The unprecedented epidemic-like scenario of dermatophytosis in India: III. Antifungal resistance and treatment options

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Abstract

One of the canonical features of the current outbreak of dermatophytosis in India is its unresponsiveness to treatment in majority of cases. Though there appears to be discordance between *in vivo* and *in vitro* resistance, demonstration of *in vitro* resistance of dermatophytes to antifungals by antifungal susceptibility testing is essential as it may help in appropriate management. The practical problem in the interpretation of antifungal susceptibility testing is the absence of clinical breakpoints and epidemiologic cutoff values. In their absence, evaluation of the upper limit of a minimal inhibitory concentration of wild type isolates may be beneficial for managing dermatophytosis and monitoring the emergence of isolates with reduced susceptibility. In the current scenario, most of the cases are unresponsive to standard dosages and duration of treatment recommended until now. This has resulted in many ex-cathedra modalities of treatment that are being pursued without any evidence. There is an urgent need to carry out methodical research to develop an evidence base to formulate a rational management approach in the current scenario.

Key words: Antifungal agents, antifungal susceptibility testing, clinical breakpoints, epidemiologic cutoff values, the upper limit of minimal inhibitory concentration of wild type isolates

Introduction

There has been a significant increase in the incidence of chronic, relapsing, recurrent cases of superficial dermatophytosis in India that are also often unresponsive to conventional drugs and doses of recommended antifungal treatment. Almost 15–20% of the outpatient department cases are those of chronic dermatophytosis. Recurrences and relapses after completion of full doses of treatment and resistance to major classes of antifungal drugs have been observed.[1-6]

The reasons for this phenomenon are not clear but the proposed reasons are the abuse of irrational combination creams containing potent corticosteroids, inadequate duration of treatment, difficulties in eliminating predisposing factors and reinfection due to inadequate source control.[7] This section of the review deals with the mechanisms of the emergence of antifungal resistance, antifungal sensitivity testing and management of dermatophytosis in the current situation.

Antifungal Agents and Antifungal Resistance

The plethora of antifungal agents available for the management of dermatophytosis include imidazoles (clotrimazole, miconazole, ketoconazole, bifonazole,

How to cite this article: Verma SB, Panda S, Nenoff P, Singal A, Rudramurthy SM, Uhrlass S, *et al*. The unprecedented epidemic-like scenario of dermatophytosis in India: III. Antifungal resistance and treatment options. Indian J Dermatol Venereol Leprol 2021;87:468-82.

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Received: March, 2020 Accepted: August, 2020 Published: June, 2021

DOI: 10.25259/IJDVL_303_20 **PMID:** ***

econazole, sertaconazole, luliconazole and tioconazole), triazoles (fluconazole, itraconazole, posaconazole, voriconazole, isavuconazole and lanoconazole), allylamines (terbinafine, naftifine and butenafine), morpholines (amorolfine), griseofulvin, ciclopirox and tolnaftate. These antifungals are available either in topical or oral formulations. Current management of dermatophytosis includes topical and oral formulations of antifungal therapy for difficult to treat infections.[8] With the increase in the use of antifungal agents for dermatophytosis, resistance to different classes of antifungals is also on the rise. Though there appears to be discordance between *in vivo* and *in vitro* resistance, demonstration of *in vitro* resistance of dermatophytes to antifungals by antifungal susceptibility testing is essential as it may help in appropriate management.

Antifungal resistance mechanisms

Antifungal resistance in dermatophytes could be due to several mechanisms like activation of signaling pathways to antifungal stress response, modification in the target site, increased drug efflux and decreased drug uptake.[9,10]

Environmental stress

Fungi have evolved to adapt themselves to the various environmental stresses including antifungal exposure. Many signaling pathways such as cell wall integrity pathway, calcineurin signaling pathways and high osmolarity glycerol pathways are shown to be activated following antifungal exposure to neutralize drug-induced stress.[11] Molecular chaperone, heat shock protein 90, modulates the stress responses leading to tolerance to antifungal agents through calcineurin and mitogen-activated protein kinase in the cell integrity pathway.

Efflux pumps

Overexpression of the drug efflux pumps is one of the major mechanisms of acquiring resistance, especially for azole agents. Azoles that bind to the different efflux cell membrane transporter proteins, are extruded from the cell. Overexpression of these efflux pumps is one of the major reasons for resistance to azoles and treatment failure. Common drug efflux systems that modulate azole resistance are the adenosine triphosphate-binding cassette superfamily, the major facilitator superfamily and pleiotropic drug resistance families.[10,12] The adenosine triphosphate-binding cassette superfamily encompasses the medium-chain dehydrogenases/reductases superfamily that is well studied with *Trichophyton interdigitale* H6 strain (earlier identified as *Trichophyton rubrum*).[9] Increased transcription of *mdr1* and *mdr2* genes have been noted after exposure to the different class of antifungal agents.[13] *Mdr2* gene has also been associated with terbinafine resistance as it has been demonstrated that disruption of *mdr2* gene renders mutants susceptible to terbinafine.[14] However, it has been hypothesized that *mdr2*, *mdr4* and *pdr1* genes act synergistically by compensating one gene with others during drug efflux activity.[9]

Mutations in squalene epoxidase gene, especially responsible for allylamine resistance

