IJBPAS, July, 2023, 12(7): 2932-2942

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

A REVIEW ON DIAGNOSIS & THEIR TREATMENT: FUNGAL INFECTIONS

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Received 10th July 2022; Revised 15th Sept 2022; Accepted 10th Oct. 2022; Available online 1st July 2023

https://doi.org/10.31032/IJBPAS/2023/12.7.7020

ABSTRACT

Non- systemic or systemic fungal infections affects the individuals who make him seriously ill with confirmed risk factors such as those frequently found in transplant recipients. Unfortunately, they are mostly diagnosed late, when the efficacy of the available treatments is low, often less than 50%, and the cost in terms of lives lost, hospital length of stay, and total hospital costs is substantially increased. The choice of a prophylactic agent should be based upon its ease of administration, lack of adverse effects, reduced likelihood of potential drug interactions, and its efficacy in patients with established risk factors and comorbid disease processes that include renal, hepatic, and chronic pulmonary disease. The indications for the use of currently available antifungal agents, their adverse effects, drug interactions, ease of dosing, and applicability in patients with preexisting disease states, and especially in liver transplant recipients, are presented in this review paper.

Keywords- Non- systemic, systemic fungal infections, treatments

INTRODUCTION

More than 600 fungal strains are correlated with humans as pathogens that provoke some of the most deadly contagious disease. Particular with weaken immune system are the most unsafe, healthy persons are also at danger from widely known and emerging pathogens Mainly in circumstances in which infection include a large inoculum. Worldwide rise in the occurrence of invasive fungal infections and the evolution and spreading of fungal parasite resist to all modern classes of antifungal these microorganism cause an acute threating to the human health. However many fungi are related with humans nearly few are dangerous pathogens. The fungal kingdom grow at ambient temperature find in nature since the normal body temperature of humans are high so the most fungi don't invade inside the body as a result, fungi like the ones that induce athlete's foot, ringworm and other skin problems are usually found on the external surface or outer side of the body. A small number of species grow inside the body under usual environment. Here almost few species of fungi that give rise to most human disease of host with an intact immune system. Several fungi can give rise to disease in hosts who are immunocomprised **[1]**. The majority of individuals in their life span were develop external fungal infection. Fungal sepsis of the skin, hair and nails are a usual worldwide problem 20-25% of the global population has skin mycoses that are generally caused by *dermatophytes, C. albicans* infections are persistent in babies, weaken immune system individuals, diabetic and obese individuals. Invasive fungal infection have usually a lower disease incident than superficial infections, but invase fungal infection have high mortality rates **[2]**. Pathogenic fungi also infect human beings although superficial fungal infection are normally benign, invasive infections are much difficult to cure and they have an astonishing effect on human health, whereas the majority of recent studies evaluate that they were responsible for the death of more than 1.6 milllion people annually. Universally fungal infections are very hard to treat and the mortality remains very high even when approved antifungal treatment can be used. The first difficulty is that no vaccine is still available and the arsenal of antifungal molecule accessible is limited and not present in most countries. A very small number of antifungal molecules are utilized to cure fungal infection. Echinocandins class of antifungal drug has been developed over the last 15 years weakening of a host

immunity due to aids and cancer disease with change in immune response and mostly infected by aggressive fungal pathogens also describe therapeutic failures. The guideline for the cure of issued *cryptococcocal meaningitis* is issued by the world health organization in 2018 are Amphotericin B deoxycholate and flucytosine and the long term fluconazole treatment although the cost and the absence of license strongly limit the acquirer of these drugs in countries the most affected by this disease. In order to combat with fungal disease novel antifungal drugs with improved efficiency are required **[3]**.

CLASSIFICATION

There are two major classifications of fungi filamentous fungi and yeast on the basis of their morphological property. They are categorizing into five phyla using a fusion of morphological character and the reproductive mechanism. The kingdom fungi comprise of one subkingdom, Dikarya, involving phyla Ascomycota and Basidiomycota seven phyla .That is – Ascomycota, Basidiomycota, Chytridiomycota, Glomeromycota, Blastocladiomycota, Neocallimastigomycota. and Microsporodia. Numerous human pathogen fungi are discover in the phyla Ascomycota, Basidiomycota, and microsporidia along with fungi incertae sedis along with the prospect of a medical mycologist, human pathogenic fungi are efficiently seperated seven subgroups **[4]**.

