FUNGAL INFECTIONS - A CHALLENGE IN GERIATRIC AND IMMUNOCOMPROMISED POPULATION

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One of the most significant demographic trends of the 20th century was what has been described as "Greying of Population". Of all the people who have ever lived to age 65, more than two thirds are currently alive. Advances in medical and surgical therapy over the past three decades have increased the longevity of life. Fungal infections have increasingly become a problem among older adults as increasing longevity and affluence have enabled retirees to travel and participate in outdoor activities . Opportunistic fungal infections have increased because older patients are now receiving transplanted solid organs or bone marrow, undergoing aggressive treatment of malignancies, and taking immunosuppressive medications for dermatologic and rheumatologic diseases. Newer technology and therapies result in immune compromised individuals. Use of invasive monitoring devices, parenteral nutrition, broad spectrum antimicrobial agents and assisted ventilation have helped to treat patients suffering, provides life to non-viable but in turn results in proliferation of nosocomial invasive fungal infection in severely ill, immunocompromised, hospitalized patients, with fungi which were previously considered of low virulence. Older patients are also less able to handle invasive endemic or opportunistic infections, and outcomes of infection are frequently worse for patients who are elderly if not recognized and cared early .

Fungi are remarkable organisms. They are eukaryotic, rank in animal rather than in the plant kingdom. Aspergillus and Candida are found everywhere on earth. In past candida was known as Monilia (Monilia albicans and Odium albicans) the term first used by John Hill in 1751 while in 1890 Zopf termed it Monilia albicans to the fungus causing thrush in humans. Pathogenic fungi may be divided on the basis of their pathogenicity into true pathogens and opportunistic pathogens. While Candida albicans is the major pathogen most commonly isolated from ICU patients, other species of Candida include C. glabrata, C. parapsilosis, C. tropicalis, C. kruzi etc. Apart from Candida species and Aspergillus the other fungi which are frequently isolated from ICU patients include Fusarium, Mucor, Rhizopus, Penicillium, Trichosporon, Cryptococcus sps. etc. Data on the burden of opportunistic mycoses in India is not clear though the climate in this country is well suited for a wide

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variety of fungal infections; yet a definite rising trend has been noted.

The major factors which increase the risk of developing severe fungal infections in ICU patients include major abdominal surgery, perforation of G.I. tract, broad spectrum antibiotics, candida colonization, immunosuppression, burns, total parenteral nutrition, mechanical ventilation, central venous lines and other invasive procedures. To improve and optimize the level of predictive validity and specificity of tests analyzing colonization, two indices namely Candida Colonization Index [CCI] and Corrected Candida Colonization Index [CCCI] have been developed. In candidiasis, prevalence of disease depends on various factors. Candida reservoir is endogenous, as Candida albicans colonizes mucosa of G.I. tract and Vagina. Alteration in host-defence mechanism associated with altered intestinal barrier function and decreased immunity characterizes critically ill patients and results in life threatening fungal infections. Use of broad spectrum antibiotics eliminates bacteria of G.I. tract which confer colonal protection. After colonization, there is proliferation of organisms followed by translocation and invasion of mucosal barrier. This is followed by a period of inapparent candidaemia and finally invasive candidiasis and pathological manifestations of invasiveness. Thus, colonization is an independent risk factor and also a prerequisite for candida infection. This has been proved in neutropenic and nonneutropenic critically ill patients. Signs and symptoms of systemic candidiasis are variable and nonspecific. Clinical presentation varies from fever to septic shock. Other manifestations include skin nodules, myopathy, endophthalmitis, meningitis etc. Although the usual presentation is an unremitting fever that fails to respond to standard antibiotics within 96 hours of initiation of therapy.

It is essential to understand the host defence processes involved in initiating immune responses at mucosal surfaces and how it discriminates between the "commensal" and "pathogenic" states of this fungus. Nearly all studies investigating the epithelial response to C. albicans utilise cytokine and chemokine production as the sole read-out mechanism. We and others have shown that infected ECs produce cytokines/chemokines with a proinflammatory profile, including IL-1α/β, IL-6, G-CSF, GM-CSF and TNF α as well as the chemokine RANTES, IL-8 and CCL20.Infection of epithelial cells by C. albicans results in the production of cytokines and chemokines which recruit and activate various other immune cells. The best documented of these networks is initiated by IL-8. IL-8 recruits circulating neutrophils (PMNs) that are then activated by a variety of cytokines including GM-CSF, G-CSF and IL-1 family members. Activated PMNs then produce TNF α which then affect epithelial gene transcription. TGF β is produced constitutively by epithelial cells and will act with IL-1β and IL-6 to induce T

cell differentiation to the Th17 phenotype. Mucosal homing cells including Th17 T cells and activating dendritic cells will also be recruited by the increased expression of CCL20 and β-defensin 2, acting through the CCR6 receptor. This will lead to the presence of active Th17 T cells in the region to combat the fungal infection. Finally, infection of epithelial cells leads to the production of IL-20 family cytokines including IL-19, IL-20 and IL-24. These cytokines will function in an autocrine fashion, although their role in fungal immunity is not fully understood.

