



IJPPR

INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203



Human Journals

Review Article

March 2020 Vol.:17, Issue:4

© All rights are reserved by Jnanamba P et al.

Fungal Infections in Man



IJPPR
INTERNATIONAL JOURNAL OF PHARMACY & PHARMACEUTICAL RESEARCH
An official Publication of Human Journals

ISSN 2349-7203



Jnanamba P*¹, Krishan Pal Singh², Raghavendra³

¹*Research Scholar OPJS University, Churu, Rajasthan, India*

²*Research Guide OPJS University, Churu, Rajasthan, India*

³*Research Scholar OPJS University, Churu, Rajasthan, India*

Submission: 25 February 2020
Accepted: 2 March 2020
Published: 30 March 2020

Keywords: Antifungal agents, Drug resistance, Pharmacology

ABSTRACT

The incidence and spectrum of local as well as systemic fungal infections have increased dramatically over the past two decades. Various factors which predispose patient to invasive fungal infections are advances in medical technology, use of invasive monitoring devices, mechanical ventilation, parenteral nutrition, broad spectrum antimicrobial agents, intensive cancer chemotherapies, corticosteroid and other immunosuppressive. Traditionally, many invasive fungal infections were associated with a poor prognosis, because effective therapeutic options were limited. The recent development of new antifungal agents has significantly contributed to the successful treatment of fungal diseases. These drugs offer novel mechanisms of action and expanded spectrums of activity over traditional treatment options. However, with these new agents comes the need for increased awareness of the potential interactions and toxicities associated with these drugs. Therefore, an understanding of the pharmacokinetic and pharmacodynamic properties of the classes of antifungal compounds is vital for the effective management of invasive fungal infections. This review provides a summary of the pharmacologic principles involved in treatment of fungal diseases.



www.ijppr.humanjournals.com

INTRODUCTION

Fungi are heterotrophic organisms which are able to reproduce sexually as well as asexually. About 100 infectious fungal agents have been detected in man. Although the existence of fungi dates back a billion years, the history of medical mycology and human mycoses as reviewed by Espinel-Ingroff began in the early 19th century in Italy with the discovery of tinea favosa¹

Pathogenic fungi are fungi that cause disease in humans or other organisms. The study of pathogenic fungi is referred to as "medical mycology." Although fungi are eukaryotic organisms, many pathogenic fungi are also microorganisms².

A member of the Eukarya, fungi lives by absorptive nutrition in which they secrete digestive enzymes to break down large molecules in the environment. They are composed of rapidly growing filamental hyphae and are distinguished by their cell walls which contain microscopic fibrils of chitin, a nitrogen containing polysaccharide.

There are 5 broad groups of fungal infections in man (fungi are the main cause of plant disease as well). Fungal infections can be grouped as follows:

- Thrush (i.e. vaginal thrush, oral thrush (AIDS and cancer patients, antibiotic treatment) and severe nappy rash)
- Skin infections ie athlete's foot, ringworm, dandruff, cradle cap, nappy rash and nail infections
- Invasive and life-threatening infection ie candidiasis (intensive care, prematurity, leukemia, diabetes, dialysis), invasive aspergillosis (leukaemia, transplantation and steroid treatment) and cryptococcal meningitis (AIDS).
- Allergic fungal disease ie allergic fungal sinusitis (normal people with chronic sinusitis) and allergic bronchopulmonary aspergillosis (asthma and cystic fibrosis) and severe asthma with fungal sensitization.
- Chronic fungal infections³⁻⁸ ie chronic pulmonary aspergillosis, chronic invasive or granulomatous sinusitis and Madura foot.

