Journal of Bangladesh College of Physicians and Surgeons
Vol. 41, No. 2, April 2023

Common Invasive Fungal Infection in Bangladesh and Available Management

HAMN AHASAN[a], N NOOR[b]

Abstract

Invasive fungal diseases are an important cause of mortality in immunocompromised patients and in patients with chronic illnesses. Multiple studies in Bangladesh have documented the frequency of fungal infections in our country and results varied. However, better understanding of the invasive fungal infection includes learning about the epidemiology, clinical features, and diagnostic method which is integral part of improving outcomes. In this review, we discuss the common invasive fungal infection that are prevalent in our country along with the clinical pictures, diagnosis, and treatment. It is hoped that this article will highlight the burden of fungal infections on public health and promote effective diagnosis and therapy.

Key words: Fungal infection, Deep mycoses, Aspergilloma, Mucor mycosis, Blastomycosis, Histoplasmosis, candidaemia, Systemic fungal infection

(J Bangladesh Coll Phys Surg 2023; 41: 164-169)
DOI: https://doi.org/10.3329/jbcps.v41i2.65105

Introduction:

Historically communicable diseases remain one of the leading causes of death worldwide. Unfortunately, some of these "microbial threats" have been underestimated and neglected, although they endanger millions of lives worldwide. The epidemiology of deep fungal infections is currently at a critical stage. However, Mortality rates attributable to invasive mycoses are increasing. Fungal infections (FIs) represent an example of neglected emerging diseases. Recent estimates indicate that more than 300 million people are affected by severe fungal diseases worldwide, accounting for approximately 1.7 million deaths annually[1].

Fungal pathogens are a widely diverse group of highly infectious agents, including yeast or yeast-like species (e.g., Candida, Cryptococcus species) and molds (e.g., Aspergillus species). Moulds and yeasts are widely distributed in the environment, and of the 100,000 fungal species present, only 300 have been linked to diseases in humans and animals. Human mycoses are caused by true or opportunistic fungal pathogens. These widely diverse group of pathogens are responsible for a range of diseases with variable prevalence and clinical outcomes. Aspergillus species cause 3 million cases of chronic lung disease. This species also causes substantial cause of fungal-associated asthma in approximately 10 million people. Invasive fungal diseases caused by Cryptococcus, Candida, Aspergillus, and Pneumocystis species are associated with high mortality rates, ranging from 30%- 90%, depending on the fungal pathogen and patient group[2]. These species are currently the most common cause of fungal diseases. Nevertheless, new and emerging fungal pathogens are being identified that are considered a significant threat to human health. Thus, FIs are increasing day by day and becoming a global health problem associated with high morbidity and mortality rates leading to devastating socioeconomic and health consequences.

Method:

The epidemiology of invasive fungal infections has been difficult to glean from the literature because of the different definitions used, the different risk groups studied, and variation from institution to institution. 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, deep mycoses, histoplasmosis, candida infection, aspergillosis, mucormycosis etc. in the search engines from 2000-2023. This article aims to review the epidemiological features, clinical presentation,

a. Prof. H.A.M. Nazmul Ahasan, Professor of Medicine, Popular Medical College, Dhaka, Bangladesh.

b. Dr. Nawsabah Noor, Registrar, Department of Medicine, Popular Medical College, Dhaka, Bangladesh.

Address of Correspondence: Professor HAM Nazmul Ahasan, Professor of Medicine, Popular Medical College and Hospital, Dhaka. Email: ahasanhamn@yahoo.com.

Received: 11 January, 2023 **Accepted:** 04 February 2023

investigation modalities, management scopes, and prognosis of fungal infections to provide the physician with updated information on this adversary to humanity.

Bangladesh Perspective:

Invasive fungal infection is now a recognized emerging threat to Bangladesh. Over the past 20 years, the number of invasive fungal infections has continued to persist, due primarily to the increased numbers of patients subjected to severe immunosuppression e.g. 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 Bangladesh [3]. 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 Shiekh Mujib Medical University (BSMMU), and Rajshahi Medical College. They concluded that deep fungal infections are an emerging problem in our country [4]. A recently published article, "Burden of serious fungal infections in Bangladesh," showed the 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 5 per 100,000 rates (8100 cases) [5].

