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REVIEW ARTICLE

REVIEW ON COMMON FUNGAL DISEASES OF HUMANS

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ABSTRACT
In this review article we had discussed about the common fungal diseases which occur in Human beings. The infections which are caused due to fungal pathogens are having worldwide distribution. As the fungal infections and diseases are increasing day by day so the deep study about these infections is very important especially for control and treatments. The information about these fungal diseases was collected from research papers and review articles of different journals available on Google Scholar. We discussed twelve common fungal infections which cause infection in humans include Fungal nail infection, Vulvovaginal candidiasis, Tinea pedis, Oral candida, Aspergillosis, Blastomycosis, Candida auris infection, Cryptococcosis, Mucormycosis, Talaromycosis, Mycetoma and Keratitis. The epidemiology of the infection of causative agents which causes the specific disease, pathology and diagnostic techniques to identify the infection are discussed. Suitable treatment for the cure of infection and prophylaxis of these fungal infections are also stated. There are higher chances of the infection to be occurred in the immunocompromised patients.

INTRODUCTION

There are almost 1.5 million fungal species on Earth (Hawksworth, 2001). However, only small portion of these species cause infection or diseases in human beings. These disease-causing pathogens produce different kinds of infections, allergies and mycoses in humans. There are higher chances of fungal infections to occur in immunocompromised patients who are having weak immune system (Otto and Green, 2020). The rate of invasive fungal diseases is increasing day by day (Horn *et al.,* 2012). The most common disease-causing pathogens are *Candida albicans* and *Aspergillus fumigatus.* They cause invasive mycoses. About 200 of species of Aspergillus are reported to cause infection in humans (Brakhage, 2005). Skin and nail infection due to fungal microbes is also very common in the world. It causes this infection in approximately 1.7 billion people worldwide (Havlickova *et al.,* 2008). The most common reason of these infections is Dermatophytes which cause athlete's foot mostly in adults. Dermatophytes may also cause ringworm of scalp usually in children. It affects 200 million people worldwide. It also causes nail infection in adults and the chances of infection increases with age (Thomas *et al.,* 2010). Many fungal pathogens cause invasive infection. These infections may kill 1.5 million people annually (Firacative, 2020). Fungal infections are having worldwide distribution and are increasing in different regions in different ways according to the conditions of the area and cultural habits of the people. The death rate and impact of these fungal infections on people is difficult to calculate especially in developing nations (Brown *et al.,* 2012). In this review article we are going to study briefly about the epidemiology, prevalence of the infection, causative agents, pathology, diagnostic techniques and treatment of twelve different fungal diseases. The names of these diseases, causative agents and distribution in the world are presented in Table 1.

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Fungal nail infection

Fungal nail infection is most common fungal infection in the humans. This infection is also known as onchomycosis. The most common reason for this infection is dermatophytes. The dermatophytes include fungi from genus Microsporum and Trichophyton. It is prevalent in the humid areas. It is common in Europe and its prevalence is 23 % (Ogasawara, 2003). It is also common East Asia and North America (Ghannoum and Isham, 2014). It is not prevalent in the tropical regions. It is most common in immunocompromised people. This infection can also cause diabetic foot syndrome (Nenoff *et al*., 2012). This infection can cause Athlete's foot and it is most common in wet areas of the world. This infection invades the nail bed and penetrates into the lateral margins or from the above side of the nail forming white surface on the nail (Berker, 2009). Fungal nail infection causes thickening of the nail. The skin around this infection becomes scaly. It forms discoloration of nails and forms white markings (Muth, 2017). The onchomycosis is diagnosed by microscopic and staining techniques using Chlorazol Black E (Lilly *et al*., 2006). The nail infection can be cured by chemical treatments or by surgery. Different medicines are used to treat onchomycosis including Terbinafine, Fluconazole, Itraconazole but they also have some side effects (Elewski and Tavakkol, 2005). The new treatment used to cure onychomycosis is Laser treatment (Gupta and

Simpson, 2013). Topical and systemic therapies are also used for their treatment. Relapse may also occur in fungal nail infection. It is most common in people who are immunosuppressed or having diabetes (Scher and Baran, 2003).

