Impact of fungi on public health – A review

Impacto dos fungos na saúde pública – Uma revisão

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ABSTRACT
Fungi belong to a diverse group of organisms. Most fungi are harmless and are found in soil or organic matter. However, many species manage to relate to the Human Being causing him pathologies[1,2]. Much of the population, for part of their life, has suffered from superficial fungal infections that are easily treated. However, millions of individuals fall victim to life-threatening invasive fungal infections, which are much more difficult to diagnose and treat[1,3]. Currently, the diagnosis of invasive mycoses, especially in immunocompromised patients, remains problematic due to the nonspecificity of the symptoms, and the available diagnostic methods [4,5].

Keywords: Fungi, Health, Human.

RESUMO
Os fungos pertencem a um grupo diverso de organismos. A maioria dos fungos é inofensiva e encontram-se no no solo ou matéria orgânica. Contudo, muitas espécies conseguem relacionar-se com o Ser Humano causando-lhe patologias[1,2]. Grande parte da população, durante uma parte da sua vida, já sofreu de infeções fúngicas superficiais que são facilmente tratadas. Contudo, milhões de indivíduos são vítimas de infeções fúngicas invasivas potencialmente fatais, muito mais difíceis de diagnosticar e tratar[1,3]. Atualmente, o diagnóstico das micoses invasivas, principalmente em doentes imunocomprometidos, continua a ser problemático devido à inespecificidade dos sintomas, e aos métodos de diagnóstico disponíveis [4,5].

Palavras-chave: Fungo, Saúde, Humano.

1 INTRODUCTION

Fungi belong to a diverse group of organisms. Most fungi are harmless and are found in soil or organic matter. However, many species manage to relate to the Human Being causing him pathologies[1,2]. Much of the population, for part of their life, has suffered from superficial fungal infections that are easily treated. However, millions of individuals fall victim to life-threatening invasive fungal infections, which are much more difficult to diagnose and treat[1,3]. Currently, the diagnosis of invasive mycoses, especially in immunocompromised patients, remains problematic due to the nonspecificity of the symptoms, and the available diagnostic methods [4,5].

Invasive fungal infections affect sterile tissues, organs, or fluids such as blood or cerebrospinal fluid (CSF). In recent years, its incidence in immunocompromised and/or hospitalized patients has been

increasing, leading to high morbidity and mortality rates. Microorganisms such as *Candida spp*, *Cryptococcus neoformans* and *Aspergillus spp.* are among the most isolated[6].

Superficial mycoses are restricted to the skin, its appendages and mucous membranes. They are estimated to affect around 25% of the world's population and are the most common fungal infections worldwide[1,7]. Fungal infections of the genital and oral mucosa are quite common, especially in HIV+ patients[8]. Onychomycosis and tineas are considered aesthetic problems, devaluing their clinical importance. In reality, this type of mycoses can cause pain, emotional and occupational discomfort in addition to being a constant source of contamination[9]. Most cases of tinea are caused by *Trichophyton rubrum*. Not least, the *Microsporum canis*, with a high incidence in tineas capitis[7].

2 GOAL

Conduct a review of the most prevalent fungi among the human population;

Analyze the prevalence of the most frequent fungal infections and forms of transmission;

Integrate the prevalence of fungal infections as public health problems.

3 METHODOLOGY

Literature review based on scientific articles searched in databases – Pubmed, B-on, SienceDirect and SciELO – with the following keywords: Fungal infections, epidemiology, *Candida*, Cryptococcus, Aspergillus, *dermatophytosis.*

4 DEVELOPMENT

Various species of *Candida spp.* constitute a group of commensal fungi of the mouth, gastrointestinal tract and vagina of the Human Being causing, in certain situations, candidiasis[10]. The change of this fungus from commensal to pathogenic is complex and is related to changes in the flora that lead to the expression of its virulence factors[11]. However, other transmission mechanisms are known, mainly contamination through health professionals[10,12,13]. According to the *Centers for Disease Control and Prevention* (CDC), a *Candida spp.* represented about 11% of infections associated with the hospital environment reported between 2006-2007, being the fourth most cited microorganism[13].