1- Dermatophytes
    a- Epidermophyton
    b- Microsporum
    c- Trichophyton
2- Yeast
    a- Blastoschizomyces
    b- Candida
    c- Cryptococcus
    d- Lacazia
    e- Malassezia
    f- Rhadotorula
    g- Saccharomyces
    h- Trichosporon
3- Dimorphic fungi (represented by blastomyces, coccidioides, histoplasma, Parcoccidioides)Hyaline hyphomycetes (hyaline molds) represented by Acremonium, Aspergillus, chrysoporium, Beauveria, Cylindrocarpon, Fusarium, Geotrichum, Gliochladium, Graphium, Madurella, Mall branchea, Onychocola, Paecilomyces, Penicillium, Scedosporium, scopulariopsis, sepedonium, Trichoderma, Trichothecium and verticillium.
4- Dematiaceous hyphomycetes (represented by Acrophialophora,

Alternaria, Aureobasidium, Bipolaris, Cladophialophora, cladosporium, Curvularia, Drechslera, Exophiala, Exserohilum, fonsecaea, Hortae, Lecythopora, Ochroconis, Phaeoacremonium, Phialophora, Ramichloridium, Rhinocladiella, scedosporium, sporothrix, Ulocladium and veronaea.

5- Coelomycetes represented by colletotrichum, Lasiodiplodia, Nattrasia and Phoma.
6- Zygomycetes (reprsented by Apophysomyces, Basidiobolus, Conidiobolus, cunninghamella, Mortierella, Absidia, Rhizo mucou, Rhizopus, Saksenaea, Syncephalestrum.
7- Basidiomycetes **[5]**.

ARISING FUNGAL WARNINGS TO HUMANS

The effect of fungi on human wellbeing has been under appreciated, although that these eukaryotic pathogens cause infection to the billions of people globally. Systematic fungal diseases were limited in humans until the 1950s when antibiotics and the evolution of ICU reform modern medicine. Immunosupressive agents are used in the start of 1950s such as corticosteroids the advancement of cancer chemotherapies, and the inception of catheters that allow entry for microbes on the surface of a body to the body's interior. These aspects permit the fungi to exploit humans in new ways. Superficial infections are the most usual and involve the one billion humans with skin, nail infection and hair infection. Candida is a fungal infection caused by so called yeast additionally very common with over 135 million females **[6]**.

FUNGAL INFECTION CAUSED IN HUMAN BEINGS

Fungi also cause the superficial fungal infection, which can enter various aspects of the human body. These infections involve dermatophytes which infect keratinized epithelium, hair follicles, nail apparatus. Candida which require hot, humid environment., Malassezia which needs a moist microenvironment Dermatophytes infect stratum corneum, nails, & hair an epidermis dermatophytosis infection is known as epidermomycosis, Dermatophytosis of hair & hair follicles is called trichomycosis and the dermatophytosis of nail is known as onchomycosis **[7]**.

A. Tinea Pedis

Dermatophytes infections are distinguished by body areas. This is the infection of foot.

Disease	Definition	Treatment
Tinea Pedis	**This is the infection of foot.**	**1-Topical Agents** **a- Clotrimazole** **b- Miconazole** **c- Ketoconazole** **2- Systemic antifungal agents** **a- Terbinafine,250mg tablet for 14 days** **b- Itraconazole 200mg tablet for twice daily for 6 days** **c- Fluconazole 150mg once weekly for 2-6 week.**

B. Tinea Cruris

Tinea jockitch medically named as tinea cruris, a rise in warm weather after extreme sweating and wearing moist clothes. The encouraging factor is existence of warm and moist conditions. Mostly male are affect more than females. Itching turn into worse as moisture gather and the contributing condition to this inflamattory process is overweight and moisture **[8]**.

Disease	Definition	Treatment
Tinea cruris	**Fungal infection at groin**	**Fluconazole 50-100 mg daily or** **Fluconazole 150 mg once weekly × 2-3 wk** **Itraconazole 100 mg daily × 2 wk** **Itraconazole 200 mg × 7d** **Terbinafine 250 mg daily × 1-2 wk** **Griseofulvin 250 mg thrice a day for 14 days**

C. Tinea Corporis

This disease arises at any group and is more widespread in warm weather. A wide range of explaination exist with lesions varied in size, degree of infection, and depth of involvement **[9]**.

