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Resistance of filamental fungi in opportunistic mycoses: literature review

Resistência de fungos filamentosos em micoses oportunistas: revisão de literatura

Resistencia de hongos filamentales en micosis oportunistas: revisión de literatura

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Abstract
Fungal diseases need to be better known and studied, as they are not the first diagnostic hypotheses and are the main causes of morbidity and mortality among immunocompromised patients. Main agents involved in opportunistic mycoses: *Cryptococcus* spp., *Candida* spp., *Aspergillus* spp. and *Pneumocystis* spp., present epidemiological data of these infections are modest, due to incorrect or incomplete diagnoses. adding to this the indiscriminate use of antifungal agents contributed to a change in the epidemiological profile and selecting resistant fungal strains, increasing the mortality rate in affected patients. Thus, this study aims to review the literature on the main opportunistic fungi and address important aspects of the resistance profile of filamentous opportunistic fungi. A search was carried out in the scientific literature based on the electronic database Pubmed, MedlinePlus, Scientific Electronic Library Online (Scielo), Academic Google., using as descriptors: Filamentous Fungi, Antifungals; *Aspergillus* spp.; *Candida albicans*; *Cryptococcus neoformans; Sporothrixs chenckii*; resistance, resistance in opportunistic mycoses and resistance profile. Studies indicate that rapid diagnosis and the choice of the correct drug can increase the recovery rates of patients with fungal infections. The delay in diagnosis and even the use of drugs with low efficiency has aggravated and, at the same time, increased the mortality of patients infected with these mycoses. This study aims to increase the bibliographic base on opportunistic mycoses cases and their resistance to the main antifungal drugs available.
Keywords: Opportunistic mycoses; *Cryptococcus* spp.; *Candida* spp.; *Aspergillus* spp.; *Pneumocystis* spp.

Resumo
As doenças fúngicas, precisam ser mais conhecidas e estudadas, pois, não estão como as primeiras hipóteses diagnósticas e são das principais causas de morbidade e mortalidade entre pacientes imunocomprometidos. Principais agentes envolvidos em micoses oportunistas: *Cryptococcus spp.*, *Candida spp.*, *Aspergillus spp.* e *Pneumocystis spp*., apresentam, dados epidemiológicos dessas infecções são modestos, devido a diagnósticos incorretos ou incompletos. somando se a isso o uso indiscriminado de antifúngicos contribuiu para mudança no perfil epidemiológico e selecionando cepas de fungos resistentes, aumentando a taxa de mortalidade nos pacientes acometidos. Assim, esse estudo tem por objetivo fazer uma revisão da literatura sobre os principais fungos oportunistas e abordar aspectos importantes sobre o perfil de resistência de fungos filamentosos oportunistas. Foi realizado pesquisa na literatura científica com base no banco eletrônico Pubmed, MedlinePlus, ScientificElectronic Library Online (Scielo), Google acadêmico., utilizando como descritores: Fungos Filamentosos, AntiFúngicos; *Aspergillus spp.; Candida albicans; Cryptococcus neoformans; Sporothrixs chenckii;* resistência, resistência em micoses oportunistas e perfil de resistência. Os estudos indicam que o diagnóstico rápido e a escolha da droga correta, pode aumentar os índices de recuperação de pacientes com infecções fúngicas. A demora no diagnóstico e mesmo a utilização de drogas com baixa eficiência tem agravado e ao mesmo tempo aumentado a mortalidade de pacientes infectados com essas

micoses. Este estudo visa aumentar a base bibliográfica sobre casos de micoses oportunistas e sua resistência às principais drogas antifúngicas disponíveis.
Palavras-chave: Micoses oportunistas; *Cryptococcus spp.; Candida spp.; Aspergillus spp.*; *Pneumocystis spp*.

