

A REVIEW ON UNDERLYING CONDITIONS AND RISK DETERMINANTS OF INVASIVE AND OPPORTUNISTIC FUNGAL INFECTIONS

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ABSTRACT

Over time, fungal diseases have become a serious threat to human health worldwide, and thus predicting fungal diseases that may lead to pandemics in the future is very important if we are to have efficient preparedness and reaction plans. Fungi are eukaryotic organisms that are found everywhere in nature. Fungal infections are the diseases caused by fungus. The Fungal species are categorized based on the part of the body effected i.e. superficial, sub-cutaneous and systemic. The fungal organisms that infect humans such as *Cryptococcus*, *Coccidioidomycosis*, *Aspergillosis* etc. Patients who are suffering with diabetes, HIV/AIDS, cancer, organ transplant, and prolonged hospital stays, are among the immunocompromised are the more at risk for developing fungal infections. Obesity, environmental exposure, and the overuse of antibiotics or corticosteroids are the factors that contribute to people becoming more at risk of developing infections. The major fungal infections that are occurring in humans are Candidiasis, oral thrush, fungal nail infection, keratitis etc. The risk factors can be modifiable and some are non-modifiable. The modifiable risk factors include antibiotics, corticosteroids, long term hospital stays, diabetes, obesity and indoor environment exposure. The non-modifiable risk factors include cancer, AIDS, chronic lung disease, organ transplants, stem cell transplants, kidney failure, extensive burns and environmental changes.

KEYWORDS: Fungal infections, types, risk factors, modifiable and non modifiable risk factors.

INTRODUCTION

Fungi are eukaryotic organisms that are found everywhere in nature. Fungal infections are the diseases caused by fungus. The Fungal species are categorized based on the part of the body effected i.e. superficial, sub-cutaneous and systemic. In the early 1840s, the Hungarian microscopist based on parries David Grubby first reported that human disease could be caused by fungi. In 2003 approximately 14.8- 33% of people effected and 25- 73.7% of people were died due to SARS (severe acute respiratory syndrome) outbreak. Fungi are present everywhere in nature, but fungal infections are majorly caused due either inhaling, direct contact with skin or enter the body through the cut, wound, or injection on skin and immunocompromised patients like HIV and people with cancer treatment. Fungi that cause infections in people includes Yeast and Molds. *Candida* is one of the fungal species that lives inside the body without causing any problem to human but over production may leads to an infection.

Cryptococcus, *Coccidioidomycosis*, *Histoplasmosis*- Affect people who lives or visit certain parts of the world like Southern United States, Mexico, Arizona and California.

Aspergillosis, *Pneumocystis pneumonia*, *Candidiasis*, *Mucormycosis*, *Talar Mycosis*- Effect people who has less immunity.^[1]



Fungal Infections



A wide range of fungal infections occur in the other animals, and some can be transmitted from animal to people. World-wide, every year fungal infections affect more than one billion people. An estimated 1.6 million deaths were reported in 2017. The figure has been increasing with an estimated 1.7 million deaths in 2020. According to global action fund for fungal infections, every year there are over 10 million cases of fungal asthma, around 3 million cases of long-term aspergillosis of lungs, 1 million cases of blindness due to fungal keratitis, more than 200,000 cases of meningitis due to cryptococcus, 700,000 cases of invasive candidiasis, 5000,000 cases of pneumocystis of lungs, 250,000 cases of invasive aspergillosis and 100,000 cases of histoplasmosis. Fungal infections are caused by yeast, Molds and some fungi that can exist as both Molds and yeast. Fungal infections can be prevented by keeping skin clean and dry as well as maintaining good hygiene, it is important to wash after touching other people or animals.^[1]

