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Emerging fungal infections of man

Abstract

Many fungi are now emerging as important causes of superficial and deep seated infections of man. The indiscriminate use of broad spectrum antimicrobials by oral and topical routes and prolonged hospital stay have led to emergence of many new fungal pathogens like *Candida auris, Histoplasma spp*. and *Emergomyces spp.*. Of these, *C. auris* is an established nosocomial pathogen now and can colonize hospital surfaces very commonly. Immunocompromised status of the patients due to various causes like HIV infection, Diabetes mellitus and anticancer chemotherapy, have added to the problems of emerging mycoses. Other risk factors can be exposure to soil and vegetation, and aquatic animals, in case of Lobomycosis. Some of these emerging mycoses are caused by dimorphic fungi. Also, some of these pathogens are really not fungi but algae, like *Prototheca spp*. Many a times these fungal pathogens are very difficult to identify accurately and treat. Treatment options are limited and surgical excision may have to be tried. Some of them may not be culturable at all, and need histopathology to confirm diagnosis. Their taxonomy is also being revised and reviewed constantly. These aspects are very important and should be studied and reviewed. Here we have reviewed available information in this aspect.

Keywords: emerging, fungus, pathogens

Volume 8 Issue 2 - 2023

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Received: May 31, 2023 | **Published:** June 19, 2023

Introduction

The term "emerging infection" may be used to denote an infection that has newly appeared in the population or one that is rapidly increasing in incidence or geographic range. New therapeutic modalities for malignant and autoimmune diseases have also inadvertently led to emergence of new risk factors for unusual mycoses. In clinical mycology, just as in other arenas of healthcare, the only thing which is now constant is change. The epidemiology of invasive fungal infection has changed during the past 20 years. The incidence of mycoses has increased, and the population of patients at risk of acquiring such mycoses has expanded to include those with a broad list of medical conditions. These conditions are solid-organ and hematopoietic stem cell transplantation (HSCT), cancer, immunosuppressive therapy, premature birth, advanced age, AIDS, and major surgery. Medical advances have improved quality of life and also averted death, but have also increased the pool of individuals vulnerable to fungal disease; among these, new therapies for old diseases like monoclonal antibodies for autoimmune disease and small-molecule inhibitors like receptor tyrosine kinase inhibitors , namely ibrutinib for B-cell malignancies, have also led to reports of atypical and exceptionally severe fungal infections. In fact, immunotherapy has changed lives of patients suffering from various cancers and autoimmune diseases. Their infectious risks, however, are only now being fully appreciated. Invasive fungal infections are now important complications of some of these new immunomodulators. For example, the Bruton's tyrosine kinase inhibitor, ibrutinib, which is used to treat B-cell malignancies, is linked with severe and very unusual fungal infections, especially due to *Aspergillus* and *Cryptococcus* . Fingolimod, a syphingosine-1-phosphate receptor which is used for the treatment of relapsing-remitting multiple sclerosis, has been recognized as a putative risk factor in some patients who reported cryptococcosis and histoplasmosis . Invasive candidiasis is now increasingly caused by non-albicans *Candida spp.,* including *C. auris*. The latter a multidrug-resistant yeast with the potential for nosocomial transmission that has hence rapidly spread globally. Over the last few decades, fungal infections have become very common due to many factors like the HIV pandemic, over the counter use of antimicrobials and very few classes of antifungals available.[1] In the 1980s, yeasts, particularly *Candida albicans* were the most common causative agents behind invasive mycoses. In recent years, however, molds have become more frequent in certain subsets of patients, such as HSCT recipients. In patients in whom candidiasis is still the most frequent invasive mycosis, non-albicans species of Candida account for about 50% of infections. The application of triazole pesticides in agriculture, has also driven the emergence of azole-resistant *A. fumigatus* in environmental as well as clinical isolates. The widespread use of topical antifungal agents along with corticosteroids in India has resulted in *Trichophyton mentagrophytes* causing recalcitrant dermatophyte infections. Overall, diagnosis and also management of these emerging mycoses is thus often confusing and quite difficult. Also, diagnosis needs many new and advanced techniques which are not always available in all areas. Some of these emerging mycoses that are now upcoming, are described below.