Among the most prevalent species found in the oral cavity, both in the commensal state and in cases of oral candidiasis, the *C. albicans* is the most frequent. Studies estimate that this species represents more than 80% of oral yeasts[11]. Several studies point to oropharyngeal candidiasis as the most prevalent opportunistic fungal infection in individuals infected with the Human Immunodeficiency Virus (HIV). Research has identified *Candida spp.* in approximately 50% of the HIV patients studied, with the most common infection being oral candidiasis (71.25%) and *C. albicans* was the most isolated species[8]. Other

research shows that in these individuals, this type of infection remains common, mainly due to *C. albicans* (62%). However, other species such as *C. glabrata* (17%) and *C. dubliniensis* (12%) have also been frequently isolated[14].

On the other hand, the epidemiology of vaginal infections is not well characterized. It is not a notifiable disease, being often diagnosed without mycological confirmation and treated with over-the-counter drugs, thus contributing to antifungal resistance[15]. A survey conducted on 612 women showed that 20.1% of them are colonized by yeast, being the predominant one; *C.albicans* (68.3%) followed by *C.glabrata* (16,3) and *C. parapsilosis* (8,9%)[16]. More recent studies show that about 47.9% of patients with symptoms suggestive of vulvovaginal candidiasis have *Candida spp.* in laboratory tests. Among the isolated strains it is evident once again *C. albicans* (71.5%) followed by *C. tropicalis* (8,5%), *C. parapsilosis* (5,3%), *C. krusei* (3.2%), and *C. glabrata* (2,1%)[17].

The incidence of invasive candidiasis has been increasing in recent years, and the *Candida spp*. It is among the ten most frequently isolated microorganisms in blood cultures[6, 18]. In a study carried out in Spain - FUNGEMYCA, 1357 episodes of funguemia were recorded. Among causative agents, the *C. albicans* was the most frequently isolated species (44.7%), followed by *C. parapsilosis* (29,1%), *C.glabrata* (11,5%), *C. tropicalis* (8.2%) and *C. krusei* (1,9%)[19]. Invasive fungal diseases by *Candida spp*. they also represent a complication of hospitalized patients, especially patients admitted to intensive care units (ICU). A study carried out by the AURORA project in Italy, covering 5561 patients of whom 105 were diagnosed with fungal infection, showed similar data to the previous ones. In this study, the only fungal infection caused by yeast was candidiaemia (87.6%), and once again the *C.albicans* the most isolated species (40.2%). Among the species not *albicans* The most isolated species was *C. parapsilosis* (61.8%) followed by *C.glabrata* and *C. tropicalis* (16,4%). The observed mortality rate was 40.2%, and species did not *albicans* achieved higher mortality rates, namely: *C. tropicalis* (77,8%)[20]. According to the results of the *Transplant-Associated Infection Surveillance Network* (TRANSNET): invasive candidiasis is also the main invasive fungal infection in transplant patients (52.9%), with an associated mortality rate of 66%[21].

It is possible to state that changes have been reported in the species of the genus *Candida spp.* involved in invasive diseases because more and more species have been isolated that do not *C. albicans*, chiefly *C. parapsilosis*, *C. glabrata*, *C. tropicalis* and *C. krusei*[12, 18, 20]. Several reasons have been studied to find out the reason for the emergence of these species[18].

Gender *Aspergillus spp.* encompasses a group of filamentous fungi with high diversity that are dispersed worldwide being the *Aspergillus fumigatus* the species most often isolated in the clinic[22]. This genus of fungi is widely distributed in nature, and its conids are the main fungal element present in the air[23]. Or *Aspergillus spp.* It is an opportunistic fungus, capable of causing a wide spectrum of pathologies ranging from hypersensitivity reactions to invasive infections. The fungus can invade the respiratory system

of humans through inhalation of its conids, causing extrapulmonary infections involving the central nervous system, skin or liver [24].