Vulvovaginal Candidiasis

It is mucosal opportunistic infection caused by *Candida albicans*. It mostly affects women of reproductive ages. It is having worldwide distribution but it is most common in North America. The acute infection is common during the pregnancy and causes morbidity in women. It can also occur at the luteal phase of menstrual cycle (Russo *et al*., 2019). Mostly when there is an increase in progesterone or estrogen level (Fidel *et al*., 2000). *C. albicans* is dimorphic fungal specie. It is present in gastrointestinal and reproductive tract. Approximately 75% women in their reproductive ages are affected due to this infection (Fidel, 2005). In 5 to 10 % of cases recurrent vulvovaginal candidiasis is also common (Sobel, 1992). It causes infection of vaginal lumen and may also affect the vulva. The symptoms of the infection include itching, soreness and abnormal vaginal discharge. It also causes erythema, edema and external dysuria. Gram staining of vaginal discharge can be done for diagnosis. The symptomatic and asymptomatic vulvovaginal candidiasis can be differentiated by wet mount technique (Sobel, 2016). The vulvovaginal candidiasis can be treated by regimens of Fluconazole and Itraconazole. Some other drugs are also used for example Clotrimazole, Miconazole, Terconazole etc. (Donders *et al*., 2008).

Tinea pedis

Tinea pedis is the form of dermatophytosis, is also known as athlete's foot. It is a chronic fungal infection. It is one of the most common fungal infections in United States (Weinstein and Berman, 2002). This infection is very common and having worldwide distribution. It causes infection of the toes and foot. The causative agents of the tinea pedis include *Trichophyton rubrum*, *Epidermophyton floccosum* and *Trichophyton interdigitale* (Ilkit and Durdu, 2015). The risk of this infection is most common in the adults of age 31 to 60 years (Drakensjö and Chryssanthou, 2011). It rarely affects children. It is mostly common in men as compared to women and also common in the developed countries. This infection mostly occurs in soldiers, miners and marathon runners (Lacroix *et al*., 2002). This infection causes interdigital tinea pedis. This infection is reported in East Asia and Europe (Beguin *et al*., 2012). It causes lesions in between the toes. Extensive spreading of infection occurs in immunocompromised patients (Glick and Khachemoune, 2012). The second type of tenia pedis is inflammatory or vesiculobullous tenia pedis. It forms lesions in the epidermis and the bullae formed are lemon yellow in color (Hasan *et al*., 2004). In ulcerative tenia pedis lesions and ulcers are formed on the foot. It is most common in diabetic and immunocompromised patients (Legge *et al*., 2008). Tinea pedis also causes chronic hyperkeratotic also known as moccasin and may cause two feet one hand syndrome (Ilkit and Durdu, 2015). Tenia pedis also causes cellulitis, id reactions and lymphangitis etc. Tenia pedis is mostly diagnosed by microscopy technique using Potassium Hydroxide. It can be treated by using Topical antifungal agents. Terbinafine is most commonly used (Schäfer-Korting *et al*., 2008). Oral antifungal medicines for example fluconazole can also be used for its treatment. By improving personal hygienic conditions Tenia pedis can be controlled.

Oral candida

Oral candida is also known as oral thrush. The causative agent of this infection is *Candida albicans*. This pathogen was found in 1900 in the oral cavity of the people infected due to this infection (Barnett, 2008). This infection causes severe pain and restlessness in the patients especially in immunocompromised patients. The causative agent can cause oropharyngeal and esopharyngeal candidiasis (Sherman *et al*., 2002). It is more common in extreme ages. It also causes infection in AIDS and cancer patients. The change in salivary gland secretions or its dysfunction can cause oral candidiasis (Turner and Ship, 2007). The local factors which can cause this infection include dental prostheses, topical medication, smoking and unbalanced diet. The systemic factors which can increase the chances of this infection are nutritional deficiency especially of iron, use of systemic drug, malignancies, endocrine and immune disorders (Patil *et al*., 2015). There are different forms of this infection. In pseudomembranous candidiasis causes white yellow plaques and consist of fungal hyphae and necrotic material (Lalla *et al*., 2013). The other form is erythematous candidiasis but it is very rare (Ashman and Farah, 2005). Other form is hyperplastic candidiasis. Candida associated lesions include denture stomatitis which causes chronic inflammation (Lund *et al*., 2010). The other forms are angular cheilitis, median rhomboid glossitis, linear gingival erythema and secondary oral candidiasis also called as chronic mucocutaneous candidiasis. Diagnosis of this infection can be done by the symptoms and clinical signs. Identification can be done by examination of smear taken by lesions. Biopsy and serological tests can also be performed (Ellepola and Morrison, 2005). Oral candidiasis can be treated by using antifungal agents. Different medicines are used for example nystatin, miconazole, fluconazole and caspofungins etc. (Pappas *et al*., 2004). Proper cleaning of mouth and teeth can prevent oral candidiasis.

