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ARTIGO ORIGINAL

Clinical characteristics, epidemiology, and mortality of patients receiving antifungal therapy at a university hospital of the Triângulo Mineiro, Brazil

Aspectos clínicos, epidemiológicos e mortalidade de pacientes em uso de terapia antifúngica em um hospital universitário do Triângulo Mineiro, Brasil

Aspectos clínicos, epidemiológicos y mortalidad de pacientes en uso de terapia antifúngica en un hospital universitario del Triângulo Mineiro, Brasil

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ABSTRACT

Background and Objectives: Invasive fungal infections are associated with high morbidity and mortality in patients admitted to hospital, including those receiving appropriate therapy. The aim of this study was to evaluate the use of prophylactic and preemptive antifungal therapy; clinical and epidemiological features; and mortality of patients admitted to an infectious disease ward of a public high complexity hospital in Uberlandia, Minas Gerais, Brazil. **Methods:** This is a retrospective study carried out in the infectious diseases ward of a public university hospital in Brazil. Data from patients hospitalized in 2019 and 2020 who received azole antifungals (fluconazole, itraconazole, or voriconazole), echinocandin (anidulafungin), and polyene (amphotericin B) were collected from medical records. **Results:** During the study period, 111 patients received one or more antifungal agent. The length of hospital stays of patients (29.35 days; p=0.0252), mean number of days of antibacterial drug use (23.5 days; p=0.0164), a diagnosis of AIDS (p=0.0397), mechanical ventilation (MV) (p<0.001), and presence of a nasoenteral tube (p<0.01) were variables that were associated with death. Fungal infection was confirmed in 79 (71.2%) patients who used antifungal drugs. The most frequent fungi isolated were *Candida* spp. (36; 32.4%) and *Cryptococcus* spp. (22; 19.8%), and there was an association between infection with these fungi and mortality (p<0.05; OR: 7.61 and 5.53, respectively). Regarding antifungal therapy indication, 56 (50.4%) patients received it as empirical therapy, 33 (29.7%) as targeted therapy, and 22 (19.8%) as preemptive therapy. **Conclusion:** The factors that contributed to mortality of the patients were longer hospital stays, AIDS, antibacterial medication use, mechanical ventilation, and presence of a nasoenteral tube. The type of antifungal therapy used did not influence the mortality in these patients.

Keywords: *Antifungal therapies, Invasive fungal infection, Mortality, Drug therapy.*

RESUMO

Justificativa e Objetivos: As infecções fúngicas invasivas apresentam alta morbimortalidade para pacientes hospitalizados, inclusive para aqueles em uso de terapia apropriada. O objetivo foi avaliar a terapia antifúngica profilática e preemptiva, as características clínicas e epidemiológicas, e a mortalidade de pacientes internados em uma enfermaria de doenças infecciosas de um hospital público de alta complexidade de Uberlândia, Minas Gerais, Brasil. **Métodos:** Trata-se de estudo retrospectivo realizado em uma enfermaria de doenças infecciosas. Os dados coletados dos prontuários foram referentes aos pacientes internados nos anos de 2019 e 2020 e que fizeram uso de antifúngicos azólicos (fluconazol, itraconazol ou voriconazol), equinocandinas (anidulafungina) e poliênicos (anfotericina B). **Resultados:** Durante o período, 111 pacientes usaram um ou mais antifúngicos. O tempo de internação (29,35 dias, p= 0,0252), média de dias de uso de antibacterianos (23,5 dias; p=0,0164), aids (p=0,0397), uso de ventilação mecânica (VM; p <0,001) e uso de sonda nasoenteral (p<0,01) foram variáveis que se relacionaram com desfecho morte. A infecção por fungos foi confirmada em cultura para 79 (71,2%) pacientes em terapia antifúngica. Os fungos mais frequentes foram *Candida* spp. (36; 32,4%) e *Cryptococcus* spp. (22; 19,8%), mostrando relação da infecção por esses fungos com a mortalidade (p<0,05; OR: 7,61 e 5,53, respectivamente). Quanto à terapia, 56 (50,4%) pacientes estavam em terapia empírica; 33 (29,7%) usaram como terapia alvo; e 22 (19,8%) usavam como terapia preemptiva. **Conclusão:** A mortalidade foi mais frequente entre os pacientes com maior tempo de hospitalização, que tinham aids e que fizeram uso de antibióticos, de ventilação mecânica e de sonda nasoenteral em algum momento da internação. O tipo de terapia antifúngica não influenciou a mortalidade desses pacientes.