Resumen
Las enfermedades fúngicas necesitan ser mejor conocidas y estudiadas, ya que no son lãs primeras hipótesis diagnósticas y son lãs principales causas de morbilidad y mortalidad entre los pacientes inmunocomprometidos. Principales agentes implicados enmicosis oportunistas: *Cryptococcus* spp., *Candida* spp., *Aspergillus* spp. y *Pneumocystis* spp., presentes, los datos epidemiológicos de estas infecciones son modestos, debido a diagnósticos incorrectos os incompletos. Además, el uso indiscriminado de antifúngicos contribuyó a un cambio enel perfil epidemiológico y La selección de cepas fúngicas resistentes, aumentando latasa de mortalidad en los pacientes afectados. Por lo tanto, este estudiotiene como objetivo revisar la literatura sobre los principales hongos oportunistas y abordar aspectos importantes del perfil de resistencia de los hongos filamentosos oportunistas. Se realizó una búsquedaenla literatura científica basada en la base de datos electrónica Pubmed, Medline Plus, Scientific Electronic Library Online (Scielo), Google académico, utilizando como descriptores: Filamentous Fungi, Antifungal; especies de *Aspergillus; Candida albicans; Cryptococcus neoformans; Sporothrixs chenckii*; resistencia, resistência em micosis oportunistas y perfil de resistencia. Los estudiosindican que el diagnóstico rápido y La elección del fármaco correctopued en aumentar lastas as de recuperación de los pacientes con infecciones fúngicas. El retraso enel diagnóstico e incluso el uso de fármacos de baja eficaciahan agravado yala vez aumentado La mortalidad de los pacientes infectados por estas micosis. Este estudio pretende aumentar la literatura sobre casos de micosis oportunistas y su resistencia a los principales antifúngicos disponibles.
Palabras clave: Micosis oportunistas; *Cryptococcus* spp.; *Candida* spp.; Especies de *Aspergillus*; *Pneumocystis* spp.

1. Introduction

Fungal diseases need to be better known and more studied, because, even knowing the epidemiology of these diseases, they are not the first diagnostic hypotheses of infectious diseases and are not reported (Brown *et al*., 2012). Not all doctors who analyze etiology in serious infections, the fungal origin. In addition, those who suspect a possible fungal etiology, need hospital and laboratory structure, as this reality may not offer the necessary tools for the diagnosis of fungal diseases (Fioravanti, 2016). Among the microorganisms, filamentous fungi are the most resistant and persistent in atmospheric air. Due to this characteristic, they can colonize all sorts of environments, regardless of their constitution. The presence or suspicion of fungi colonizing an environment requires immediate attention, since they can certainly bring risks to people who have direct contact with environments where they can be contaminated and complications in people at risk (Karam, 2016).

Over time, more than 100,000 species of fungi have been recognized and described. However, less than 500 of these species have been associated with disease in humans, and no more than 100 can cause infection in healthy individuals, so most are only capable of causing disease in debilitated or immunocompromised individuals (predisposing factor) (Kauffman; 2011). The genus Candida is reported as the third cause of septicemia in general in the world (Pappas et al., 2018). In a survey in the United States, which evaluated the epidemiology of nosocomial infections in 183 hospitals, it was shown that *Candida* spp. was the most frequent etiology among primary bloodstream infections, with an estimated 15000 cases per year (Magill, 2014).

Jesus *et al.* (2021) cited a prevalence of 45.9% of the patients in their study who had opportunistic fungi. It is known that 90% of reported cases of death from fungal infections are caused by the following agents: *Cryptococcus spp., Candida spp., Aspergillus spp. and Pneumocystis spp*., however, the epidemiological data of these infections are modest, primarily due to incorrect or incomplete diagnoses. (Brown *et al.,* 2012). Agents such as *Candida* species, *Aspergillus, Cryptococcus and zygomycetes*, previously considered environmental contaminants and therefore of little clinical importance, are now known to cause systemic diseases (Rokas, 2021).

On the other hand, systemic mycoses are a major cause of morbidity and mortality among immunocompromised patients, particularly those with onco-hematologic disorders, cancer, bone marrow or solid organ transplant recipients, and patients on therapy with immunosuppressive agents (Dignani, 2014). Advances in medicine that have allowed greater survival of critically ill and immunocompromised patients, use of broad-spectrum antimicrobials, implementation of solid organ and

bone marrow transplant techniques are some of the factors that have transformed the diagnostic routine of microbiology and mycology laboratories. The genus Candida being the most frequent in these infections, among the main opportunistic fungal pathogens, some genera stood out *Cryptococcus spp., Sporothrix spp. e Aspergillus spp.* (Rokas, 2021). During the SARS-CoV2 epidemic, the Aspergillus genus has emerged as an agent of infection and has been associated with increased hospital stays and poor outcomes (Tavares et al., 2021). Zuo et al. (2020) mentioned that patients with COVID-19 are more susceptible to infection by Candida spp., Aspergillus, Mucorales and other fungi, due to intense antimicrobial therapy and intense immunosuppressive condition.

