

REVIEW ARTICLE

FUNGAL INFECTION: A RECENT CONCERN FOR PHYSICIAN

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Abstract:

Fungal diseases are an important determinant of survival in immunocompromised patients and in patients with chronic illnesses. Fungal infections in Bangladesh are diverse, and many studies have documented their frequency. A better understanding of the epidemiology, clinical features, and diagnostic method of fungal infection is integral to improving outcomes. In this review, we discuss the emergence of fungal infection along with the clinical pictures, diagnosis, and treatment of different fungal infections that are prevalent in our country. It is hoped that this article will create greater awareness of the burden of fungal infections on public health and promote effective diagnosis and therapy.

Keywords: Fungal infection, Deep mycoses, Aspergilloma, Mucor mycosis, Blastomycosis, Histoplasmosis, Candidaemia, Superficial fungal infection, Systemic fungal infection

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Introduction:

Worldwide, communicable diseases remain one of the leading causes of death. Infectious diseases throughout history have plagued humankind, and the ongoing COVID-19 pandemic is a reminder that this susceptibility persists even in our modern time. Some of these “microbial threats” unfortunately have been underestimated and neglected by healthcare authorities, although they endanger millions of lives worldwide. Fungal infections (FIs) represent an example of neglected emerging diseases, accounting for approximately 1.7 million deaths annually¹.

Nearly one-quarter of the world’s population is estimated to have superficial skin, hair, and nail fungal infections caused primarily by dermatophyte fungi. Oral and genital mucosal fungal infections are also exceedingly common, with 75% of women experiencing at least one vulvovaginal fungal infection caused by *Candida* species during their lifetime². *Aspergillus* species are responsible for 3 million cases

of chronic lung disease and are a substantial cause of fungal-associated asthma, affecting 10 million people. While significantly less common, invasive fungal diseases caused by *Cryptococcus*, *Candida*, *Aspergillus*, and *Pneumocystis* species are associated with exceedingly high mortality rates, ranging from 30% to 90%, depending on the fungal pathogen and patient group³. Thus, FIs are increasing with time and becoming a global health problem associated with high morbidity and mortality rates and devastating socioeconomic consequences.

Methods:

We systematically searched to identify published English literature on fungal infections at the national and international level using the search engine Google, PubMed, MEDLINE, MSD Manual, Med Facts, Bangladesh Journals Online (BanglaJOL), and different sets of keywords, viz. Bangladesh, mycoses, superficial mycoses, deep mycoses, histoplasmosis,

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candida infection, aspergillosis, mucormycosis etc. in the search engines. This article aims to review the epidemiological features, clinical presentation, investigation modalities, management scopes, and prognosis of fungal infections to provide the physician with updated information on this adversary to humanity.

Emerging Problem:

The number of fungal cases continues to constantly rise and many new and emerging fungal pathogens are being identified, poised to significantly threaten human health. Several factors contribute to the escalating emergence of human fungal pathogens in the modern era. Fungi are commonly opportunistic pathogens: exploiting susceptibilities presented by a host with a compromised immune system, an altered microbiome, or breached physical barriers, to cause infection. Specifically, the growing prevalence of fungal infections is directly associated with ever-increasing rates of (1) medical vulnerabilities, including immunosuppression due to HIV/AIDS, hematologic cancers and cancer chemotherapeutics, the use of immuno-suppressive agents for organ and bone marrow transplantation, and an aging population; (2) pervasive dysbiosis of the human micro-biome associated with exposure to broad-spectrum antimicrobials; and (3) breached barriers linked to the frequent use of modern medical devices such as ventilators, stents, and catheters⁴. Aside from medical factors, environmental fluctuations such as global climate change are contributing to geographic spread of many fungal crop pathogens and may be associated with the emergence of pathogenic fungal species. Conventional many anti-fungal are found to be resistant to these emerging potentially fatal fungal strains. Early recognition and minimize the major factors associated with the fungal infection is very important to combat the issue.

