REVIEW ARTICLE

Uncommon opportunistic fungal infections of oral cavity: A review

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ABSTRACT
The majority of opportunistic oral mucosal fungal infections are due to *Candida albicans* and *Aspergillus fumigatus* species. *Mucor* and *Cryptococcus* also have a major role in causing oral infections, whereas *Geotrichum, Fusarium, Rhodotorula, Saccharomyces* and *Penicillium marneffei* are uncommon pathogens in the oral cavity. The broad spectrum of clinical presentation includes pseudo-membranes, abscesses, ulcers, pustules and extensive tissue necrosis involving bone. This review discusses various uncommon opportunistic fungal infections affecting the oral cavity including their morphology, clinical features and diagnostic methods.

Key words: Immunocompromised patients, opportunistic fungi, oral cavity

INTRODUCTION

Humans are exposed to hundreds of fungal spores daily, usually not producing any harmful effect on their health. This protection is by various pulmonary defense mechanisms that effectively eliminate the fungal spores.[1]

Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidis, Paracoccidioides brasiliensis and dermatophyte fungi can infect healthy, immunologically competent individuals.[1] By contrast, species such as *Candida*, *Aspergillus*, *Rhizopus* and *Fusarium* are normally avirulent in healthy people, but can cause disseminated fatal infections in patients with suppressed immunity. These are called opportunistic pathogenic fungi. The fungus *Cryptococcus neoformans* can be considered both as a true and opportunistic pathogen since it can cause infections in immunologically competent as well as immunocompromised hosts.[1]

The occurrence of superficial as well as invasive opportunistic fungal infections has increased significantly over the past two decades. This increase can be attributed to the growing number of immunocompromised patients- including those with AIDS, neoplastic disease, advanced age, long-standing diabetes mellitus, undergoing blood and marrow transplantation, solid-organ transplantation, major surgery, receiving immunosuppressive therapy and premature infants.[2] Genetic predisposition to invasive fungal infection has been reported recently owing to defective NADPH oxidase activity, abnormal production of tumor necrosis factor- α, interleukin 10 and other cytokines.[3,4]

The spectrum of opportunistic fungal infections is changing. The majority of invasive fungal infections are still due to *Aspergillus* and *Candida* species; but infections due to mycelial fungi other than *Aspergillus* and non-*albicans* species of *Candida* are becoming increasingly common.[5] Any fungus present in the environment can be potentially pathogenic in immunocompromised patients.[6]

This review considers the main general and oral aspects of these emerging uncommon opportunistic fungal infections such as Candidiasis due to *Candida* species other than *C. albicans*, Aspergillosis due to non-fumigates species of *Aspergillus*, *Mucormycosis*, *Cryptococcosis*, *Geotrichosis*, *Rhodotorula* infection, *Saccharomyces* infection, Fusariosis and Penicilliosis.

CANDIDIASIS DUE TO *CANDIDA* SPECIES OTHER THAN *C. ALBICANS*

Oral candidiasis is the most common human fungal infection.[7] Even though *C. albicans* is the most common pathogen responsible for candidiasis, other *Candida* species causing oral infections have also been identified including

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C. glabrata, *C. krusei*, *C. parapsilosis*, *C. dublieniesis*, *C. tropicalis*, *C. kefyr* and *C. guilliermondii*.[8-11] Less commonly isolated species are *C. inconspicua, C. lusitaniae, C. norvegensis* and *C. rugosa*.[12] These species are resistant to the commonly used azole antifungal drugs.[13] These non-*Candida albicans Candida* species lack many of the virulence factors present in the virulent *C. albicans* i.e. the ability to form hyphae and phenotypic switching. They have low adherence capacity to buccal epithelial and vascular endothelial surfaces. They secrete less proteinases. Thus they are thought to cause candidiasis of less severity.[14]

C. dublieniesis is a species associated with oral lesions in HIV-infected individuals. It is morphologically and genotypically closely related to *C. albicans*.[15,16] *C. dublieniesis* is the only *Candida* species other than *Candida albicans* that forms true hyphae. They show decreased susceptibility to fluconazole.[17]

C. glabrata is emerging as an important pathogen in both mucosal and blood stream infections and is commonly isolated from the oral cavity of HIV-infected individuals.[11,14] *C. glabrata*-associated oropharyngeal candidiasis in HIV infection and cancer patients is more severe and more difficult to treat due to their quick development of resistance to fluconazole.[18]