The research conducted by the AURORA project revealed that 12.4% of invasive fungal diseases were caused by filamentous fungi, and approximately 92.3% of these were caused by *A. fumigatus*. This study also determined a mortality rate of 61.5% in infected individuals[20]. An evaluation carried out between 2006 and 2008 in 38 UCIs in Italy reports data similar to the previous ones. About 16.4% of the reported fungal infections were caused by filamentous fungi of which 82% belonged to the species *A. fumigatus.* The mortality rate for this fungus was 63%, a value significantly higher than in Candidiasis (44%)[25].

Invasive aspergillosis is recognized as a complication of the post-transplant period. Studies report that cases of invasive aspergillosis by *Aspergillus* spp. stand out in patients who have undergone lung transplants and in hematological patients, thus becoming the two risk groups;[26]. A survey in the United States, including 17 transplant centers and 429 patients, identified 515 invasive fungal infections. The evaluation declared invasive aspergillosis (24.8%) as the second most common invasive fungal infection after *Candida spp*. This type of infection was more common among lung transplant recipients (59.7%), and is also considered a late complication with 61.8% of patients developing infection within more than one year of transplantation[27]. The values obtained by TRANSNET are similar to those previously mentioned, where invasive aspergillosis has an incidence of 18.8% and a mortality rate of 59%[21]. Surveys *Prospective Antifungal Therapy Alliance* (PATH) found that invasive aspergillosis is also the main infection in patients undergoing stem cell transplantation. In this study, 59.2% of invasive infections were invasive aspergillosis.

Despite the constant exposure of man to this fungus, cases of aspergillosis by *Aspergillus spp.* in immunocompetent patients are not common [29]. Although most cases of aspergillosis are sporadic, outbreaks associated with the hospital environment often arise. Inadequate ventilation systems, poorly maintained air filters, contamination of false ceilings or insulation and construction material in and around the hospital are the main causes of these outbreaks[13, 30]. Surveillance studies of invasive aspergillosis show that of the cases studied, 30% were nosocomial invasive aspergillosis. The same study suggests that the origin of these cases is due to the lack of protective measures, namely filters for air treatment because 80.9% of infections occurred in areas with no of these filters[31].

Gender *Cryptococcus spp.* It comprises several species of which only two - *Cryptococcus neoformans* and *Cryptococcus gattii* – show important clinical relevance when commonly infecting humans and animals[32, 33]. These two species have different environmental niches. *C. neoformans* it is associated essentially with bird droppings and *C. gattii* It has its main reservoir in the bark and leaves of numerous species of trees in the soil and surrounding air[32].

Or *Cryptococcus spp* It is usually acquired from the environment and its transmission occurs through the inhalation of cells of the fungus. However, it has not been proven that this is the only source of infection.

Other routes of infection, such as ascending infections through the urinary tract or ingestion of contaminated water or food, have been proposed[33]. The transmission of the disease between individuals occurs in occasional cases as is the case of transplants[34]. The consequences of infection with this microorganism range from asymptomatic colonization of the airways to disseminated infections that may involve the central nervous system, eyes and skin[32]. Only a small percentage of people exposed to this microorganism actually develop the disease[35].

Gender *Cryptococcus* It is the second cause of yeast-invasive fungal diseases after *Candida spp*, however, presenting relatively low prevalences in two different studies 0.72% and 4%[19,21]. In one of the studies previously mentioned, carried out by TRANSNET, cryptococcosis had a prevalence of 8% of the cases, 45% of which involved only the central nervous system and 39% represented a disease limited to the lungs. In fact, infections with this microorganism are more prevalent in HIV-infected individuals. Surveillance programs conducted in Colombia conclude that the biggest risk factor for cryptococcosis is HIV infection (83.5%), and the estimated incidence rate for these patients is higher than for the general population. These programs also reported that most of the identified cases (81.8%) were cryptococcal meningitis and the *C. neoformans* where. *grubii* as the most prevalent agent (95.6%), followed by *C. gattii* (3.4%) and last *C. neoformans* where. *neoformans* (1%)[36]. Another study conducted over a period of 13 years, found that 90.83% of patients diagnosed with *Cryptococcus spp.* were in the AIDS phase. Once again, cryptococcal meningitis was the most observed (78.6%), followed by funguemia (11.45%). Most patients (91.26%) diagnosed with cryptococcal meningitis had a previous diagnosis of HIV. Of the species isolated in the CSF of patients with meningitis, 94.5% belonged to the species: *C. neoformans* and 5.6% to the species *C. gattii*[37].