Emerging yeast infections

Candida auris infections

Candida auris is an emerging yeast pathogen. Discovered in 2009 from the external ear discharge of a Japanese patient, although in retrospect review of candida strain collection it was found that the earliest known strain of *C.auris* dates to 1996 in South Korea. It was initially missidentified as Candida haemulonii. It is emerging as a potential cause behind the next possible pandemic.[1] *C. auris* is commonly found on hospital surfaces and is thus a very important cause behind nosocomial infections. It is difficult to identify and refractory to most available antifungal agents. It also persists in the hospital environment and is not affected by common disinfectants used in the laboratory. Cells are large, oval shaped and rarely form short pseudohyphae. Germ tube is negative but yeasts grow well at and above 42 degree C, and fails to grow in presence of 0.01% or 0.1% cycloheximide. Virulence factors include biofilm formation, phospholipase and protease.

Now *C. auris* strains are distributed worldwide and based on Single nucleotide polymorphism analysis using the next-generation sequencing, global *C. auris* strains are grouped into four clades: East Asia, South Asia, South Africa, and South America.[2] Every major

clade except Clade II has been associated with invasive infections.[3] Japanese strains all belong to the East Asian clade and have not been generally associated with disseminated infection. *C. auris* has been recovered from blood, urine, sputum, ear discharge, cerebrospinal fluid, and soft tissue. Mortality of fungemia due to *C. auris* can be as high as 30-60%. *C. auris* is also more severe in hospitalized COVID positive patients. In fact, in Indian hospitals it has been seen that chances of Candidemia is twice as common in COVID positive patients than in COVID negative ones.

Candida auris can be misidentified by common phenotypic automated systems as *C. famata* and *C. haemolunii*, *C.sake*, *Rhodutorula glutinis, C lusitaniae, and C .parasilosis*.[4] C. auris produces white to cream colonies with a smooth edge on Sabouraud's dextrose agar and pink colonies on CHROMagar . We have also encountered a few suspected strains of *C. auris* from various samples, but confirmation was difficult. It ferments dextrose, dulcitol and mannitol. The most reliable method to identify suspected *C. auris* strains is matrix-assisted laser desorption/ionization time-of-flight mass spectrometry (MALDI-TOF MS) along with genome sequencing.[1] Sequencing of the internally transcribed spacers and D1/D2 regions of the 26S rDNA can also help in detection.[2] People have also attempted T2 magnetic resonance (T2MR; T2 Biosystems, Inc.) technology for identification. Treatment is difficult and the pathogen may only respond sometimes to Echinocandins. Now a phase 2 or 3 trial on ibrexafungerp (SCYNEXIS, Inc., formerly named SCY-078) is going on. Ibrexafungerp is a 1,3-β-D-glucan synthase inhibitor. It has good activity in vitro against *C. auris* strains which show echinocandin resistance . Rezafungin , a newer evhinocandin derivative, is also promising. Skin colonization by *C. auris* can pose a substantial risk of surgical site infections. Environmental sanitation, disinfection and hygiene can help eliminate and control *C. Auris* (Figure 1).

Figure 1 Pink colonies of *Candida auris* on CHROM Agar. (source:- www.cdc.gov)

Colonization screening for *C. Auris*

Colonization occurs most commonly in axilla, followed by groin and rectum. Specially patients with diarrhoea may be at higher risk at persistent colonization. Screening sites suggested are axilla , groin, oral mucosa, urine/ urethral swab, sputum, endotracheal secretion, drain fluid(abdominal/pelvic/mediastinal),cannula sites, wounds. These sites should be tested in periodic intervals. If a site is positive there is no need for retest for next three months.[4,5]

Decolonization methods to remove Candida auris from surfaces:-

1. Skin- sponging with 2% chlorhexidine gluconate
2. Oral- 0.2% chlohexidine mouthwash or 1 % chlorhexidine dental gel for patients on ventilator support
3. Oropharyngeal- oral nystatin
4. Central vascular catheter - chlorhexidine impregnated protective disk.