C. guilliermondii cause infection in patients undergoing surgical procedures, endocarditis, in intravenous drug users and fungemia in immunocompromised patients.[19] They show resistance to amphotericin B.[20]

C. krusei infection occurs in critically ill patients mainly in hematology patients with severe neutropenia. It is an uncommon pathogen causing candidemia. The increase in *C. krusei* infection in HIV-infected patients is thought to be due to the widespread use of fluconazole prophylaxis.[21]

C. lusitaniae mainly causes infection in immunocompromised hosts with prolonged antibiotic administration, hospitalization, cytotoxic or corticosteroid treatment, granulocytopenia and low-birthweight babies.[22,23]

C. parapsilosis mainly affects critically ill neonates and patients in intensive care units i.e. prematurity and low birth weight are recognized as the risk factors.[24]

C. tropicalis is the most virulent of the non-*albicans Candida* species. This may be due to its ability to adhere to epithelial cells *in vitro* and to secrete moderate levels of proteinases.[14] It is usually isolated from oral cavity and skin and can cause infections in esophagus in patients with systemic diseases.[25]

Diagnosis

The diagnosis of candidiasis is often made on the basis of clinical suspicion of the typical mucosal changes and angular cheilitis. These are almost always associated with some degree of discomfort.[26] Microscopic examination of the smears stained with periodic acid Schiff's method (PAS), or KOH preparation can reveal candidal hyphae and blastospores.[27]

Qualitation is accomplished by culture on Sabouraud's dextrose agar (SDA) at 25-30ºC for 48-72 hours.[28] Germ tube growth can be used for identification of *C. albicans* whereas carbohydrate assimilations can be employed for other species.[26] Culture on CHROMagar can be used to identify *C. albicans, C. krusei* and *C. tropicalis*. *C. albicans* forms green colonies, *C. krusei* form fuzzy, rose-colored colonies and *C. tropicalis* show steel-blue colonies.[13,29,30] CHROMagar-PAL is a new method which combines CHROMagar Candida and Pal agar that can easily differentiate between *C. albicans* and *C. dublieniesis* even in mixed cultures. ELISA and polymerase chain reaction (PCR) may also be used for the same. Multiplex PCR, which identifies yeast directly in clinical samples is a more recent advancement.[31] Further speciation can be done by conventional biotyping techniques or with the aid of commercially available systems like Micronaut-Candida, API ID32C, RapID yeast plus system, Auxocolor, Vitek, Api Candida, etc.[32,33] Quantitation is done by collecting whole saliva and plating on SDA, incubating and counting the colony-forming units.[28]

Biopsy is mainly done to rule out hyperplastic candidiasis. In hyperplastic candidiasis, histopathological examination will reveal epithelial parakeratosis with polymorphonuclear leukocytes in the superficial layers. PAS-staining will show the presence of Candidal hyphae in these areas.[34]

ASPERGILLOSIS

Aspergillosis has been reported as the second most prevalent opportunistic fungal infection.[35] *Aspergillus* species are universally found in humid areas, damp soil, grain, cereal, mouldy flour and organic decaying or decomposing matter.[36] In the hospital setting, construction activities, rotten leaves or insufficient cleaning of dust can increase the risk of developing aspergillosis.[37] *Aspergillus fumigatus* is the most familiar pathogen of the species. Human infections are also caused by less common *Aspergillus* species, such as *Aspergillus flavus, Aspergillus glaucis, Aspergillus terrus, Aspergillus parasiticus, Aspergillus repens, Aspergillus nidulans, Aspergillus niger* and *Aspergillus tubingensis*.[38,39] In India, the most common species encountered is *A. flavus* followed by *Aspergillus fumigatus* and *A. niger*.[40]

Rowe Jones in 1994 classified aspergillosis into three chief variants: Invasive, non-invasive and non-invasive destructive type. Invasive type represents true fungal tissue invasion that can be either slow progressive and destructive (non-fulminant) or highly aggressive and lethal (fulminant). Non-invasive type is further classified into Aspergilloma, Fungal ball, Mycetoma (usually affecting one sinus) or allergic Aspergillus

sinusitis (involving more than one sinus). Destructive non-invasive variant is locally destructive but shows no tissue invasion.[41]

