Clinical Failure of Antifungal Therapy of Dermatophytoses: Recurrence, Resistance, and Remedy

The epidemiology and clinical outcome of any disease depends on host, environment, and agent factors. In infectious diseases, the exposure to a causative organism is the main prerequisite irrespective of the presence of any of these factors. All the living organisms over period of time adapt to resist their killing by evading immune response through various mechanisms and developing resistance to drugs. To contain the epidemic of infectious diseases such as dermatophytoses, identifying and understanding various factors related to host, environment, and agent are essential. At the same time, it is crucial to analyze whether the clinical failure of antifungal therapy is due to recurrence and/or resistance. The development of any management strategy to treat dermatophytoses must take into account of these factors.

Factors Responsible for Clinical Failure of Antifungal Therapy

Recurrence
In most of the cases, the clinical failure of antifungal therapy can be attributed to either persistent or recurrence of infection presenting clinically as initial response followed by extension and/or spread of lesions elsewhere or as complete clinical remission followed immediately by reappearance of lesions or as in minority of cases, no clinical response to antifungal therapy. Such clinical situations indicate, other than drug resistance, the presence of recalcitrant clinical types, persisting predisposing factors and other factors related to treatment.[1]

Recalcitrant clinical types
The chronic nature of some of the clinical types can result in extension and spread of lesions in the presence of inadequate treatment. In addition, they can act as reservoir of infection. Involvement of vellus hairs can lead to clinical failure of topical antifungal therapy of dermatophytic infection involving glabrous skin. Infection with nonanthropophilic fungi and prior use of topical corticosteroid predispose to tinea of vellus hairs. The fungi parasitize hairs and become inaccessible to the effect of topical antifungal agents. In such cases, systemic antifungal therapy is effective.[2] Similarly, invasive dermatophytosis and tinea unguium can result in chronic infection and act as reservoir of infection. The former is commonly seen in the setting of severe immunodeficiency, internal malignancy, hepatic failure, and organ transplant patients.[3]

Persisting predisposing factors
Several factors related to host and environment promote recurrence or persistence of infection. Comorbid conditions such as diabetes, internal malignancies, anemia and organ dysfunctions, and their treatment can predispose an individual to immunosuppression. Since last few years, there has been a lot of change in the climate, lifestyle, and attitude toward health in general population. The hot and humid climate and working conditions and tight-fitting clothes such as jeans, leggings, and synthetic undergarments provide moist and occlusive milieu where dermatophytes thrive. The attitudinal changes such as reluctance to seek expert opinion, noncompliance, unrealistic demand of quick relief, and self-medication further augment the existing problem. As long as these factors persist in an individual, the chances of recurrent or persistent infection increase.

Inappropriate antifungal therapy
Griseofulvin and terbinafine are effective only against dermatophyte whereas fluconazole is weakly active. Inappropriate selection of antifungal agents in addition to inadequate dose and duration of therapy can result in partial response or rapid recurrence of infection. It also facilitates the development of drug resistance.[4] Inappropriate application methods of topical preparations can result in prolonged or recurrent infections.

Self-medication
The majority of patients seek consultation of dermatologist only after applying over the counter topical preparations for a month or two. They are influenced by the advertisements promoting the creams claiming dramatic cure of cutaneous fungal infection. Many of these creams contain steroids which provide rapid relief of symptoms and hence lead to subsequent abuse. The prolonged application of steroid-based creams results in increased prevalence of recalcitrant clinical variants as mentioned above.

Quality of drugs
There has been a sudden increase in availability of several brands of a particular antifungal agent either manufactured and/or marketed by numerous pharmaceutical companies. Generic brands of these drugs are also available. Hence, the issues related to quality control of these drugs are a real concern. The use of less efficacious molecules can lead to clinical failure and drug resistance.

Resistance
Naturally, the selective pressure of immune response and antifungal agents results in selection of resistant strains which becomes prevalent in a population. There are several mechanisms by which dermatophytes develop drug resistance. These include decrease in drug uptake, structural alterations in target site, increase in intracellular targets, and increased
drug efflux. The resistance to azoles and terbinafine has been attributed predominantly to increased drug efflux. Another important mechanism is formation of biofilm. The persistence or progression of infection despite adequate antifungal therapy indicates clinical resistance. The *in vitro* drug resistance of dermatophytes is determined by minimum inhibitory concentration (MIC). In dermatophytosis, the *in vitro* resistance based on MIC does not always correlate with the clinical resistance. Hence, the MIC of an antifungal agent is not the only factor that predicts the clinical success or failure.\[^4\]

**Remedy**

The modification in pharmacotherapy is not the only solution for current problems associated with dermatophytosis. The clinical response also depends on the choice of antifungal agent, topical/systemic/both, type, site, and extent of infection, comorbidities, and immune status of the host. In the current scenario, it is of paramount importance to prevent or remove the various factors related to host and environment that are responsible for extensive dermatophytosis. We need to focus more on developing an effective strategy to literate the population regarding predisposing factors, adverse effects of over the counter drugs, need of expert consultation, and importance of following expert’s advice on management of the disease. It is also essential to literate general physicians about ill effects of steroid combinations and adequate dosage duration of appropriate antifungal drug. Simultaneously, the antifungal agents should be used judiciously.

**Ideal antifungal agent**

At present, the antifungal therapy of dermatophytosis has its own limitations. As dermatologists, we wish all the antifungal drugs to have certain attributes which make them ideal [Table 1]. The search for ideal antifungal agent which can rescue both the dermatologists and patients from the menace of dermatophytosis continues. Meanwhile, we need to critically review and use the antifungal agents rationally.