Dermatophytes belong to a group of filamentous fungi responsible for superficial skin diseases. In general, dermatophytes remain located on surfaces with keratin, not invading deeper tissues[38]. Dermatophytoses, also called *tíneas*, affect different anatomical sites of the human body having specific agents of infection[39]. Although dermatophytes are pathological agents worldwide, the most prevalent species or the most frequent form of infection changes depending on the geographic region. Despite everything, its distribution is not static, changing due to environmental and/or cultural factors[38,39].

It is estimated that onychomycosis affects about 20 to 25% of the population, representing about 60% of nail pathologies. This type of pathologies is more common in adults and is related to predisposing factors (basic pathology, social class, aesthetic treatments, age or climate)[9]. Not many studies have been conducted at this level however, one on the incidence of dermatophytes in a hospital considered that the most common infections were related to the nails and the sole of the foot. In conclusion, yeasts were the main cause of infection (61.6%), followed by dermatophytes (32.7%) and the remainder caused by non-dermatophyte filamentous fungi (5.7%)[40]. A more recent Spanish multicenter study analyzed a total of

5961 samples (fingernails and toenails) from 5663 patients, 66% of whom were female. Of the clinical forms of onychomycosis, the most common was distal and lateral subungual onychomycosis, with 29% prevalence in the fingernails and 54.8% in the toenails. As for the predominant microorganisms in the toenails, dermatophytes stand out (82.8%). On the fingernails the yeasts of the genus *Candida spp.* were more frequently isolated (75%) than dermatophytes (17%). Inside the Dermatophytes, *T. rubrum* was elected the most isolated agent (86.5%), followed by the *T. mentagrophytes* (10%)[41].

Around the world, thousands of children are affected by tinea capitis. Its clinical manifestations range from asymptomatic carriers to scalp lesions and/or alopecia[42]. The inflammatory form of the tinea capitis is usually associated with genera *Trichophyton* and *Microsporum*[39]. A study that evaluated the frequency of dermatophytoses in children identified the tinea capitis as the most frequent tinea (72.9%) with the *Trichophyton tonsurans* identified in 121 of the 153 cases and *Microsporum canis* in 24 cases[43]. A study conducted in Tunisia allowed us to evaluate the epidemiology and prevalence of inflammatory tinea capitis. In this study, inflammatory tinea capitis represented 13.73% of the total number of cases, being more prevalent in males (68.6%) and in patients from rural areas (49.6%). It was also observed that about 71.9% of the cases occurred in children under the age of 10 years. Of the 121 cases studied, 35 reported contact with animals[42]. Other studies show that fungi responsible for tinea capitis (as is the case of *T. mentagrophytes e M. canis*) have been frequently isolated in domestic animals even when they do not present clinical signs of disease[44, 45].

Fungi are currently among the microorganisms very often isolated in immunocompromised patients. However, certain filamentous fungi, namely dermatophytes, can infect healthy individuals[2]. Invasive infections are among the most worrisome fungal infections achieved high morbidity and mortality rates[6].

Of the microorganisms that cause invasive infections, we can highlight the *Candida spp.* mentioned in several studies as the main responsible for most of this type of infections, especially candidiaemia;[19-21]. Another study conducted in Chile corroborates the data obtained, considering the *Candida albicans* as the most isolated species[46]. This human commensal microorganism becomes easily pathogenic in cases of immunosuppression. Therefore, the *Candida spp.* it also becomes an important player in healthcare-associated infections[13].