Clinical presentation

Aspergillosis generally occurs after inhalation of spores, that can result in both upper and lower respiratory tract infection- bronchopulmonary aspergillosis.[42] From lungs, infections may spread to the brain, bone or endocardium.[43] Paranasal sinuses, larynx, eyes, ears and the oral cavity may be involved in primary aspergillosis.[43,44] *A. fumigatus* is the usual agent of sinus aspergillosis, whereas *A. flavus* is more common in invasive lesions in immunosuppressed individuals.[45] Orofacial aspergillosis is relatively common in patients undergoing treatment for malignancies of the blood and blood-forming organs.[44,46-48]

Aspergillus does not contain chlorophyll, thus light is not required for growth. Aspergillus exhibits a centrifugal linear growth unless inhibited by natural or artificial barriers. This is why Aspergillus in the paranasal sinus eventually develops into a ball-shaped mass.[49] The centre of the mass contains calcium phosphate and therefore mimics a foreign body on radiography.[50]

In most cases, oral aspergillosis lesions are yellow or black in color, with a necrotic ulcerated base, classically located on the palate or posterior tongue.[46,51] *Aspergillus hyphae* invade host tissues through the release of various toxins. These include various proteases, phospholipases, hemolysins, gliotoxin, aflatoxin, phthioic acid and other toxins.[52] The hyphal elements of the fungus may invade the oral mucosa and penetrate the walls of small to medium-sized blood vessels, producing thrombosis, infarction and necrosis, finally leading to systemic spread.[53]

Diagnosis

Histopathologically, invasive lesions show chronic granulomatous reactions. In hematoxylin and eosin-stained sections hyphal forms can be seen faintly in the center of an area of necrosis. They may go unnoticed unless special stains like methanamine silver are used. The fungi appear as septate hyphae, showing branching at 45° angles and are about 2-4 mm in diameter.[54] Conidiospores and fruiting bodies are also seen. This fungus should be differentiated from mucor which shows broader non-septate hyphae with branching at 90°.[55,56]

MUCORMYCOSIS

Mucormycosis (Zygomycosis or Phycomycosis) is an opportunistic mycotic infection caused by Mucorales.[57] It is considered as the third most common opportunistic fungal infection after candidiasis and aspergillosis.[58] The common genera causing disease are Rhizopus, Rhizomucor and Absidia. Rhizopus is the chief pathogen accounting for 90% of the cases of rhinocerebral mucormycosis.[59]

This fungus is widespread in soil, manure, vegetables and as bread mould.[60] This pathogen may be cultured from the oral cavity, nasal passages, throat and stool of healthy patients without clinical signs of infection.[59] The infection usually results from inhalation of fungal spores, contamination of traumatized tissue, ingestion or direct inoculation.[61] An area of ulceration or an extraction socket in the mouth can be a port of entry for mucormycosis into the maxillofacial region, chiefly when the patient is immunocompromised.[62]

Up to 40-50% of patients suffering from mucormycosis have diabetes mellitus (DM).[63,64] Acidosis in DM reduce the phagocytic ability of granulocytes thereby affecting the immunological capability to resist mucormycosis.[65,66] During the state of diabetic ketoacidosis, the acidic environment and the increase in the levels of free ferric ions support the growth of mucorales.[67] In diabetic patients there is a high occurrence of mucormycosis caused by Rhizopus oryzae, because they produce the enzyme ketoreductase, which enables them to make use of the patient's ketone bodies.[68]

Mucorales have the ability to damage and penetrate endothelial lining of blood vessels. This accounts for the most characteristic feature of mucormycosis i.e. widespread angioinvasion resulting in thrombosis and tissue necrosis.[69]

Clinical presentation

Eisenberg *et al*. described six clinical variants- rhinocerebral (rhinomaxillary), pulmonary, cutaneous, gastrointestinal, central nervous system and disseminated type.[68] Rhinocerebral form is the most common clinical variant which has been further divided into two subtypes: (i) A highly fatal rhino-orbito-cerebral form which is invasive involving the ophthalmic and internal carotid arteries, (ii) A less fatal rhino-maxillary form which involves the sphenopalatine and greater palatine arteries, resulting in thrombosis of the turbinate and necrosis of the palate.[59,70,71]