This review is necessary due to the lack of knowledge about data on opportunistic mycoses associated with resistance in Brazil, many of these microorganisms are agents of opportunistic diseases, being described the most isolated species Candida albicans and Aspergillus spp., in addition to other species such as Cryptococcus spp., Sporothrixs spp. as well as knowing the drugs that best respond to treatment. In addition, the lack of epidemiological data and research on invasive fungal diseases throughout Brazil makes it difficult to find information to better diagnose and manage.

2. Methodology

This is a study of a qualitative and exploratory study with the purpose of deepening the discussion about opportunistic filamentous fungi, were carried out according to Köche (2016), who reported that the objective of the bibliographic research is to know and analyze the main existing theoretical contributions on particular theme or problem., as well as printed books related to the theme and equal methodology used in the study by Tavares et al. (2021), The search for articles was carried out from August to October 2021, out from August to October 2021. To this end, 1047 articles were analyzed, for this; the articles were initially selected based on the full availability of the work in the electronic databases PubMed, MedlinePlus, Scientific Electronic Library Online (Scielo), Google academic. Thus, the literature review was carried out through the selection of the following descriptors: Filamentous Fungi; Antifungal; *Aspergillus spp.; Candida albicans;* resistance; resistance in opportunistic mycoses; resistance profile and fungal resistance in Brazil. Both articles written in Portuguese or English, fieldwork and laboratory work were included in the search. Scientific articles from 1990 to 2021 were searched. As an inclusion criterion, the studies were available in full and were correlated with the proposed theme. Moreover, the exclusion criteria were articles that are not related to the objective of the study, articles with inadequate methodology, incomplete articles and articles not available in full in the evaluated databases (Figure 1).

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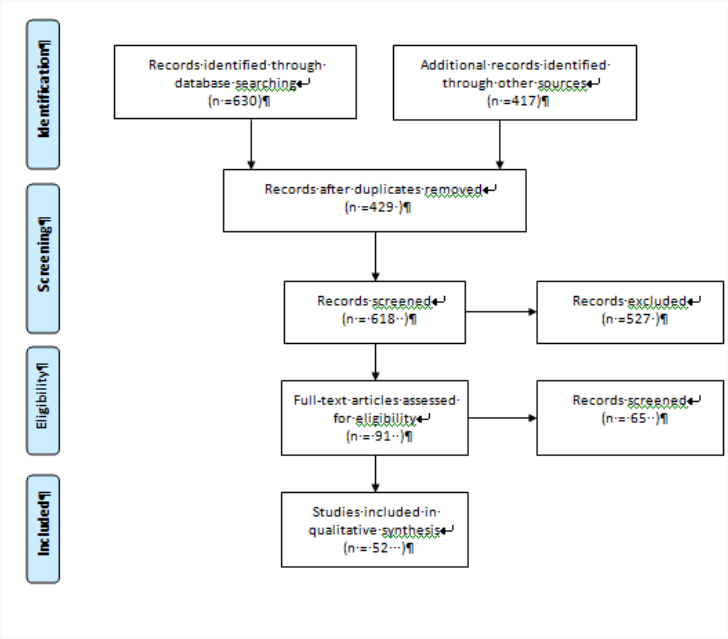
Figure 1. Flowchart of identification and selection of records.



Source: Authors (2022).

3. Theoretical Framework

Tavares *et al.* (2021) cited that the incidence of opportunistic fungal infections varies according to the patient's condition and depends on variables such as exposure time, site of infection and use of antibiotic therapy, but they report that mortality varies between 36 and 44 % in hospitalized patients. Morbidity and mortality rates are in a period of growth, being accompanied by an increase in the number of patients with weakened immunity (Wattier *et al.*, 2015). Mycology is the science that studies fungi, which are heterotrophic living beings that have a worldwide distribution. They have macroscopic representatives, such as mushrooms, and microscopic representatives, such as yeasts and filamentous fungi (Benchimol & Sá, 2004).