Descritores: *Antifúngicos*; *Infecções Fúngicas Invasivas*; *Mortalidade*; *Tratamento Farmacológico*.

RESUMEN

Justificación y Objetivos: Las infecciones fúngicas invasivas presentan una alta morbilidad y mortalidad en los pacientes hospitalizados, incluidos aquellos que utilizan la terapia adecuada. El objetivo fue evaluar la terapia antimicótica profiláctica y preventiva, las características clínicas, epidemiológicas y la mortalidad de pacientes ingresados en una sala de enfermedades infecciosas de un hospital público de alta complejidad en Uberlândia, Minas Gerais, Brasil. **Métodos:** Este es un estudio retrospectivo realizado en la sala de enfermedades infecciosas de un hospital universitario público en Brasil. Los datos recogidos de las historias clínicas se referían a pacientes hospitalizados en 2019 y 2020 y que utilizaban antifúngicos azoles (fluconazol, itraconazol o voriconazol), equinocandinas (anidulafungina) y polienos (anfotericina B). **Resultados:** Durante el período, 111 pacientes usaron uno o más antifúngicos. El tiempo de estancia hospitalaria (29,35 días, p= 0,0252), promedio de días de uso de antibacteriano (23,5 días; p=0,0164), SIDA (p=0,0397), uso de ventilación mecánica (VM; p<0,001) y uso de sonda nasoenteral (p<0,01) fueron variables que se relacionaron con el desenlace de muerte. La infección por hongos se confirmó en cultivo en 79 (71,2%) pacientes que usaban medicamentos antimicóticos. Los agentes fúngicos más frecuentes fueron *Candida* spp. (36; 32,4%) y *Cryptococcus* spp. (22; 19,8%), mostrando relación entre la infección por estos hongos y la mortalidad (p<0,05; 7,61 y 5,53, respectivamente).

En cuanto a la terapia, 56 (50,4%) pacientes estaban en terapia empírica; 33 (29,7%) la utilizaron como terapia diana; y 22 (19,8%) la utilizaron como terapia preventiva. **Conclusión:** La mortalidad fue más frecuente entre los pacientes con mayor tiempo de internación, que tenían SIDA y que utilizaron antibióticos, ventilación mecánica y sonda nasoenteral en algún momento de la internación. El tipo de terapia antifúngica no influyó en la mortalidad de estos pacientes.

Palabras clave: *Antifúngicos*; *Infecciónes Fúngicas Invasoras*; *Mortalidad*; *Quimioterapia*.

INTRODUCTION

Invasive fungal infections (IFI) are a growing problem in hospitals, and it is estimated that more than 300 million people worldwide acquire fungal infections each year. Fungal infections are associated with an estimated one to two million deaths per year, a figure approaching the number of deaths due to malaria or tuberculosis. [1,2]

The prevalence of fungal infections is influenced by several factors related to the agent and the host. One of the most key factors contributing to the increase in number and severity of IFI is permanent or transient immunosuppression. [1,3] The infectious load and virulence of the fungus are principal factors which allow the fungus to establish itself in the tissue and cause infection. [3]

Although the epidemiology of fungal diseases has changed in recent decades, *Candida* spp., *Cryptococcus* spp., *Aspergillus* spp. and *Histoplasma capsulatum* continue to account for the majority of IFI. [1,4] These infections have high mortality rates: 38–75% in infection with *Candida* spp.; [5,6] 20–70% with *Cryptococcus* spp.; [7–9] 30–95% with *Aspergillus* spp.; and 26.2–47.4% in infection with *Histoplasma* capsulatum. [7,10,11]

Despite recent advances in the diagnosis and treatment of IFI, the morbidity and mortality from these infections remains very high, mainly due to delays in diagnosis and initiation of antifungal treatment. These two factors are the most important predictors of survival in patients with these infections. [4,12] Antifungal therapy is initiated according to clinical suspicion, the clinical setting, and the infectious agent. [13]