Amongst these host factors could be local and/or systemic. Wearing dentures, inadequate care of appliances, disturbed oral microbial flora due to long term use of antibiotics or corticosteroids, change in dietary factors and diseases like oral cancers or xerostomia are few important local factors. While extremes of age, chronic smoking, immunosuppression, nutritional deficiency, long term use of systemic antibiotics or diseases like diabetes mellitus, Cushing's syndrome, malignancies, severe blood dyscrasias, radiation to head and neck, oral epithelial dysplasia are systemic factors.

People are living longer, and older people are more likely to have compromised immune systems, a major risk factor for fungal infection. Similarly, the widespread use of broad spectrum antibiotics has contributed to the growing infection rate as fungal infections are known to occur after antibiotic therapy, which has the effect of killing the normal commensal bacteria. The global change in spectrum of candida species is also observed in India; cases with non-albicans Candida especially with C. tropicalis are commonly seen. Candida infections can spread to vulnerable people with depressed immune systems who are in the hospital, where the fungus is commonly found on the hands of caregivers and where indwelling catheters, central IV line, can allow an infection to take hold. Infection rates in intensive care units (ICUs) have been documented to be the highest of all hospital acquired infections in large multicentre studies. This is related to the use of large numbers of invasive monitoring devices, endotracheal and tracheostomy tubes; patient factors including extremes of age, immunocompromised state, malnutrition and severe underlying disease; and to a high incidence of cross infection. Bloodstream infections cause substantial morbidity and mortality. Increasing rates of antimicrobial resistance, changing patterns of antimicrobial usage, and the wide application of new medical technologies (e.g., indwelling catheters and other devices) may change the epidemiology and outcome of bloodstream infections. It is therefore important to continually review and update the epidemiology. These infections are costly to treat, prolong ICU stay and increase mortality rates. The three most common nosocomial infections are ventilator-associated pneumonias,

urinary tract infections and bloodstream infections.

Infection of skin, mucous membranes and nails by endogenous Candida can be caused by conditions that result in chronic maceration of these areas, physiologic changes in the host or a compromised immune status. Patients with chronic mucocutaneous candidiasis are generally immunocompromised adults undergoing treatment with steroids, cytotoxic drugs or antibacterial antibiotics.Oral candidiasis is an opportunistic infection of the oral cavity which is caused by an overgrowth or infection of the oral cavity by a yeast-like fungus, candida and often referred to as thrush. The lesions may be singular, patchy or confluent and a whitish pseudo membrane composed of yeasts and pseudohyphae may cover the tongue, soft palate and oral mucosa.. There are various strains of oral candidiasis but the important ones are C. albicans, C. tropicalis, C. glabrata, C. pseudotropicalis, C. guillierimondii, C. krusei, C. lusitaniae, C. parapsilosis and C. stellatoidea. C. albicans, C. glabrata, and C .tropicalis represent more than 80% of isolates from clinical infection. Incidence of oral candidiasis is 54-93% in HIV positive patients with history of chronic smoking. CR-3 like protein enhances adherence of candida with epithelial cells in HIV positive patients. Vaginal thrush, patches of grey-white pseudo membrane develop on vaginal mucosa and a yellow-white discharge may accompany the infection especially in elderly diabetic females or those who are on hormone therapy.

Invasion of nail plate by fungus is known as onchomycosis, which is derived from the Greek word “onyx”, a nail and “mykes” a fungus. There is considerable difference in prevalence of onchomycosis in various geographical areas. In India, Pakistan, Korea, Canada and UK dermatophytes are major causative pathogens while Yeasts are frequently reported in Spain, Italy, Saudi Arabia and Iran. Saprophyte moulds are common cause of toenail infections .Onchomycosis are usually caused by dermatophytes and rarely by Candida or some saprophytic fungi .Patients who are diabetic, in extremes of age, having hyperhydrosis or frequent trauma suffers with onchomycosis frequently. Onchomycosis is being viewed as cosmetic problem, more prone to have secondary bacterial infections, cellulitis, idiopathic reaction and chronic urticaria. Infected toenail in elderly population may act as reservoir for fungus and in female patients social and emotional impairments are seen.