Agents such as *Aspergillus, Candida, Cryptococcus and zygomycetes* species are now known to cause disseminated disease, such as endocarditis, pulmonary infections, keratitis, among others, in immunocompromised patients (ANVISA, 2017). *Candida spp. and Pneumocystis carinii*, are widely known to be opportunistic pathogens in immunocompromised patients. Most systemic infections are opportunistic and tend to occur more frequently in immunocompromised individuals, such as those with AIDS and now with SARS-CoV2 (Tavares et al., 2021, Zuo et al. 2020, Guarner, 2017).

Giacomazzi (2016) cites a survey carried out in Brazil, in which the highest prevalence of the disease was cases of candidiasis, aspergillosis, cryptococcal meningoencephalitis and pneumonia caused by *Pneumocystis*. Also, according to the study, it reveals a discrepancy with data obtained from the Ministry of Health website. The incidence of fungal disease and species is related to socioeconomic, demographic and cultural conditions (Brown *et al.*, 2012). Part of the importance of knowing fungal diseases is an accurate diagnosis, through the isolation of the fungus in culture and / or histopathological techniques are methods of investigation and diagnosis, however, both cases have many limitations, which implies a delay in diagnosis definitive (Valero *et al.*, 2016).

4. Prevalent Fungi

Among the more than 250,000 known species, less than 150 have been described as pathogens to humans (Rokas, 2021). The development of contaminating fungi indoors and the adverse health problems triggered by them are directly related to favorable environmental factors such as humidity and temperature at each stage of fungal development: germination, growth and sporulation. (Vujanovic, 2001). The proliferation of these genera in closed environments is among the growing problems of modern medicine, as these microorganisms are highly invasive and infectious, especially for people with risky behavior who suffer from immunodeficiency (Bennet, 2010). There is a wide spectrum of diseases that fungi can cause, depending on the patient's immune status.

4.1 Candidiasis

The *Candida* genus is reported as the third cause of septicemia in general in the world. Candida albicans remains over the years the species most found in infections caused by species of the genus *Candida*, prevailing in 65.3% of infections by this genus around the world (Rocha *et al*., 2021) Systemic candidiasis It is a disease with high morbidity and mortality (Pappas et al., 2018) and that affects the hospitalized population more frequently. Candidiasis is caused by the infection of the fungus of the genus *Candida spp*., which present clinical manifestations from localized mucosal infection to dissemination to multiple organs, and the individual's immune response determines the type of infection. It is observed that the most important risk factors are malignant hemopathies, transplant recipients and patients undergoing chemotherapy (Silva, 2010). Disseminated candidiasis and candidemia are divided into: candidemia, invasive candidiasis, and chronic disseminated candidiasis. Furthermore, the most isolated species in the infectious context is *Candida albicans* (Seghir *et al*., 2017).

Data in 2013 show that *Candida glabrata* is one of the most worrisome among the infectious agents in the hospital, as it shows resistance to almost all antifungals, such as, for example, Fluconazole, which causes a mortality of almost 50% of patients hospitalized in ICU (Fioravanti, 2016). The great importance of *Candida albicans* is that, in addition to its high incidence of infections in adults, it is associated with high mortality, due to the increase in resistance to available antifungals and especially to the azoles and echinocandins (Rocha *et al.* 2021).

4.2 Aspergillosis

Aspergillosis is a disease caused by fungi of the genus *Aspergillus spp*., the infection occurs via inhalation of conidia through aerosol, which reach the lungs, germinate and form hyphae (invasive filaments) (Aspergillus, 2021; Goldman, & Schafer, 2015). *Aspergillus spp.* is the most common filamentous fungus causing invasive fungal disease with a mortality rate greater than 80% (Tavares *et al.*, 2021). The most common symptoms are coughing, sneezing and dyspnea, with pleuritic pain and hemoptysis (Silva, 2010). *Aspergillus* can cause various diseases, depending on the individual's immune status. Among the manifestations, the most serious is invasive pulmonary aspergillosis, which has increased its prevalence (Gavronski et al., 2016).