In Brazil, the classes of antifungals that are approved by the National Health Surveillance Agency (ANVISA) include imidazoles (ketoconazole), triazoles (fluconazole, itraconazole, isavuconazole, posaconazole, and voriconazole), polyenes (amphotericin B deoxycholate, amphotericin B complex lipid, and liposomal amphotericin B), and echinocandins (micafungin, caspofungin, and anidulafungin). [14–16]

Antifungal therapy can be prophylactic, empirical, preemptive, or targeted. [13] Prophylactic therapy aims to reduce the frequency of infection, particularly severe ones,

when there is no currently suspected or diagnosed fungal infection, only an increased possibility of its occurrence. [13] Empirical therapy is proposed to treat a possible fungal infection before it progresses to overt disease. [13] The preemptive strategy is used when there is at least one marker of infection, such as a positive test for 1-3-β-D-glucan or for galactomannan; detection of the fungus by molecular techniques such as by polymerase chain reaction (PCR); or radiological data such as chest and sinus scans and clinical data suggesting infection. [13,17,18] Targeted therapy is used when the presence of the infective agent has been demonstrated and it has been identified by culture. [13]

Studies have been conducted to produce evidence about prophylactic and pre-emptive antifungal therapy, mainly in populations that are at high-risk of fungal infections. [19] A study by Çaglar et al. [20] evaluated antifungal therapy use in a pediatric population in Turkey. In their sample, 48.8% of patients used prophylactic therapy and another 51.2% had used the treatment (50% empirical therapy; 18.8% preemptive; 31.2% targeted therapy). Antifungal treatment strategies aim to implement the most appropriate therapy for the patient, at the right time, to reduce the risk of death. However, they also promote the safe and rational use of drugs and avoidance of excessive use, especially among immunocompromised and high-risk populations, such as transplanted and neutropenic patients. [20]

Given the high morbidity and mortality of IFI and the increase in the occurrence of patients at risk of developing these infections, the use of antifungal medications has increased. These treatments are largely empirical, such that the frequency of inappropriate prescription may also have increased. [1,12,13,19,20] Appropriate antifungal therapy impacts on the clinical outcomes of the patient, leading to shorter hospital stays, fewer complications, reduced risk of hospital outbreaks, and reduced hospital costs. This study aimed to explore the association between the outcomes of patients hospitalized in an infectious diseases' unit and the type of antifungal therapy they were treated with, by evaluating prophylactic and preemptive antifungal therapies, clinical and epidemiological features, and the mortality of patients admitted to an infectious diseases ward of a public high complexity hospital in Uberlandia, Minas Gerais, Brazil.

METHODS

This is a retrospective and observational study conducted in the specialized infectious diseases ward of the Clinical Hospital of the Uberlandia, Federal University of

Uberlandia, a public high complexity university hospital in the state of Minas Gerais, Brazil. The hospital has 520 beds, 16 of which belong to the infectious diseases ward.

Patient demographic and clinical data, laboratory and imaging test results, medical reports, and other information contained in the medical records were collected from the Hospital Information System (HIS). The data collected were: age; sex; length of hospitalization; diagnosis; chief complaint; whether they were a transplant patient; comorbidities such as HIV/AIDS, diabetes, systemic arterial hypertension, neoplasms, or other comorbidities; vital data; use of invasive mechanical ventilation; parenteral nutrition; use of a catheter or probe during hospitalization; results of blood culture, urine, cerebrospinal fluid (CSF), bone marrow aspirate, bronchial aspirate, sputum, imaging and biopsy results; microorganisms isolated; antifungals and antibacterial drugs prescribed and the time of use; corticosteroid use; and outcome.

Fungal infections were identified from the culture results of clinical samples, as found in patient records. The analyses (culture and identification of fungi) were carried out in the hospital's mycology laboratory. Sample collections were conducted according to the hospital's internal protocol and identifications were carried out using classical methodology and the Vitek® system (bioMérieux-Durham, USA).

Patients aged 18 years or older who were hospitalized between January 2019 to December 2020, and taking antifungal medications (amphotericin B [deoxycholate, lipid complex, and/or liposomal], anidulafungin, fluconazole, itraconazole, micafungin, or voriconazole), were included in this study. Patients whose records were incomplete, who were discharged or died within 48 hours of admission, and those who took antifungal medications to treat leishmaniasis were excluded.

