Cutaneous fungal infections affect more than one-fourth of the world’s population. The pathogenesis and severity of fungal infection depend on various immunological and nonimmunological factors. The rampant use of antifungal therapy in immunocompromised individuals marked the onset of antifungal drug resistance. Fungal resistance can be microbiological or clinical. Microbiological resistance depends on various fungal factors which have established due to genetic alteration in the fungi. Clinical resistance is due to host- or drug-related factors. All these factors may cause fungal resistance individually or in tandem. In addition to standardized susceptibility testing and appropriate drug dosing, one of the ways to avoid resistance is the use of combinational antifungal therapy. Combination therapy also offers advantages in increased synergistic action with enhanced spectrum activity. Newer insights into mechanisms of drug resistance will help in the development of appropriate antifungal therapy.

**Key Words:** Antifungal resistance, dermatophytes, mechanisms

**Introduction**

Fungi have been present for around 1500 million years with more than 1.5 million species out of which only about 300 species are known to cause human infections.[1,2] Fungi were recognized earlier than bacteria as a pathogenic agent of human disease with David Gruby describing etiological agent of favus, ectothrix, and endothrix into three genera, *Epidermophyton*, *Microsporum*, and *Trichophyton.*[3] Despite their early discovery, most widespread infectious diseases in the 19th century were attributed to bacterial, parasitic, and to viral origins.[4] From the mid-20th century, the incidence of severe systemic fungal infections increased significantly, mainly due to increase in the number of patients with compromised immune system such as acquired immunodeficiency syndrome (AIDS) or postorgan transplantation and chemotherapy. The indiscriminate use of antibiotics added to the worsening of this picture, leading to the installation of fungal infections.[5]

Among all fungal infections, superficial mycoses are the most frequent forms of human infections, affecting more than 20%–25% of the world’s population.[6] It is also estimated that 30%–70% of adults are asymptomatic carriers of these pathogens.[7] In addition, species of dermatophytes are divided into zoophilic, geophilic, or anthropophilic, depending on their primary habitat (animals, soil, or humans, respectively). Zoophilic species are responsible for about 30% of human dermatophytoses and usually cause acute inflammatory features. Anthropophilic species represent about 70% of infections on these hosts, causing a chronic infection of slow progression, suggesting that the fungus has adapted to the human host.[8]

**Pathogenesis of Fungal Infections**

The successful initiation of infection is a process closely related to the capability of the infecting dermatophyte to overcome the host resistance mechanisms.[9] Factors affecting fungal virulence are:

a. Defect in normal physiological barriers such as physical and chemical structure of skin, normal microflora present, exposure to ultraviolet light, temperature, and humidity[6]

b. Adherence of dermatophytes and hyphae penetration – adherence of dermatophytes is due to arthroconidia, which are genetically programmed disarticulated septate hyphae. It occurs 3–4 hours

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Antifungal resistance

Clinical resistance is defined as the failure to eradicate a fungal infection despite the administration of an antifungal agent.

Microbiological resistance refers to nonsusceptibility of a fungus to an antifungal agent by in vitro susceptibility testing, in which the minimum inhibitory concentration (MIC) of the drug exceeds the susceptibility breakpoint for that organism. Microbiological resistance can be primary (intrinsic), where the fungi are resistant to a drug before exposure and secondary (acquired), which develops in response to exposure to an antimicrobial agent. Certain fungal species are intrinsically resistant such as Candida krusei to fluconazole and Cryptococcus neoformans to echinocandins and nonalbicans Candida to 5-flucytosine (5FC).

Secondary resistance develops among previously susceptible strains after exposure to the antifungal agent and is usually dependent on altered gene expression, for example, terbinafine resistance in T. rubrum, fluconazole resistance among C. albicans.

Clinical resistance is defined as the failure to eradicate a fungal infection despite the administration of an antifungal agent.
agent with in vitro activity against the organism. Although clinical resistance cannot always be predicted, it highlights the importance of individualizing treatment strategies on the basis of the clinical situation.\(^{[10]}\)

Fungal factors, host factors, and drug pharmacology play a role in fungal resistance in isolation or in association with other. The fungal molecular mechanism can result from gene amplification, gene transfer, gene deletion, point mutations, loss of cis- and trans-acting regulatory elements, and transcriptional activation. All these effects could be on genes directly involved in the combat against the cytotoxic compounds and/or could be on genes involved in their regulation or processing.\(^{[5]}\)

The genes responsible for ergosterol synthesis is given in Figure 2.\(^{[13]}\)