Tavares *et al.* (2021) cited in their study that Italian researchers reported that about 25% of COVID-19 deaths were associated with Aspergillus sp. And they reported that the prognosis becomes unfavorable in patients with orotracheal intubation. Among the fungal pneumonias, the most responsible is *Aspergillus spp.*, therefore, aspergillosis is more restricted to the lung and invasive aspergillosis has progressively increased in prevalence (Silva, 2010).

4.3 Cryptococcosis

Cryptococcal disease is caused by fungi of the genus *Cryptococcus spp*., The infection occurs by inhalation of aerosol conidia present in the environment. Thus, in immunocompetent individuals, a pulmonary infection occurs and remains

localized, however, in immunocompromised individuals, the failure of the defense mechanism causes the microorganism to spread to other organs and systems, with a tendency to the central nervous system. (Goldman & Schafer., 2014).

Currently, it is understood that Cryptococcosis is primarily pulmonary, and may be asymptomatic and controlled by the host's immune system, or disseminated, reaching the central nervous system. The pulmonary form follows either acutely or chronically. In the meningoencephalitis form, symptoms vary according to the location, and may even resemble meningeal tuberculosis, but the most frequent symptom is headache. The cutaneous form is also possible, which is, in most cases, secondary to pulmonary dissemination. In the bone form, in a longer course of the disease, it is manifested by pain and inflammation, which can last for months before diagnosis. (Oliveira, 2014).

4.4 Penicillium

Fungi of the *Penicillium* genera are present in soil, air and decaying plant material. *Penicillium*is also reported as an opportunistic plant pathogen, species of this genus are widely distributed, presenting negative and positive impacts. Many species of *Penicillium* are recognized for producing toxic metabolites (Pitt, 2000). The climate in tropical and subtropical regions allows agricultural production throughout the year, however, these same conditions, high humidity and great temperatures are also conducive to the development of fungi. Deterioration of stored grain is a problem for the economy (Ribeiro *et al.*, 2003).

4.5 Pneumocystosis

Pneumocystosis, also called *Pneumocystis jirovecii* Pneumonia (PJP), is a common opportunistic infection in the respiratory tract, often found in patients with HIV, and it can be a definitive diagnosis of AIDS (Brown *et al*., 2012). *Pneumocystis* is globally distributed. Its transmission is through the respiratory route; however, the infection of immunocompetent people does not cause any significant disease (Goldman, & Schafer, 2014). The symptoms are like those of atypical pneumonia and the histological substrate of a plasmacytosis, characterizing “plasma cell interstitial pneumonia”. Chest X-ray shows interstitial infiltrate in the lungs, preferentially located in the lower 2/3. Bronchial lung biopsy can be performed, which reveals alveolitis with edema and inflammatory infiltrate with lymphocytes, plasma cells and macrophages, in addition to foamy material in the alveolus lumen with 23 numerous parasites. (Oliveira, 2014).

4.6 ***Trichophytosis***

It is a disease caused by fungi of the genus *Trichophyton*. They are fungi considered to be dermatophytes associated with the skin and nails, but are mainly isolated from infections of the scalp, especially in school-age children and immunosuppressed patients. In Brazil, we observed a predominance in the isolation of this fungus in the North and Northeast regions, but it is also isolated as an agent of scalp ringworm (Tinea capitis) in different regions of the country: Southeast and South (Chimelli *et al.,* 2003). Jesus *et al.* (2021) reported in their study that *Trichophyton rubrum* was the most prevalent fungus in rural patients with diabetes mellitus, causing dermatomycosis.

5. Antifungal Susceptibility

According to Berto *et al.* (2018), the discovery of new drugs is minimizing the problem of susceptibility of fungi, the development of resistance to antifungal drugs is very evident. This is clearer when patients who receive long treatments, or receive antifungals in a prophylactic way, where, in both cases, there can be selection and change in the microbiota, giving rise to a favorable environment for species resistant to antifungals to increase. As for *in vitro* sensitivity, according to Castro *et al.* (2006), there has been an increase in the number of commercially available antimycotics in recent years. However, the analysis

of antifungal resistance has represented a major challenge for clinical processes. These microorganisms have developed several mechanisms to prevent the action of antifungal agents, such as, for example, alteration of the site of action and permeability, difficulties in detecting resistance and low clinical correlation are major limitations for correct diagnostic. (Cuenca-Estrella & Rodríguez-Tudela, 2002).