Bangladesh Perspective:

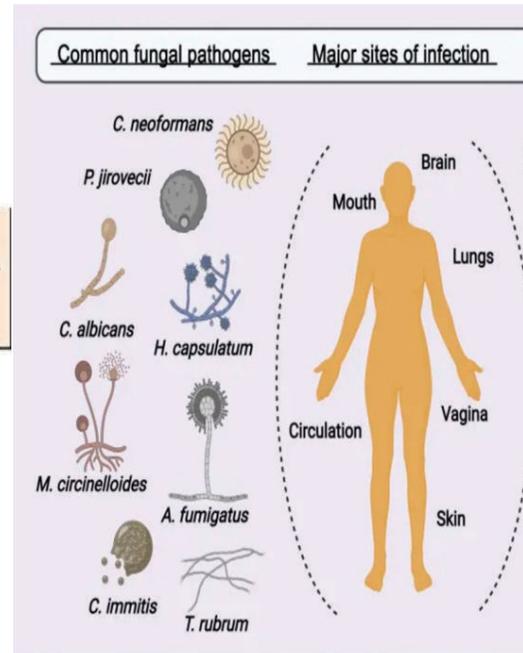
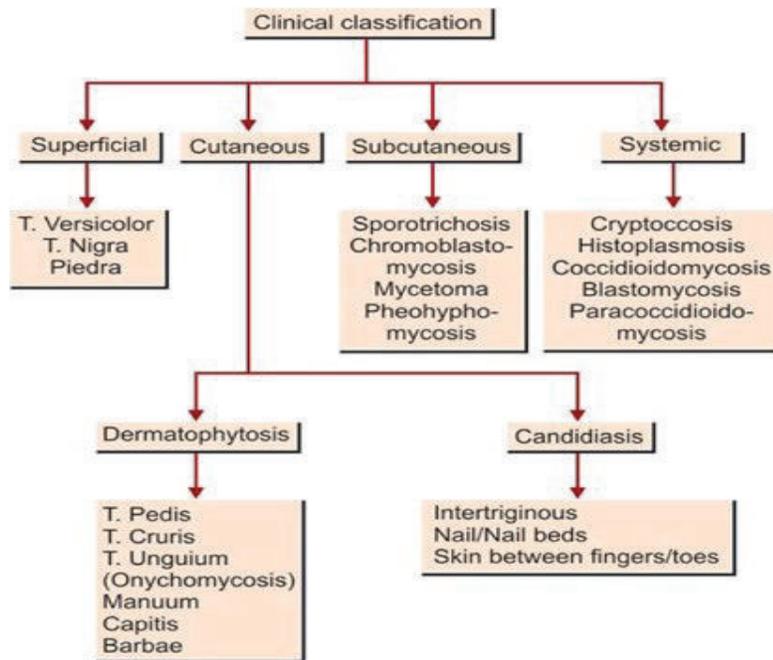
Deep fungal infection is now a recognized emerging threat to Bangladesh. With the increasing number of patients with tuberculosis, organ transplant, HIV, COVID-19 Pandemic, and other chronic conditions and the widespread use of immunosuppressive medications in Bangladesh, a large population is now at risk of deep fungal infections. Most of the disseminated infections have similar clinical features of chronic inflammatory process and malignancy, so a high index of suspicion is required to diagnose the cases.

Many case reports of fungal infections from Bangladesh published in local and international

journals bear testimony to this emerging problem. Back in 1962 and after 1971, N. Islam et al. conducted two surveys of Histoplasmosis and they confirmed Histoplasmosis was highly prevalent in Bangladesh⁵. Ahasan HN et al. showed several case reports of deep fungal infection, including Histoplasmosis, pulmonary blastomycoses, mucormycosis, and pulmonary aspergilloma from Dhaka Medical College, Bangabandhu Sheikh Mujib Medical University (BSMMU), and Rajshahi Medical College. They concluded that deep fungal infections are an emerging problem in our country⁶. A recently published article "Burden of serious fungal infections in Bangladesh" showed prevalence of 30,178 people with chronic pulmonary aspergillosis, 80% attributable to TB and an anticipated 90,262 and 119,146 patients have allergic bronchopulmonary aspergillosis or severe asthma with fungal sensitization. Candida bloodstream infection was estimated based on a 5 per 100,000 rates (8100 cases). Superficial mycoses were found very common with *Trichophyton rubrum* as the predominant etiological agent (80.6%)⁷.

