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Update on Fungal Disease: From Establish Infection to Clinical Manifestation

Wanessa CMA de Melo, Liliana Scorzoni, Suélen Andréia Rossi, Caroline Barcelos Costa-Orlandi, Mônica Yonashiro, Maria José Soares Mendes-Giannini and Ana Marisa Fusco Almeida*

Faculdade de Ciências Farmacêuticas, UNESP-Universidade Estadual Paulista, Campus Araraquara, Departamento de Análises Clínicas, Laboratório de Micologia Clínica São Paulo, Brazil

Abstract

Fungal diseases have emerged as an important cause of morbidity and mortality, especially among immuno-compromised patients. Pathogenic fungi have evolved an array of virulence factors to survive within the host and to outwit immune defenses. Fungi may cause a wide range of diseases in humans that range in extent from superficial to disseminated infections. Generally, the site of infections classifies the type of fungal disease, which can be divided into superficial, cutaneous, subcutaneous and systemic. In addition, the fungal virulence factors determine whether the infection will become established in the host. A primary pathogen may infect an immunologically normal host, whereas, an opportunistic pathogen requires some compromise of the host immune defenses in order for the infection to become established. This article covers the main fungi that are responsible for the increase of the fungal infections.

Keywords: Fungal infections; Virulence; Yeast; Opportunistic infections; Endemic mycosis

Fungal Infections

Fungal diseases have changed constantly in the last years. The virulence of these microorganisms has been adapted according to the human host, promoting a range of clinical manifestation. Several are the ways by which fungi promote a disease depending on human body part involved by the microorganism and the immunologic system of the host [1].

In this review, we discuss the main fungal pathogens responsible for causing several diseases, highlighting on their virulence associate to clinical manifestation and the difficulty to accomplish the treatment.

Superficial and cutaneous fungal diseases

Superficial and cutaneous fungal infections are very common and occur worldwide affecting millions of people, especially immunocompromised patients. The most common types of these infections are dermatophytosis (tinea or ringworm), pityriasis versicolor (formerly tinea versicolor) and candidiasis (moniliasis). These occur by fungal invasion into the skin, keratinized tissues and mucous membranes [2]. Trichosporon and Fusarium species also cause superficial fungal infection, but also may be considered an invasive pathogen that may cause a systemic infection [3,4].

Dermatophytosis: Dermatophytes are fungi that invade keratinized structures of humans and animals producing a condition called dermatophytosis or, more commonly, tinea [5,6]. These fungi belong to three main genera Trichophyton, Microsporum and Epidermophyton, of these *T. rubrum* is the most prevalent species worldwide [7,8]. The mechanisms of pathogenicity of these fungi are not yet well understood. There are several studies focusing on keratinolytic proteases (keratinases) produced by dermatophytes, but it is not known how these fungi regulate the use of these proteases to obtain nutrients from the stratum corneum substrate they invade, and whether there are additional roles of these proteins in adhesion and immunomodulation [9].

To establish the infection, the contact of arthroconidia or hyphal fragmens with the host skin is essential. The fungi express specific carbohydrate adhesins on the surface of the microconidia that recognize specific sugars such as mannose and galactose. Other species such as *T. mentagrophytes* develop long and short fibrillar projections that anchor and connect the arthroconidia to the keratinocytes and to other arthroconidia [10]. Proteases such as subtilisins, dipeptidyl peptidases and metalloproteinases are directly involved in the adhesion to keratinocytes and invasion of stratum corneum. This adherence is time dependent and may vary for each species of fungi [9,11]. Subtilisins and fungalisins are keratinases responsible for the digestion of keratin into assimilable oligopeptides or amino acids. During keratin degradation, the dermatophytes secrete sulfite (using a sulfite efflux pump encoded by the gene SSU1). The sulfite is a reducing agent that cleaves disulfide bonds of keratin into cysteine and S-sulphocysteine, leaving the proteins capable of being digested by many endo and exo-proteases secreted by fungi. The high expression of the SSU1 gene is characteristic of dermatophytes and assists in the efficient degradation of keratinized tissue by dermatophytes [11].

High keratolytic activity is directly correlated to the production of more symptomatic infections and activation of the immune response. Dermatophyte infection induces delayed type hypersensitivity (DTH) reactions, which are characterized by the action of macrophages as effector cells and secretion of some cytokines, such as interferon-γ (INF-γ) [9]. The pattern of protease secretion plays a key role in the immune and inflammatory responses [12]. The intensity of inflammation depends on the depth of the skin damage caused by the infection, and the damage is dependent on the high or lower secretion of proteases. Other species such as *T. rubrum* and *T. tonsurans* are highly adapted to

***Corresponding author:** Almeida AMFA, Faculdade de Ciências Farmacêuticas, UNESP-Universidade Estadual Paulista, Campus Araraquara, Departamento de Análises Clínicas, Laboratório de Micologia Clínica São Paulo, Brazil, Tel: +551633014638; E-mail: ana.marisa@uol.com.br

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the human host and can evade or damp down the immune response, causing chronic dermatophytosis [9].