The incidence of opportunistic fungal infections has increased concomitantly with the emergence of strains resistant to antifungal therapy, and the use of empirical and prophylactic treatments in neutropenic patients is one of the main factors related to the emergence of resistant species (Dignani, 2014). In the last decade, infections caused by other non-*albicans* and resistant *Candida* species have increased greatly. The intrinsic resistance observed in some *Candida* species and the development of acquired resistance during treatment have made it difficult to control candidiasis. (Catana *et al.*, 2013 e Silva *et al.*, 2010).

Berto *et al.* (2018) state that *Candida* samples isolated from patients admitted to ICUs have decreased susceptibility to antifungal agents due to their excessive empirical use. The institution of late and inappropriate antifungal therapy is associated with increased mortality and the likelihood of cross-contamination. (Avila-Aguero *et al.*, 2005). The determination of the antifungal susceptibility of the etiologic agents is important in the choice of the therapeutic conduct and treatment efficacy (Pfaller *et al.*, 2005).

6. Antifungal and Resistence

Queiroz-Fernandez (2021) reported in their study that among the main opportunistic fungal pathogens, several studies have shown that there is already resistance to amphotericin B, ketoconazole, miconazole, econazole, flucytosine, voriconazole, fluconazole, itraconazole and multi azoles, in these studies *Candida* species showed antifungal resistance, reaching 50% and pointed out that inadequate use of some antifungals has contributed to the increase in the incidence rates of opportunistic infections, mainly by resistant strains, worsening the prognosis of these patients. In Brazil, according to the recommendations of the Brazilian Medical Consensus, amphotericin B, fluconazole and caspofungin are options for the treatment of *Candida*. In addition to these drugs, voriconazole and anidulafungin appear as a treatment option for species resistant to fluconazole and when the patient's clinical condition does not allow the use of highly toxic drugs (Hazen; Howell, 2007).

Hazen and Howell (2007) mentioned that since 2007, amphotericin B was one of the most used drugs. More recently Ferreira *et al.* (2012), report that amphotericin B and fluconazole are the two most used drugs for the treatment of invasive yeast infections of the genus *Candida*. They also report that routine use has been associated with the development of resistant *Candida* species, and they also indicate that about 10% of *C. albicans* isolates from blood samples are resistant to fluconazole. Resistance to antifungals of the Echinocandin class is still quite uncommon among *Candida* species (Rocha et al. (2021).

Corrêa (2019) analyzed fungi isolated in pigeon feces, and filamentous fungi of clinical importance were identified. *Cryptococcus neoformans* showed sensitivity to Amphotericin B 2μg/ml and Voriconazole 1μg/ml, and resistance to Amphotericin B 0.5μg/ml, 5-flucytosine 4 and 16μg/ml, Itraconazole 0.125 and 0.5μg/ml and Fluconazole 8 and 32μg /ml. The data also showed other strains of medical importance sensitive to some of the antifungals tested and described in the literature. Demillto *et al*. (2012) performed strain analysis of clinical samples, 38 *Candida* showed that, for these strains, the antifungals amphotericin B, voriconazole and anidulafungin were effective, but highlighted that resistance was different according to the dosage of each antifungal.

Fluconazole, an azole derivative belonging to the family of first-generation triazoles, began to be widely used in the 1980s, these antifungals have a fungistatic action, acting to inhibit cell growth (Berto *et al*., 2018). In 2006, as reported by Sabatelli *et al*. (2006), resistant strains of non-*albicans Candida* begin to emerge, such as *C. krusei* and *C. glabrata,* and the occurrence of resistance in isolates of *C. parapsilosis* and *C. tropicalis* is also reported to a lesser extent (Berto *et al*., 2018).

Pfaller *et al*. (2005) state that isolates of *C. albicans, C. parapsilosis and C. tropicalis* are sensitive to fluconazole. However, the occurrence of resistance in *C. tropicalis* isolates can be detected and *C. glabrata* strains show considerable resistance to this drug.

