDIDA* SPP. ISOLATED FROM INFANTS AND CHILDREN

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All authors approved the final version of the text.	
Conflict of interest:	There is no conflict of interest
Financing:	Fundação de Amparo à Pesquisa a ao Desenvolvimento Científico e Tecnológico do Maranhão (FAPEMA), Bolsa de iniciação científica (BIC-00815/21)
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Editor:	Matias Nunes Frizzo PhD
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