There are few types of fungal infections are there in mycosis they are superficial, systemic and subcutaneous, cutaneous mycoses fungal infections. Mycoses refers to a group of disease caused by various species of fungi. Superficial and cutaneous mycoses are fungal infections that primarily effects the outermost layer of skin, hair, nails. They are usually caused by the dermatophytes, which are a specific group of fungi capable of colonizing these areas. Subcutaneous mycoses the dermis, subcutaneous tissues, muscles are all affected by the subcutaneous mycoses. It was generally caused by Chromoblastomycoses. These are long lasting infections that can be brought on by puncturing injuries to the skin, which lets the fungi penetrates. Systemic mycoses is caused by species of Deuteromycetes and Schizomycosis. Systemic mycoses are fungal infections that spreads throughout the body often affecting internal organs.^[5] Candidiasis is a type of fungal infection that is caused by the any Candida species. In some countries it is commonly called thrush when effects the mouth. Signs and symptoms include white patches on the tongue or other areas of the mouth and throat. In Candidiasis includes Vulvovaginal candidiasis and oral candida. Vulvovaginal Candidiasis is mucosal opportunistic infection caused by Candida Albicans. It is mostly effects women of reproductive ages. Approximately 75 % of women in their reproductive ages are affected due to this infection. The symptoms of this infection include itching, soreness, and abnormal vaginal discharge. Oral candida is also known as 'ORAL THRUSH' and the causative organism is Candida albicans. This infection causes severe pain and restlessness in patients especially in immunocompromised patients.^[6] The Aspergillosis is one of the fungal infections, the causative agent of aspergillosis is Aspergillus fumigates. Aspergillus can cause invasive fungal infection mostly in immunocompromised patients. The symptoms include fever, cough, sputum production, malaise, pain in chest.^[6] Fungal nail infection is the most common fungal

infection in the humans. This infection is also called as onychomycosis, the most common reason for the for this infection is dermatophytes. It is most common in immunocompromised people it was also cause diabetic foot syndrome. Fungal nail infection causes thickening of the nails. The skin around this infection becomes scaly.^[2,6] Cryptococcus also the type of fungal infection in that Cryptococcus Neoformans is the fungus which causes cryptococcus. It is facultative, intracellular and opportunistic, encapsulated pathogen. It primarily effects individuals with weakened immune system, such as those with AIDS or undergoing immunosuppressive therapy. It enters into lung, extra pulmonary tissues and brain. It Causes Lung, Skin, Prostate, CNS And Eye Infection.^[2,6] Histoplasmosis is the type of fungal infection and it is caused by the histoplasma capsulatum. It is dimorphic fungi found in soil contaminated with the large amount of bird or bat dropping. Histoplasma capsulatum microconidia penetrates the respiratory tract by inhalation and due to their small size, manage and reach the alveoli of the host, where at 37⁰c they become yeast. The disease has a special predilution for the reticuloendothelial system that mainly affects the spleen, liver, lymph nodes and bone marrow oral lesion appear nodular, ulcerative or vegetative on the vestibular mucosa, gums, tongue, lips.^[2,4,20] Pneumocystis jirovecii it is opportunist fungal pathogen that primarily effects immunocompromised individuals, particularly those with weakened immune system such as AIDS patients. It is transmitted through respiratory droplets and has potential for the human-human transmission.^[2] Keratitis is the fungal infection it is rare but serious ocular infection, also known as Keratomycotic. It is common among people who used to wear contact lens. Trauma, use of topical drugs, dry eye syndrome. It causes ulcerative corneal infection which may results in reduced vision and blindness. Sporotrichosis is an implantation mycosis caused by species of the sporothrix genus that usually effects the skin at the cutaneous and subcutaneous levels. Infection generally occurs by traumatic inoculation of soil, plants and organic matter.^[6]

Risk factors

The predisposing factors that are responsible for fungal infections include Diabetes, Obesity, AIDS/HIV, Bronchiectasis, Kidney transplantation, Corticosteroids, Long term hospital stays, Cancer, Antibiotics, Extensive burns and Environmental changes.

DIABETES

Fungal infections are more frequent in diabetic patients, due to increase in blood glucose levels in blood which favors the fungal growth. This alters the leucocyte function and immune responses are weakened. So, the immune system cannot fight against fungal infections. When a woman with diabetes is more risk to get fungal infections is due to the presence of yeast and high blood sugar inhibits the body's ability to fight against other bacteria and viruses. Angular stomatitis due to Candida is a classic complication in diabetic children caused due to increased concentrations of salivary glucose.^[7]

OBSESITY

Obesity initiates skin changes and conditions like inflammation based and hypertrophic which are often associated with increased growth of fungi. The adipose tissue actively participates in inflammation and immunity producing and realizing a variety of proinflammatory factors like Adiponectin, leptin, cytokines and chemokines. Prolonged, low-level immune stimulation initiates hypertrophy of adipose tissue that partly liberates the immune system as a result susceptible to fungal infection.^[8]