Common fungi⁹⁻¹¹

About 30 different species of fungi cause the vast majority of human fungal infection. In all about 600 species out of an estimated 1 million species worldwide cause human infection; others are implicated in allergic disease. Common fungi causing disease are:

- Candida (thrush and invasive candidiasis)
- Aspergillus (allergic fungal disease and invasive aspergillosis)
- Trichophyton (athlete's foot and nail infections)

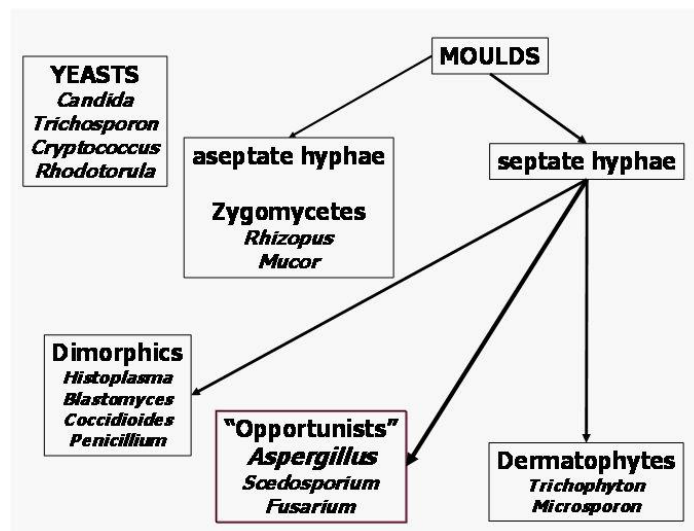


Figure No. 1: Classification of Fungi

Pathogenic Fungi [12, 13, 14 – 15]

Diseases Caused by Fungi

Though *S. cerevisiae* is normally considered a non-pathogenic micro-organism, occasional infections may occur. Furthermore, budding yeast can serve as a model to learn more about pathogenic fungi, in particular with regard to regulatory features and drug therapy, because yeast as a fungal species shares many characteristics with its pathogenic relatives.

Fungal infections or mycoses are classified depending on the degree of tissue involvement and mode of entry into the host. These are:

Superficial - localised to the skin, the hair, and the nails.

Subcutaneous - infection confined to the dermis, subcutaneous tissue or adjacent structures.

Systemic - deep infections of the internal organs.

Opportunistic - cause infection only in the immunocompromised.

Human fungal infections in Europe and large parts of the world are uncommon in normally healthy persons, being confined to conditions such as candidiasis (thrush) and dermatophyte skin infections such as athlete's foot. However, in the immunocompromised host, a variety of normally mild or nonpathogenic fungi can cause potentially fatal infections. Furthermore, the relative ease with which people can now visit "exotic" countries provides the means for unusual fungal infections to be imported into Western countries.

Superficial Mycoses

In superficial mycoses, infection is localised to the skin, the hair, and the nails. An example is "ringworm" or "tinea", an infection of the skin by a dermatophyte. Ringworm refers to the characteristic central clearing that often occurs in dermatophyte infections of the skin. Dermatophyte members of the genera *Trichophyton*, *Microsporum* and *Epidermophyton* are responsible for the disease. Tinea can infect various sites of the body, including the scalp (tinea capitis), the beard (tinea barbae) the foot (tinea pedis: "athlete's foot") and the groin (tinea cruris). All occur in Europe although tinea infections, other than pedis, are now rare. *Candida albicans* is a yeast causing candidiasis or "thrush" in humans.

As a superficial mycoses, candidiasis typically infects the mouth or vagina. *C. albicans* is part of the normal flora of the vagina and gastrointestinal tract and is termed a "commensal". However, during times of ill health or impaired immunity, the balance can alter and the organism multiplies to cause disease. Antibiotic treatment can also alter the normal bacterial flora allowing *C. albicans* to flourish.

Subcutaneous Mycoses

These are infections confined to the dermis, subcutaneous tissue or adjacent structures. Infection may arise following the wounding of the skin and the introduction of vegetable matter. These mycoses are rare and confined mainly to tropical regions. They tend to be slow

in onset and chronic in duration. An example is sporotrichosis caused by *Sporothrix schenckii*. The fungus is dimorphic, being a mould that can convert to a yeast form at 37°C on rich laboratory media or in infection. Sporotrichosis was once common in Europe but cases are now rare. The disease is most prevalent the Americas, South Africa and Australia. Infection usually follows an insect bite, thorn prick or scratch from a fish spine. Certain occupation groups appear to have increased risk from infection. These include florists, farmworkers and others who handle hay and moss. The most common symptom is an ulcerative lesion that may develop into lymphangitis.