**Systemic versus topical antifungal agents**

Dermatophytes being keratinophilic are incapable of invasive infection beyond epidermis under normal circumstances. Unlike bacteria or virus, dermatophytes do not enter systemic circulation or any viscera. Hence, irrespective of mode of administration, the antifungal agents have to reach epidermis to eliminate the fungi.

There are a few important issues need to be considered before using oral antifungal agents. Currently, terbinafine and itraconazole are used for the treatment of dermatophytosis. The latter is also an important systemic antifungal agent used in the treatment of deep fungal infections. The risk of fungi causing deep fungal infections developing drug resistant to itraconazole cannot be ruled out even if it is used rationally in the treatment of dermatophytosis. This clinical situation can be compared to some extent with rise of multidrug-resistant tuberculosis. The remaining systemic agents, ketoconazole and amphotericin-B, are generally not used because of potential risk of hepatic and renal toxicity, respectively. The fluconazole is less effective against dermatophytes compared to other drugs, and voriconazole is reserved for invasive fungemia in intensive care unit (ICU) setup and deep fungal infections. Other issue is treatment of infection with drug-resistant dermatophytes. It has been shown that in recurrent oropharyngeal candidiasis caused by same *Candida albicans* strain, with every recurrence, the MIC has increased. The dose of fluconazole increased progressively from 100 mg/day to 800 mg/day to maintain necessary MIC to achieve clinical and mycological cure after each relapse.\[^5\] The high dose of antifungal agents increases the risk of toxicity, especially in patients with comorbidities. Hence, in such scenario, it is not reasonable or possible to increase the dose of the drug beyond certain limits. Moreover, systemic antifungal agents do not meet many of the characteristics of ideal antifungal agents.

Though topical antifungal agents score over systemic agents in many of the characteristics of ideal agents, the currently available topical agents except a few agents are not effective in maintaining adequate levels in the skin, hair, and nail for prolonged duration which is essential for the management of recalcitrant or resistant dermatophytoses. The development of novel delivery systems addresses this limitation of topical agents.\[^6\]

In the absence of novel delivery systems readily available for clinical use, appropriate oral antifungal therapy that can maintain effective MIC against infecting organism for adequate duration is the mainstay of treatment of recalcitrant, invasive, or extensive dermatophytoses.

**Future of antifungal therapy**

The cellular targets for antifungal action are limited because both human and fungi are eukaryotic organisms.\[^4\] Hence, the strategy to prevent or control of drug resistance is critical [Table 2].\[^1\] Considering the mechanisms of drug resistance,

### Table 1: Characteristics of ideal antifungal agent

| Characteristic                  | Ideal Antifungal Agent |
|--------------------------------|------------------------|
| Highly effective against all dermatophyte |                        |
| Strong anti-inflammatory action   |                        |
| Rapid action/response             |                        |
| Good penetration                  |                        |
| Good reservoir effect             |                        |
| Minimal systemic absorption       |                        |
| No side effects                   |                        |
| Short duration of therapy         |                        |
| Risk of development of resistance |                        |
| Cost-effectiveness                |                        |
| Safe use in pregnancy and lactation|                        |
| Safe use in renal and hepatic failure |                    |

### Table 2: Prevention or control of antifungal resistance

| Precaution                              | Recommendations                          |
|-----------------------------------------|------------------------------------------|
| Judicious use of antifungal agents      | Avoiding treatment with low dose of antifungal agents |
| Combination therapy using drugs with different mechanisms of action | Surveillance studies to identify true nature of antifungal resistance |
new drug targets have been identified [Table 3].[4] The new drug should act efficiently against wide range of fungal with no or minimal toxicities to host. The cellular target should be essential and conserved in variety of fungi and more importantly its counterpart should not be present in the host.[7]

Combination therapy using drugs with different mechanism action may be considered to prevent drug resistance. The immunosuppressive drugs such as cyclosporine and D-octapeptides have been found to counteract drug resistance due to efflux pumps. In immunocompromised patients, antifungal agents can be combined with cytokines.[8] Physical modality of treatment such as photodynamic therapy, lasers (fractional CO$_2$, 0.65 ms-pulsed 1064 nm neodymium-doped yttrium aluminum garnet), and iontophoresis can also be combined to improve the penetration of antifungal agent, especially in onychomycosis.[9]

Considering the characteristics of ideal antifungal agent, development of novel drug delivery system appears to be the suitable option for management of dermatophytoses [Table 4].[6] They ensure prolonged pharmacological effect by achieving high local concentration of drug in epidermis and dermis through controlled release of drug from the formulation.

### Table 3: Putative targets for new antifungal agents

| Genes and proteins: Involved in infection of host tissues | Virulence factors: Keratinases, elastases, DNase, proteases, lipases, mucolytic enzymes | Sulfite transporters: Involved in proteolytic digestion of hard keratin | Heat shock protein 90 | ATP-binding cassette transporters: Involved in drug efflux | ATP: Adenosine triphosphate |
|--------------------------------------------------------|---------------------------------|-----------------------------|-----------------|---------------------------------|-----------------------------|

### Table 4: Novel delivery system for topical antifungal therapy

- Micelles
- Solid lipid nanoparticles
- Nonstructured lipid carriers
- Microemulsions
- Vesicular delivery systems
  - Liposomes
  - Niosomes
  - ethosomes
  - Transfersomes
  - Penetration-enhancer vesicles

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