Discussion on Deep or Systemic Fungal Infection:

Histoplasmosis

In 1905, Samuel Taylor Darling, a North American pathologist first described histoplasmosis but thought it was due to a protozoan. Histoplasmosis is also known as Darling disease and is a systemic endemic mycosis caused by the thermally dimorphic fungus: *Histoplasma capsulatum*. *Histoplasma capsulatum* is normally found in soil as a mould and has been often recovered from soil contaminated with bat or bird droppings, especially those found under bat caves or bird roosts. Infection occurs through the direct inhalation of microconidia (spores) from the environment which passes through the bronchioles and end up in the alveoli, giving rise to a primary pulmonary infection. It is the most frequently diagnosed systemic mycoses, and globally it affects over 10,000 people [6].

The spectrum of the clinical manifestation is diverse, ranging from an asymptomatic or minimally symptomatic acute pulmonary disease to chronic pulmonary disease in patients with underlying structural lung disease to acute progressive disseminated disease in patients with severe immunodeficiency. Immunocompromised patients are at risk of invasive, disseminated disease. It is a neglected disease with worryingly under-diagnosed and often misdiagnosed as cancer or tuberculosis with fatal consequences.

Rahim MA et al., in a retrospective data analysis of histoplasmosis in/or from Bangladesh from 1962-2017, showed the most common manifestations are chills, fever, malaise, sore throat, oral ulcer, loose motion, abdominal pain, cough, hemoptysis, anorexia, and weight loss and during physical examination hepatomegaly, splenomegaly, lymphadenopathy, anemia, abdominal mass, oral ulcer, ascites, creps, spastic paraparesis erythema nodosum, erythema multiforme, cavitary lesion in lungs, organomegaly was found [7]. If the symptoms last less than 1 month indicate acute disease, symptoms 1-3 months indicate subacute disease and symptoms above 3 months indicate chronic disease.

Lab investigations may show thrombocytopenia in disseminated disease; serology may be helpful in testing immunocompetent individuals with the acute or subacute disease. Antigen testing is useful in immunosuppressed infiltrative or chronic disease; urine antigen has around 60%, serum antigen has ~60%, and both combined have above 80% sensitivity. Tissue biopsy or bronchoalveolar lavage may be necessary to obtain histology specimens. Microscopic histopathology can strongly suggest the diagnosis; intracellular yeasts may be seen in Wright- or Giemsa-stained specimens.

Mild cases of histoplasmosis that are limited to the lungs will resolve without specific treatment in about a month.

If there is no spontaneous improvement after 1 month, itraconazole 200 mg orally is given 3 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:

Mucormycosis (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 rhinocerebral mucormycosis in Bangladesh was reported by Rafiqueddin AM et al. in 1994 [8].

These fungi are ubiquitous worldwide in soil, manure, and decaying organic matter such as bread, compost bins, and animal excreta. Infection is typically by inhalation of spores, though ingestion or via the cutaneous route (e.g., trauma or burns) is also recognized. Most had an underlying disease including diabetes, malignancy, solid organ transplantation, deferoxamine therapy, renal failure, HIV infection.

Types of Mucor Mycosis are Rhinocerebral mucormycosis, 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. Diagnostic limitations remain (i.e, culture and histology) and recognized fungal biomarkers such as â-D-glucan and galactomannan remain negative in infections caused by these organisms. However, the epidemiology of these infections is increasingly better understood with the introduction of molecular methods for diagnosis (e.g., 18S rRNA PCR) and genomic sequencing studies.