Disease	Definition	Treatment
Tinea Corporis	**Any part of body**	**Fluconazole 150-200 mg once weekly for 2-4 weeks.** **Itraconazole 200 mg × 7 days.** **Terbinafine 250 mg daily for 1 week.**

D. Tinea capitis

This fungal infection arises most of the time in prepubertal children at the age of between 3 and 7 years of age. Anthropophilic species spotted in humans is the most probably species of dermatophyte to cause this disease. Human get infection after they come in contact with a infected pet or infected person **[10]**.

Drug	Dosage	Duration
Griseofulvin 250 mg	**20-25 mg /kg/d (microsize formulation)** **10-15 mg / kg/d (ultramicrosize formulation)**	**6-12 week** **6-12 week**
Terbinafine 250 mg tablet	**Weight 10-20 kg 62.5 mg** **Weight 20-40 kg 125 mg** **Weight > 40 kg 250 mg**	**4-6 week** **4-6 week** **4-6 week**
Itraconazole 100 mg tablet	**3-5 mg / kg/d** **5 mg /kg/d for 1 week every month** **3 mg /kg /d (oral suspension)**	**4-6 week** **2-3 month** **2-3 month**

E. Tinea versicolor

Dimorphic lipophilic yeast give rise to infection of skin tinea versicolor, Pityrosporum orbiculare and Pityrosporum ovale both of them were formerly known as Malassezia. They both are the part of a skin flora and they are seen where the sebaceous activity is high **[11]**.

Disease	Definition	Treatment
Tinea versicolor	**Tropical part of body**	**Ketoconazole 2 % shampoo is the first choice of mepdication. The shampoo should be rub to the whole skin surface from scalp area down to the thighs. Left the shampoo for five minutes on the surface of a skin and then rinsed completely all over the skin**

INVASIVE FUNGAL DISEASE

Globally IFD are rising fastly and very difficult to cure and mortality rate is high based on the pathogen and patient population. *Candida albicans, Aspergillus fumigatus, Cryptococcus neoformans*, *Pneumocystis jirovecii* endemic dimorphic fungi and mucormycetes they are the most dangerous fungal pathogens which cause fungal infection or disease. Although the capability of these fungi to triggered the infection depend upon their virulence factor and pathogenic ability, along with the interrelation with the host. Fungal disease can be begin by breach of fungi microbiota into the mucosa by the Intake of fungal spores from the surrounding **[12]**.

RISK FACTORS OF AN INVASIVE FUNGAL DISEASE

Risk factor	Specific condition	Most common pathogens.
Medical intervention	**Catheters, intravascular or intracranial devices**	***Candida albicans, Candida spp.***
	Broad spectrum antibiotic used	***C. albicans, Candida spp.***
	Neurosurgical procedures contaminated devices and drug preparations	***Candida spp, saprophyte fungi.***
Treatment induced immunosupression	**Several prolonged neutropenia**	***Aspergillus fumigatus, Aspergillus spp.***
	Solid organ transplantation	***C. albicans, Candida spp, A. fumigatus, Cryptococcus neoformans***
	Haematopoietic stem cell transplantationl	***A . fumigatus, C.albicans,***

		Candida spp, Pneumocystis jirovecii, Mucormycetes
	Biological agent	***Candida spp., Aspergillus spp., Cryptococcus spp, P. Jirovecii , Dimorphine fungi, Mucormycetes***
Disease induced immunosupression	**Hiv infection**	***P. Jirovecii, C.neoformans Histoplasma capsulatum, Talaromyces marneffei***
	Uncontrolled Diabetes	***Rhizopus oryzae, Mucormycetes,***
	Chronic obstructive pulmonary disease	***A.fumigatus***
Co-infection	**Tuberculosis**	***A fumigatus, Aspergillus niger, H. capsulatum, C. neoformans, C. albicans***
	Cytomegalovirus	***P. jirovecii, Aspergillus spp, non Aspergillus molds.***
	SARS COV-2 infection	***A. fumigatus***
Environmental exposure	**Trauma**	***R. oryzae, Mucormycetes***