A study conducted by Youngchim et al. [13] showed melanin production by various species of dermatophytes. It is known that fungal melanin is a virulence factor in many fungal species, since it protects the microbes against host defense mechanisms and also from the environment; however there is insufficient evidence to suggest that melanin exerts a crucial role in the pathogenesis of these fungi. Recently, Costa-Orlandi et al. [14] characterized biofilm formation by *T. rubrum* and *T. mentagrophytes*, Biofilm formation could explain the persistence of infection caused by these fungi, especially in onychomycosis, but more studies are needed in order to correlate biofilm formation with pathogenesis.

Pityriasis versicolor: Pityriasis versicolor (formerly tinea versicolor), is one of the most common pigmentary disorders worldwide, that especially occurs in adolescence and early adulthood [15]. This superficial fungal infection is caused by dimorphic lipophilic yeasts of the genus *Malassezia* spp., such as *Malassezia furfur*, which is part of the normal cutaneous flora [16,17]. The frequency and density of this pathogen is related to patient's age, regional sebaceous glands, and genital secretions. In both their normal and pathological forms, these fungi reside within the stratum corneum and hair follicles, where free fatty acids and triglycerides from sebum and the keratinised epidermis might be altered in some way to provide a desirable host environment to allow primary or recurrent infection [18]. *Malassezia* spp. occasionally act as opportunistic pathogens especially in patients receiving intravenous fat emulsions for parenteral nutrition. However other factors that enhance patient susceptibility are not fully defined [19].

Infections caused by *Malassezia furfur* occur due a change of the saprophytic phase of this yeast to its pathogenic phase, colonizing the stratum corneum [20,21]. Several factors could be the cause of the transformation to the mycelian phase, including endogenous (sweating, greasy skin or immunosuppression) and exogenous factors (high temperature and humidity) [20].

The clinical manifestation of tinea versicolor is characterized by many irregularly shaped slightly scaled macules and patches, generally covering large areas of the body and separated by intercalated regions of normal skin. Flaking is evident, although in larger lesions this may occur only at the border. Lesions may be round or oval, becoming confluent in advanced cases of the disorder [17]. The macules and patches can appear hypopigmented or hyperpigmented. The hypopigmentation is related to dicarboxylic acids produced by fungi that may inhibit the dopa-tyrosine reaction that produces host melanin [22]. According to Karaoui, melanocyte damage also is caused by fungi, varying from altered melanosomes, damage to mitochondria to actual degeneration [23]. The size and distribution of melanosomes can be different between patients: when the melanosomes are abnormally small hypopigmentation occurs, while when the melanosomes are extra-large hyperpigmentation appears [22].

Fusariosis: Fusariosisis is caused by *Fusarium* species including *Fusarium oxysporum, Fusarium moniliforme* and *Fusarium verticillioides*. These pathogens are widely distributed in soil, plants and the air, being responsible for causing a broad spectrum of human diseases such as mycotoxicosis and infections which can be locally invasive or disseminated [24]. Disseminated fusariosis occurs almost exclusively in immunocompromised individuals and has recently emerged as the second most common pathogenic mould in high-risk patients suffering from hematological cancers, and in recipients of solid organ and allogeneic bone marrow or stem cell transplants [25-27].

The clinical manifestation of this disease is skin lesions with the appearance of granulomas, ulcers, nodules, mycetomas, necrosis, panniculitis and intertrigo [28]. Besides these manifestations, *Fusarium* spp. also can cause keratitis which is a frequent cause of corneal damage [29], endophthalmitis that may occur after fusarial keratitis or following surgical trauma [30] and onychomycosis which can invade the large toenails after soil contamination [31].

Fusarium spp. infections belong to a wide group of infections named hyalohyphomycosis, a term that describes fungal infections caused by moulds whose basic tissue morphology is hyaline, light-colored, hyphal elements that can be branched or non-branched, occasionally toruloid and without pigment in their cell walls [32,33].

Several virulence factors of this fungal species include: 1) the capacity to produce mycotoxins that suppress humoral and cellular immunity causing tissue breakdown; 2) the ability to adhere to abiotic surfaces and to produce proteases and collagenases [28].

Trichosporonosis and white piedra: Trichosporon species are responsible to cause the diseases trichosporonosis and white piedra. These fungi also can be involved in systemic or disseminated mycoses, particularly in patients with underlying hematological malignancies, AIDS, large area burns, and solid tumors [34]. There are several species of Trichosporon responsible for these diseases, especially: *Trichosporon asahii* (more common in cases of systemic mycosis), *Trichosporon asteroides, Trichosporon cutaneum, Trichosporon beigelii* (the main fungi responsible for white piedra), *Trichosporon inkin, Trichosporon jirovecii, Trichosporon mucoides* and *Trichosporon ovoides* [35,36].