About target modification, a mutation in the *Erg11* gene which encodes the enzyme lanosterol 14-alpha-demethylase, has been well associated with azole resistance in *Candida* species. Several studies demonstrated substitution or deletion of amino acid in the region of protein Erg1, *Erg11* causes resistance to terbinafine and azoles, respectively[10,15-18] The terbinafine resistance in dermatophytes is attributed to single nucleotide polymorphisms in squalene epoxidase gene. In 2005–2006, Osborne *et al*., for the first time, reported terbinafine resistance due to a single missense amino acid substitution at L393F and F398L in squalene epoxidase enzyme gene of *Trichophyton rubrum* that imparts resistance to allylamines.[18] Squalene epoxidase is a catalytic enzyme required for the conversion of squalene to 2,3-oxidosqualene during ergosterol biosynthesis which is the major target for terbinafine.[15,19-21] Deficiency of ergosterol synthesis leads to a decrease in cell wall integrity and growth of the fungi and ultimately death due to the accumulation of toxic compound, squalene.[19,21-24] Squalene epoxidase is also responsible for the biosynthesis of cholesterol (analog of ergosterol) in higher eukaryotes, while terbinafine shows a lower binding affinity for mammalian squalene epoxidase enzyme.[23] Fungi use different modes to overcome drug action by substitution of amino acid following mutation which hinders the binding of terbinafine to squalene epoxidase.

Biofilm and antifungal resistance

Biofilm formation by the dermatophytes can confer resistance/tolerance to antifungal agents. Only limited studies are available on biofilm formation in dermatophytes. The biofilm matrix produced by dermatophytes acts as the physical barrier and contributes to resistance by preventing the access of the microbial community by drugs and host immune cells.[25] Biofilm association is documented more with onychomycoses. Its role in skin tinea infection needs to be explored further. Lastly, the capacity of dermatophytes to form arthroconidia *in vivo* has been attributed to the antifungal resistance due to the highly resistant nature of arthroconidia compared to hyphae or microconidia. However, *in vitro* studies show contrasting results[25] which needs further confirmation.

Resistance to different antifungal agents

Griseofulvin resistance

Antifungal resistance to griseofulvin was first reported by Michaelides *et al.* in 1960 in patients with *Trichophyton rubrum* and *Trichophyton tonsurans* infection.[26,27] A study from north India also reported tinea capitis patients not responding to the systemic antifungal agent, griseofulvin.[28] Increasing reports of treatment failures with griseofulvin led to a shift in the treatment of choice towards azoles and allylamines,[19] but still, some recommend it for the treatment of tinea capitis. Increased *in vitro* resistance to griseofulvin has been reported from across the world.[4] Two

major studies from north India reported high minimum inhibitory concentration to griseofulvin supporting the earlier findings.[7,29] *Trichophyton interdigitale* was the predominant agent in both those studies and griseofulvin was the most inactive drug with modal minimum inhibitory concentration of 32 μg/mL and 98% of isolates exhibiting minimum inhibitory concentrations of ≧ 2 μg/mL.[29]

Azole resistance

Though clinical trials have shown that fluconazole is effective for the treatment of dermatophytosis,[30] high minimum inhibitory concentrations demonstrated by *in vitro* studies, especially from recent studies from India[7,29] criticizes its utility as the preferred agent and it needs clinical trials to confirm its effectiveness. Itraconazole is considered as one of the most effective azoles for the treatment of dermatophytosis.[31] *In vitro* data also indicates that resistance to itraconazole is a rare phenomenon. *In vitro* antifungal susceptibility results showed that itraconazole was the most effective oral azole agent effective against dermatophytes isolated from north India.[7,32] Most of the studies on *in vitro* susceptibility testing on topical azoles such as luliconazole, sertaconazole, efinaconazole and lanoconazole have shown that all have very potent *in vitro* activity with low minimum inhibitory concentrations.[9] Gupta and Kohli concluded that increased exposure of azoles may be indicative of the development of azole resistance in dermatophytes after repeated exposure.[33] A study from a Mexican hospital reported increased resistance as high as 19% to azoles using the E-test method, whereas, Sarifakioglu *et al.* reported the greatest variation in the minimum inhibitory concentration values of itraconazole and fluconazole.[34]