Aspergillosis

The causative agent of aspergillosis is *Aspergillus fumigates*. It is a saprophytic fungus, consists of vegetative mycelium present in soil and produce asexual spores (Tekaia and Latgé, 2005). Lung infection is caused

due to the inhalation of conidia of *A. fumigates* (Wéry, 2014). Aspergillus can cause invasive fungal infection mostly in immunocompromised patients (Perfect *et al*., 2001). In immunocompromised patients, chronic pulmonary aspergillosis occurs. The inflammatory and fibrotic reactions occur during this condition (Alastruey-Izquierdo *et al*., 2018). This can cause allergic broncho pulmonary aspergillosis (ABPA) in atopic patients (Agarwal *et al*., 2013). The symptoms include fever, cough, sputum production, malaise, pain in chest etc. It may also lead to chronic pulmonary secretions. Aspergillus can also cause invasive pulmonary aspergillosis (IPA). It is one of the most common invasive fungal infections. For its diagnosis Galactomannan (GM) antigen can be used. PCR amplification can also be used for its diagnosis but it is used in only few laboratories (White *et al*., 2015). Antifungal drugs are used for the treatment of Aspergillosis. They consist of three classes of antifungal agents including ergosterol, parts of fungal membrane and β1, 3glucan (Holt and Drew, 2011). Amphotericin B medicine is used for Aspergillosis treatment.

Blastomycosis

The causative agent of this infection is *Blastomyces dermatitidis*. This disease is most common in North America and some southern states of United States (Smith and Kauffman, 2010). It is also endemic in some Canadian provinces. *Blastomyces dermatitidis* cause subclinical infection. But it can also cause serious complications which can be fatal. The symptoms include fever, influenza, cough, pleurisy and may also cause myalgia arthralgia. This infection causes weight loss and fatigue which are the most common symptoms. In pulmonary blastomycosis patients have alveolar infiltrate. However, it is not advantageous for diagnostic purposes (Patel *et al*., 1999). Extrapulmonary blastomycosis also involves cutaneous infection in 40-80 % of cases. Osseous blastomycosis can also occur in some patients. As men are more affected due to this infection so when it affects genitourinary tract, they cause disease in prostate, testicle and also affect epididymis (Sarosi and Davies, 1979). Blastomycosis causes meningitis when it affects central nervous system. The most common method for its diagnosis is cultural method and yeast cells are identified for its diagnosis. Fluorescence microscopy technique and PCR can also be used for specie identification (Pounder *et al*., 2006). For its treatment antifungal therapy and Amphotericin B are used. Other medicines for example ketoconazole, voriconazole and fluconazole can also be used. Vaccine is not currently available for its prevention.

Candida auris infection

A new species of yeast, Candida auris was discovered in 2009 (Rhodes and Fisher, 2019; Satoh *et al*., 2009). It is also called fungemia or candidemia and isolated from discharge of ear canal of a patient in Japan. It is worldwide and is prevalent in more than 30 countries and 6 continents including Pakistan. It is a sporadic and nosocomial disease and outbreaks easily. It can persist easily on human host and inanimate surfaces and causes infection in patients of all ages. It causes blood stream infections, wound infections, and otitis as well as has been cultured from sites like respiratory tract and urine (Chowdhary *et al*., 2016). It is more prevalent in patients having infections with other candida species, immunocompromised, recent surgeries, recent antibiotics and those using central venous or urinary catheters and using antifungals. Biochemical tests are used for diagnosis. On Microscopic examinations its isolates are ovoid with no pseudo hyphae. Presently, the most consistent methods for its identification are MALDI-TOF MS both the Bruker and the MS-VITEK platforms (Kathuria *et al*., 2015). It might be hard to differentiate it from other species of Candida. Prevention can be carried out with hand hygiene, use of protective equipment in hospitals, patient's isolation and careful environmental cleaning (Jeffery *et al*., 2018; Sarma and Upadhyay, 2017).