This fungal species can be found in soil, decomposing wood, air, rivers, lakes, seawater, cheese, scarab beetles, bird droppings and so on. Also, occasionally it may be part of the gastrointestinal and oral cavity microbiota and can transiently colonize the respiratory tract and skin [37].

According to Colombo et al. [38], the *Trichosporon* spp. have the ability to form blastoconidia, true mycelia, and, most importantly, arthroconidia, asexual propagules that detach from true hyphae. The presence of multilamellar cell walls and dolipores with or without parenthesomes is an important characteristic of *Trichosporon* spp. [39].

The most important virulence factors of this fungal specie include: 1) the ability to produce and secrete enzymes such as hemolysins, proteases, and lipases that allow protein degradation and destabilization of the membranes of the host cell, increasing fungal pathogenicity [40]; 2) cell wall components such as glucuronoxylomannan (GXM) that can attenuate the phagocytic capability of neutrophils and monocytes *in vivo* [41]; 3) capacity to adhere and form a biofilm providing an extra-protection against host defenses and antifungal drugs [42]. Usually the biofilm of Trichosporon species are associated with central venous catheters, intravesical catheters, and peritoneal catheter-related devices [38].

Most clinical infections with Trichosporon strains are correlated with episodes of colonization or superficial infections. The condition called white piedra is the most common superficial infection in which white nodules are formed due to the aggregation of conidia around each hair shaft. The fungi remain in contact with the hair cuticle, without invading either the hair medulla, scalp or skin [36,43].

This infection mainly affects head hair; however the infection may manifest itself in the hair in armpits, pubis, and to a lesser degree moustaches and beards. Humidity and poor hygiene are among the risk factors for this disorder. The principal agents causing white piedra are *T. asahii*, *T. inkin*, *T. cutaneum*, *T. mucoides* and *T. ovoides* [44].

In the last few years, there has been an increase in the occurrence of onychomycosis associated with *Trichosporon* spp., especially caused by *T. asahii, T. mucoides* and *T. inkin* [45].

Trichosporon spp. also has been recognized as an opportunistic agent causing emerging, invasive infections known as trichosporonosis. According to Colombo et al. [37], trichosporonosis is considered to be an endogenous disease since the pathogen is commonly found as a part of the normal flora in the gastrointestinal tract, lungs, and skin. The main clinical manifestations are fever and fungemia and some instances of inflammation and abscesses can be found in different organs and tissues, such as heart, brain, liver, spleen, esophagus, urinary tract, joints and peritoneum [46,47]. The most common species responsible for causing this disease are *T. asahii*, *T. asteroides*, *T. cutaneum*, *T. inkin* and *T. mucoides* [48].

Candidiasis: Candida species are components of the normal microbiota of a healthy individual, being present in mucosal oral cavity, gastrointestinal tract and vagina. However, in certain conditions Candida, especially *Candida albicans*, can undergo overgrowth to infect the skin and mucosa. Conditions encouraging this overgrowth include hot, humid weather, poor hygiene, diabetes or patients with a weak immune system and so on [49]. Among risk factors for developing candidiasis there is also prolonged antibiotic therapy [50].

Superficial candidal infections cause significant morbidity in older adults, which becomes a particular problem with the use of certain types of medication, poor self-care, and decreased salivary flow. Age alone is not sufficient for the development of candida infection; however, increased morbidity is associated with both superficial and invasive forms of disease. There is an increased risk in patients in an immunosuppressed state, such as malignancy [51].

The various Candida species have the ability to invade the skin and cause a number of diseases. The clinical manifestations vary depending on the location of the infection and particularly affect intertriginous areas, such as infra-mammary skin, groin and abdominal skin folds. Also, it can occur in interdigital sites (interdigital candidiasis). The symptons comprise pruritus, pain, and erythema [52].

C. albicans is the yeast most commonly involved with superficial candidiasis, however there are reports that non-albicans Candida, such as *C. glabrata*, *C. parapsilosis*, *C. tropicalis* and *C. guilliermondii,* may be etiologic agents. Generally, these pathogens cause cutaneous candidiasis, oral candidiasis (thrush), vaginal candidiasis, *Candida* onychomycosis, oropharyngeal candidiasis and chronic mucocutaneous candidiasis [53,54].

Candidiasis symptoms vary depending on the location of the infection. Infections in skin folds or in the navel usually cause a bright red rash. Small pustules or pimples may appear which may ooze white fluid. The rash may feel like burning, and can be very itchy.

Candida pathogenicity is associated with a number of virulence factors including the ability to evade host defenses, adherence, biofilm formation (on host tissue and on medical devices) and secretion of hydrolytic enzymes (e.g. proteases, phospholipases and haemolysin) [55].