Allylamine resistance

Primary resistance to terbinafine in *Trichophyton rubrum* that resulted in treatment failure was first reported by Mukherjee *et al.*, in 2003[35]; it was also demonstrated that the isolate exhibited mutation in the squalene epoxidase gene (L393F).[15] Later, the same group described another mutation in the squalene epoxidase gene resulting in the amino acid change F397L in the squalene epoxidase protein.[18] Since then, resistance to terbinafine was rarely reported and terbinafine remained the preferred drug for the systemic management of dermatophytosis. In 2017, Yamada *et al*. performed antifungal susceptibility testing of 2,056 clinical isolates of *Trichophyton rubrum* and *Trichophyton interdigitale* and reported terbinafine resistance in 1% of these, indicating the rarity of terbinafine resistance. The resistant *Trichophyton* isolates had single amino acid substitution at Leu393, Phe397, Phe415 and His440.[36] Eight of the 17 patients from whom terbinafine-resistant *Trichophyton* was isolated were already on terbinafine therapy while the sample was collected for culture. Though it is difficult to interpret whether the resistance was primary or secondarily acquired due to therapy, a high frequency of resistance in those exposed to terbinafine suggests secondary or acquired resistance to this drug. Following these results, two reports from India reported a high prevalence of resistance to terbinafine. Both the reports demonstrated mutations in squalene epoxidase gene as the mechanism of terbinafine resistance.[7,29] In 2018, high terbinafine resistance was reported in 15 (17%) *Trichophyton interdigitale* (which can be considered to be the currently defined *Trichophyton mentagrophytes* VIII) and five (14.3%) of *Trichophyton rubrum* isolates. Among those 20 *Trichophyton* spp., only six isolates showed amino acid substitution at 397th position and the remaining 14 isolates did not show any mutation in squalene epoxidase.[7] They also analyzed the effect of the amino acid substitution conferring resistance to terbinafine using 3-dimensional homology modeling of squalene epoxidase and demonstrated that missense mutation causes structural destabilization of the protein interfering binding of terbinafine with squalene epoxidase.[7] Following this report, higher (32%, 20 isolates) terbinafine resistance *Trichophyton interdigitale* were reported from northern India in which, all the isolates carried either L393F (60%) or F397L (40%) amino acid substitutions.[27] Resistant *Trichophyton mentagrophytes* strains have been found to harbor missense mutations with subsequent amino acid substitutions, most frequently Phe^{397}Leu, either as a single substitution or in combination with Ala^{448} Thr^{87}. Recently, two novel (Ser^{395}Pro and Ser^{443}Pro) amino acid substitutions were reported in the squalene epoxidase gene of *Trichophyton* species. They also reported that Ala^{448}Thr missense substitution was associated with increased minimum inhibitory concentrations of itraconazole and voriconazole.[37] Khurana *et al.* from India further correlated the patients infected with isolates with high terbinafine minimum inhibitory concentrations to their clinical response to terbinafine and concluded that patients infected with *Trichophyton* spp. having terbinafine minimum inhibitory concentration of ≦ 1 μg/mL were 2.5 times more likely to respond to terbinafine treatment compared to patients infected with strains of higher minimum inhibitory concentrations. Absence of mutation in SQE (squalene epoxidase) gene in terbinafine resistant isolates,[7] higher expression of efflux pumps pdr1, mdr1, mdr2 and mdr4 in the isolates exposed to a subinhibitory concentration of terbinafine[38] and reduction of terbinafine minimum inhibitory concentration from 32 μg/mL to 4μg/mL after addition of efflux pump blocker FK 506,[38] all suggest the role of efflux pumps in conferring resistance to terbinafine. Recently, 2% of clinical dermatophytes resistant to terbinafine were reported from Iran.[39] In addition to *Trichophyton rubrum*, a mutation in the squalene epoxidase gene conferring resistance in *Trichophyton tonsurans* and *Epidermophyton floccosum* were also reported.[39] Reports on mutation in squalene epoxidase gene conferring resistance to terbinafine are provided in Table 1. Recently, an amplified refractory mutation system polymerase chain reaction assay was developed that could detect C to A transversion and T to C transition responsible for amino acid substitution in the 397th position of squalene epoxidase gene in terbinafine resistance *Trichophyton* isolates. Amplified refractory mutation system polymerase

Table 1: High minimum inhibitory concentration terbinafine isolates with their mutation pattern in squalene epoxidase gene

Study	Number of terbinafine high MIC isolates	Change in amino acids leads to higher MICs to terbinafine											
		L393F	L393S	F397L	F397I	F397V	F415I	F415S	F415V	H440Y	H440Y/F484Y	I121M/V237I	No mutation
Osborne *et al.*, 2005[15]	2	2											NM
Osborne *et al.*, 2006[18]	1				1								NM
Rudramurthy *et al.*, 2018[7]	20			6									14
Singh *et al.*, 2018[29]	20	8		12									NM
Yamada *et al.*, 2018[36]	17	4	2	5	1	1	1	1	1	1			NM
Salehi *et al.*, 2018[39]	5	2											3
Saunte *et al.*, 2019[90]	14	2	2	7				1			1	1	NM

MICs: Minimum inhibitory concentrations, NM: No mutation

chain reaction assay was a simple and convenient tool for the rapid detection of wild type isolates from non-wild type isolates with a consensus gene-specific internal control.[40]

Antifungal susceptibility testing

Given the increasing resistance of dermatophytes to the various groups of available antifungal agents, antifungal susceptibility testing against dermatophytes is gaining importance. Minimum inhibitory concentration of antifungal agents helps to predict the likelihood of efficacy of the antifungal therapy. The susceptibility profile of implicated dermatophytes to the antifungal agents can guide the clinician to choose the best antifungal agent with maximum efficacy, less toxicity and less expense. Besides, the reproducible standard antifungal susceptibility testing technique is essential to determine the epidemiological cutoff value and define clinical breakpoints for the development of the newer antifungal agents, and to determine pharmacokinetics/pharmacodynamics parameter of the drug. The goal of antifungal susceptibility testing is to generate the data for the treating clinician regarding the susceptible or resistant phenotype of the drug-species combination.

Standard broth microdilution method of antifungal susceptibility testing

Currently, the broth microdilution method described by Clinical Laboratory Standard Institute and European Committee on Antimicrobial Susceptibility Testing (EUCAST) are considered as standard reference methods to measure the minimum inhibitory concentration of antifungal agents against yeasts and molds/filamentous fungi. The test can be performed using a two-fold dilution of the antifungal in test tubes (macrobroth) or microtiter plates (microbroth). Microbroth technique is preferred over the macrobroth dilution technique as it requires less amount of media and drugs making it relatively cheaper than the macrobroth technique. However, for testing dermatophytes such as *Microsporum* and *Epidermophyton* spp. which produce numerous large macroconidia, some prefer the macrobroth technique rather than the microbroth format of testing. The Clinical Laboratory Standard Institute, for the first time, described a standard protocol for antifungal susceptibility testing of dermatophytes, and recently (in 2017) released a new protocol (Clinical Laboratory Standard Institute M38) for testing molds, in which a specific modification for testing dermatophytes has been provided.[41] In this method, Roswell Park Memorial Institute 1640 media is used for testing and diluting the antifungal agents. For antifungal susceptibility testing of dermatophytes, the cultures of all dermatophytes except *Trichophyton rubrum* should be grown on the potato dextrose agar to obtain the number of conidia required for testing (inoculum), whereas *Trichophyton rubrum* which is generally known to produce fewer conidia, should be grown on oatmeal agar.