Mycotic keratitis manifested as corneal ulcer or hypopyon or both, precipitated due to corneal trauma, tear deficiency, lid abnormality or chronic dacrocystitis, are commonly seen in elderly population. The mycosis has emerged into prominence since the advent of antibacterial antibiotics and the use of steroid ointment as they tend to enhance mycotic activity if spores of fungi are present on abraded cornea or in eye, surgical intervention or

antibacterial medication has altered normal host response. Fusarium solani, Aspergillus and Candida sp. are commonest causative agents. Most strains of F. solani are isolated from plants; they multiply rapidly at 370C and survive at 400C and causes mycotic keratitis in elderly due to trauma by vegetative plants.

Though Aspergillus is responsible for pulmonary aspergillosis which is typical invasive form with eventual haematogenous dissemination to other organs commonly caused by A.flavus, A.niger, A.clavus, A.terreus while A. niger and A. fumigates may colonise an ectatic bronchus ,without invasion of lung parenchyma , forming a compact "fungus ball" known as Aspergilloma. In elderly Aspergillus can also lead to chronic fibrosing granulomatous reaction, allergic reactions as allergic asthema,allergic bronchopulmonary aspergillosis , sinusitis and otomycosis, CNS,sino-orbital infection or GIT-infarction(rarely). Mucormycosis are commonly seen in elderly with endocrinopathies (e.g. uncontrolled diabetes).

Candida biofilm is difficult to treat as they show resistance to antifungal treatment through slow penetration of drugs through the bio film, expression of resistance genes and presence of persister cells. Antifungal drug resistance especially with fluconazole, Amphotericin- B and newer triazoles are rapidly becoming major therapeutic challenge in immunocompromised patients. Newer antifungal agents, such as the echinocandins and liposomal formulations of Amphotericin B, have shown increased activity against candida bio films.

Numerous systemic manifestation of candidiasis may follow introduction of Candida into the blood stream. Candidaemia may result from contamination of indwelling catheters, surgical procedures, and trauma to the skin or gastrointestinal tract. The extent and severity of the infection is determined by the inoculum size and virulence of organism and most importantly the host defences. Clinical indications of acute systemic candidiasis include candiduria (in the absence of catheterization and an imbalanced flora), candida endophthalmitis and maculonodular skin lesions. Although Candida albicans is the most common agent of candidiasis, C.guilliermondii, C.parapsilosis and C. tropicalis are frequent causes of endocarditis. Prophylaxis is considered for a selected group of patients in whom the frequency of Candidaemia is high enough to make such treatment beneficial. On the other hand, presumptive antifungal therapy should be given to individuals with well known risk factors and a known degree of Candida colonization. Currently, active and extensive investigation is focused on preventive strategies for invasive fungal infections.

Fungal infections are common in elderly patients admitted to intensive care unit due to impaired immunity and presence of multiple risk factors. These infections have a profound effect on morbidity and mortality

rates of ICU patients. Appropriate interventions must be undertaken to hasten the recovery of patients and to decrease the health care cost. More than 20% of Candidaemia cases are associated with increased morbidity and mortality rates. Persons at extremes of age are most susceptible to fungal colonization. Because of their dependency in personal hygiene, dentures responsible for mucocutaneous infection, vulnerability for getting injured while outdoors due to diminished vision because of age related ocular changes, along with co morbid diseases of old age. Physical dependency becomes more relevant for the institutionalized or admitted elders who may find it difficult to get assistance from the caretakers. Use of invasive monitoring devices, parenteral nutrition, broad spectrum antimicrobial agents and assisted ventilation have helped to treat patients' suffering, provides life to non-viable elderly but in turn results in proliferation of severely ill, immune-compromised, hospitalized patients which are at higher risk of acquiring nosocomial fungal infections which were previously considered of low virulence. Fungal infection in these patients is often severe, rapidly progressive and difficult to diagnose or manage.

While Candida albicans species are the most common cause of severe fungal infections in ICU, the incidence of candida non-albicans and Aspergillus infection are rapidly rising due to the increased spectrum of patients at risk for developing mould infections. These fungal infections increase both morbidity and mortality to a significant extent in ICU patients and also prolong the duration of stay in ICU and increase health care cost. Candidaemia means isolation of Candida species in the blood and candidiasis means tissue invasion demonstrated by culture or histology at nonadjacent, normally sterile sites. Proven invasive Candida infections include Candidaemia and histological evidence of tissue invasion and positive Candida blood culture from sterile site .In the United States, Candida is reported to be the fourth leading organism responsible for nosocomial blood stream infections, accounting for 10-20% of infections in ICU patients. There are very few data available regarding the incidence of fungal infections in ICU patients in India, but the overall incidence is said to range from 10 to 16%.