Subcutaneous mycoses: Subcutaneous mycoses are fungal infections that primarily involve the dermis and subcutaneous tissues and rarely disseminate into systemic disease. Disease is caused by a variety of pathogens, which are often restricted to tropical and subtropical regions of the world. The main fungi responsible for subcutaneous mycoses are called dematiaceous or black yests.

Dematiaceous fungi, so-called darkly pigmented fungi, black yeasts, melanized fungi, comprise a heterogeneous group of organisms that have darkly pigmented (brown to black) cell walls of their hyphae or conidia [56,57].

The pathogenic mechanisms by which many of these fungi cause disease are not yet completely understood, particularly in immunocompetent individuals. One of the likely candidate virulence factors is the presence of pigment in the cell wall, which is common to all dematiaceous fungi [56]. Generally, this pigment is melanin, more specifically dihydroxynaphthalene melanin, a broadly stable compound that is important to pathogenicity, since it is resistant towards destructive physicochemical processes [57-59]. Several mechanisms have been proposed by which melanin may act as a virulence factor including: 1) a protective advantage against free radicals and hypochlorite which are produced by phagocytic cells in their oxidative defenses; 2) melanin may bind to hydrolytic enzymes preventing their action on the fungal plasma membrane; 3) the production of allergic reactions that can also cause disease [60].

Chromoblastomycosis, eumycetoma and phaeohyphomycosis are the clinical syndromes caused by dematiaceous fungi, and are distinguished according to their histological characteristics [59]. In addition, sporotrichosis is an infection caused by *Sporothrix schenckii* and involves subcutaneous tissue at the point of traumatic inoculation [61].

Chromoblastomycosis: Chromoblastomycosis (CBM) is a chronic and progressive subcutaneous mycosis presenting nodular, tumoral and verrucous lesions, plaque and cicatricial lesions caused by the traumatic transcutaneous inoculation of fungal species of the Herpotrichiellaceae family. The species responsible for this mycosis are *Fonsecaea* spp., *Cladophialophoracarrionii*, *Phialophora verrucosa*, *Rhinocladiella aquaspersa* and *Exophiala spinifera* [62-64]. Histopathologically, CBM specimens contain muriform cells (resembling courses of bricks in arrangement) or sclerotic cells associated with pus and granulomatous tissue reaction [62,65,66].

Eumycetoma: Eumycetoma, similar to CBM, is a chronic subcutaneous inflammatory disease caused by *Madurella mycetomatis* (70% of cases), *Leptosphaeria senegalensis*, *Madurella grisea*, *Exophiala jeanselmei* and *Pseudallescheria boydii*. Lesions consist of a painless subcutaneous mass, presence of sinuses and sero-purulent discharge, colored grains and aggregates of the fungal hyphae. The progression of the disease can lead to the involvement of the skin, deep structures, fascia, and bones with consequent deformity and disability [67-69].

Phaeohyphomycosis: Phaeohyphomycosis is a term used to cover the remainder of clinical syndromes caused by dematiaceous fungi [57,59]. These are opportunistic diseases whose predisposing factors are organ transplantation, leukemia, lymphoma, peritoneal dialysis, AIDS/HIV, corticosteroid therapy, and intravenous drug abuse. The etiological agents include Exophiala, Phialophora, Cladosporium, Wangiella, Fonsacaea, Alternaria, Bipolaris and Curvilarias species [70].

According to the severity (extent and invasion), phaeohyphomycosis can be classified into superficial (cutaneous, otitic and ophthalmic), subcutaneous, cerebral and disseminated or systemic forms. Commonly cutaneous or subcutaneous disease occurs through skin trauma caused by thorns and wood splinters. In cerebral and systemic infection, the microorganism is inoculated via the airways and then spreads from the lungs to the brain [70,71].

The clinical manifestations depend on the degree and location of invasion of the fungal cells. Subcutaneous nodular phaeohyphomycosis is the most characteristic form of this infection, and occurs predominantly in immunosuppressed patients. This infection starts on the upper or lower limbs and spreads over the body surface, causing nodular lesions that form verrucous plaques, which can be partly ulcerated and super-infected. The most common subcutaneous form is the mycotic cyst which presents a firm tumor with sharp borders with an intact skin surface above it [72].

Cerebral phaeohyphomycosis is another fungal infection that is characterized by black necrotic tissue, black pus, and black cerebrospinal fluid. Most of the pathogens that cause this infection belong to Chaetothyriales group, which may reach the brain through blood or lymphatic vessels, by directly spreading from adjacent lesions, or by accidental inoculation [73].

Generally, the fungi disseminate to the central nervous system (CNS) through blood vessels, and might also reach the brain through lymphatic vessels. Clinical presentations of cerebral phaeohyphomycosis include, seizures, headache, cerebral irritation, fever, and psychotic behavioral changes, although hemiparesis and hemisensory loss can occur [71,74].

