The rising threat of Invasive fungal infections

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Fungi are ubiquitous. Fungal Infections have been known for decades. Superficial fungal infections are common in tropical countries. Over the last two decades, there has been a constant increase in the burden of fungal infections worldwide and in India. Over 300 million people worldwide are affected by invasive fungal Infections. Most of the patients have one or more co-existing conditions. Although some fungal infections are endemic to particular geographical areas, most fungal infections depend on multiple risk factors [1].

Invasive fungal Infections have become a global threat, and it is a challenge for clinicians to suspect, diagnose, and manage invasive fungal infections.

The burden of Invasive fungal infections

An estimated 57 251 328 of the 1 393 400 000 people in India (4.1%) suffer from a serious fungal disease. The prevalence (in millions) of recurrent vulvovaginal candidiasis is 24.3; allergic bronchopulmonary aspergillosis is 2.0; tinea capitis in school-age children is 25; severe asthma with fungal sensitization is 1.36; chronic pulmonary aspergillosis is 1.74; and chronic fungal rhinosinusitis is 1.52. The annual incidence rates of *Pneumocystis* pneumonia (58 400), invasive aspergillosis (250 900), mucormycosis (195 000), esophageal candidiasis in HIV (266 600), candidemia (188 000), fungal keratitis (1 017 100), and cryptococcal meningitis (11 500) were also determined. Histoplasmosis, talaromycosis, mycetoma, and chromoblastomycosis were less frequent [2].

The common invasive fungal infections:

Invasive **Candidiasis** is most common in intensive care units. This is mainly because of the wide use of Broad-spectrum Antibiotics and long-standing indwelling catheters and abdominal surgeries. Followed by Candida and **Aspergillus spp**. The predisposing factors include prolonged neutropnia due to chemotherapy or hematologic malignancies and Graft-Versus-Host Disease in Transplant recipients. Invasive **Mucormycosis** was seen more commonly in patients with diabetic ketoacidosis. In the last 20 years, the incidence of invasive mucormycosis has increased significantly. It primarily affects immunocompromised patients. We experienced a sudden upsurge of invasive mucormycosis during the post-COVID-19 epidemic period, probably because of the wide use of Steroids in the treatment of severe COVID-19 infections.

Who is at Risk?

Patients with hematologic malignancies risk acquiring infections with Candida, Aspergillus, Zygomycosis, and Scedosporium.

Mortality with invasive fungal Infections due to Cryprococcal meningitis, Pneumocystis pneumonia, invasive Asperigillosis, candidemia, and Chronic allergic Aspergillosis is very high.

Because of an increase in the immunocompromised population, like patients with HIV, patients with autoimmune diseases on immunosuppresive therapy, patients with hematological malignancies, neutropenic patients, the recipients of organ or allogenic Hematopoetic stem cell transplants, and Patients with GVHD.

Now we have some emerging groups that are at risk of acquiring invasive fungal infections, which include patients on immunomodulating drugs, COPD patients, Patients with CLL or other lymphoproliferative diseases, patients in the ICU, and patients with respiratory infections such as Influenza or COVID-19 [3].

How do you define an invasive fungal Infection?

The invasive fungal Infections were based on Host factors, Clinical manifestations, and Mycological evidence. The fungi causing infection of internal organs, tissue, or any sterile site are demonstrated by Histology or blood culture in patients with one or more risk factors like prolonged neutropenia, more than three weeks of corticosteroids, T-cell immune suppression, HSCT, or inherited severe Immunodeficiency [4].

After considering the host factors, clinical features, and mycology, one can think of invasive fungal infections in terms of After considering the host factors, clinical features, and mycology, one can think of invasive fungal infections in terms of "proven," probable, probable, probable, or possible. Direct mycological evidence involves Culture positivity from BAL or sputum. Antigen detection in BAL, Sputum, blood, or CSF serum is positive for markers like Galactomannan, B-D Glucan, or a positive molecular test.

Drug resistance to Antifungal Agents

Candida, *Aspergillus*, *Cryptococcus*, and *Pneumocystis* genera are the most commonly involved fungal species in invasive fungal infections. [5] Three main classes of antifugal agents, so far, exist. These include azoles (fluconazole, itraconazole, voriconazole, posaconazole, etc.), echinocandins (caspofungin, micafungin, and anidulafungin), and polyenes, such as amphotericin B (AMB).

Antifungal drug susceptibility testing is cumbersome and time-consuming. In the absence of Clinical breakpoints for many fungal species, only MICs can be reported. The resistance to antifungal agents is steadily increasing. Azole resistance in Candida spp. Resistance to itraconazole in Aspergillus fumigatus. Echinocandin resistance has been observed in many Candida and Aspergillus spp [5].

Advances in the Diagnosis of Invasive Fungal Infection:

Predisposing factors, clinical symptomatology, radiological findings, and tissue or blood cultures are routine methods for the diagnosis of invasive fungal Infections. But most of them have limitations that may lead to inappropriate decision-making. Blood cultures are good for diagnosing Candida infections but have a sensitivity of 50% and do not grow molds. Blood cultures are not a good method for treating tissue infections. Radiological findings are often nonspecific.

Rapid diagnostic tests like the detection of B-D-Glucon have good negative predictive value but have only 30% positive predictive value. Mannan is specific for Candida, but the sensitivity varies depending on the Candida species. Galactomannan is specific to Aspergillus. False-positive results occur in therapy with Tazobactum or plasma lyte-40. BAL is more sensitive than blood.

Fungal Nucleic Acid detection by PCR has higher sensitivity and specificity. MALDI-TOF can help identify Candida species directly from blood specimens [6].

Management of Invasive Fungal Infections

Management of Invasive fungal infections includes appropriate diagnosis using microbiological tests, radiological investigations, and serological tests. Evaluation of host factors, test results, and initiation of prophylactic or targeted therapy

In conclusion, fighting invasive fungal infection in low-resource countries is an uphill battle. The diagnosis is difficult, and treatment endpoints are difficult to find. The population affected is very vulnerable because of this the management of Invasive fungal infections becomes multi-factorial. the mortality rate is very high. The management guidelines need regular monitoring and improvements. With increasing resistance to antifungal agents, there is a need to develop new antifungal agents that are less toxic and effective. Therapeutic drug monitoring methods be made available to centers that face high rates of invasive fungal infections. We will need to develop infrastructure development to diagnose fungal infections with availability for antifungal drug susceptibility testing. Stewardship for appropriate use of antifungal drugs would help reduce drug resistance. Reliable infection data may help reduce the threat of invasive fungal infections.

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