The clinical presentation of rhinocerebral mucormycosis includes malaise, headache, facial pain, swelling an irregular black eschar, exudation of pus from the eye and nose and low-grade fever.[64] The disease usually starts in the nasal mucosa or palate and spread through the surrounding vessels to the paranasal sinuses, frequently involving maxillary and ethmoid sinuses. In addition, mucormycosis can involve the retro-orbital region by direct extension.[61,63,72] Orbital involvement can impair the functions of cranial nerves III, IV and VI resulting in proptosis, ptosis, pupillary dilatation, orbital cellulitis and loss of vision. Direct penetration and growth of the fungi through the walls of blood vessels can result in thrombosis and extensive tissue necrosis.[57] Hematogenous

spread to the cavernous sinus can lead to fatal cavernous sinus thrombosis.[61,64,73] Rhinocerebral mucormycosis can also spread by perineural invasion.[74]

Diagnosis

Suspicion of mucormycosis necessitates a CT scan of the maxilla, orbits and brain. In particular, evidence of intracranial brain abscesses and orbital extensions is critical. Sinus and orbital extensions are recognized by membrane or periosteal thickenings as well as bony disruption.[75]

Routine blood studies will show leukocytosis in the 12,000-20,000/ mm^3 range and usually a shift to the left. If the patient is diabetic, a full workup of serum glucose, electrolytes, blood chemistries and blood gases is required. Serological assays for Mucor antigens have been developed.[75]

Histopathologically broad, irregularly shaped, nonseptate hyphae with right angle branching are seen invading the tissue in H and E-stained sections; but are better visualized with PAS or methanamine silver stains. Ideally the biopsy specimen should be obtained from the junction of necrotic and non-necrotic tissue. The organisms are mainly seen within the walls of necrotic blood vessels.[75] Culturing can be done on Sabouraud's glucose agar and sporulation of fungal hyphae within 24-48 hours helps to identify mucor.[76]

CRYPTOCOCCOSIS

Cryptococcus neoformans and *Cryptococcus gattii* are commonly considered as the causative agents of cryptococcosis.[34] *C. neoformans* generally affects immunocompromised hosts whereas *C. gattii* is isolated more from immunocompetent individuals.[34,77]

Clinical presentation

C. neoformans infections usually occurs after inhalation of fungal spores from the soil and excreta of birds like pigeons, parrots and canaries.[78] In immunocompetent individuals the infection remains subclinical within the lungs. In the immunocompromised host, the fungus produces rapid disseminated infection involving central nervous system, skin, mucous membranes and many other tissues.[79]

The face, scalp and neck are the common sites of cutaneous lesions, presenting as papules, acne form pustules, abscesses, ulcers, superficial granulomas or sinus tracts.[80] Dissemination may occur from reactivation of dormant disease or a primary infection.[81] The most common clinical presentation is meningo encephalitis. The increased occurrence of cryptococcosis in HIV-infected individuals has been reduced by the implementation of Highly Active Anti Retro viral Therapy (HAART).[81]

Cryptococcosis in oral cavity may arise from hematogenous spread of the infection localized in the lungs of AIDS patients. However, oral cryptococcosis can be the initial presentation of a disseminated infection.[81] Violaceous nodules, swellings or ulcers have been reported on the gingiva, hard and soft palates, pharynx, oral mucosa, tonsillar pillar and in tooth socket after extraction.[82]

Diagnosis

Histopathology varies according to the immunological status of the host. In immunocompetent hosts, typical granulomas are formed at the site of cryptococcal infection, with multinucleated giant cells containing intracytoplasmic cryptococci in budding forms. In immunosuppressed patients, proliferating cryptococci present as extra- and intracellular yeast cells with some budding forms with reactive macrophages, minor lymphocytic and neutrophilic infiltrate. The definitive diagnosis of cryptococcosis is established with periodic acid Schiff (PAS), methanamine silver and mucicarmine-stained preparations. The fungal cytoplasm appears bright magenta by PAS stain and mucicarmine stains the fungal capsule.[81,83] Culture and assay of serum or cerebrospinal fluid for capsular antigen is useful.[84]