Sporotrichosis: The thermally dimorphic *Sporothrix schenckii* is the most common etiologic agent of sporotrichosis, which can mainly be found in tropical and subtropical regions of Latin America, although there are some reports of infections outside these regions [75,76]. Recent phylogenetic studies determined the geographic distribution, biochemical properties, virulence and antifungal susceptibility of distinct *Sporothrix* spp. [77-80].

This infection causes cutaneous and lympho-cutaneous mycoses and can affect both humans and animals [81]. Both the cutaneous and lympho-cutaneous clinical forms can be acquired by injuries, thorns and scratches from animals [82], while pulmonary infection occurs by inhalation of spores. Immunosuppressive therapy contributes to the increased prevalence [83].

Virulence factors of *Sporothrix* spp., have been described. The thermotolerance of the fungus is correlated with the clinical form of the disease. Isolates able to grow at 35°C are able to produce cutaneous lesions, while lymphatic sporotrichosisis is caused by isolates that could withstand higher temperatures [84,85]. Melanization has also been described in *Sporothrix* spp. and may be related to protection against harmful environmental conditions and phagocytosis [86,87]. Adhesins are another important virulence factor for the development of sporotrichosis [88]. A 70 kDa glycoprotein has been described as an important adhesion [89].

Systemic Mycoses

Opportunistic infections

Candidiasis and candidaemia: In recent years, the incidence of infections by *Candida* species has substantially increased, especially in immunocompromised individuals, (transplant patients, surgery, diabetes, HIV, antibiotic therapy, steroids and chemotherapy). Epidemiological data show that Candida yeasts are the most important group responsible for mycoses in humans and can cause simple superficial infections to severe systemic infections that can lead to death [90]. *C. albicans* is the most important and prevalent yeast pathogen. However, other species, termed non-albicans Candida (NAC), such as *C. glabrata, C. krusei, C. parapsilosis, C. tropicalis* and *C. dubliniensis* are increasingly being found as causative agents of mycoses [91-93].

C. albicans is a polymorphic fungus, and is a constituent of normal human microbiota that colonizes skin, oropharynx, genital and gastrointestinal mucosa. Usually this yeast is considered harmless; however, when there is an imbalance with other microflora or with the host cells, it becomes a pathogen. The steps in pathogenesis comprise colonization of mucosal surfaces and skin, fungal overgrowth, host tissue invasion and finally spread through bloodstream [94,95].

The opportunist yeast *C. glabrata* is considered the second most important cause of candidemia and has emerged as a serious health threat, especially due to its ability to develop resistance to several classes of antifungal drugs [96,97]. *C. glabrata* has a size between 1-4 µm, does not have the ability to form pseudohyphae, and always occurs as blastoconidia. It is a comensal species that colonizes the oral cavity and human gut, and as a pathogenic agent can cause diseases such as vulvovaginitis and systemic infections [98,99]. Its pathogenic process is not so aggressive as other fungal pathogens, for example *C. albicans*, however *C. glabrata* can still invade and colonize the host, with immune evasion and persistence [100]. It is able to survive and reproduce inside macrophages with little cell death, leading to cytokine release [101].

Different from most other species of the Candida genus that have ovoid morphology, *C. krusei* cells are usually elongated resembling long grain rice [102]. Approximately 2 to 4% of candidemia cases are caused by this fungal pathogen, mostly affecting patients with bone marrow transplants or hematological malignancies such as leukemia. *C. krusei* can also cause endocarditis, osteomyelitis, endophthalmitis, and can colonize the urinary and gastrointestinal tracts, and the vagina. The virulence factors of *C. krusei* are very similar to *C. albicans* and comprise modulation of the system immune, adherence to surfaces, production of enzymes, such as proteinases and phospolipases, antigenic variability, dimorphism and phenotypic changes. In addition *C. krusei* is naturally resistant to fluconazole [99,103].

Aspergillosis: Invasive aspergillosis (IA) is a serious infection caused by saprophytic fungi of the genus Aspergillus, resulting in high mortality in immunocompromised individuals. After an early report of disseminated aspergillosis by Rankin in 1953 [102], subsequent years showed an increase in incidence of IA, particularly in individuals with some type of immunosuppression, such as malignancies, AIDS, solid organ transplantation and immunosuppressive treatment [104-106].

A. fumigatus is the main causative agent of IA, followed by *A. flavus, A.niger, A. terreus, A. nidulans* and other species with morphological similarity to *A. fumigatus* [107].