Cryptococcosis

C. neoformans is a fungus which causes cryptococcosis. It is a facultative intracellular, opportunistic and encapsulated pathogen. It causes disease in immunocompromised and T-cell deficient patients (Kwon *et al*., 1992). It is worldwide and inhabits on debris and soil contaminated with chicken and pigeon's wastes and droppings. It enters into lungs, extra pulmonary tissues and brain. Most commonly it causes lungs, skin, prostate, central nervous system and eye infections. It causes cryptococcal meningoencephalitis and is fatal if untreated. Diagnosis can be carried out by direct microscopic examination, fluorescent microscopy, serology (enzyme immunoassays, EIAs) (Knight, 1992), blood culture, molecular identification (PCR, gel electrophoresis, blotting) (Ingram *et al*., 1993), radiology (Computed tomography (CT) and magnetic resonance (MR) scans. Treatment includes use of antifungal drugs like, flucytosine, Intraventricular miconazole (used rarely nowadays), standard doses of ketoconazole (Levitz *et al*., 1994), fluconazole (which target CSF to treat AIDs and cryptococcosis) and itraconazole. Combination therapy with AMB and flucytosine is widely used to treat cryptococcal meningitis (Bicanic *et al*., 2008). It is difficult to control the disease because it has sporadic nature but active immunization can be possible by developing a vaccine against it (Buchanan and Murphy, 1998).

Mucormycosis

Mucormycosis is an infection which is caused by a fungus called *Rhizopus oryzae* (Hibbett *et al*., 2007). It belongs to the order Mucorales. It is most prevalent in the United

States 500 cases per year (Ibrahim *et al*., 2009). There are six categories of mucormycosis based on site of infection namely rhino cerebral, pulmonary, cutaneous, gastrointestinal, disseminated, and miscellaneous. It is suggested that iron uptake is directly related to the pathogenesis of the disease (Ibrahim *et al*., 2012). Patients with neutropenia and dysfunctional phagocytes (due to hyperglycemia and acidosis) are at higher risk of developing the disease (Spellberg *et al*., 2005). Like cryptococcosis, mucormycosis pathogenesis is also related to elevated serum iron of patient. Rapid and early diagnosis is very important for the treatment of the disease. Currently there are no PCR based or serological tests available for rapid diagnosis (Mori *et al*., 2003). Treatment includes the rapid diagnosis, removal of the infected tissue with surgery to prevent it further invasion, use of antifungal drugs such as polyene class, including amphotericin B deoxycholate and its lipid derivatives, azoles such as itraconazole, voriconazole, posaconazole and ravuconazole, investigational triazoles, echinocandins such as caspofungin (Sun *et al*., 2002).

Talaromycosis

Talaromycosis is caused by an opportunistic fungus called *Talaromyces marneffei* which is thermally dimorphic specie (Cooper and Haycocks, 2000). It is an invasive mycosis which is endemic in South and Southeast Asia and also prevalent in mainland China and the subcontinent of India (Pruksaphon *et al*., 2020). It occurs in individuals with advanced human immunodeficiency virus (HIV) disease. The pathogenesis of the disease is nonspecific and skin lesions are very common in this infection. It may be like other dimorphic fungal infections e.g., histoplasmosis thus making its diagnosis very difficult and challenging (Widaty *et al*., 2020). It can be diagnosed by culture method which takes up to 14 days (Thu *et al*., 2021). Rapid diagnosis can be carried out with the detection of a specific *T. marneffei* antibody and antigen with the help of immunoblotting, immunodiffusion and indirect ELISA. It can initially be treated with amphotericin B deoxycholate with substantial side effects which is very costly and limitedly available. Itraconazole is another drug for treatment which is easily available and has fewer side effects than amphotericin (Le *et al*., 2017).