As per Clinical Laboratory Standard Institute, suggested ranges of dilutions to be tested include ciclopirox 0.06–32 μg/mL; fluconazole and griseofulvin 0.125–64 μg/mL; itraconazole, voriconazole and terbinafine 0.001–0.5μg/mL; and posaconazole 0.004–8 μg/mL. Unlike other molds, the dermatophytes antifungal susceptibility testing reading should be read after four days of incubation at 28 or 35°C and end point should be read as 80% inhibition of growth compared to the control for fluconazole, flucytosine, ketoconazole, itraconazole, posaconazole, voriconazole, isavuconazole, griseofulvin, ciclopirox, terbinafine and 100% inhibition for amphotericin B.[41]

Other methods of antifungal susceptibility testing

The major limitation of the standard broth dilution techniques is that it is technically cumbersome and difficult to perform in a routine diagnostic laboratory. Though other methods such as agar-based E-test (AB Biodisk, Solna, Sweden),

and antifungal susceptibility testing using automated system (Vitek 2 system; biomerieux, Marcy I'Etoile, France) and broth dilution by SensititreYeastOne (SYO; Thermo Fischer Scientific, Waltham, MA, USA) are available, these are yet to be recommended for testing dermatophytes.

Clinical breakpoints

Clinical breakpoints are generally used to predict the clinical success. Clinical breakpoint is the minimum inhibitory concentration of antifungal that categorize an organism into susceptible, susceptible dose-dependent or resistant. Unfortunately, for dermatophytes the clinical breakpoints have not been established. For determination of the clinical breakpoints, data on minimum inhibitory concentration distribution and pharmacokinetics/pharmacodynamics modeling of the antifungal (in animal and/or human subjects) along with outcome data from clinical trial is essential.[42]

Epidemiological cutoff values

In the absence of the clinical breakpoints, alternative minimum inhibitory concentration values (such as, epidemiological cutoff value) which determine whether the given isolate is wild-type or non-wild type can be used for appropriate management of dermatophytosis. An epidemiological cutoff values is the minimum inhibitory concentration value that generally indicates to the clinician whether the given antifungal will be successful or not; however, unlike clinical breakpoints it will not predict clinical success. Wild type is the epidemiological cutoff value interpretative category that describes the isolates without any known mechanism of acquired resistance or reduced susceptibility to given antifungal agent. The non-wild type is the epidemiological cutoff value interpretative category that describes the isolates with presumed or known mechanism of acquired resistance and reduced susceptibility to given antifungal agent. As the data required for the determination of clinical breakpoints are difficult to generate, epidemiological cutoff values are described and used for management of patients. Species-specific epidemiological cutoff value for different antifungal agents can be determined by testing the minimum inhibitory concentration of a given antifungal against a large number of defined species originating from geographically diverse regions. Recently, Khurana *et al.* classified patients into three groups based on the therapy and recovery rate. They found that out of 30 patients only two cases responded to a standard dose of terbinafine (250 mg OD for three weeks), and 13 patients took longer time to cure (250 mg OD for 28 to 66 days) considered under group 1. Thus, they suggest that the level of drugs in tissue is more important than the plasma level in case of dermatophytes. In group 2, upon updosing (250 mg BD), six patients showed complete cure, linear pharmacokinetics for terbinafine profile suggesting that increasing doses of terbinafine increases the plasma level proportionately and also helps to achieve the required level for tissues. Another nine patients fell under group 3 as they did not show any sign of cure with the use of terbinafine and in this condition, therapy changed to itraconazole. Thus, in this study, due to a small number of sample size, the investigators did not find any significant correlation between the clinical response to terbinafine and individual minimum inhibitory concentrations.[43] Hence, there is need for multicentric studies to determine the clinical outcome, compare it with the minimum inhibitory concentration data generated from isolates of those patients and pharmacokinetics/pharmacodynamics parameters. In view of difficulty to obtain all these data to determine clinical breakpoints, at least minimum inhibitory concentration data of a large number of dermatophytes of geographically diverse regions is warranted to determine the epidemiological cutoff values.

In a recently published multicentric study from India, a total of 498 isolates of the *Trichophyton mentagrophytes/interdigitale* complex were collected from six medical centers over a period of five years (2014–2018). Antifungal susceptibility testing of the isolates was carried out for itraconazole, fluconazole, ketoconazole, voriconazole, luliconazole, sertaconazole, miconazole, clotrimazole, terbinafine, amorolfine, naftifine, ciclopiroxolamine and griseofulvin. The minimum inhibitory concentrations (in mg/L) comprising >95% of the modeled populations were as follows: 0.06 for miconazole, luliconazole, amorolfine; 0.25 for voriconazole; 0.5 for itraconazole, ketoconazole, ciclopiroxolamine; One for clotrimazole, sertaconazole; eight for terbinafine; 16 for naftifine; 32 for fluconazole; and 64 for griseofulvin. High percentage of isolates above the upper limit of wild type minimum inhibitory concentration were observed for miconazole (29%), luliconazole (13.9%), terbinafine (11.4%), naftifine (5.2%) and voriconazole (4.8%). They were low for itraconazole (0.2%). The authors concluded that, since the minimum inhibitory concentrations of itraconazole were low in *Trichophyton mentagrophytes/interdigitale* complex, it may be considered as the choice of first-line treatment. F397L mutation in squalene epoxidase gene was observed in 77.1 % of isolates with terbinafine minimum inhibitory concentration of ≥1 mg/L. However, no mutation was seen in isolates with terbinafine minimum inhibitory concentration of <1 mg/L. Thus, in the absence of clinical breakpoints, evaluation of upper limit of wild type may be beneficial for managing dermatophytosis and monitoring the emergence of isolates with reduced susceptibility.[44]

Management of Dermatophytosis

Management of dermatophytosis is the biggest challenge faced by dermatologists today. Herein, we have summarized the available therapeutic options, and have provided the rationale of using different molecules in the appropriate dose and duration.