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 caused by dimorphic fungus Blastomyces dermatitidis resulting from inhaling spores. The first case of pulmonary blastomycosis in Bangladesh was reported by Ahasan HAMN et al. back in 1995 in a chain smoker patient who presented with approximately 3 months' history of a dry cough and fever [9]. *B. dermatitidis* is the asexual form of this holomorphic fungus and the sexual phase is termed *Ajellomyces dermatitidis*. It occurs in the mycelial form at 30 °C and as a yeast at 37 °C (tissue phase). This transition is also affected by nutrients.

Blastomycosis occurs mainly in two clinical forms: pulmonary and extra-pulmonary. 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.

Invasive aspergillosis is a major cause of invasive fungal disease which tends to affect the immunocompromised. The majority of Aspergillus isolates causing invasive aspergillosis is often attributed to *Aspergillus fumigatus*. The increase in the incidence of invasive fungal infection is largely attributed to the prolonged neutropenia in hematological regimes due to the intensification of cytotoxic chemotherapy, the use of corticosteroids, the increased use of allogeneic hematopoietic stem cell transplantation, the increased incidence of graft-versus-host disease (GvHD) and the widespread use of immunosuppressive agents. Mortality of invasive aspergillosis in non-neutropenic patients has been estimated to be approximately 63–72%, primarily due to delays in recognition and diagnosis. Poor prognostic factors associated with invasive aspergillosis include age, corticosteroids prior to ICU admission, mechanical ventilation, septic shock, and hemodialysis.

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 bloostream 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/k/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

Treatment of Systemic fungal infection:

INDICATION	PRIMARY THERAPY	SECONDARY THERAPY
Disseminated candidiasis	Flucanazole or Voricanazole	Amphotericin B, Capsofungin
Invasive Aspergillosis	Voricanazole	Itraconazole, Amphotericin B, Capsofungin, Poscanazole
CNS Apergillosis	Voricanazole	Amphotericin B
Cryptococcal meningitis	Liposomal Amphotericin B + Flucytosin	Flucanazole
Mucor mycosis Persistent neutropenic patient not responding to antibiotics	Amphotericin B, Capsofungin	Poscanizole, Amphotericin B

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.

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.

Reference:

1. Bongomin F, Gago S, Oladele RO, Denning DW. Global and multi-national prevalence of fungal diseases—estimate precision. Journal of fungi. 2017 Oct 18;3(4):57.
2. Kainz K, Bauer MA, Madeo F, Carmona-Gutierrez D. Fungal infections in humans: the silent crisis. Microbial Cell. 2020 Jun 6;7(6):143.
3. Islam N, Chowdhury NA. Histoplasmosis from Bangladesh: a case report. Bangladesh Medical Research Council bulletin. 1982 Jun;8(1):21-4.
4. Parvin R, Amin R, Mahbub MS, Hasnain M, Alam MB, Ahasan HN et al. Deep fungal infection-an emerging problem in Bangladesh. Journal of Medicine. 2010;11(2):170-5.
5. Gugnani HC, Denning DW, Rahim R, Sadat A, Belal M, Mahbub MS. Burden of serious fungal infections in Bangladesh. European Journal of Clinical Microbiology & Infectious Diseases. 2017 Jun;36(6):993-7.
6. Bongomin F, Kwizera R, Baluku JB, Asio LG, Otu AA. Treatment of Histoplasmosis. InHistoplasma and Histoplasmosis 2020 Jun 25 (p. 69). IntechOpen.
7. Rahim MA, Zaman S, Amin MR, Uddin KN, Chowdhury J. Histoplasmosis: An emerging or neglected disease in Bangladesh? A systematic review. Oman Medical Journal. 2020 Jan;35(1):e91.
8. RAFIQUEUDDIN AM, NAZMUL AHASAN HAM, JALIL CHOWDHURY MA, Quashem A, Kundu NC. Mucormycosis (zygomycosis). Tropical doctor. 1994;24(1).
9. NAZMUL AHASAN HAM, MASHIUR RAHMAN K, JALIL CHOWDHURY MA, AZHAR M, RAFIQUEUDDIN AM. Pulmonary blastomycosis. Tropical doctor. 1995;25(2):83-4.