A. fumigatus can be easily distinguished from other less common agents, through the characteristic morphology of its conidial structures [108]. Differentiation of atypical strains of *A. fumigates* can be performed by growth and appearance of colonies, ease of production of conidia, conidial surface markings, the presence or absence of septation in phialides and maximum growth temperatures [108,109]. In a study using multilocus sequence data, it was reported that several atypical strains of *A. fumigatus* were genetically identified as new distinct phylogenetic species such as *A. lentulus* and *A. felis* [108,110]. In recent years, using molecular techniques, other *A. fumigates*-related species have been re-classified as *Neosartorya udagawae*, *A. novofumigatus*, *N. pseudofischeri* and *A. viridinutans* [111-113]. These cryptic species were found to be less sensitive to antifungal agents, including amphotericin B (AmB) and the azoles [112,114]. Thus, the correct identification of the etiologic agents of IA that resemble *A. fumigatus* is of great importance because the clinical presentation and response of invasive infections caused by these species may differ from that observed for *A. fumigatus* [115].

Aspergillus infection is an opportunist mycosis and occurs by inhalation of fungal spores, after which the development of disease depends on the immune status of the host. Usually, when the individual is healthy, the infection is countered by the host immune system causing only allergic reactions, but when the patient has immunosuppression, an infection can develop causing invasive disease [116]. *Aspergillus* spp. are responsible for a range of infections with the most common clinical presentations involving the lungs (i.e., acute or chronic IA and allergic bronchopulmonary aspergillosis) and the disease can disseminate via the bloodstream and eventually involve distant organs [107]. The central nervous system (CNS) is one of the most frequent sites of dissemination [117].

The pathophysiology and virulence determinants of *A. fumigate* are not well understood. The identification of pathogenic virulence factors has been hampered by the redundancy of genes with the same function, the pleiotropic effects of several genes, and complex enzymatic systems encoded by gene clusters [107].

According to Chotirmall et al. [118] the virulence factors can be divided into classical and non-classical. Classical virulence factor refers to a specific component of the pathogen, whereas the non-classical virulence factor refers to fungal structure, growth capacity, stress adaptation, ability to damage to the host, and the mechanisms used to evade the immune system. Virulence factors of *A. fumigatus* include conidial melanin and gliotoxin expression [119-121]. The acquisition of iron and zinc is very important for the growth of *A. fumigatus*. As a result, genes encoding proteins involved in the acquisition of these metal ions are essential to cause disease [122,123].

Cryptococcosis: Infections caused by C*ryptococcus* spp. [124] such as *C. neoformans* and *C. gattii*, (ubiquitous environmental fungi) are the main etiologic agents of cryptococcosis. However other Cryptococcus species, which are not classically considered to be pathogenic, such as *C. albidus* and *C. laurentii*, have been emerging as opportunistic pathogens over the years [125,126].

Cryptococcal disease primarily affects individuals with impaired immunity [127,128]. The infection occurs through inhalation of the infectious forms of the yeast, called basidiospores, which are commonly found in the environment [129-131]. After inhalation of the basidiospores, there is the involvement of the alveolar tissue, initiating a primary lung infection. In healthy people, the infection often is effectively contained, but in immunocompromised patients, the yeast can disseminate via the hematogenous route and reach its preferred site of infection, the central nervous system (CNS) [132]. CNS infections comprise more than 70% of cases of cryptococcosis in patients with AIDS and may be fatal if not treated appropriately [133].

C. neoformans has a worldwide distribution and is the major species causing CNS infections in individuals with AIDS [134]. However *C. gattii* is more geographically restricted and infects both immunocompromised and normal immunocompetent patients [135]. *C. gattii* has been associated with outbreaks in humans and animals, and has been isolated in temperate countries, showing that the fungus can adapt to new environments previously unknown [136-138].

Several studies have shown that *C. neoformans* and *C. gattii*, share the same key virulence factors already known [139,140], although there are reports that some virulence attributes are specific for each species [141-144]. In this context, it can be mentioned that superoxide dismutase (Sod1, a prominent antioxidant) is required for virulence of *C. gattii,* but not for *C. neoformans* [145].

The combination of virulence factors and host susceptibility is crucial for survival and proliferation of *Cryptococcus* spp. [146,147]. Among the main virulence factors described, it is possible to highlight the fungal capacity to grow at 37°C, the polysaccharide capsule, laccase activity, which is responsible for the production of melanin, and the production of urease and phospholipases.

The polysaccharide capsule is considered to be a major virulence factor in both *C. neoformans* and *C. gattii*. This capsule is a complex structure which surrounds the cell and is composed of mannoproteins (MP), glucuronoxylomannogalactan (GalXM) and glucuronoxylomannan (GXM). Each of these components may have an effect on the host immune system [134,148,149]. The capsule protects cells from phagocytic activity by macrophages and neutrophils, and interferes with normal T cell function [150,151].

Cryptococcus spp. is facultative intracellular pathogens and previous studies have shown that these yeasts can adapt and survive within the host in a latent state for long periods of time [150,152,153]. In addition, other virulence factors contribute to the development of infection, such as the appearance of different phenotypic forms when in contact with the host [154-156] and the ability to survive and replicate within phagocytic cells [157-159].