According to the various authors, the species of *Candida spp.* more often isolated remains the *C. albicans*. However, in two of the studies addressed in this review, the percentage of species did not *albicans* tends to be larger, thus suggesting a change in the epidemiology of this microorganism[19,20]. This fact may be justified by the prophylactic use of antifungals and the consequent gain of resistance by these species. The observation of this alteration has been recorded in other studies that, contrary to those studied in this review, indicate the *C. tropicalis* as one of the most frequent. This small disagreement may be justified by the fact that certain strains are associated with outbreaks in neonatal centers, burn units and ICUs such as

C. parapsilosis, The most isolated species in the reviewed studies[47,48]. Associated with the emergence of these species, there are also higher mortality rates justified by the ineffectiveness of the therapy due to acquired resistance [20].

Also the genre *Aspergillus* excels in invasive infections[20]. Although studies show that its incidence rate is lower than that of *Candida spp.*, apparently this microorganism has a higher associated mortality rate with regard to critically ill patients[25]. Invasive aspergillosis has been shown to be the most prevalent fungal infection in stem cell transplant patients, most possibly due to recorded cytopenia and immunosuppressive therapy[28].

Gender *Cryptococcus*, although it also plays an important role in invasive infections, it is present with a lower incidence, especially in cases of disseminated infection. However, cases of invasive cryptococcosis seem to be associated with higher mortality rates than the fungi mentioned above[21]. As mentioned, the most prevalent cases of cryptococcosis involved only the central nervous system or the respiratory system. This can be explained by the fact that this microorganism has an attraction to the cells of the nervous system or by the fact that the respiratory system is the main gateway. In addition, these cases were very prevalent in HIV+ individuals[36, 37].

The studies mentioned in the course of this review, as well as others observed, then seem to demonstrate a relationship between invasive fungal infection/etiologic agent and the patient's underlying pathology or immunosuppressive status. The PATH Alliance even publishes studies in which it is possible to observe a prevalence of certain infections in certain risk groups. Thus, infections by *Candida spp.* were more prevalent in patients in internal medicine, surgery or with solid tumors; infections by *Aspergillus spp.* in patients undergoing stem cell transplantation and *Cryptococcus spp.* in patients with HIV[49].

For superficial fungal infections, the *Candida spp.* stands out once again, being responsible for oral candidiasis, namely in patients with HIV+ [8]. Vulvovaginal infections represent another of the pathologies caused by fungi, namely *Candida spp.*. As mentioned, studies show that about 52.1% of patients with symptoms suggestive of vulvovaginal candidiasis do not present *Candida spp.* in laboratory tests. Thus, the diagnosis is often carried out only on the basis of the signs and symptoms and can lead to unnecessary therapies[17].

Onychomycosis represents a large percentage of nail pathologies and can be caused by dermatophytes, non-dermatophyte filamentous fungi and yeasts. Epidemiological studies refer to dermatophytes as the most common implicated representing 90% of infections of the toenails and 50% of the fingernails, being *T. rubrum* responsible for most cases[7,50]. In the studies addressed, dermatophytes continue to appear among the most isolated microorganisms in onychomycosis. However also the *Candida spp.* has been shown to play a very important role in infections with a higher prevalence [9,40,41].

A *tinea capitis* It is the dermatophytosis whose alteration of the epidemiology is more significant. In recent decades its incidence has increased significantly. Along with this fact, the emergence of species not as frequent as for example *T. tonsurans* may pose new challenges to public health in the future[7]. Most of these cases are also associated with rural areas or contact with infected animals[42].

5 FINAL CONSIDERATIONS

Fungi such as *Candida spp.*, Aspergillus spp. *and* Cryptococcus neoformans, are among the main opportunistic fungi, infecting mainly immunocompromised. In addition to these, dermatophytes were also highlighted, among them the genera *Trichophyton and Microsporum*, affecting the general population with a high incidence rate.

Developments in healthcare, new immunosuppressive therapies and the incidence of HIV/AIDS have increasingly contributed to the increase in opportunistic fungal infections. In addition to these, a large part of the population is faced with milder fungal infections, often undervalued and most often treated empirically.

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