Systemic Mycoses (primary and opportunistic)

These are invasive infections of the internal organs with the organism gaining entry by the lungs, gastrointestinal tract or through intravenous lines. They may be caused by: (i) primary pathogenic fungi or (ii) by opportunistic fungi that are of marginal pathogenicity but can infect the immune compromised host.

Primary Pathogenic Fungi

Infection occurs in previously healthy persons and arises through the respiratory route. Examples include histoplasmosis, blastomycosis, coccidioidomycosis and paracoccidioidomycosis. The fungi occur throughout the world but not in large parts of Europe.

Histoplasmosis. This is caused by *Histoplasma capsulatum*. The organism is dimorphic (being a mould that can convert to a yeast form). *H. capsulatum* is endemic in many parts of the world including North and South America. It is found in the soil and growth is enhanced by the presence of bird and bat excreta. Environments containing such material are often implicated as sources of human infection. The lungs are the main site of infection but dissemination to the liver, heart and central nervous system can occur. Pulmonary infection can resemble symptoms seen in tuberculosis.

Opportunistic Fungi: Here, patients usually have some serious immune or metabolic defect, or have undergone surgery.

The diseases include aspergillosis, systemic candidosis and cryptococcosis. Exceptionally, other fungi that are normally not pathogenic, such as *Trichosporon*, *Fusarium* or *Penicillium*, may cause systemic infections.

Aspergillosis. This is the name given to a number of different diseases caused by the mould *Aspergillus*. It produces large numbers of spores and occurs worldwide. In Europe, *A. fumigatus* is the most common species causing disease. The organism can infect the lungs, inner ear, sinuses and, rarely, the eye of previously healthy persons. In the immunosuppressed host, *Aspergillus* can disseminate throughout the body.



Figure No. 2: Aspergillus (allergic fungal disease and invasive aspergillosis)

Candidosis. In severely immunocompromised patients (e.g. those receiving chemotherapy) *C. albicans*, that is part of the normal human flora (see above), can proliferate and disseminate throughout the body.

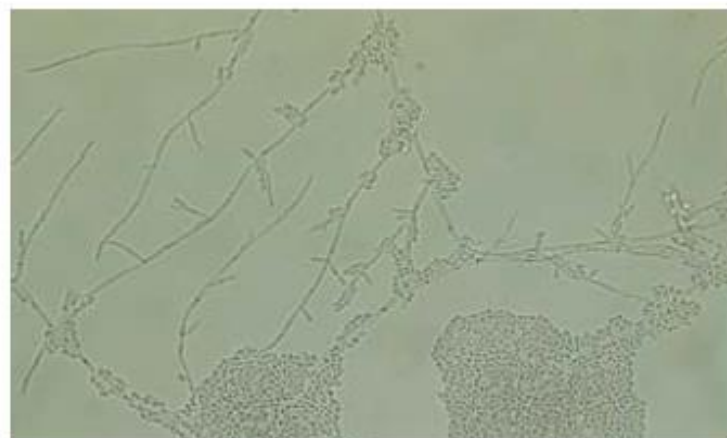


Figure No. 3: Candia (trush and invasive candidiasis)

Cryptococcosis. This is a systemic infection caused by the yeast *Cryptococcus neoformans*. The commonest manifestation is a subacute or chronic form of meningitis resulting from the inhalation of the organism. Pulmonary infection can also occur. The disease affects both healthy and immunosuppressed individuals and occurs worldwide. *C. neoformans* can be isolated in large numbers from pigeon droppings in the environment, although such birds do not appear to harbour the yeast.