Mycetoma

Mycetoma is a tropical disease which is caused by certain fungi (eumycetoma) or bacteria (actinomycetoma) (Fahal *et al*., 2015). It is also reported in some temperate regions. It is a specific, chronic, progressive subcutaneous inflammatory and granulomatous disease (Bonifaz *et al*., 2014). Pathogenesis of mycetoma includes painless subcutaneous swelling, formation of sinus tract and the discharge that contain grains usually on foot. Diagnostic methods include radiology, ultrasonic imaging, fine needle aspiration cytology, culture for identification, histology of the stained sections of tissues and serodiagnosis. Treatment depends upon the causative agent and severity of the infection. Mycetoma is treated with antibiotics and chemotherapy. Combination of streptomycin sulphate and diaminodiphenylsulphone (dapsone) orco-trimoxazole is very effective (Mahgoub, 1994). Rifampicin, sulfadoxine-pyrimethamine (fansidar) and sulphonamides are also used in case of drug resistance. Eumycetoma is treated with ketoconazole and itraconazole.

Keratitis

Fungal keratitis is a rare but serious ocular infection, also known as keratomycosis. It is common among people who used to wear contact lens (Gower *et al*., 2010). Trauma, use of topical drugs, dry eye syndrome, bullous keratopathy, photorefractive keratectomy and Lasik are also associated with onset of the infection (Srinivasan, 2004). The fungal causative agents belong to genera including Fusarium, Aspergillus and Curvularia (Kredics *et al*., 2015). It is most prevalent in the United States, Asia, South India, China and South Florida. It causes ulcerative corneal infection which may result in reduced vision and blindness. Corneal epithelium and stroma get infected primarily which results in tissue necrosis of the area (Ansari and Galor, 2013). In case of severe infection, the endothelium and anterior chambers of the eye are affected (Tuli, 2011). It can be diagnosed with the help of smear, staining and culture of the fungus. PCR and confocal microscopy are used for rapid diagnosis. Treatment includes use of the polyenes such as natamycin and amphotericin B and use of the azole compounds such as triazole, clotrimazole, imidazoles, fluconazole, and voriconazole (Prajna *et al*., 2003). Surgical therapy such as penetrating and lamellar keratoplasty is also used for treatment (Xie *et al*., 2002).

CONCLUSION

From the above information we can conclude that fungal diseases are increasing very rapidly. The diagnosis of these infections is not very easy. In the near future these diseases might become more dangerous and life threatening to the mankind. Changes might come in the fungal pathogens due to the climate change which can make them even more pathogenic. So, we should improve the diagnostic techniques. Funding should be increased for the purpose of new treatment methods. Antifungal drugs with better results and fewer side effects should be produced. Awareness about the fungal pathogens and its harmful diseases related to human beings should be increased. The development of vaccines for different fungal diseases can play a vital role in the prevention and control of fungal infections.

Table 1: Diseases, causative agents and distribution in the world

Name of disease	Causative agents	Distribution	References
Fungal nail infection (onchomycosis)	Dermatophytes (Trichophyton, Epidermophyton, Microsporum, *T. rubrum*)	Europe, East Asia, North America	(Ghannoum and Isham, 2014)
Vulvovaginal candidiasis	*Candida albicans*	Worldwide	(Russo *et al*., 2019)
Tinea pedis	*Trichophyton rubrum*, *Epidermophyton floccosum* and *Trichophyton interdigitale*	Worldwide	(Weinstein and Berman, 2002)
Oral candida	*Candida albicans*	Worldwide	(Rhodes and Fisher, 2019)
Aspergillosis	*Aspergillus fumigates*	Worldwide	(Tekaia and Latgé, 2005)
Blastomycosis	Blastomyces	United States, Canada	(Smith and Kauffman, 2010)
Candida auris infection	*Candida albicans*	Worldwide	(Rhodes and Fisher, 2019)
Cryptococcosis	*Cryptococcus neoformans*	Worldwide	(Maziarz and Perfect, 2016)
Mucormycosis	Mucor sp, Rhizopus sp, Fusarium sp	Worldwide	(Ibrahim *et al*., 2009)
Talaromycosis	*Talaromyces marneffei*	South and Southeast Asia, China and the subcontinent of India	(Pruksaphon *et al*., 2020)
Mycetoma	Eumycetoma or by bacteria Actinomycetoma	tropical and sub-topical subcontinents	(Fahal *et al*., 2015)
Keratitis	Fusarium, Aspergillus and Curvularia.	United States, Asia, South India, China and South Florida	(Ansari and Galor, 2013)

In the nut shell we can say that by expanding time and money for the control and management of the fungal infections we can save the world from some of the major global issues which can occur in the future.

Declaration of interest

The authors report no declarations of interest.

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