Data analysis was performed using the Statistical Package for the Social Sciences (SPSS, software version 20). Categorical variables were reported as simple and relative frequencies. For continuous variables, measures of central tendency and dispersion (mean and standard deviation) were used. The significance level adopted was 5% ($p \leq 0.05$). The association between death/discharge (outcome) and independent variables was verified using simple and multiple logistic regressions, with a significance factor of 5%, to obtain the *Odds Ratio* (OR) and 95% confidence interval (95% CI).

This research was conducted in accordance with the required ethical standards - Resolutions 466/2012 - 510/2016 - 580/2018, of the Ministry of Health, Brazil; it was approved by the Research Ethics Committee of the Federal University of Uberlandia,

Brazil (CAAE number 38317520.3.0000.5152 and approval protocol number 4.321.218 on October 5, 2020).

RESULTS

From January 2019 to December 2020, 567 patients were admitted to the specialized infectious disease ward. Of these, 111 (19.58%) received antifungal therapy. The majority were male (69.4%), with a median age of 40 years (from 18 to 88 years). Male patients had a higher frequency of survival than females (Table 1).

The length of hospital stay ($p=0.0252$), mean number of days of anti-bacterial use ($p=0.0164$), prevalence of AIDS ($p=0.0397$), use of mechanical ventilation (MV) ($p<0.001$) and use of a nasogastric tube (NGT) ($p<0.01$) were variables that were related to death (Table 1). AIDS was the comorbidity most strongly associated with death ($p=0.0397$; OR= 8.78) and was the independent variable for death occurrence ($p=0.0165$; OR=77.0) (Table 1).

Among the patients who underwent to invasive procedures, MV and NGT were associated with the occurrence of death ($p<0.0001$; OR=20.8 and $p=0.0020$; OR=9.10, respectively), but only MV was associated with death on multivariate analysis ($p=0.0241$; OR=8.8) (Table 1). Of the 111 patients who took antifungal medications, 79 (71.1%) had a fungal infection confirmed on laboratory tests or imaging. The remaining patients (n=32) received empirical therapy. The antifungal drugs fluconazole and amphotericin B were the most prescribed for both patients who had (81 and 65, respectively) and who not had a confirmed fungal infection (26 and 22, respectively). The use of anidulafungin was directly related to the occurrence of death, being statistically significant on univariate analysis for both fungal infection ($p<0.01$ and OR 8.36) and absence of fungal infection ($p<0.01$ and OR=23.7). Patients who used three different antifungal classes simultaneously had a higher occurrence of death compared to those who used only one ($p=0.3027$ and OR=3.72). The mean length of antifungal use was 16 days, and 76 patients (68.4%) used only one class of antifungal (Table 2).

Table 1. Demographic and clinical characteristics of patients admitted to the infectious diseases ward who received antifungal therapy, and relationships with mortality.

Features	Survivors N=96		Deaths N=15		Univariate Analysis		Multivariate analysis	
	N	%	N	%	p-value	OR	p-value	OR
Male	70	72.9	7	46.7	0.0471	0.33	0.0157	0.04
Female	26	27.08	8	53.3			-	-
Age (average)	43.01±15.41		39.07±14.42		0.3526	0.98	-	-
Hospitalization time (average/days)	27.46±17.06		41.47±35.04		0.0252*	1.03	-	-
Time of antibiotic use (mean/days)	20.95±19.4		39.8±40.87		0.0164*	1.03	-	-
Comorbidities								
AIDS	59	61.5	14	93.3	0.0397*	8.78	0.0165*	77.00
Diabetes mellitus	8	8.3	1	6.7	0.8263	0.79	-	-
Kidney transplantation	2	2.1	0	0	0.0993	0.00	-	-
Neoplasia	10	10.4	2	13.3	0.7358	1.32	-	-
Hypertension	22	22.9	2	13.3	0.4087	0.52	-	-
Invasive procedures								
Mechanical ventilation	5	5.2	8	53.3	0.0001*	20.80	0.0241*	28.80
Nasoenteral tube	5	5.2	5	33.3	0.0020*	9.10	-	-
Hemodialysis	0	0	3	20.0	0.9893	1.00	-	-
Parenteral Nutrition	1	1	1	6.7	0.1845	6.79	-	-

*Statistical $p \leq 0.05$; AIDS: Acquired immunodeficiency syndrome.