AIDS/HIV

Human immunodeficiency virus is a class of retro virus that mainly effects the body's immune system. HIV targets and destroys CD4 white blood cells which are essential in the prevention of infection or disease. The advanced form of HIV is referred to as AIDS and a CD4 cell count below 200 cells/mm³ is one of the indicators used in the diagnosis of AIDS. Since the CD4 cell count is less in the patients it weakens the immunity of that individual, it is due to the CD4 cells play a key role in immunity. So, HIV/AIDS patients are susceptible to Opportunistic fungal infections. Oral candidiasis or thrush is the primary sign of fungal infection in these patients. Common fungal species associated with oropharyngeal fungal infections in HIV/AIDS patients are *Candida albicans*, *C. Para psilosis*, *C. tropicalis*, *C. guilliermondii*, *C. krusei*, *C. glabrata*, *C. stellatodies* and *Talaromyces*.^[9]

BRONCHIECTASIS

Bronchiectasis is defined as chronic inflammatory bronchial disease with irreversible dilation of the bronchial lumen and it can occur for a number of reasons. since, the airways are widened and are constantly exposed to a environmental fungi. As, the size of spore is very small it gets easily deposited in airways and some reaches the alveolus. Due to the presence of deteriorated mucociliary clearance, thick mucus the fungal growth is increased and the fungus capacity to avoid the hosts immune mechanisms. The most commonly isolated fungal organisms in bronchiectasis patients are *Candida albicans* and *Aspergillus* species.^[10]

KIDNEY TRANSPLANTATION

During the process of transplantation, immunosuppressants are administered to patients to prevent graft rejection which increases the risk of opportunistic fungal infections. Increased risk of infections is observed in patients who require prolonged dialysis before transplantation or who have delayed graft function post-transplant, as dialysis led to bacterial and fungal colonization, which may result into fungal infections. The most common fungal pathogens in kidney transplant recipients include *Candida* species, *Aspergillus* species, *Pneumocystis jirovecii* and *Cryptococcus* species.^[11]

CORTICOSTEROIDS

Corticosteroids are a class of immunosuppressive drugs. As these drugs suppress immune system there is high chance of causing fungal infections. Pulmonary Aspergillosis is a fungal infection caused in pulmonary non-tuberculous mycobacterium patients due to the administration of corticosteroids. Topical steroids are regarded a major risk factor for the development of fungal keratitis. The most common fungal diseases are Aspergillosis, Candidiasis, Cryptococcal meningoencephalitis, fungal keratitis, fusariosis, mucormycosis, allergic fungal; rhinosinusitis.^[12]

LONG TERM HOSPITAL STAYS

In hospitals, fungal pathogens can enter the human body through cuts, wounds, burns, surgical sites and inhalation. *Candida* and *Aspergillus* coinfections are more commonly seen in ICU patients. During COVID-19 administration of steroids and other drugs are negatively impacted the patient's immune system to fight against fungi and then increased the risk for invasive fungal infections. In hospital patient's fungal pathogens such as *Aspergillus*, *Candida* and *Mucor* were commonly seen during COVID-19 pandemic. Due to extended use of gloves, gowns and changes in disinfection practices *C. auris* infection was seen in acute care hospitals.^[16]

CANCER

Many severe fungal infections develop in immunodeficient individuals with conditions such as HIV, solid organ transplantation and cancer. Cancer patients will be at greater risk for developing fungal infections and treatment strategies become more aggressive. Chemotherapy induced immune suppression is frequently associated with opportunistic fungal infections, often through drug-induced neutropenia and mucositis.^[15] The changes include immunosuppression (induced by drugs), imbalance in the oral flora (e.g., secondary to antibiotic therapy), decreased salivation (induced by drugs, disease or radiation therapy) and local tissue damage. Among general population cancer patients receiving chemotherapy or radiation therapy are more prone to all the predisposing factors and are therefore considered to be at higher risk for oral fungal infection. The most common forms of intra oral candidiasis reported in oncology patients are Pseudomembranous candidiasis (thrush), Chronic hyperplastic candidiasis, Erythematous candidiasis and Angular cheilitis.^[14]