Emerging mold infections

***a. Emergomyces* infections:** *Emergomyces spp.* are dimorphic fungi that are now emerging as causes of systemic mycoses. First discovered in an Italian patient with advanced HIV in 1994, it is now found in many countries. It has now been regarded as the commonest dimorphic fungal pathogen in South Africa.[6] Morphologically it resembles Emmonsia cristianus very closely. Initially classified under genus Emmonsia, a taxonomic revision in 2017 based on DNA sequence analyses placed five Emmonsia-like fungi under a new genus, *Emergomyces*. *Emmonsia spp*. produce adiaspores while *Emergomyces spp*. produce yeasts at 37 degree C. Clinical disease often resembles histoplasmosis. There are 5 species of *Emergomyces*:- *E. pasteurianus* whih has caused cases in Europe, Asia including India, *E. africanus* which is common in South Africa and *Lesotho, E. canadensis, E. orientalis and E. europaeus*. Except *E. africanus* that commonly affects skin, lungs and lymph nodes, all other species cause disseminated infection. Diagnosis can be achieved by histopathology and sequencing the internal transcribed spacer region of the rDNA.

b. New Blastomyces spp. are also coming up in North America and Africa, like *Blastomyces helicus*. Previously it was called *Emmonsia helica*. It causes fatal encephalitis in man and also systemic disease, and cases have ne been reported from Canada.[7] Cases are mostly reported from immunosuppressed patients.

Other emerging fungal infections

a) Lobomycosis: Lobomycosis or Jorge Lobo's disease is a subcutaneous mycosis caused by *Lacazia loboi*, an uncultivable fungus. Previously it was known as *Loboa loboi.* Bottlenose dolphins of the Atlantic ocean (*Tursiops truncatus)* can serve as reservoir hosts of this pathogen as they are infected and human cases are also found along the distribution of this animal, though the true natural reservoir is yet to be determined. Hence it can be called an emerging zoonotic fungal pathogen. Cases are found mostly in the Amazon basin of Brazil (Matto Grosso), and also the Atlantic coastline of the USA. Microscopy of skin lesions shows round cells of size 6 -10 µm joined in chains, that are actually spherical intracellular yeasts.[8] Papules or plaque-like lesions appear first on exposed areas of skin that rapidly progress to keloid-like lesions. Sometimes squamous cell carcinoma may develop from such lesions, especially in Cayabi Indians and lesions often recur.[9] Autoinoculation is reported. Diagnosis is achieved by skin biopsy showing fungal cells embedded in histiocytes and giant cell granulomas. The fungus does not grow on culture. Treatment is by wide surgical excision, and limited success has been achieved by use of agents like clofazimine, itraconazole, and posaconazole (Figure 2).

b) Protothecosis: It is caused by an alga, *Prototheca wickerhamii* and also *P. zopfii*.. These algae are achlorophyllic. Infection usually occurs after traumatic inoculation. It can cause infections

Citation: Bhattacharyya S, Kumar A, Chakraborty M, et al. Emerging fungal infections of man. *MOJ Biol Med.* 2023;8(2):77–80.
DOI: 10.15406/mojbm.2023.08.00188

like olecranon bursitis. Infections can be classified as (i) cutaneous lesions, (ii) olecranon bursitis, and (iii) disseminated or systemic manifestations.[10] Infections are more severe in immunocompromised individuals.

c) Pythiosis: *Pythium insidosum* is a oomycete or fungus-like microorganism. It is a fungal pathogen producing motile zoospores, which are also the infective forms.[11] Phylogenetically they are more closely related to diatoms and algae, rather than fungi. Infections occur mostly in the tropical and subtropical areas, commonly in horses, dogs and man.[11] The infection, though called emerging, have been depicted since 1884. It was earlier termed bursattee (derived from the Indian word meaning rains), espundia and equine *phycomycosis*. Keratitis is often reported. The agent is found mostly in inland water and soil, and cases are found mostly after rains. Injured areas in skin come in contact with the ecological niche of *Pythium spp*. and a glycoprotein helps in attachment of the encysted zoospores to the injured site.[12] It can be classified under the Phylum *Chytridiomycota*. The agent can grow on SDA (Sabouraud's dextrose agar) as submerged hyphae after a few days of incubation. Microscopy shows slender hyphae. From tissue, potassium iodide–sulfuric acid (IKI-H2SO4) stain is done, which is cost-effective, simple, sensitive, as well as specific for diagnosing the oomycete of *Pythium spp.*[13] The Pythium hyphae are seen as blue/bluish-black and can be labelled as positive, and yellow or yellowish brown is considered negative staining. However, it is not a true fungus because it does not have ergosterol in its cell membrane or chitin in its cell wall.