The emergence of fluconazole resistance begins to have clinical relevance, associated with doses greater than 2 µg/ml (Berto *et al*., 2018). Some authors report the occurrence of resistance in isolates of *C. glabrata, C. parapsilosis, C. krusei* (Pfaller *et al*., 2005), *C. lusitaniae* (Berto *et al*., 2018), *Paecilomyceslilacinus, Scedosporium apiospermum, S. prolificans, Aspergillus terreus, A. ustus, Sporothrixs chenckii, Penicillium marneffei* and species of *Alternaria, Fusarium* and *Phialophor*a (Espinel-Ingroff *et al*., 2007). Queiroz-Fernandez (2021) reported that there was an increase in infections by Cryptococcus spp. who did not respond to fluconazole, the drug of first choice. Currently, the drugs of first choice for long-term therapy are still azole derivatives, but the emergence of fluconazole-resistant *C. enformas* and *C. gattii* isolates represents a major challenge.

In 2018, Goulart *et al*. (2018) evaluated HIV positive patients and found that 84% of the isolates were *Candida spp.*, and only 1% showed resistance to fluconazole and ketoconazole and 4% to itraconazole. Queiroz-Fernandez (2021) reported that there was an increase in infections by *Cryptococcus spp*. who did not respond to fluconazole, the drug of first choice. Currently, the drugs of first choice for long-term therapy are still azole derivatives, but the emergence of fluconazole-resistant *C. neoformans* and *C. gattii* isolates represents a major challenge.

Silva *et al*. (2010) evaluated the sensitivity to antifungal agents and detected two isolates of *C. gattii* resistant to itraconazole and two *C. neoformans* to amphotericin B. Already Oliveira *et al*. (2015) evaluated the sensitivity of *S. albicans, S. brasiliensis, S. globosa, S. Mexicana* and *S. schenckii* to terbinafine in combination with itraconazole, ketoconazole and voriconazole and observed that all *S. schenckii* and *S. brasiliensis* isolates were sensitive to itraconazole, but *S. albicans, S. globosa* and *S. mexicana* showed resistance to the combinations, the most relevant of which was observed in relation to voriconazole

Voriconazole is another azole derivative, a second-generation triazole, which broadens the spectrum of activity of this group of drugs. Voriconazole has good efficacy against *Candida* species involved in invasive infections (Pfaller *et al*., 2005). According to Martinez (2006), voriconazole is indicated as the drug of choice for the treatment of invasive aspergillosis, and the intravenous formulation is recommended for serious patients. This drug is also widely used in the treatment of invasive mycoses caused by filamentous fungi, showing better efficacy than fluconazole. The treatment of infections caused by *A. terreus* must is performed with triazole derivatives, mainly voriconazole, due to the resistance of this fungus to amphotericin B (Berto *et al.*, 2018).

The findings of this study showed that *A. fumigatus* isolates were resistant to itraconazole, posaconazole and voriconazole. And that an isolate of *A. brasiliensis* showed resistance to itraconazole (Alastruey-Izquierdo, *et al.*, 2015). Echinocandins began to be marketed in Brazil in 2000, with the arrival of caspofungin. Later in 2009, anidulafungin was introduced as an alternative for the treatment of invasive candidiasis in non-neutropenic adult patients. Resistance to anidulafungin is rare, even in isolates resistant to fluconazole or amphotericin B. this drug has 15.4% better efficacy against *Candida* species than fluconazole (*Berto et al.*, 2018).

7. Conclusion

As presented in this review, opportunistic mycoses are important infections and their frequency is increasing, especially among immunosuppressed patients, further aggravating the condition of these patients and becoming a serious public health problem, due to the difficulty of diagnosis, increased resistance and availability of effective drugs. The aim of this review was, in addition to increasing the bibliographic base on the subject, to serve as a warning about the increase in the number of cases of opportunistic mycoses and resistance to the main antifungalagents available, and studies related to warn

that, in addition to rapid diagnosis, the choice of the correct drug may increase the recovery rates of patients with fungal infections. Therefore, there is a need for further studies on rapid diagnosis, preventive treatment mechanisms, as well as research for the search for new antifungal drugs and treatment of these infections in high-risk patients, as in the case of COVID.

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