Classification of Fungal infection:

Fungal infections are classified into three categories according to the site of infection, type of virulence, and route of acquisition. According to the site of infection, they are further classified as superficial, cutaneous, subcutaneous, and deep. When mycoses are limited to the stratum corneum only and elicit no inflammation, they are considered as 'Superficial mycoses.' Cutaneous infections involve integuments and the appendages, including hair and nails. Subcutaneous mycoses involve infection of the subcutaneous tissues usually at the point of traumatic inoculation. Deep mycoses involve the internal organs including the lungs, central nervous system, abdominal viscera, bones. The most common portals of entry of fungal infections are the respiratory tract, gastrointestinal tract, and blood vessels. According to the acquisition route, mycoses are designated as exogenous or endogenous. Exogenous infections may be transmitted by airborne, cutaneous, or percutaneous routes. Colonization or reactivation of a fungus from a latent infection results in an endogenously-acquired fungal infection. Fungi may also be classified according to virulence as primary or opportunistic pathogens. A primary pathogen may establish infection in an immunologically normal host; whereas an opportunistic pathogen requires some compromise of host defenses for infection to become established⁸.



times a day for 3 days, then once a day for 6 to 12 weeks. Severe pneumonia requires more aggressive therapy with amphotericin B. For chronic cavitary histoplasmosis, itraconazole 200 mg orally is given 3 times a day for 3 days, then once a day or 2 times a day for 12 to 24 months. For severe disseminated histoplasmosis, liposomal amphotericin B 3 mg/kg IV, once a day (preferred) or amphotericin B 0.5 to 1.0 mg/kg IV once a day for 2 weeks or until the patient is clinically stable is the treatment of choice. Patients can then be switched to itraconazole 200 mg orally 3 times a day for 3 days, then 2 times a day for 12 months after they become afebrile and require no ventilatory or blood pressure support. For mild disseminated disease, itraconazole 200 mg orally 3 times a day for 3 days, then 2 times a day for 12 months can be used.

Mucor Mycosis:

Mucor Mycosis (sometimes called zygomycosis) is an angioinvasive, severe but rare fungal infection caused by a group of molds called mucormycetes. It usually affects patients with altered immunity. The first ever case of rhinocerebralmucormycosis in Bangladesh was reported by Rafiqueuddin AM et al. in 1994 ¹¹.

These fungi are ubiquitous worldwide in soil, manure, and decaying organic matter. Types of Mucor Mycosis are Rhinocerebralmucormycosis, Pulmonary mucormycosis, Gastrointestinal mucormycosis, Cutaneous mucormycosis, and Disseminated mucormycosis. The most common presentation is skin induration with surrounding erythema rapidly

progressing to necrosis. The diagnosis of mucor mycosis relies upon identifying the organisms in tissue by histopathology with culture confirmation.

Treatment of mucor mycosis involves a combination of Surgical debridement of involved tissues, antifungal therapy, and elimination of predisposing factors for infection. Intravenous (IV) amphotericin B (lipid formulation) is the drug of choice for initial therapy. Posaconazole or isavuconazole is used as step-down therapy for patients who have responded to amphotericin B.

Blastomycosis:

Blastomycosis is a pulmonary disease caused by dimorphic fungus Blastomyces dermatitidis resulting from inhaling spores. The first case of pulmonary blastomycosis in Bangladesh was reported by Ahasan HN et al. back in 1995 in a chain smoker patient who presented with approximately 3 months' history of a dry cough and fever ¹².

Occasionally, the fungi spread hematogenously, causing extrapulmonary disease. Patients with blastomycosis may present as an asymptomatic, flu-like illness and nonproductive cough. Chronic illness may occur and simulate tuberculosis or lung cancer, with symptoms of low-grade fever, a productive cough, night sweats, and weight loss. Extrapulmonary features may include gray verrucous lesions with heaped borders, ulcers in the skin, bony lytic lesions, osteomyelitis, prostatitis, orchitis, and epididymitis.

If blastomycosis is suspected, a chest x-ray should be taken. Focal or diffuse infiltrates may be present. A urine antigen test is useful, but cross-reactivity with *Histoplasma* is high. Molecular diagnostic tests (e.g., polymerase chain reaction) are approved for *Blastomyces*. Amphotericin B and itraconazole continue to be the main drugs used in blastomycosis. Itraconazole is the drug of choice in mild-to-moderate pulmonary blastomycosis.

Aspergilloma Syndromes:

Aspergillosis is an opportunistic infection and is caused by inhaling spores commonly present in the environment. The spores germinate into hyphae, which enter blood vessels and, with invasive disease, cause hemorrhagic necrosis and infarction.