d) Zoonotic sporotrichosis: In Brazil, zoonotic sporotrichosis caused by *Sporothrix brasiliensis* has now emerged as an important disease of cats and humans.[14] Originally described in 1898, sporotrichosis is a chronic granulomatous infection having a worldwide distribution. It is caused by the thermally dimorphic fungus *Sporothrix spp*. Until the early 2000s, *S. schenckii* was the only known species implicated in disease. However, genetic analyses have recently led to the description of additional species, like *S. globosa, S. mexicana, S. luriei* and *S. Brasiliensis*.[15] *Sporothrix brasiliensis* causes infections spreading from cat to man. Infections are very common, especially in Rio Grande de Sul and Rio De Janeiro.

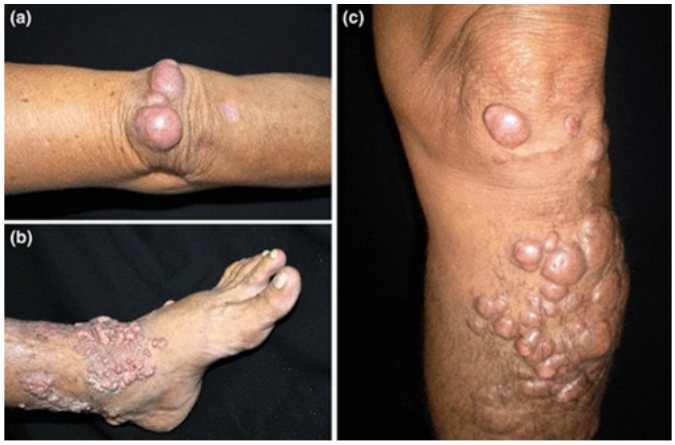

Figure 2 *Lobomycosis.* Source:- Wiley online library

Discussion

Factors like overcrowding, more international travel, immunosuppressed conditions and coexistence with animals has led to emerging mycoses mentioned above. Other factors like new modes of immunotherapy may also contribute to the high burden of emerging mycoses. *Candida auris* is such an emerging fungal infection that can cause several types of infections, including surgical site infections. Surgical site infections can occur after any surgical procedure, and *Candida auris* is becoming a more common cause of these types of infections. One of the challenges with *Candida auris* is that it is resistant to multiple antifungal medications. This can make treating surgical site infections caused by this fungus challenging. To prevent surgical site infections, healthcare facilities should follow strict infection control protocols, including proper hand hygiene, disinfection of surfaces, and appropriate use of prophylactic antibiotics. Additionally, patients undergoing surgery may be screened for the presence of *Candida auris* to prevent transmission to other patients in the healthcare setting. Overall, preventing surgical site infections caused by *Candida auris* requires a multifactorial approach, including infection prevention measures, early identification and diagnosis, and appropriate treatment. The HIV pandemic and close contact with pets and aquatic animals may also be a powerful contributing factor behind other emerging mycoses delineated above, like *Emergomycosis* and *Lobomycosis*. Unless one is vigilant, one may miss many of these cases. Both clinicians and laboratory scientists need to be vigilant about these emerging fungi.

Conclusion

Many factors have led to emergence of fungal zoonoses now. Whenever there is unexplained fever and systemic symptoms in immunocompromised patients, one should look for detecting these systemic emerging fungi. Also, one should look for exposure to aquatic animals in case of papule-like or keloidal fungal lesions over skin. There should be more scientific research regarding these emerging fungal infections so that students and researchers n medical Mycology get to know about these fungi more. Misdiagnosis or false diagnosis of infections caused by these pathogens should be avoided as much as possible.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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DOI: 10.15406/mojbm.2023.08.00188