GEOTRICHOSIS

Geotrichosis is caused by *Geotrichum candidium* which is a component of the normal microflora of the skin and the mucosa of the respiratory and digestive tracts. It can also be isolated from vegetables, fruits, soil and plants.[85] Oral lesions are caused by *G. candidum* and *G. capitatum*.[86-89]

Clinical presentation

Geotrichosis can present as pseudomembranes, mucosal ulcerations, edematous and erythematous gingivae. Easily scrapable creamy-white pseudomembranous plaques with an erythematous background can be seen mainly on the tongue, resulting in glossitis and on the cheeks. The most common symptoms are burning pain and impaired swallowing.[90] Angular cheilitis and palatal ulcers appearing similar to the ulcers caused by zygomycosis and aspergillosis have been reported. Palatal ulcers can result in a very aggressive palatine- cerebral condition with poor prognosis.[90,91]

Diagnosis

Direct examination and staining will reveal multiple septate hyphae with rectangular arthroconidia. But some arthroconidia may have rounded appearance (clavata cells) and may be easily mistaken for Candida. Hence culture is recommended for the accurate diagnosis.[90]

In culture *G. candidum* and *G. capitatum* are seen as white, membranous, villous, wet colonies. In chromogenic culture

media their villous wet growth with slight pink pigmentation distinguishes them from the major *Candida* species.[90] Various biochemical tests can also aid the diagnosis; but molecular biology is the most accurate technique for species identification by internal transcriber spacer (rDNA).[86,92]

RHODOTORULA INFECTION

The genus Rhodotorula is a pigmented yeast classified under the family Cryptococcaceae. Three main species are actually known: *Rhodotorula glutinis*, *Rhodotorula minuta* and *Rhodotorula mucilaginosa*.[93] *R. mucilaginosa* is the current name for the species formerly known as *Rhodotorula rubra*. Rhodotorula is found in air, soil, lakes, ocean water and dairy products. It may colonize plants, humans and other mammals.[94,95] Rhodotorula produce moist, smooth to mucoid, glistening, pigmented colonies. Salmon-pink to coral red color of the colony is due to the carotenoid pigment, torularhodin.[96] This pigment blocks certain wavelengths of light which can damage the yeast cell.[94,95]

Clinical presentation

Rhodotorula can cause meningitis, endocarditis, ventriculitis, peritonitis, fungemia, central venous catheter infection and keratitis.[97] Non-healing oral ulcers and white patches are the reported oral presentations of Rhodotorula infection.[98]

Diagnosis

Gram stain will show Gram-positive round, budding yeast cells of 4-8 μm in diameter with clear halo around them. India ink preparation of the smear will demonstrate encapsulated budding yeast cells.[99]

Rhodotorula are pigmented yeasts easily identified as coral pink, smooth, sometimes reticulate, rugose or corrugated and moist to mucoid yeast-like colony forms when grown on SDA. The germ tube test is negative. Rhodotorula produces urease enzyme and does not ferment carbohydrates.[100]

SACCHAROMYCES INFECTION

Saccharomyces cerevisiae (also known as "baker's yeast" or "brewer's yeast") is widespread in nature and is a commensal inhabiting the gastrointestinal tract of humans, which has an important role in maintaining the normal homeostasis of the lower gastrointestinal tract.[101,102] *S. cerevisiae* is now included in some diet or health foods. Fungemia from *S. cerevisiae* can follow the use of live yeast capsules of *Saccharomyces boulardii* which are used as probiotics for the prevention and treatment of various diarrheal disorders.[103]

Clinical presentation

Lesions resemble invasive candidiasis due to the presence of choreoretinitis and esophagitis in both conditions. Fever may be present in majority of patients. Deep site involvement with necrosis and granulomatous reaction has also been reported.[104] Intra-oral manifestations include ulcers with associated painful swallowing, dry mouth and burning sensation.[102]

Diagnosis

Direct Gram stain from the swab will show majority of Gram-positive budding yeast cells. The culture will give creamy-white yeast-like growth. The Gram staining from the colony will show budding yeast cells without any capsule. The organism can be identified using corn meal agar and carbohydrate assimilation test.[102]

FUSARIOSIS

Fusarium species are important plant pathogens causing various diseases on cereal grains, occasionally causing infection in animals.[105,106] In humans, *Fusarium* species cause both superficial infections (such as keratitis and onychomycosis), allergic diseases and disseminated diseases.[107]