Table 2. Antifungal use in relation to the presence of laboratory-proven infection and mortality.

Antifungals	Proven fungal infection present				Proven fungal infection absent			
	Survivors N=96	Deaths N=15	Univariate Analysis		Survivors N=96	Deaths N=15	Univariate Analysis	
	N (%)	N (%)	p-value	OR	N (%)	N (%)	p-value	OR
Fluconazole	67 (69.7%)	14(93.3%)	0.0888	6.06	23 (23.9%)	3 (20%)	0.7368	0.79
Time of use (days)	12.06 ± 10.43	13.36± 10.75	0.6715	1.01	4.7 ± 1.69	6 ± 1.73	0.2343	1.68
Amphotericin B	57 (59.3%)	8 (53.3%)	0.4410	0.78	19 (19.7%)	3 (20%)	0.9850	1.01
Time of use (days)	18.12 ± 15.29	17 ± 13.04	0.8412	0.99	4.89 ± 2.4	6.33 ± 0.58	0.3176	1.34
Voriconazole	4 (4.1%)	0 (0)	0.7863	0.66	0 (0)	0 (0)	0.3650	6.22
Time of use (days)	23.5 ± 8.06	-	-	-	-	-	-	-
Anidulafungin	4 (4.1%)	4 (26.6%)	0.0062	8.36	1 (1.04%)	3 (20%)	0.0080*	23.75
Time of use (days)	6.86 ± 4.98	6 ± 6.16	0.7811	0.96	4 ± 0	3 ± 1.73	0.5265	0.53
Itraconazole	4 (4.1%)	0 (0)	0.7863	0.66	1 (1.04%)	0 (0)	0.6638	2.05
Time of use (days)	15.5 ± 10.75	-	-	-	4 ± 0	-	-	-
Number of antifungals								
One antifungal [a]	67 (69.8)	9 (60)	-	-	12 (12.5%)	0	-	-
Two antifungals [b]	27 (28.1)	5 (33.3)	0.5941	1.38	16 (16.6%)	3 (20%)	0.2842	5.30
Three antifungals [c]	2 (2.1)	1 (6.7)	0.3027	3.72	0 (0)	1 (6.6%)	0.0475*	75.00

*p≤0.05; [a]Amphotericin B; Fluconazole; Itraconazole; Voriconazole; [b] (Concomitant) Amphotericin B + Fluconazole; Fluconazole + Anidulafungin; Amphotericin B + Anidulafungin; [c] (Concomitant) Amphotericin B + Fluconazole + Anidulafungin.

When the occurrence of deaths was evaluated by fungal microbial agent, they were found to have occurred more frequently in patients who were infected with *Candida* spp. or *Cryptococcus* spp. Patients infected with *Candida* spp. were seven times more likely die (OR=7.61; p<0.0179) and those infected by *Cryptococcus* spp. were five times more likely to die (OR=5.53; p<0.0375) compared to other fungal agents (Table 3). Most of the fungi were isolated from blood (51 patients; 64.5%), followed by gastric aspirate (34 patients; 43%) and lung biopsy (20 patients; 25.3%). *Candida* spp. were isolated from 36 patients (32.4%), *Cryptococcus* spp. from 22 patients (19.8%), and *Histoplasma capsulatum* from 20 patients (18%). *Candida* spp. were responsible for 32.4% of infections, with *Candida albicans* being the most frequent species (21.6%). Less frequent non-*C. albicans* species were *Candida parapsilosis* (4.5%), *Candida krusei* (1.8%), *Candida glabrata* (1.8%), *Candida tropicalis* (0.9%), *Candida dubliniensis* (0.9%), and *Candida kefir* (0.9%). Figure 1 shows the frequency of fungi isolated by clinical sample type.