Zygomycosi: Zygomycosis is an opportunistic fungal infection caused by genera from the Zygomycetes class, which is divided into the orders Mucorales and Entomophthorales. Rhizopus, Mucor, Absidia, Rhizomucor, Apophysomyces, Saksenaea, Cunninghamella, Cokeromyces, Syncephalastrum and *Basidiobolus* spp. are some of the species of Zygomycetes that can cause human disease [160]. Zygomycetes is a ubiquitous class of saprophytes, which can easily be found in the environment. The epidemiology of zygomycosis is still unclear because of the difficult diagnosis [161]. The mortality of zygomycosis is high and has been estimated at 50-100%, giving a higher mortality index than either systemic candidiasis or aspergillosis [160,162-164].

Zygomycosis can be acquired by inhalation of spores, and takes the form of rhinocerebral or pulmonary zygomycosis [165].Traumatic innoculation has also been described as a route of infection [166-168]. Gastrointestinal zygomycosis is a rare infection that has been described in neonates [169,170].

Zygomycosis affects immuno-compromised patients with neutropenia, diabetes mellitus with ketoacidosis, solid organ transplantation, trauma, and dialysis patients using iron chelators (deferoxamine) [164,171-176]. Moreover, the use of voriconazole as a prophylaxis or for treatment of aspergillosis represents a risk factor for zygomycosis, because Zygomycetes are intrinsically resistant to this antifungal drug [177-179].

The acquisition of iron is an important factor in the pathogenesis of zygomycosis [180]. Patients with diabetic ketoacidosis or other metabolic acidosis have a higher availability of iron in their tissues, and therefore are more susceptible to zygomycosis [160,181]. The importance of iron could be explained by a study that carried out inactivation of the gene *FTR1* of *R. oryzae*, encoding an iron permease. When this gene was inactivated they generated non-pathogenic *Rhizopus oryzae* [182]. Nevertheless the use iron chelation in combination with antifungal drugs as a treatment has been inconclusive [183].

Endemic Mycoses

Blastomycosis

Blastomycosis is a potentially fatal infection in humans, dogs and

other mammals caused by the thermally dimorphic fungi *Blastomyces dermatitidis* [184]. It is frequent in adults around 40 years but uncommon in children, and is more predominant in male patients due to occupational factors [185]. In North America, most cases of blastomycosis occur in the valleys of the Ohio and Mississippi rivers, in the southeastern states and in Canadian provinces around the Great Lakes [186]. There are some reports of blastomycosis occurring in Mexico, Africa, India, Lebanon, South Arabia and Israel [185]. The ecological factors that determine the presence or absence of *B. dermatitidis* in the environment are poorly understood because this fungus has rarely been isolated from the environment [186].

Blastomyces virulence factors include thermal dimorphism, the presence of an adhesion factor called BAD1 (blastomyces adhesion 1) which allows the onset of infection and at the same time suppresses the activity of tumor necrosis factor α (TNF-α). The major virulence factor of the fungus is due to the presence of α-1,3 glucan in 95% of the yeast cell walls, while the cell walls of the filaments contains both α and β- glucans in the same proportions. Furthermore, the fungus produces melanin, to protect itself from oxidative attack by leukocytes. The presence of numerous yeast cells within tissues induces delayed hypersensitivity reactions producing abscesses, hemorrhagic lesions, fibrosis, and granulomas in the chronic form of the disease [185].

Infection occurs by inhalation of conidia or fragments of fungal mycelium, which come in contact with the lungs, where they are converted to the yeast form. In the lungs there may be an asymptomatic infection, a localized pneumonia, or severe acute respiratory distress syndrome (ARDS). The yeasts that escape phagocytosis can spread to other tissues such as bone, central nervous system, liver, spleen, bone marrow, skin and genitourinary tract [184]. There are also reports of sexually transmitted infections, by intrauterine route and through bites from infected dogs [185,187-189]. Disseminated blastomycosis occurs more often in immunosuppressed individuals such as organ transplant recipients and patients infected with HIV [190].

Coccidioidomycosis

Coccidioidomycosis is a systemic mycosis, also known as "Valley fever", "San Joaquin Valley fever", "San Joaquin fever", "desert fever" and "desert rheumatism", and affects both immunocompetent and immunocompromised hosts [191]. It is caused by dimorphic fungi *Coccidioides immitis* and *C. posadasii*, which are both human respiratory pathogens. *Coccidioides* spp. has a unique parasitic life-cycle that is not found in any other fungi that cause systemic mycoses [192]. The small spores dispersed in the air (arthroconidia) are launched into the air by the mycelium present in the soil in the southwestern United States, northern Mexico, Central America and South America. Inside the lung, the spores are converted into small round multinucleated cells called spherules, which grow and become larger parasitic cells. The large parasitic cells undergo an elaborate cell wall growth process with compartmentalization of the cytoplasm leading to the formation of a multitude of endospores, smaller than the parasitic cells. These endospores grow and differentiate into second-generation spherules, also called mature spherules that escape phagocytosis as they are too large to be ingested by neutrophils, macrophages, and dendritic cells [192]. There are two clinical forms of coccidioidomycosis: the first causes an influenza-like illness, which may resolve itself or may progress to a moderate to severe disease, followed by cure of the infection and the establishment of a strong immunity against re-infection. The second form is a rare form in which the infection becomes established and is followed by a chronic or acute fatal dissemination to the meninges, bones, joints and skin and subcutaneous tissues. In most cases the immune system resolves the infection without the need for pharmacological intervention; but without proper diagnosis, the disease can disseminate, and therefore, symptoms may become more severe [191,193].