Fusarium solani was most frequent species followed by *Fusarium oxysporum* and *Fusarium verticillioidis* and *Fusarium moniliforme*.[105] *Fusarium* species are the second-most common mould causing invasive fungal infections in immunocompromised individuals.[108,109]

Clinical presentation

The clinical presentation of fusariosis depends principally on the immune status of the host and the portal of entry of the infection.[110] The main routes of entry for *Fusarium* species are the airways and the skin. Risk factors are persistent neutropenia, severe depletion of T- lymphocytes and previous fungal infections.[111] Disseminated infection and skin involvement leading to cellulitis are seen in immunocompromised patients. These lesions may frequently appear as multiple erythematous papules or nodules with central necrosis.[110]

Fusariosis presenting as a necrotic ulceration of the gingiva, extending to the alveolar bone has been reported in a granulocytopenic patient.[112]

Diagnosis

Skin lesions (cellulitis and metastatic lesions) and positive blood cultures for mold can suggest disseminated fusariosis. Due to the dissemination of yeast-like structures, blood cultures are often positive in fusariosis.[113] In histopathology the hyphae are similar to those of Aspergillus species, with hyaline and septate filaments that typically dichotomize in acute and right angles. The finding of hyphae and yeast-like structures together is highly suggestive of fusariosis.[114] From cultures, *Fusarium* can be identified by the presence

of hyaline, banana shaped multicellular macroconidia with a foot cell at the base.[115] But species identification is difficult and needs molecular techniques like PCR.[115]

PENICILLIOSIS

Penicilliosis is caused by *Penicillium marneffei* which can cause fatal infection in HIV-infected individuals.[116] It is a dimorphic fungus that can exist in mycelia form at 25ºC and yeast form at 37ºC.[117] It was first identified in 1973, as an opportunistic infection in a patient with Hodgkins lymphoma.[118] In South-east Asian countries like Thailand, Penicilliosis is the third-most common opportunistic infection in people with AIDS.[116]

Clinical presentation

Penicilliosis is mostly seen in late HIV infection with CD4+ count less than 100/μL.[119-121] Inhalation of air-borne conidia is the most common mode of transmission.[122] Most of the patients have fever, weight loss and malaise. Skin manifestation such as subcutaneous abscesses, molluscum contagiosum-like lesions and papule-like ulcers may be present.[123] Respiratory involvement is characterized by productive cough, dyspnea and hemoptysis.[124] Oral lesions include papules, erosions or shallow ulcers covered by yellow necrotic slough which are mainly seen on the palate, gingiva, labial mucosa, tongue and oropharynx.[125]

Diagnosis

The diagnosis of penicilliosis may be made through examination of cytology or biopsy specimens.[126] In fungemia, yeast cells may be seen inside monocytes in peripheral blood smear and are best demonstrated by PAS/methanamine silver stain.[127] Detection of non-budding yeast cells with characteristic central transverse septum is the key to diagnosis which should be confirmed by microbiological culture.[126] isolation of *P. maneffei* is the gold standard for diagnosis. Culture on SDA at 25ºC for 3 days will give granular colonies with greenish-yellow color and a characteristic red diffusible pigment.[126] In histopathologically occult cases, methanamine silver stain can aid in the diagnosis.[127] Various types of antigen-antibody testing and PCR assay specific to *P. marneffei* have been developed in research laboratories, but are not widely available.[126]

CONCLUSIONS

Fungi are opportunistic infectious agents and most of them are not usually pathogenic. But when they infect an immunocompromised host, can cause a wide range of diseases ranging from superficial to disseminated infections involving the vital internal organs. The outcome of invasive fungal infections depends on various factors such as the clinical condition of the patient, immunological status, pathogenicity and virulence factors of the invading fungal species and the location of the infected area.[128]

The range of patients at risk for invasive fungal infections continues to expand beyond the normal host to encompass patients with acquired immunodeficiency syndrome; diabetes mellitus, those undergoing therapy for cancer and organ transplantation and major surgical procedures. As the population at risk continues to expand, so also does the spectrum of opportunistic fungal pathogens infecting these patients.

Inhalation of spores of these microorganisms is the most common mode of infection in a susceptible host. Hence, prevention of the same would be an excellent prophylactic measure to contain opportunistic fungal infections especially in immunocompromised individuals.

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