Four main syndromes:

1. Allergic bronchopulmonary aspergillosis (ABPA)
2. Chronic necrotizing *Aspergillus* pneumonia (also termed chronic necrotizing pulmonary aspergillosis [CNPA])
3. Aspergilloma
4. Invasive aspergillosis-
 - Acute invasive pulmonary aspergillosis
 - Chronic invasive pulmonary aspergillosis
 - Invasive aspergillus sinusitis
 - Cerebral aspergillosis
 - Other- endocarditis (BCs usually negative, and valve replacement is necessary to achieve cure), pericardial, intestinal, oesophageal, renal, vascular graft, and bone.

Diagnosis is primarily clinical but may be aided by imaging, histopathology, specimen staining, culture and Galactomannan antigen test on serum and bronchoalveolar lavage fluid.

Treatment of ABPA includes oral corticosteroids (inhaled steroids are not effective), and adding oral itraconazole to steroids in patients with recurrent or chronic ABPA may be helpful. Sinusitis is treated with Itraconazole 200g twice daily for months, along with surgical debridement. Aspergilloma is treated when patients become symptomatic, usually with hemoptysis. Oral itraconazole may provide partial or complete resolution of aspergillomas in 60% of patients and intracavitary treatment, using CT-guided, percutaneously placed catheters to instill amphotericin alone or in combination. Surgical resection is curative and may be considered for massive hemoptysis if there is adequate pulmonary function.

Systemic Candidiasis:

Candidiasis is an infection by *Candida* species (most often *C. albicans*), manifested by mucocutaneous lesions, fungemia, and sometimes focal infection of multiple sites and the bloodstream infection is a life-threatening one with high morbidity and mortality. Risk factors include neutropenic patients (e.g. complicating cancer chemotherapy), prolonged hospitalization, and bloodstream infection related to central venous catheters, major surgery, broad-spectrum antibacterial therapy, IV hyperalimentation, or IV line.

Symptoms depend on the site of infection and include skin and mucosal lesions, vaginal symptoms (itching, burning, discharge), dysphagia, blindness, fever, shock, disseminated intravascular coagulation, and oliguria. Diagnosis is confirmed by histopathology and cultures from normally sterile sites. Other investigation modalities include blood cultures, serum beta-glucan testing, Mannan antigen, and antimannan immunoenzymatic tests.

Delaying antifungal treatment in systematic candidiasis significantly increases mortality; even a 12–24 h delay can result in a two-fold increase in crude mortality rate. In patients with invasive candidiasis, predisposing conditions should be reversed or controlled. Less critically ill patients who have never been exposed to azole; intravenous fluconazole 800mg loading then fluconazole 400mg daily should be given. In the case of moderate to severe critically ill patients with recent azole exposure, one of the following drugs can be used: Caspofungin – 70mg i/v loading then 50 mg i/v daily, Micafungin - 100mg i/v daily or Anidulafungin -200mg i/v loading then 100 mg daily. The duration of treatment is the parenteral drug for 14 days from the last positive blood culture and resolution of symptoms and signs of infection. Then, once a patient has become clinically stable oral fluconazole 200–400mg daily. Chronic disseminated Candidiasis is treated with prolonged several months of oral fluconazole and adjuvant steroid treatment. Candidal endocarditis requires combined medical and surgical therapy and medical therapy includes liposomal amphotericin B 3–5mg/kg/day or deoxycholate amphotericin 0.6–1mg/kg/day.

CNS Cryptococcosis:

Cryptococcosis is a pulmonary or disseminated infection which is acquired by inhalation of soil contaminated with the encapsulated yeasts *Cryptococcus neoformans* or *C. gattii*. The most common manifestations are subacute or chronic meningitis and meningoencephalitis. This infection

is invariably fatal without appropriate therapy; death may occur from 2 weeks to several years after symptom onset. The most common features are headache, altered mental status, including personality changes, confusion, lethargy, obtundation, and coma. After lung and CNS infection, the most commonly involved organs in disseminated cryptococcosis include the skin, prostate, and the medullary cavity of bones. Risk factors for cryptococcosis include AIDS, Hodgkin lymphoma, other lymphomas, Sarcoidosis, long-term corticosteroid therapy, and solid organ transplantation.