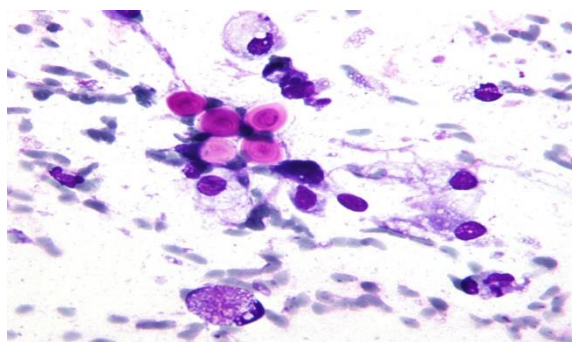


Figure No. 4: Cryptococcosis (acute, pulmonary, systemic or meningitis)

Other Fungal Related Disease: Constant exposure to fungal spores in the atmosphere can induce respiratory allergies. Elevated antibodies to a range of common spore forming fungi have been demonstrated in occupational diseases such as Humidifier fever, Malt workers' lung and Wheat threshers' disease. Certain fungi, such as mushrooms, can produce poisonous toxins that may prove fatal if ingested (e.g. *Amanita phalloides*: "death cap"). Others (*Psilocybe*) affect the central nervous system inducing hallucinogenic responses. Many moulds produce secondary metabolites (mycotoxins) that are highly toxic to humans.

Ergotism is caused by eating bread prepared from rye infected with the fungus *Claviceps purpurea*. Historically, several large scale outbreaks of madness in local populations have been attributed to ergotism.

Pneumocystis. This is an infection of the lung caused by *Pneumocystis carinii*. The organism is a common cause of fatal pneumonia in AIDS patients. An intracellular parasite, with a life cycle of trophozoite and cyst, it was formerly considered to be a protozoan. However, comparison of DNA and RNA sequences have established that it is one of the group of ascomycetes red yeast fungi. The cysts contain 8 nuclei which can be seen in smears of pulmonary aspirates. *P. carinii* is a commensal of many wild and domestic animals and evidence suggests that human infection is commonly derived from dogs.

Other Pathogenic Fungi

A brief survey of pathogenic fungi that are 'prominent' inducers of severe diseases, mostly outside Europe, Some virulence factors in these pathogens have been described, but more detailed information will be available when genome sequences will have been accomplished in the near future.

Histoplasma capsulatum

Histoplasma is a primary pathogenic dimorphic fungus forming macroconidia and microconidia. The yeast form is required for propagation in human tissues. The fungus is endemic worldwide (mainly in North and South America) and is found in soil. It enters macrophages or trachea epithelial cells, whereby the cell surface of the fungus is modified. The proliferation occurs in phagolysosomes. This causes pneumonia similar to tuberculosis and affects the renal cortex and nervous system.

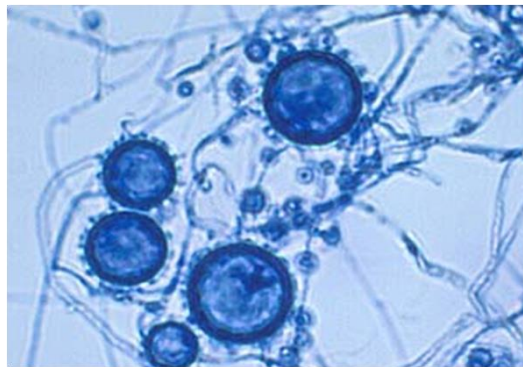


Figure No. 5: *Histoplasma capsulatum*

Cryptococcus performance

Cryptococcus cells are encapsulated by polysaccharide layers (mannose) like bacteria. The negative charge contributed by N-acetyl-neuramic acid and sialic acid prevents phagocytosis of the infecting agent. Virulence is caused by secreted phospholipase B, and possibly by melanine produced by the fungus, which protects against heat and cold. Also, calcineurin is required for virulence. The synthesis of melanin and capsula are regulated by a transduction pathway involving a G-protein (GPA1) and cAMP. By knocking out the GPA1 ge, Cryptococcus remains a virulent. By inhalation, Cryptococcus cause a chronic, subacute to acute pulmonary, systemic or meningitic disease. Infection suppresses the immune response and gives a poor inflammatory response. The mannoproteins of C. performance induce a

proliferative response in human peripheral blood mononuclear cell therapy enhancing HIV replication.