Little is known about the virulence factors of *Coccidioides* spp. However, Sharpton and collaborators (2009) compared the genomes of *C. immitis* and *C. posadasii* with the nearest nonpathogenic species *Uncinocarpus reesii* and with the most distant pathogenic fungus *H. capsulatum*. Specific genes were identified in the genus Coccidioides that were: related to the spherules; involved in energy metabolism; required for the use of allantoin as a nitrogen source; related to the membrane; and others that may be involved in host-parasite interactions [192,194,195]. Furthermore, it is believed that metalloproteinases such as (Mep1), which are secreted during endosporulation phase, are able to digest the immunodominant cell surface antigen (SOWgp), preventing host recognition of the endospores during the development phase [196]. There is an emerging hypothesis that *Coccidioides* spp. is associated with animals in both the environmental and parasitic stages of the life cycle. This hypothesis explains the unequal distribution within the soil of endemic areas, and could be attributed to the unequal distribution of carcasses of dead animals in the soil. In these carcasses, high temperatures and high carbon dioxide concentrations favor the production of spherules, that then revert to hyphae and then to arthroconidia [197].

Paracoccidioidomycosis

Paracoccidioides brasiliensis and *P. lutzii* are thermally dimorphic fungi which are etiologic agents of paracoccidioidomycosis (PCM). This infection is an endemic fungal disease in Latin America [198,199]. Outside the endemic areas cases are found after migration of individuals originating in these endemic areas, or in travelers who visited these regions [200].

The infection occurs by inhalation of the fungal conidia or mycelial propagules. Paracoccidioidomycosis presents two main clinical forms: a chronic form affecting adult men between 30 and 60 years (most of them being rural workers); and an acute/subacute form that affects mainly children or young adults [201-203].

For a successful *Paracoccidioides* spp. infection the fungi have to be able to adhere to host cells. In this context, many adhesions have been described for *Paracoccidioides* spp. [204-217]. Important virulence factors for these fungi include thermal dimorphism which allows the pathogen to adapt/survive inside the host, and the capacity to produce biofilm *in vitro,* expression of phospholipase and melanin production [218-223].

Histoplasmosis

Histoplasmosis is a systemic mycotic infection caused by dimorphic fungus *Histoplasma capsulatum* var. *capsulatum*. This disease is endemic in areas of the USA (Ohio and Mississippi valleys) and in most Latin American countries [224].

Infection by *H. capsulatum* is primarily acquired via inhalation of infective microconidia or hyphal fragments. A respiratory disease may occur if the yeast can survive and replicate within the alveolar macrophages. Depending on the host immune system the yeast can disseminate from the lungs to other organs (spleen and liver), causing the most lethal form of histoplasmosis [225].

This saprophytic fungus exhibits pathogenesis attributes including the mold-to-yeast transition, ability to gain entry into host phagocytes,

intracellular survival, and proliferation during clinically non-apparent infection, and sometimes demonstrating a reactivation mechanism after an apparent cure. In addition, the capacity of *H. capsulatum* to grow showing different morphologies makes this microorganism able to adapt in various living conditions [224].

According to Pitangui et al. [224], *H. capasulatum* has virulence factors such as mechanisms for iron acquisition, a secreted small protein that is able to bind Caþþ at a low concentration (Cbp1), an extracellular yeast phase-specific protein (Yps3), and the cell wall polysaccharide, α-(1,3)-glucan. Besides that, these authors suggested that this fungus has the ability to form biofilms, and the yeast form is able to adhere to epithelial A549 cells.

The clinical manifestations of this disease depend on the immunological status of the patient and may range from asymptomatic infection in an immunocompetent host, or may take a more invasive nature in immunosuppressed individuals presenting three types of lesions such as pulmonary, oral and mucocutaneous [225].

Conclusion

Fungal diseases have significantly increased in the worldwide causing emergence in human health. This increase is related to differences factors, especially, the virulence changes of the fungi which difficulty the access of antifungal to combat the infections. So, the understanding of association between the disease establishment, fungal specific virulence and clinical manifestation improves the diagnostic methods and allows the development of new strategies to combat the fungal diseases.

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