Clinical diagnosis of cryptococcosis is suggested by symptoms of an indolent infection in immunocompetent patients and a more severe, progressive infection in immunocompromised patients. Chest x-ray, urine collection, and lumbar puncture are done first. The culture of *C. neoformans* is definitive. Apart from the Culture of cerebrospinal fluid (CSF), sputum, urine, and blood, the followings also help in diagnosis; fixed-tissue specimen staining and CSF testing for cryptococcal antigen.

For cryptococcal meningitis, Liposomal amphotericin B 0.7-1mg/kg/d for 14 days with or without flucytosine, followed by additional 8 weeks of fluconazole 400mg/day is indicated. For nonmeningeal cryptococcosis, fluconazole is usually adequate.

Systemic fungal infections:

Systemic fungal disease is associated with increased morbidity and mortality, and timely recognition and treatment of invasive fungal diseases are essential to decrease mortality. The clinical manifestations of systemic fungal infection are not specific, and like other infective diseases, a high degree of suspicion is required for the early diagnosis and optimal management of these infections.

If any patient has the following risk factors or clinical features, the physician should have high clinical suspicion for fungal infection; prolonged fever, severe neutropenia, immunosuppression; fever resistant to broad-spectrum antibiotics in a neutropenic patient; symptoms & signs of new resistant or progressive lower RTI; prolonged severe lymphocytopenia in chronic GVHD & immunosuppression; palatal ulcer or perforation; features of focal neurologic deficit or meningeal irritation with fever; unexplained mental changes with fever, papular or nodular skin lesions; generalized pigmentation. Diagnostic criteria for definitive systemic fungal infection single fungus positive blood culture and fungus can be cultured from a biopsy specimen, peritoneal or CSF fluid, or burn wound.

Superficial Fungal Infection:

Cutaneous fungal infections involve the skin, hair, and nails resulting from dermatophytes infection, but *Candida* species can also cause them. The prevalent dermatophytic infections include tinea pedis (foot), tinea corporis (body), tinea cruris (groin), tinea capitis (scalp), and tinea unguium (nail). *Microsporum*, *Epidermophyton*, and *Trichophyton* are three dermatophyte genera that cause infections.

The most common transmission mode is by direct contact with other people, but transmission also occurs through contact with animals, soil, and fomites. The following risk factors increase susceptibility to fungal skin infections; e.g., obesity, immunodeficiency or immunosuppression, impaired circulation, prolonged exposure to sweaty clothes or bedding, poor hygiene, and residence in warm, humid climates ¹².

Treatment of Systemic fungal infection:

Indication	Primary Therapy	Secondary Therapy
Disseminated candidiasis	Fluconazole or Voriconazole	Amphotericin B, Caspofungin
Invasive Aspergillosis	Voriconazole	Itraconazole, Amphotericin B, Caspofungin, Poscanazole
CNS aspergillosis	Voncanazoie	Ampnoiencin B
Cryptococcal meningitis	Liposomal Amphotericin B + Flucytosin	Fluconazole
Mucor mycosis Persistent neutropenic patient not responding to antibiotics	Amphotericin B, Caspofungin	Poscanazole, Amphotericin B

The classic appearance of a tinea infection is a central clearing surrounded by an active border of redness and scaling with no mucosal involvement. Proper identification and treatment of fungal skin infections remain a growing health concern. Tinea pedis, tinea corporis, and tinea cruris are typically treated topically unless the infection is extensive, severe, or recalcitrant. Tinea unguium responds best to oral therapy, and tinea capitis must be treated with oral antifungal therapy since topical agents cannot penetrate the hair shaft. Treatment may last several weeks to months, making patient adherence an essential factor in therapy selection.

Conclusion:

The epidemiology of invasive fungal infections is currently at a crucial stage. From being uncommon during the earlier part of the 20th century when the world was plagued with bacterial epidemics, fungi have evolved as a significant global health problem. In Bangladesh, most cases are underdiagnosed and underreported due to a lack of orientation and similar clinical findings caused by tuberculosis, chronic inflammatory diseases, and many malignant diseases. The morbidity and mortality from deep fungal infections can be reduced effectively if these are detected and treated early. All trends suggest that the burden of fungal diseases will increase in the 21st century, and enhanced human preparedness for this scourge will require more research investment in this group of infectious diseases.

Conflict of Interest:

The author stated that there is no conflict of interest in this study

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