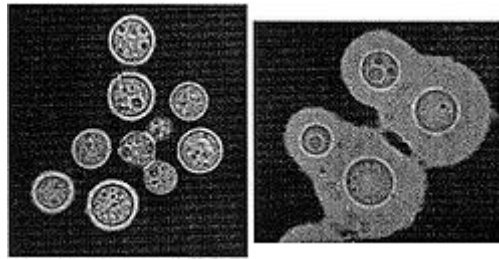


Figure No. 6: Cryptococcus performance

Blastomyces dermatitidis

B. dermatitidis is the causative agent of the 'Chicago disease'. Blastomycosis may be a benign infection or a chronic granulomatous mycosis. Primary infection occurs in the lungs, causes an influenza-like pneumonia, later affecting bones and skin. The virulence is probably caused by a 120 kDa antigen, adhesion WI-1, which is homologous to bacterial invasions from *Yersinia*. The adhesion binds CD11b/CD18 (=CR3) and CD14 on host cells, thereby interacting with macrophages.

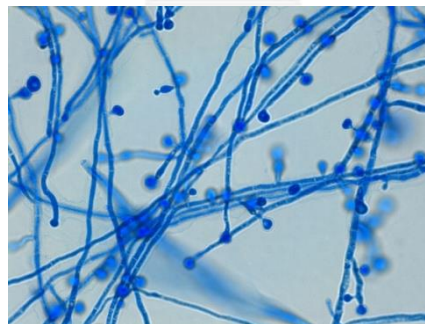


Figure No. 7: Blastomyces dermatitidis

Coccidioides

Coccidioides immitis produces mycoses ('Valley fever') that can become acute, chronic, severe or fatal and is manifest in lung, bone and joints, or may disseminate to meningitis.

Paracoccidioides brasiliensis causes a granulomatous disease that originates as a pulmonary infection. Dissemination occurs resulting in ulcerative granuloma in the nasal and buccal, occasionally in the gastrointestinal mucosa or lymph nodes.



Figure No. 8: Coccidioides

Immune response to fungal infections

The immune mechanisms of defence against fungal infections are numerous, and range from protective mechanisms that were present early in evolution (innate immunity) to sophisticated adaptive mechanisms that are induced specifically during infection and disease (adaptive immunity). The first-line innate mechanism is the presence of physical barriers in the form of skin and mucous membranes, which is complemented by cell membranes, cellular receptors and humoral factors. There has been a debate about the relative contribution of humoral and cellular immunity to host defence against fungal infections. For a long time it was considered that cell-mediated immunity (CMI) was important, but humoral immunity had little or no role. However, it is accepted now that CMI is the main mechanism of defence, but that certain types of antibody response are protective. In general, Th1-type CMI is required for clearance of a fungal infection, while Th2 immunity usually results in susceptibility to infection.

Aspergillosis, which is a disease caused by the fungus *Aspergillus*, has been the subject of many studies, including details of the immune response. Attempts to relate aspergillosis to some form of immunosuppression in animals, as is the case with humans, have not been successful to date. The defence against *Aspergillus* is based on recognition of the pathogen, a rapidly deployed and highly effective innate effector phase, and a delayed but robust adaptive effector phase. *Candida albicans*, part of the normal microbial flora associated with mucous surfaces, can be present as congenital candidiasis or as acquired defects of cell-mediated immunity. Resistance to this yeast is associated with Th1CMI, whereas Th2 immunity is associated with susceptibility to systemic infection. Dermatophytes produce skin alterations in humans and other animals, and the essential role of the CMI response is to destroy the

fungi and produce an immunoprotective status against re-infection. The resolution of the disease is associated with a delayed hypersensitive response. There are many effective veterinary vaccines against dermatophytoses. *Malassezia pachydermatis* is opportunistic yeast that needs predisposing factors to cause disease, often related to an atopic status in the animal.

Two species can be differentiated within the genus *Cryptococcus* with immunologic consequences: *C. neoformans* infects predominantly immunocompromised hosts, and *C. gattii* infects non-immunocompromised hosts. *Pneumocystis* is a fungus that infects only immunosuppressed individuals, inducing a host defence mechanism similar to that induced by other fungal pathogens, such as *Aspergillus*.