General measures

- Patients should avoid sharing of garments, linens and towels, including bathroom napkins

- All the garments including undergarments and socks must be thoroughly washed daily in hot water and sun-dried (iron-pressed reverse if sun drying is not feasible)
- It is considered prudent to wear loose fitting cotton garments. Denims, especially tight-fitting jeans, have been incriminated in India. They also lead to friction in areas like the knees, thighs, lateral aspect of hips, waist band area and submammary areas which become locus minoris resistentiae in many cases leading to appearance of dermatophytosis, in those areas. V-shaped underwear and tight-fitting brassieres cause more friction and increased sweating, because they literally "cut into" the skin. Use of breathable cottons should be emphasized
- Avoidance or minimization of close contact with child or spouse until adequate treatment is taken. Intimate contact with partner may be avoided during active infection. This is specially being advised because of the increased number of cases of genital dermatophytoses, and the behavior of the disease being similar to sexually transmitted infection, for example, a rise in conjugal cases. It is already a known fact that *Trichophyton mentagrophytes* internal transcribed spacer genotype VII, the so called Thai variant, is considered an sexually transmitted infection owing to its preference for genitalia[45]
- Avoidance of body-contact sports and swimming is preferable
- Simultaneous treatment of affected family members is vital. The patient should be instructed to ask his/her close contacts regarding the presence of similar disease or any complaints of itching in the unexposed parts of the body. Examination of nails and feet is important to rule out reservoirs of infection. The patients should be counseled using colloquial terms regarding the meaning of recalcitrant infection and the chances of developing it in the absence of poor compliance. Explaining the manifold increase in the cost of therapy due to nonadherence to prescriptions may help us in reiterating the importance of regularity in following the dermatologist's advice.[44] It needs to be explained that application of steroids suppresses the inflammation but does not reduce the proliferation of the organisms. Reinforcement of verbal explanation can be done by provision of patient information leaflets and utilization of audio-visual media to explain the condition. Patient needs to be advised to keep the skin, especially the folds, dry. Special attention should be given to toe web spaces
- If the patient is involved in physical activity or is in an environment where one tends to sweat a lot or has primary hyperhidrosis, having a bath twice daily helps.[30] It is also worthwhile to ask the patients how they have a bath. In the economically backward settings, on account of the fact that they do not have the luxury of a separate bathroom and its privacy, it is usual to encounter individuals having a bath with their undergarments on.

Pharmacotherapy

This is an unusual epidemic like situation and the newly implicated organism as well as lesions are known to behave in unusual ways. There is a paucity of studies or logic/rationale for many regimens that are being administered as a matter of course. However, lack of evidence at this point should not be considered as lack of effectiveness of many of the regimens we choose.

Topical therapy in dermatophytosis

Indications of topical therapy include single lesions, elderly patients with significant comorbidities, infants and pregnancy.

An additional topical antifungal agent in a case where oral antifungal is administered concomitantly serves three purposes: the local concentration of the topical antifungal increases the chances of clearance; the purported anti-inflammatory and antimicrobial properties of the new topical antifungals help the cause; and the patient satisfaction also increases.

It is often impractical and unaffordable to recommend topical agents in widespread disease. The cost may also preclude buying oral antifungal agents for the rest of the family in familial outbreaks.

Topical antifungals

Oldest and nonspecific agents include keratolytics-salicylic acid, lactic acid, Whitfield's ointment and so on. and antiseptics like gentian violet, Castellani's paint, potassium permanganate. These older topical agents have fallen out of favor for causing significant irritation and color changes barring Whitfield's ointment which is often used in patients of moccasin tinea pedis. Azoles act by inhibiting the biosynthesis of ergosterol (block 14α-demethylation of lanosterol and inhibit fungal cell synthesis which leads to accumulation of cytotoxic 14αmethyl sterols). These are fungistatic but in higher concentrations, these can be fungicidal as well. Besides, they possess anti-inflammatory and antibacterial properties.

Azoles useful in superficial dermatophytosis

These molecules are the first line topical agents these days, because of their promising effectiveness and low incidence of side effects.[46] The available options in India from this group include miconazole, bifonazole, clotrimazole, ketoconazole, oxiconazole, sertaconazole, luliconazoleeberconazole, fenticonazole and fluconazole. The oft-used topical azole antifungals are discussed below:

- Clotrimazole is satisfactorily effective in the management of intertriginous candidal infections[47] but