ANTIBIOTICS

A Yeast infection is a type of vaginitis caused by vaginal candidiasis. A yeast infection occurs when there is no proper balance between bacteria and yeast in the vagina. A small amount of *Candida* fungus is usually present in the vagina and beneficial bacteria help keep this fungus under control. Antibiotics work by killing bacteria that cause infection, but they can also kill beneficial bacteria in other parts of the body, including the vagina. As there are no beneficial bacteria the *Candida* yeast can multiply, causing the symptoms of a yeast infection. Yeast

infections can occur at any age, but these infections are more commonly during reproductive years. The following 3 types of broad-spectrum antibiotics, in particular, may increase the risk of yeast infections, they are Tetracyclines, Quinolones, broad spectrum Penicillin's-Ampicillin and Amoxicillin.^[16]

EXTENSIVE BURNS

Burns are serious wounds that are majorly impacting the skin and subcutaneous issues. The primary risk of infection is due to destruction of the primary barrier, the skin. The main risk factor for systemic bacterial and fungal infections includes patients with deep burns, loss of the dermis.^[17] The risk factors for fungal infections in burns are age of the patient, increased in total burned size, body surface area (30-60%), full thickness burns, inhalation injury, prolonged hospital stay, late surgical excision, open dressing, artificial dermis, central venous catheters, antibiotics, steroid treatment, long term artificial ventilation, fungal wound colonization, hyperglycemic episodes and other immunosuppressive disorders.^[18] Invasive burn wound infections due to *Candida* species, *Aspergillus* species and other opportunistic fungi are important emerging causes of late onset morbidity and mortality in patients with major burns and severely weakens immune systems.^[19]

ENVIRONMENTAL CHANGES

Fungal disease are able to thrive and spread due to several factors that are interrelated such climate change, deforestation increased population density and urbanization as well as global travel and migration favorable condition for fungal growth and transmission in winter seasons there are more favorable conditions for the growth of fungi, when persons exposed to that environment causes fungal infection due to deforestation there is an increased contact between humans and wild life as a result increasing the risk of zoonotic fungal infection.^[2]

MODIFIABLE AND NON- MODIFIABLE RISK FACTORS

Modifiable

High dose of antibiotics- Judicious use of antibiotics.
Corticosteroids or anti-inflammatory drugs- Minimize long term or high dose use when possible.
Long term hospital stays- Better infection control, hygiene.
Diabetes- Good glycemic control and lowers risk.
Obesity- Life style modification, weight management.
Indoor environment exposure- Improved ventilation, hygiene.

Non- Modifiable

Cancer- Immunosuppression due to disease and chemotherapy is unavailable.
AIDS- Chronic condition that permanently affects immunity.

Chronic lung disease- Structural lung damage predispose to fungal colonization.

Organ transplants- Require lifelong immunosuppressive therapy.

Stem cell transplants- High risk due to immunosuppressive and graft related complications

Kidney failure- Reduced immunity and frequent hospital exposure increase risk.

Extensive burns- Natural skin barrier is lost, cannot be prevented once burns.

CONCLUSION

Fungal infections are still among major health issues that have been neglected to a large extent all over the world i.e. the frequency of infections has been rising because of the number of immunocompromised patients. The risks factors such as diabetes, obesity, HIV/AIDS, cancer therapy and long hospital stays are majorly responsible for fungal infections due to weakened immune system. In such cases we have to improve immunity and carefully monitor the disease condition. In diabetic condition by lowering the blood glucose levels we can decrease the risk for fungal infections. The risk for fungal infections can be minimized by keeping the environment and body free from moisture and maintain hygiene. In case of antibiotics, we can prevent the incidence of fungal infections by appropriate use of antibiotic medications. In kidney failure, stem cell transplants and chronic lung disease we can't cease the usage of immunosuppressants. So, the risk can be minimized by using anti-fungal drugs. Fungal infections are may be caused due to changes in the environment. In previous days it is modifiable and now-a-days it is non-modifiable because such due to deforestation there is more contact between fungi and humans and animals. As, a result risk for fungal infections are increased. Rising the level of awareness, diagnostic ability and preventive measures are the main steps towards reducing the rate of infections, depth and fungal diseases worldwide.

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