CONCLUSIONS

Various factors which predispose patient to invasive fungal infections are advances in medical technology, use of invasive monitoring devices, mechanical ventilation, parenteral nutrition, broad spectrum antimicrobial agents, intensive cancer chemotherapies, corticosteroid and other immunosuppressive. Traditionally, many invasive fungal infections were associated with a poor prognosis, because effective therapeutic options were limited. The recent development of new antifungal agents has significantly contributed to the successful treatment of fungal diseases. These drugs offer novel mechanisms of action and expanded spectrums of activity over traditional treatment options. However, with these new agents comes the need for increased awareness of the potential interactions and toxicities associated with these drugs. Therefore, an understanding of the pharmacokinetic and pharmacodynamic properties of the classes of antifungal compounds is vital for the effective management of invasive fungal infections. The thesis review provides a summary of the pharmacologic principles involved in treatment of fungal diseases.

A number of new compounds, some with unidentified mechanisms of action, are under study. One group includes dication-substituted carbazoles, furans and benzimidazoles, which are aromatic dicationic compounds with antimicrobial activity. Some are quite active *in vitro* against *Candida* spp. (including azole-resistant strains), *C. neoformans*, *A. fumigatus* and *Fusarium* spp. Carbendazim, a benzimidazole derivative, was used as an agricultural fungicide but recently was shown to cure experimental histoplasmosis. Glycyrrhizin, an extract from liquorice roots, has been shown to have antifungal activity

against *C. albicans* in thermally injured mice. Recently, BAY 10-8888, a cyclic β -amino acid related to cispentacin was observed to have potent anti-candida activity both *in vitro* and in an experimental model of systemic candidosis. This compound has a dual mode of action: it is actively accumulated by amino acid permeases and it is a low-affinity inhibitor of isoleucyl-tRNA synthetase, disrupting protein biosynthesis and cell growth.

REFERENCES

1. Espinel-Ingroff A. History of medical mycology in the United States. *Clin Microbiol Rev* 9:235, 1996.
2. San-Blas G; Calderone RA, ed. (2008). *Pathogenic Fungi: Insights in Molecular Biology*. Caister Academic Press. ISBN 978-1-904455-32-5.
3. Horn *et al.*, 2009, Mean *et al.*, 2008, Nace *et al.*, 2009, Neofytos *et al.*, 2009, Pfaller & Diekema, 2007, Wenzel & Gennings, 2005.
4. Edmond *et al.*, 1999, Wisplinghoff *et al.*, 2004.
5. Pfaller & Diekema, 2007, Gudlaugsson *et al.*, 2003, Wenzel & Gennings, 2005.
6. Fridkin, 2005, Marr *et al.*, 2002, Pfaller & Diekema, 2004a, Richardson & Lass-Flörl, 2008, Nucci & Marr, 2005.
7. Safdar *et al.*, 2001, Pfaller & Diekema, 2007, Richardson & Lass-Flörl, 2008.
8. Morgan *et al.*, 2005, Pfaller & Diekema, 2007.
9. Malani *et al.*, 2005, Safdar *et al.*, 2001, Panackal *et al.*, 2006, Magill *et al.*, 2006.
10. Perloth *et al.*, 2007, Pfaller & Diekema, 2007.
11. <http://www.fungalinfectiontrust.org/Whatisfungaldisease2011.pdf>
12. Borges-Walmsley, M. I. and Walmsley, A. R. (2000) cAMP signalling in pathogenic fungi: control of dimorphic switching and pathogenicity. *Trends Microbiol.* 8, 133-140.
13. Brown, A.J.P. and Gow, N.A.R. (1999) Regulatory networks controlling *Candida albicans* morphogenesis. *Trends Microbiol.* 7, 333-338.
14. Calderone, R.A. and Fonzi, W.A. (2001) Virulence factors of *Candida albicans*. *Trends Microbiol.* 9, 327-334.
15. Haynes, K. (2001) Virulence in *Candida* species. *Trends Microbiol.* 9, 591-596.