### Table 1: Factors for fungal resistance

| Fungal factors                                      | Host factors                                      |
|----------------------------------------------------|--------------------------------------------------|
| Reducing the accumulation of the drug within the fungal cell | State of immunosuppression                         |
| Decreasing the affinity of the drug for its target   | Site of infection                                  |
| Modifications of metabolism to counterbalance the drug effect | Severity of infection                              |
| Cellular response to stress                          | Onset of treatment                                 |
| Biofilm production                                   | Drug related                                       |
| Drug related                                         | Fungistatic nature                                |
| Pharmacokinetics                                     | Dosage                                            |
| Drug-drug interactions                               |                                                  |

**Fungal Factors**

**Decreased accumulation of drug within fungi**

Reducing the accumulation of the drug within the fungal cell is done by increasing the drug efflux mechanism. Multidrug efflux transporters are membrane proteins found in all living organisms. These proteins bind to a variety of structurally and chemically dissimilar compounds and actively extrude them from the cells.\(^{[1]}\) Mutations (upregulation or overexpression) of the genes encoding these efflux pumps result in decreased accumulation of the drug in the cell.\(^{[21]}\)

Efflux systems affecting the antifungal drugs vary. Common drug efflux systems that modulate azole resistance are the ATP-binding cassette (ABC) superfamily and the major facilitator superfamily. Overexpression of *TruMDR1* and *TruMDR2* genes in *T. rubrum*, which encoded an ABC transporter was seen followingazole and terbinafine therapy.\(^{[5]}\)

**Decreasing the affinity of the drug for its target**

A mutation or overexpression of the gene coding for target enzymes is another mechanism developed by fungi.

A point mutation in the ERG11 gene that codes for lanosterol 14α-demethylase leads to the complete inhibition of the binding capacity of theazole drug to its target.\(^{[14]}\) Mutation in the squalene epoxide (SE) gene (ERG1) leads to an amino acid substitution in the SE making the fungi about 1000-fold less susceptible to terbinafine.\(^{[5]}\)

The overexpression of target enzymes is either by gene amplification or upregulation of the corresponding gene.\(^{[8]}\) In chromosomal anomalies like isochromosome formation, an increase in the number of azole-resistant genes can occur.\(^{[21]}\)

**Modifications of metabolism to counterbalance the drug effect**

**De novo synthesis of pyrimidines**

The antifungal drug 5FC competes with the regular pyrimidine intermediate metabolites for incorporation into nucleic acids.\(^{[14,22]}\) *De Novo* increase in pyrimidine synthesis leads to 5FC resistance as seen in *Candida glabrata*.\(^{[14]}\)

**Paradoxical effect**

Few yeasts and filamentous fungi are able to grow in elevated echinocandin concentrations much higher than the MICs. This phenomenon, called paradoxical effect or “eagle effect,” is strain dependent and is due to the upregulation of the chitin synthesis in the fungal cell wall after drug administration.\(^{[14,20]}\)

**Modifications of the ergosterol biosynthetic pathway**

The antifungal activity of azole drugs depends on the depletion of ergosterol from the fungal membrane and accumulation of the toxic product 14α-methyl-3,6-diol, leading to growth arrest. Alteration in the late steps of the ergosterol biosynthetic pathway through inactivation of the ERG3 gene can lead to the total inactivation of C5 sterol desaturase and also can give rise to cross-resistance to all azole drugs. This mechanism is identified in *C. albicans*.\(^{[14,20]}\)

**Plasma membrane composition variation**

A decrease or total absence of ergosterol in the plasma membrane through mutations in nonessential genes of the ergosterol is a rare mechanism of resistance among polyene drugs, for example, ERG3 mutation in clinical isolates of *C. albicans*, ERG6 mutation in *C. glabrata*.\(^{[14]}\)
**Biofilms**

Biofilms are sessile microbial communities surrounded by extracellular polymeric substances with increased resistance to antimicrobial agents and host defenses. Both *T. rubrum* and *T. mentagrophytes* are capable of producing biofilms.[23]

Biofilms by yeast and certain molds are frequently polymicrobial and are resistant to almost all the currently used antifungals, with the exceptions of echinocandins and lipid formulations of amphotericin B. Biofilm resistance is probably the result of multiple factors such as an increased expression of efflux pumps, a modification of plasma membrane composition, and the drug sequestration in biofilm-produced extracellular matrix.[14,21]