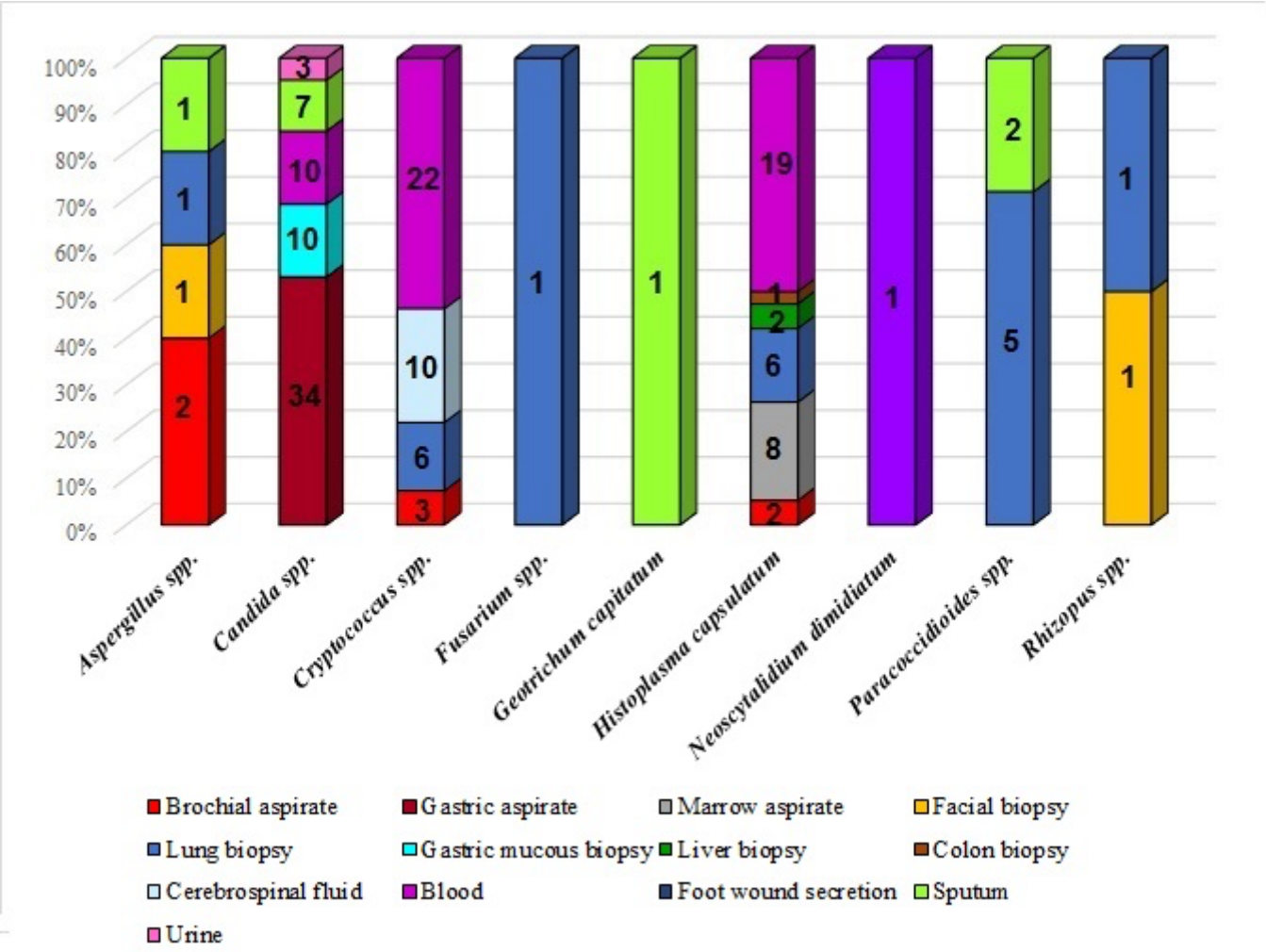

Figure 1. Frequency of fungi isolated according to clinical sample type.

Empirical antifungal therapy was instituted for 56 (50.4%) patients, followed by targeted therapy (33; 29.7%) and preemptive therapy (22; 19.8%). The frequency of death was similar among patients receiving the different types of therapy: 14.3%, 13.6%, and 12.1% of those receiving empiric, preemptive, and targeted therapy, respectively, had an outcome of death (Table 3).