its efficacy in the current scenario of dermatophytes seems doubtful

- Oxiconazole is demonstrated to be effective with once daily dosing (attributed to the persistence of the molecule in the epidermis at therapeutic levels for seven days)[48]
- Eberconazole has equivalent demonstrable activity against dermatophytes as miconazole cream[49]
- Sertaconazole is relatively lipophilic compared to other azoles, leading to a greater reservoir effect in the stratum corneum. The additional properties of sertaconazole are anti-inflammatory and antipruritic action, inhibition of release of proinflammatory cytokines from activated immune cells, apart from the prominent antibacterial action
- Luliconazole is the currently preferred topical agent amongst all the available molecules in India. In this drug, imidazole moiety is incorporated into the ketone dithioacetal structure; as a result of which luliconazole has excellent effectiveness against filamentous fungi including dermatophytes. One advantage of luliconazole is that it is effective once daily. Besides, it has demonstrated strong fungicidal activity at very low levels (minimum inhibitory concentration of < 0.001 micrograms per milliliter for *Trichophyton rubrum*. It was approved by the US Food and Drug Administration in 2013, for treatment of interdigital tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum* and *Epidermophyton floccosum* in patients 18 years of age and above. In a randomized, single-blind, two-way, parallel-group study, luliconazole 1% cream applied once daily for two weeks was found to be as effective as bifonazole 1% cream applied once daily for four weeks in tinea pedis.[50] In another study comparing luliconazole cream and terbinafine cream, both were found to be equally efficacious.[51] This finding needs to be confirmed by further studies, considering the emerging resistance with terbinafine. In one of the multicentric studies comparing sertaconazole 2%, terbinafine 1% and luliconazole 1% cream, sertaconazole was found to be slightly better than others.[52]

Allylamines, benzylamines and morpholines

The advantages of naftifine are rapid onset of action and sustained clearance of infection but it is not available in India. Butenafine (benzylamine) and terbinafine were found to have better effectiveness, in comparison to clotrimazole, oxiconazole and sertaconazole, in a meta-analysis.[53] But, the utility of terbinafine in our setting is questionable, owing to the recently discovered resistance to this group of molecules.[54] In a study, amorolfine was found to equally effective as bifonazole.[55] In another Indian study, it was found to be inferior to sertaconazole in terms of effectiveness.[56]

Hydroxypyridilones - Ciclopirox 1% cream has been found to be better than clotrimazole 1% cream in the treatment of tinea pedis. Since the molecule has a unique mechanism of action, it looks to be a promising topical agent, pending comparative studies with other topical antifungals.[57]

Comparative efficacy of topical antifungals

Azoles, allylamines and other classes of antifungals are all effective but there is no substantial evidence to suggest that one class of antifungal is superior to the other, and all of these provide similar clinical and mycological cure.[58]

In a very recent randomized double-blind trial, sertaconazole 2% was found to be superior to amorolfine 0.25%, both in terms of effectiveness and tolerability.[56]

In the past, a few other clinical trials have also been conducted, wherein one antifungal was found to be marginally superior to the other (sertaconazole better than terbinafine).[58]

Cochrane systematic review did not find significant difference in the effectiveness between azoles and benzylamines in pooled studies as well as between once daily versus twice daily application of eberconazole, terbinafine, oxiconazole and naftifine.[59]

Anecdotal topical agents in the treatment of superficial dermatophytosis

Keratolytics (topical salicylic acid 3–6%) may be used as adjuvant therapy in the management of recalcitrant infections.[32]

Some dermatologists have found gratifying results in patients of extensive dermatophytosis by prescribing short contact therapy with ketoconazole or ciclopiroxolamine lotion for 15–50 min before shower/bath, as is practiced in patients of extensive pityriasis versicolor. This has been found to provide good symptom relief to the patients, as these two agents are anti-inflammatory and aid the reduction of the spore load. This therapy awaits further validation.

The authors consider use of antifungal soaps lacking in scientific logic and also see it as an additional financial burden. This should be explained to the patients stressing on the fact that expected contact time and ultimate concentration of these preparations do not help achieve adequate levels in the stratum corneum and hence subtherapeutic levels may promote the development of resistance. Plain dusting powders may be helpful in intertriginous infections, where sweating is a major challenge to be addressed such as in cases of intertriginous tinea pedis. However, there should be an adequate gap between the cream and powder as the latter would otherwise form a layer.

Topical antifungals in pregnancy

In pregnancy, clotrimazole, terbinafine, ciclopirox, naftifine and oxiconazole are considered Category B, and these molecules can be prescribed safely.

Methodology of use of antifungals

As per the recommendations of the American Academy of Family Physicians, topical antifungals should be continued for at least one week after the clinical resolution of the lesions. Considering the current situation with increased chances of relapses, one week seems insufficient. A recently published article recommends that topical antifungal agents be continued for two weeks post clinical cure, and we are in favor of application for a further two weeks.[32] It is also recommended that the topical antifungal has to be applied on the entire affected area and at least 2 cm outside the lesion circumferentially.

Some of the upcoming topical antifungal agents include lanoconazole, efinaconazole, pramiconazole, arasertaconazole, BB2603, tavaborole, rilopirox and so on.[60]

Systemic antifungal therapy in dermatophytosis

Indications of systemic antifungals in superficial dermatophytosis

It is the general observation of dermatologists that topical antifungal therapy alone is not effective in all but very limited disease. Indications of systemic therapy are failure of topical agents, extensive lesions, involvement of multiple anatomical sites, chronic, recurrent and recalcitrant dermatophytoses, involvement of vellus hair and nail, steroid modified cases, Majocchi's granuloma and so on.[61]

Choice of systemic antifungals

There are regional differences across India in the use of systemic antifungal agents, namely, itraconazole, terbinafine, griseofulvin, ketoconazole and fluconazole. However, itraconazole is the most preferred antifungal in the current scenario due to increasing cases of terbinafine failure[37] In a recently conducted randomized controlled trial in India among chronic and chronic relapsing tinea corporis, tinea cruris and tinea faciei patients, limited effectiveness of all four oral agents – fluconazole, griseofulvin, itraconazole and terbinafine was the key finding. In terms of cure rates and the number needed to treat, among the four, itraconazole was found to be the most effective agent, followed by fluconazole daily, then terbinafine and lastly griseofulvin.[62]

Griseofulvin, fluconazole and, at times, terbinafine are the drugs usually available in government setups. Though the first two are cost effective, the need for longer duration of treatment compared to terbinafine and itraconazole is another disadvantage.[62]