ESTIMATED OCCURRENCE RATES AND DEATH RATES OF INVASIVE FUNGAL DISEASE

Mycosis	**Causative agents**	**Cases per year**	**Mortality rate**
Invasive Candidiasis	***Candida albicans***	**~750,000**	**~40**
Invasive Aspergillosis	***Aspergillus fumigatus***	**>300,000**	**30-70**
Pneumocystis pneumonia	***Pneumocystis jirovecii***	**>400,000**	**10-60**
Cryptococcal meningitis	***Cryptococcus Neoformans***	**>225,000**	**15-50**
Disseminated histoplasmosis	***Histoplasma capsulatum***	**>100,000**	**10-60**
Mucormycosis	***Rhizopus oryzae***	**>10,000**	**35-100**

PRESENT AND FUTURE PROBLEMS: THE UNKNOWN

The epidemiology of fungal disease is aggressive and modification is challenging to predict. In 2012 the CDC reported an eruption of fungal infection of the CNS that take place in the group of patient who receive epidural or paraspinal injection of methyl prednisolone. Mostly patient had meningitis caused by *Exserohilum rostratum* a rare fungal disease. The *Exserohilum rostratum* eruption of fungal disease killed over 60 people out of 750 infected patients. Sporotrichosis eruption of fungal disease in brazil is the largest outbreak in history face by Brazil caused by a fungus called *Sporothrix brasilensis*. There is also a growing sensation that weather change *Candida Auris* has revealed as a severe worldwide threat to human health causing infection resist to all class of antifungal drugs in immunosupressed patients. The evolution of *C. Auris* recommend that the fungus has recently obtain the virulence characteristic

needed to cause harm to human hosts, whereas these clarification cannot be exclude it is unlikely that these transformation take place simultaneously on three continents. In this sense it has lately been suggest that isolates of *C.auris* adjust to the human body temperature hence as a result of a global warming this would be the first exemplar of a newly human fungal pathogen that appears as a result of global warming which describe the some of its pathogenic characteristics **[13]**.

PLANT PATHOGENIC FUNGI CAUSED HUMAN DISEASE

Currently some plant pathogenic fungi have been noted pathoenic to humans it causes infection to both humans who are healthy as well as in those who are undergoing some forms of chemotherapy. Some plant pathogenic fungi involved in human disease. Several arising human disease caused by common plant pathogens fungi are listed below **[14]**.

Pathogen	Human fungi Disease
B.theobromae, C. truncatum A. Flavus, Curvularia spp.	**Corneal ulcer, keratitis , post wood trauma keratitis**
Curvularia spp., A flavus	**Sinusitis , Paranasal or granulomatous sinusitis**
Curvularia spp.	**Cutaneous infections**
B.theobromae , C. lunata	**Onchomycosis, chromoblastomycosis, Phaeohyphomycosis**
Aspergillus oryzae	**Allergic broncho-pulmonary aspergillosis**
A oryzae	**Meningitis**
A flavus	**Allergic broncho-pulmonary aspergillosis**
A tamari	**Eyelid infection**
A fumigates	**Itchy eyes, headache, cough with blood, stuffy nose**
A alliaceus; A flavus	**Post-surgery otitis externa**
A quizitongi, A beijingensis	**Maxillary aspergilloma**
C. lunata	**Mycetoma**
A flavus	**Wound infection, cutaneous aspergillosis**
A niger	**Fungal ball, otomycosis, damage to inner ear**
F culmorum	**Onychomysis, cornea infection, keratitis**
F oxysporium	**Hyalohyphomycosis , onychomycosis, inflammations**
P chrysogenum; C lunata	**Pneumonia, necrotizing pneumonia**
P chrysogenum	**Fungal ball, localized granuloma, eye infection following trauma**
Penicillium spp	**Chronic granulomatous disorder (CGD)**
P. chrysogenum	**Cerebral disease, paravertebralinfection, otomycosis, peritonitis in immune suppressed persons**
Mucor mucedo	**Necrotic zygomycosis, opportunistic infections**
Verticillium spp.	**Keratitis, subcutaneous infection, peritonitis**
Phomopsis spp.	**Osteomyelitis in diabetic patients**
Phoma spp.	**Endophthalmitis , subcutaeneous, and deep tissue infections**
Rhizopus spp	**Rhinocerebritis**
Absidia spp.	**Invasive infection in Aids and diabetic patients, rhinocerebral infection, mycotic keratitis**
Mucor indicus, M. ramosisimus And M. Circinelloides	**Invasive vascular tissue infection**
C. dematium, C. truncatum, C.crassipes, C. coccoides, C.gloeosporioides C.graminicola	**Endophthalmitis, corneal ulcers, keratitis, subcutaneous infection**
Trichoderma viride	**Pulmonary infection, peritonitis in dialysis patients. Perihepatic infection in organ transplant patients, amyloidosis**