Table 3. Relationship of fungal species isolated from patients using antifungal therapy with mortality.

	Survivors N=96		Deaths N=15		Univariate Analysis		Multivariate analysis	
Fungal species	**N**	**%**	**N**	**%**	**p-value**	**OR**	**p-value**	**OR**
Aspergillus spp.	3	3.1	0	0	0.9229	0.86	-	-
Candida spp.	28	29.1	8	53.3	0.0704	2.77	0.0179*	7.61
Cryptococcus spp.	17	17.7	5	33.3	0.1666	2.32	0.0375*	5.53

Fusarium sp	1	1.0	0	0	0.6638	0.49	-	-
Geotrichum capitatum	1	1.0	0	0	0.6638	0.49	-	-
Histoplasma capsulatum	17	17.7	3	20.0	0.8301	1.16	-	-
Neoscytalidium dimidiatum	1	1.0	0	0	0.6638	0.49	-	-
Paracoccidioides spp.	5	5.2	0	0	0.6787	0.54	-	-
Rhizopus spp.	2	2.1	0	0	0.8997	0.82	-	-
Trichosporon sp	1	1.0	0	0	0.6638	0.49	-	-
Instituted therapies								
Empirical	48	85.7	8	14.3	-	-	-	-
Preemptive	19	86.4	3	13.6	0.9409	0.95	-	-
Target	29	87.9	4	12.1	0.7730	0.83	-	-

*p≤0.05

DISCUSSION

This study evaluated clinical features and epidemiology, mortality, and different antifungal therapy strategies for treating patients in the infectious disease ward of a tertiary care hospital in Uberlandia, Minas Gerais, Brazil.

Most patients who were prescribed antifungal therapies had AIDS (65.7%), and this condition contributed to the deaths of most of them. Many of these patients were not on antiretroviral treatment and were diagnosed with the disease on admission. They generally had CD4 values below 200 cells/mm^3 (data not shown), which leads to a higher risk of developing opportunistic infections and is a predictor of mortality.[21,22]

In this study, the other risk factors that were related to higher mortality of patients were length of hospital stay, use of MV, use of NGT, and length of antibacterial use. Prolonged use of MV increases the risk of ventilator-associated pneumonia, as well as other complications such as sinusitis, tracheal stenosis, vocal fold injury, and tracheoesophageal or tracheovascular fistula. [23–25] The use of NGT also represents an increased risk of death, as has been described in the literature. [26,27] Adverse events from the use of this tube include pneumothorax, cardiorespiratory arrest, and death. [28,29] According to the Food and Drug Administration (FDA), there were 51 reports of pneumothorax between January 2012 and July 2017 related to NGT insertion. [28] The time of prolonged use of antibiotics is a relevant factor for the occurrence of co-infection by multidrug-resistant bacterial species and by fungi. [16,30,31]

IFIs are associated with high rates of morbidity, mortality, and increased length of stay and costs in the care of hospitalized patients, [16,31] so early initiation of antifungal therapy reduces complications in critically ill patients. [32,33]

Current guidelines recommend empirical antifungal therapy; however, this often offers limited benefits to patients and may result in overtreatment. [34] Some studies have demonstrated decreased mortality in patients who received empiric treatment, while others have indicated that such practice made no relevant difference in hospital mortality, suggesting that this issue is still controversial. [19,20,35] Likewise, preemptive therapy may reduce the likelihood of adverse events; the cost; and the risk of antimicrobial resistance that is associated with the use of non-selective empiric treatments. In the management of IFI, preemptive therapy has been shown to be effective. [33] However, the high costs of diagnostic tests represent a barrier to widespread use by the health system, especially in low- and middle-income countries, so the empirical strategy remains a reality in countries such as Brazil. [33]

In this study, 32 (28.8%) patients who were prescribed antifungal medications had no confirmation of IFI on laboratory or imaging tests. Data in the literature indicate a rate of 26.9 to 74% in the inappropriate use of antifungal drugs; [13,16,35] however, caution is required when comparing studies, as the clinical status of the patient, the epidemiological profile of infections, and the different institutional protocols for therapy should also be taken into consideration. In Brazil, guidelines for the control of invasive fungal infections are provided by the National Health Surveillance Agency (ANVISA), which were established in the context of the COVID-19 pandemic and published in 2021, [14] and in the Brazilian guidelines for the management of candidiasis published in 2013. [15] Institutional protocols take these documents into account, adapted according to the local context, such as patient conditions, most common fungal infections, and available antifungals. [14,15]