Practical aspects of the use of individual systemic antifungals are discussed below:

Terbinafine

According to some clinicians, terbinafine at a dose of 250 mg once daily for 4–6 weeks provides clinical cure. Presently, on account of increasing evidence of resistance, terbinafine is not preferred, although regional variability in the susceptibility and clinical responses exist. In a randomized study comparing oral itraconazole versus oral terbinafine, mycological cure was seen in 91.8% after four weeks in the itraconazole group as compared to 74.3% of patients in the terbinafine group. Authors concluded that itraconazole and terbinafine were effective and safe.[63]

In a study conducted by Majid *et al.*, clinically and mycologically diagnosed cases of tinea corporis and/or tinea cruris were administered oral terbinafine 250 mg once daily for two weeks. All clinically cured patients were then followed up for 12 weeks to look for any relapse/cure. Incomplete mycological cure as well as relapse was found to be very common after standard (two-week) terbinafine therapy in the patients.[64] Another recently conducted pragmatic prospective cohort study to determine the effectiveness of terbinafine in tinea corporis, tinea cruris and tinea faciei, concluded with an extremely disappointing result for terbinafine. The study found that the effectiveness of terbinafine in the treatment of tinea corporis, tinea cruris and tinea faciei is 2% at two weeks and 30.6% at four weeks which reiterates the fact that terbinafine has very limited use in the current epidemic like scenario of superficial dermatophytosis.[65]

Though terbinafine achieves high skin levels which is sufficiently above the minimal inhibitory concentration, patients showing a partial response to the dose of 250 mg of terbinafine have been seen to respond to 250 mg twice a day continued until complete cure. High drug exposure of terbinafine either by a longer duration or higher dosage results in higher stratum corneum levels and this may help to tide over the higher minimal inhibitory concentrations in patients. A divided dose of 250 mg twice daily is preferred over 500 mg once daily since single dose defies the basic principles of pharmacokinetics/pharmacodynamics of the drug.[66]

Itraconazole

There are constant discussions in India on many issues regarding itraconazole, starting from the bioavailability based on the size and the uniformity of the pellets, quality issues, administration with relation to food, drug interactions and finally the cost factor which is the major constraint of treatment adherence. With the increasing number of cases of recalcitrant dermatophytoses, itraconazole has undoubtedly stood out as the most favored molecule; however, the choice of a trusted brand, in an appropriate dose for an adequate duration of therapy, does play an important role.

Itraconazole at a dose of 100 mg twice daily for a minimum duration of 2–4 weeks in naïve cases, and four weeks in recalcitrant cases was recommended in a consensus statement.[32] It is probably better to err on the higher side and not stop at 14 days in even naïve cases, though this approach requires validation. The efficacy of capsules of 200 mg and 400 mg strength is not studied and hence

unproven. Itraconazole 100 mg pellet-capsule is thought to be the optimal size, allowing easy swallowing. With the same pellet size and technology, the sizes of 200 mg and 400 mg capsules would be expected to be much larger, hence affecting compliance. Change in the pellet size by altering the drug-polymer ratio or removing the PEG20000 layer leads to unstable formulations and adversely influences the bioavailability of itraconazole[67-69] Capsules of 200 mg are thought to be unstable and the molecule has an increased propensity to undergo agglutination and gel formation.[67-68] There have been animated discussions regarding the role of pellet numbers and sizes in the pharmacology of itraconazole but many other factors need to be considered, instead of focusing largely on size and number of pellets. While the study by Sardana *et al*. has merit in its observation of lack of uniformity in the pellet numbers and size, this parameter is not considered to be a critical parameter for assessing the efficacy of the product by various pharmacopeia.[69]

Scientific rationale limits the dosage of itraconazole to 100 mg twice daily. But in practice, prescriptions of a dose of 200 mg twice daily or greater are seen. Itraconazole has a nonlinear pharmacokinetics and hence increasing the dosage would result in disproportionate increase in serum levels and potentiate liver damage. Such high doses of the drug are not only unnecessary but are potentially hazardous. Optimum duration of treatment with itraconazole may be best individualized based on the clinical response. It would be safe to say that a greater number of recurrence and relapses are seen with less than four weeks of itraconazole 100 mg twice daily.

There is a need for a scientific office-based evaluation of various itraconazole brands. There is no clear evidence to suggest whether dermoscopic evaluation of pellet size/number or dissolution of pellets in an acidic pH should serve as an office-based indicator of quality of itraconazole.[70,71] Since it is virtually a novel situation for a dermatologist to be able to assess the quality of itraconazole in the office, a robust input from pharmacists and pharmacologists is vital to design a foolproof method of testing.

It is prudent to carry out investigations like liver function test and an electrocardiogram before prescribing itraconazole, especially in elderly patients and in those with a history of any hepatic or cardiovascular morbidity like congestive cardiac failure.

Itraconazole is ionized at a low pH; therefore, gastric acidity is required for dissolution and absorption of the molecule. Thus, itraconazole should be taken immediately after a full meal. Acidic beverages such as soft drinks can enhance uptake, while proton-pump inhibitors, H2-antagonists or other antacids may hinder absorption.[72-74] The use of other azoles such as voriconazole or posaconazole is discouraged considering their utility in invasive mycoses in critical care and deep fungal infections. Besides, voriconazole is not considered an impressive drug for *Trichophyton* species unlike in *Microsporum canis*.[75]

Griseofulvin

Recommended dosage of griseofulvin is 1 g per day for a period of four weeks according to western text books.[76] Hot and humid climate that is prevalent in India may necessitate an increase in the duration more than the above mentioned four weeks duration. Experience-based regimen that is currently in vogue is the administration of griseofulvin in a dose of 10–15 mg/kg body weight either as 750 mg or 1 g per day in two divided doses for six weeks.