**Cellular response to stress or stress adaptation**

Fungi are remarkably adaptive and have numerous signal-transduction pathways to sense and ensure appropriate physiological mechanisms to adapt to environmental stress following exposure to an antifungal agent.[5,21] Hsp90, Hsp104, ubiquitin, calcineurin, esterases, and oxidative-stress proteins such as glutathione synthetase are key cellular regulators critical for orchestrating cellular responses to drug-induced stress, e.g., in *T. rubrum* following azoles, griseofulvin and amphotericin B.[9]

Stress adaptation may not induce clinical resistance but stabilizes the cell in the presence of drug and allows it to develop more profound resistance mechanisms over time that are manifested as clinical resistance.[21]

**Clinical Resistance**

Clinical resistance depends on a multiple host- and drug-related factors which are as follows:[13,20]

- a. Patients with severe degree of immunosuppression with invasive fungal infections may not respond to antifungals
- b. Delay in initiation of adequate dose of antifungal results in increased chances of treatment failure
- c. Fluconazole has better cerebrospinal fluid (CSF) penetration as compared to itraconazole, therefore, making it a better choice in treating fungal meningitis. When the site of infection is necrotic with poor blood supply, a debulking surgery is essential to overcome antifungal treatment resistance
- d. Compliance in patients requiring long-term therapies.

**Drug-Related Factors**

Various factors such as the fungistatic nature of most drugs, inappropriate antifungal usage (in cases where the etiological agent is known), treatment with low antifungal dosage, long duration of treatment, drug interactions, and the cost of therapy play a role in fungal resistance.[21] Combination of polyenes and azoles with other nephrotoxic drugs can result in treatment failure.[20]

**Environmental resistance**

In recent years, the role of environment as a driver for resistance has become prominent. Fungicidal use in agriculture differs hugely between different regions, with the United States using about a tenth of as much as Europe. Azole-based fungicides are used in grape and

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**Figure 2:** The genes involved in ergosterol synthesis
cereal production in European countries. A strong link has been found between countries where azole-based fungicides are used and the incidence of antifungal resistance.[21,24]

**Antifungal susceptibility testing**

Antifungal susceptibility testing (AFST) has undergone considerable change from a nonstandardized procedure that generated results lacking clinical utility to a standardized procedure. Standardized microdilution-based procedures by the Clinical and Laboratory Standards Institute (CLSI) and the European Committee on Antibiotic Susceptibility Testing are universally accepted for performing AFST.[25] The CLSI, formerly the National Committee on Clinical Laboratory Standards has released four standard methods for antifungal susceptibility testing, namely, M27-A3 for macrobroth and microtiter yeast testing, M38-A2 for microtiter mold testing, M44-A for yeast disc diffusion testing, and M51-P for mold disc diffusion testing.[26-31]

AFST patterns in dermatophytes show individual and regional variation in their outcome. Studies on AFST showed that *T. rubrum* and *T. mentagrophytes*, which were the common species isolated, showed a higher MIC to fluconazole. Although generally itraconazole, terbinafine had lower MICs, few studies demonstrated a higher MIC to itraconazole and terbinafine. Systemic griseofulvin and topical amorolfine had lower MIC than fluconazole. A study done by Koga et al. showed the lowest MIC to be with luliconazole.[32-36] Rex and Pfaller proposed the “90–60 Rule” which states that infections caused by isolates that have MICs considered susceptible respond favorably to appropriate therapy approximately 90% of the time, whereas infections caused by isolates with MICs considered resistant respond favorably approximately 60% of the time.[37]

**Treatment**

Clinically, antifungal resistance may be suspected in patients with recurrent episodes of infection, unresponsiveness to the first line of therapy, generalized involvement, or atypical form of presentation with usual history of similar lesions in the family.

One of the important treatment measures in recurrent cutaneous fungal infections is prevention of disease among family members. Therefore, nonpharmacological measures like good hygiene play an important adjunct along with medications.[38]

Good skin hygiene measures include handwash; clipping of nail; regular bathing and complete drying of the skin; use of nonocclusive shoes, absorbent socks, and powder; avoidance of sharing of combs, towels, brushes, bedding, and hats; and avoidance of barefoot walk in public bathroom.[39,40]

Pharmacological measures like prudent use of antifungals in proper dosing and duration form the mainstay of therapy. In general, topical agents should be applied once to twice daily over the lesions and up to at least 2 cm beyond the margins of the lesions for 2–4 weeks and continued for 1 week after the rash resolves.[41] Topical allylamines maintain the mycological cure for longer periods compared to azole drugs.[42] With respect to systemic antifungals, in addition to a proper dose, duration, and knowledge of pharmacokinetics, dosage up dosing (pulse or boosted oral antifungal) and combination antifungals can be tried in recurrent dermatophytoses. Boosted oral antifungal treatment is designed to target dormant chlamydospores and arthroconidia to produce sensitive hyphae which are less refractory to antifungal treatment.[43,44]