For laboratory diagnosis of fungal infections, it is must that contamination of samples should be avoided, sterile instruments and containers should be used and appropriate sample should be ordered for a particular suspected disease .Commonly used samples are scrapings, fluids sp.CSF, BAL , pus, sputum and biopsy or blood culture to diagnose fungemia. As far as possible, swabs should be avoided as these are the poorest way to collect samples. The diagnosis of invasive candidiasis is still based on blood cultures in a substantial proportion of cases, a single positive blood culture being considered enough for a definitive diagnosis of candidaemia

and invasive candidiasis. Unfortunately, blood cultures have quite a low sensitivity value ranging between 50 to 60%, other serological methods for the detection of candida infection include (1-3)-B-D-Glucan, Mannan, D-Arabinitol, Enolase, Galactomannan detection. Germ tube test (for C.albicans confirmation), antibody or antigen detection by Polymerase chain reaction or Latex agglutination , positron emission testing scan are the newer methods used in the diagnosis of fungal infections. For diagnosis of Cryptococcal infections, Indian Ink staining along with detection of antigen in CSF or blood are confirmatory diagnostic techniques along with culture on Niger Seed Agar medium and rapid urease test positive (within 4 hours). Nowadays automated identification system like Vitek-2 helps in early identification of yeasts, along with antimycotic sensitivity testing and their MIC can be known, which combats problem of drug resistance. While in Aspergillus infection diagnosis depends upon serological or molecular techniques or high resolution CAT scan. All dermatophytes are diagnosed by 10%KOH preparation of skin, hair or nail (40%KOH) and culture is done on Sabouraud's Dextrose Agar medium (selective media for fungus culture) or dermatophyte selective agar for identification.

Among the available antifungal drugs, azole group of drugs like fluconazole, voriconazole, posaconazole are commonly used. Amphotericin-B is reserved for severe systemic infections only, owing to its high nephrotoxicity potential and other systemic side effects. Echinocandins are a new class of drugs with improved spectrum of activity and less side effect profile. But they are available in parenteral form only for administration. Due to irrational use of antifungal drugs which is associated with emergence of azole-resistant strains of Candida and also the changes in candida species i.e. increase in candida non-albicans strains compared to candida albicans strains, they must be avoided.

Prophylaxis is considered for a selected group of patients in whom the frequency of candidaemia is high enough to make such treatment beneficial. On the other hand, presumptive antifungal therapy should be given to individuals with well known risk factors and a known degree of candida colonization. Currently, active and extensive investigation is focused on preventive strategies for invasive fungal infections. Prophylaxis with antifungal drugs has been demonstrated to reduce the incidence of invasive fungal infections in immunocompromised patients specially with CD-4count <200cu/mm, nonneutropenic patients, but their role in immunocompetent, nonneutropenic patients is less well defined. Clinically useful antibiotics include Amphotericin B, nystatin, griseofulvin and the azole antifungals. Invasive fungal infections are not only observed in immunocompromised hosts, but they are increasingly recognized as a growing problem in

critically ill nonimmunocompromised patients and in patients undergoing major surgical procedures. Cases of drug resistance are commonly seen, hence antifungal sensitivity test is recommended by E-Test method or disc diffusion method.

Strictly all the following recommendations should be followed by ICU workers and doctors to minimise hospital acquired fungal infections in elderlies:

a) Hand hygiene continues to be corner stone of infection control practices
b) Judicious use of antibiotics and steroids
c) Central venous lines should be changed within 15 days
d) Minimize stay in ICU
e) Minimize civil work near OT and ICU
f) Antifungal prophylaxis should be given to high risk elderly patients
g) Avoid food that will feed the mutated Candia (A diet that is high in sugar and refined carbohydrates speeds up the process of the mutation in candida).

Fungal infection whether in ICU settings or environmentally acquired in geriatric patients is an important problem in Indian hospitals. Diagnostic delays could be shortened by more active screening for fungus especially in intensive care settings. Undiagnosed fungal infections may increase both the morbidity and mortality rates to a significant extent and increase the burden on health system in terms of cost and manpower. Correct diagnosis and prompt treatment with antifungal drugs remains a key factor in managing such patients.

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