C. gloeosporioides	**Deep soft tissue mycosis ; keratomycosis**
Pythium alphanidermatium	**Post trauma deep soft tissues mycosis invasive wound infection.**
P insidiosun	**Keratitis, haemoglobinopathy syndrome , vascular and systemic infections of the brain and other organ in leukemic patients.**
Bipolaris australiensis B. hawaiinensis, B spicifera	**Allergic and chronic sinusitis, brain fungal ball, fungemia, rhinorrhea, endocarditis, meningo encephalitis, peritonitis and osteomyelitis.**
P . capsulatum	**Fungus ball in type 2 diabetic patient**
Schizopyllum commune	**Fungus ball of the lung in a patient with pulmonary tuberculosis and diabetes.**
S .commune	**Broncho pneumonia in gastric carcinoma patient**

ANTIFUNGAL TREATMENT

During the last few years the remedial strategy of invasive candidiasis have modified. Treatment of invasive candidiasis is depend upon choosing the best effective antifungal drug that is not resist. The selection of drug is mostly based on the information accomplished from clinical trials and if achieveable by the detection of fungal species. Antifungal agents used in the patients **[15]**.

1- Azoles
- **a-** Fluconazole
- **b-** Itraconazole
- **c-** Isavuconazole
- **d-** Posaconazole
- **e-** Voriconzole

2- Polyenes
- a- Amphotericin B and its lipid formulation

3- Echinocadin
- a- Caspofungin
- b- Micafungin
- c- Anidulafungin

Azole

Miconazole and Clotrimazole (Topical agent) introduced in 1969 and econazole introduced in 1974 as well as the parentral formulation of miconazole in 1970s.They ihibit P cytochrome 450 enzyme in fungi. This enzyme are present inside the bacteria, fungi, yeast, protozoa ,insect ,vertebrates , plant. Azole inhibits the crucial enzymes 14α-demethylase **[13]**.

Echinocandin

The MOA of echinocandin is they inhibit the synthesis of 1,3 beta – gluan synthesis which leads to damage the cell wall of fungi. They are fungicidal against Candid Spp and fungistatic against Aspergillus Spp. **[18]**. Echinocandin resistance are not found in C.glabrata and C. parapsilosis. Bioavailability is poor for all echinocnadins and they are given or deliever by IV route. Caspofungin is the first drug for clinical study as well as micafungin and anidulafungin is also studied **[15]**.

Polyenes

Amphotericin B come to the polyenes class of antifungal drugs. Amphotericin B is well known to induce the cell lysis after bind to the ergosterol. Amphotericin B is more

efficient against the pathogen Candida lusitaniae. The azole antifungal drugs has enhanced therapy of C. lusitaniae infection but Amphotericin B resist strain remain to be hard to treat **[16]**.

New Antifungal Drug

Nikkomycin Z(NIK) is the novel antifungal drug show fungicidal activity. It shows inhibition of chitin synthase. The interest grow farther when NikZ confirmed to be fungicidal against dimorphic fungi, displaying remarkable clinical advantages in mammals against Coccidioides, Histoplasma, and Blastomyces Spp. Nikkamycin Z (NikZ) activity against a broad range of fungi pathogens, Li and Rinaldi inspect invitro antifungal activity of NikZ alone and combined with fluconazole and itraconazole, examining against 110 isolates of 24 species. The outcome are brief here in table **[14, 15]**.

Li Rinaldi – Selected	NikZ µg/ml		FIC	
	Range	MIC50	FCZ	ITRA
Candida Albicans	<0.5-32	4	0.48	0.2
Candida parapsilosis	1-4	2	0.32	0.46

CONCLUSION

Antifungal drug resistance having an biggest problem in treatment of fungal infections or line of treatment by view of this review have an idea to treat the specific infection with the suitable existing natural or synthetic drugs.

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