**Combination Antifungal Therapy**

The availability of new antifungal agents with unique mechanisms of action and improved tolerability has widened the possibilities for the use of combination antifungal therapy for difficult-to-treat opportunistic mycoses.[45] Combining two systemic antifungal agents has been used in invasive mycoses caused by *Candida*, *Aspergillus* and *Cryptococcus*. In dermatophytopes, combination antifungal therapy has been used, wherein topical and systemic antifungal are combined. Gupta et al. used sequential therapy with itraconazole and terbinafine pulse in toenail onychomycosis.[46,47] The advantages of combination therapy are increased rate and extent of fungal killing (synergy), enhanced spectrum of activity, and decreased likelihood of resistance or tolerance.[48] Azoles can act in a synergistic way when combined with terbinafine providing good results against *Candida*, dimorphic molds, dematiaceous fungi and yeasts, such as *C. glabrata*. Azoles with amphotericin B have mixed response.[46,49]

The disadvantages are increased toxicity, increased drug interactions, increased cost, and poorly standardized methods of testing efficacy of the combination.[45] Itraconazole and voriconazole are potent inhibitors of cytochrome P450 3A4 and associated with a greater risk of broader range of potentially severe drug interactions and hepatotoxicity than fluconazole.[48] At present, checkerboard dilution assay is the most common laboratory method for evaluating antifungal combinations.[45]

**Antifungal Drugs Plus Nonantifungal Drugs**

Combination of antifungal drugs with nonantimicrobial agents such as calcineurin inhibitors (cyclosporine A and tacrolimus), proton-pump inhibitors, antiarrhythmic agents, cholesterol-lowering agents, immunomodulators, antineoplastic drugs, antiparasitic agents, microbial metabolites, and human recombinant antibodies has
shown beneficial effects. Cyclosporine singularly is not able to inhibit the fungal growth but increases susceptibility to fluconazole due to efflux pump depletion or alteration of stress response caused by calcineurin during azole therapy.

Studies show that statins are active against Microsporum canis and T. mentagrophytes. Synergistic interactions were noticed when simvastatin was combined with terbinafine against dermatophytes.

Hemopoietic growth factors, such as granulocyte colony stimulating factor or granulocyte-macrophage colony stimulating factor and Th1 cytokines have activity on the antifungal function of phagocytes and the efficacy of antifungal agents.

Fractional carbon-dioxide laser therapy combined with topical antifungals such as terbinafine, amorolfine, or luliconazole was found to be effective in the treatment of onychomycosis.

Newer Antifungal Drugs

An efficient antifungal should act against a wide range of fungi having no or low toxicity to the host. One of the major challenges in developing antifungal drugs lies in the similarities shared between fungi and their hosts, thereby restricting the target molecules for antifungal drugs. Most newer antifungal drugs are designed considering the following:

i. Drugs having pharmacological similarity with the older drugs which share the target molecules, with lower MIC level and specific indications (e.g., isavuconazole, micafungin, luliconazole)

ii. Repurposing of established medications where an old compound with a known pharmacology is used alone or in combination with another drug for a newer indication, for example, calcineurin inhibitors, target of rapamycin inhibitors, Hsp90 inhibitors, in synergy with azoles

iii. Recent advances in fungal genomics and proteomics have revealed target genes, proteins, or virulence factors required during infection of the host tissues by dermatophytes, for example, efflux pump inhibitors (derived compounds of milbemycin), the transcription factor PacC, a wide-domain regulatory protein involved in pathogenicity events or the sulfite transporters were proposed as interesting targets for antifungal drugs in dermatology because of their role in the proteolytic digestion of hard keratin.

Conclusion

While deeper mycoses are still difficult to treat, common fungal infections in dermatology were considered easily treatable. Lately, fungi causing superficial mycoses also have evolved to develop resistance against commonly used drugs. Current solutions to this could be good skin hygiene measures, prudent use of antifungals in proper dosing and duration, appropriate use of susceptibility testing, usage of older molecules such as griseofulvin or topical keratolytics in combination with newer drugs and in appropriate dosages and combination therapy with two systemic antifungals or systemic antifungal with topical antifungals and/or topical keratolytics.

The key to managing the widespread nature of this emerging problem would involve development of drugs with newer targets, decreased drug interactions, at affordable price, which at this stage appears distant in our scenario, knowing the resources required and the economics involved. However, newer insight on drug resistance mechanisms could lead to advanced treatment strategies in managing fungal infections.

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