Patients who used three antifungal drugs simultaneously had a higher occurrence of death, and this association was greater among patients who had no proven fungal infection (OR=75.00; $p<0.0475$), and was likely related to the severity of the patients' conditions and empirical therapy for fungal infection. In addition to the patient's conditions (immunosuppressed, use of antifungals with recurrence, and underlying diseases), which interfere with the clinical response to antifungal therapy, tolerance or resistance to the antifungal may have contributed to the outcome. [36] Anidulafungin was the only antifungal

drug whose use was correlated with death. In the hospital where the study was carried out, the indication for starting therapy with anidulafungin includes only patients who are not responsive to previously instituted antifungal treatment, or when another antifungal is contraindicated (such as amphotericin), and in those who are severely ill. In general, factors such as greater severity of the patients and late initiation of anidulafungin therapy may have contributed to higher mortality in this group.

Invasive candidemia is a condition of concern, particularly because of its high mortality rate, [35] which ranges from 52.0% to 55.9%. [37–41] The mortality in the present study was 53.3% ($p<0.05$ and OR=7.61). Cryptococcosis and histoplasmosis were two other diseases diagnosed among patients in the infectious disease award. Cryptococcosis is a systemic mycosis frequently diagnosed in AIDS patients and is associated with a large number of deaths. [9,42] In the present study, cryptococcosis correlated independently with the occurrence of death ($p<0.05$ and OR=5.53). In Brazil, mortality rates for this infection range from 26% to 70%. [42–44] Disseminated histoplasmosis is also one of the most common opportunistic diseases in HIV/AIDS patients. [45] In recent studies, the mortality caused by AIDS-associated histoplasmosis was reported to be between 33 and 56.5%. [46,47]

The incidence of patients with IFI has increased, as well as the use of antifungal drugs, mainly empirically, such that the frequency of inappropriate prescription is increasing. The appropriate and rational use of antifungal medications requires adequate protocols that are periodically reviewed to improve clinical outcomes, reduce the risk of adverse events (from drugs or drug interactions), and reduce costs to the healthcare system, adjusted to each institution's setting and considering local epidemiology. The impact of interventions should be quantified to provide feedback to programs and to be comparable with other institutions.

Some limitations of this study should be noted. Firstly, the number of patients in each group was small, especially in the monotherapy and combination therapy groups. Secondly, this was a single-center study and therefore the results may not reflect the outcome of combination therapy of antifungal agents in patients at different institutions. Thirdly, the retrospective study may bias the results. On the other hand, this study has used an approach infrequently found in the literature, which was the association between the type of fungal therapy and the outcome of the patients. Thus, new studies based on the presented protocol could be performed and improved, contributing to well-designed

randomized controlled trials to address this issue in a more robust way by different institutions in different regions of the world.

In this study, mortality among patients who used antifungal therapy during hospitalization was more frequent among those with AIDS; those who had longer hospital stays; had prolonged antibiotic use; who used three different antifungal classes simultaneously; were submitted to invasive procedures (MV and NGT); and were infected by *Candida* spp. and *Cryptococcus* spp. Most of the patients who used antifungal treatment (including empirical therapy) had a confirmed fungal infection. In conclusion, the factors that contribute with mortality of the patients were longer hospital stays, AIDS, antibacterial drug use, mechanical ventilation, and nasoenteral intubation. The type of antifungal therapy did not influence the mortality of patients.

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Flávia Maria Pinto Monteiro Antonieti, **Denise Von Dolinger de Brito Roder** and **Reginaldo dos Santos Pedroso** contributed to the conception, design of the article, analysis and writing of the article.**Flávia Maria Pinto Monteiro Antonieti**, **Denise Von Dolinger de Brito Roder**, **Lúcio Borges de Araújo** and **Reginaldo dos Santos Pedroso** contributed to the planning and design of the article, review and final approval of the article.

All authors approved the final version to be published and are responsible for all aspects of the work, including ensuring its accuracy and integrity.