Fluconazole

Though not a preferred antifungal in the current scenario according to recent evidence, fluconazole has certain advantages like good oral absorption and lower cost. Recommended dosage of fluconazole is 50–100 mg/day for a period of 2–4 weeks. Weekly regimens are strongly discouraged and use of fluconazole 100 mg daily for at least 2–4 weeks beyond clinical clearance is recommended. However, even daily dosage does not give satisfactory results in many patients. Therefore, fluconazole is recommended to be used only in cases where other molecules cannot be prescribed, due to underlying comorbidities, obvious contraindications and in lactating mothers.

Various systemic agents and their salient features are summarized in the Table 2.

The adverse effects[77,78] contraindications and drug interactions of systemic antifungal agents are summarized in Table 3.

Adjunctive systemic/interventional therapeutic modalities in the treatment of superficial dermatophytosis

Recently, some cosmetosurgical procedures have been tried for the management of dermatophytoses. In a recent article by Saoji and Madke, salicylic acid peel was found to be a cheap and useful option.[79] Lack of follow-up and small sample size are the major limitations of the study.

Relieving itch is a major concern. The anti-inflammatory effect of H1-antihistamines can be helpful to combat the high degree of inflammation. This itch is also partially attributable toxerosis within the eczematous lesions of tinea. Besides, luliconazole has been observed to cause xerosis and that, in turn, may add to itching. Use of light emollients in such cases is found to be beneficial.

There have been isolated reports of use of isotretinoin in recalcitrant dermatophytosis.[80] However, since terbinafine and itraconazole are primarily lipophilic and isotretinoin reduces sebum production, the concomitant therapy appears antagonistic. The potential for cumulative liver

Table 2: Systemic antifungals in the treatment of systemic dermatophytosis

Drug	Mechanism of action	Spectrum of action	Dose and duration	Comments
Griseofulvin	Disruption of microtubule spindle formation leading to inhibition of synthesis of nucleic acids. This causes an arrest of mitosis at the stage of metaphase, and subsequent inhibition of cell wall synthesis	*Trichophyton*, *Microsporum* and *Epidermophyton* species	500–1000 mg per day after fatty meal at least 2 weeks beyond clinical cure	Griseofulvin is preferred in situations when one cannot use itraconazole. Since the results are inferior to itraconazole. Appears in the startumcorneum 4–8 h after oral administration. Sweat plays an important role in transfer to and from the horny layer. Heat-induced sweating decreases the mean SC concentration by 55%, hence prolonged durations are required to render the fungi inviable. There is no residual effect Most useful in cases with tinea capitis caused by the microsporum species
Fluconazole	Inhibition of lanosterol 14α-demethylase, leading to impairment of biosynthesis of ergosterol. Besides, the accumulation of 14αmethyl sterols in the fungal cell impairs the functions of metabolic enzymes	*Trichophyton*, *Microsporum* and *Epidermophyton* species; *Malassezia*, *Candida*, systemic mycoses	Tinea corporis and cruris: Tablet fluconazole 150 mg biweekly for 6–8 weeks or till cure Tinea manuum and pedis: Tablet fluconazole 150 mg biweekly for 8–10 weeks or till cure	Fluconazole is preferred when there is a need to use oral antifungal in infants and lactating mothers Bioavailability is>90% unaffected by gastric acidity The secretion in the sweat is high with undetectable levels in the serum with high levels in the stratum corneum but low keratin adherence
Itraconazole		Like fluconazole Besides, it is also effective in subcutaneous mycoses	All cases: 100 mg twice daily after food for 4–6 weeks or till cure	Bioavailability is around 55% when taken immediately after a full meal. It is highly lipid-soluble and well distributed in the sebum It accumulates in the plasma during multiple dosing by nonlinear pharmacokinetics Drug persists in SC for 3–4 weeks after cessation of drug Metabolized in liver extensively by CYP3A4 Contraindicated in known hypersensitivity, ventricular dysfunction, congestive cardiac failure Effective contraception throughout the therapy and until 2 months after cessation of the drug should be adopted
Ketoconazole		*Trichophyton*, *Microsporum* and *Epidermophyton* species; *Malassezia*, *Candida*	Not recommended unless no other option is available Dose is 200–400 mg for 4–8 weeks	Can be tried in cases nonresponsive to all other azoles and terbinafine. But it has to be kept in mind that this drug is not approved by FDA for tinea due to its idiosyncratic hepatotoxicity
Terbinafine	Inhibition of squalene epoxidase enzyme leading to accumulation of squalene and depletion of ergosterol	*Trichophyton*, *Microsporum* and *Epidermophyton* species, subcutaneous mycoses	All cases: 250 mg OD for a longer duration or 250 mg twice daily for 3–4 weeks or till cure	Preferred in pregnancy and when the patient is on multiple medications that interact with itraconazole. Increasing resistance to drug identified Keratinophilic and lipophilic properties Absorption not affected by food Bioavailability – 40% and reaches high concentration in the sebum Drug concentration in the SC is 70 times more than that achieved in plasma

FDA: Food and Drug Administration, SC: Stratum corneum

toxicity is also higher. Hence, this combination should be discouraged.[81]

Dermatophytic infections, especially in frictional areas, heal with variable hyperpigmentation. It is not clear whether the pigmentation is entirely post-inflammatory or whether other factors are involved. Experience suggests that it is self-limiting and it resolves within a variable period of time. Use of depigmenting agents is not recommended.

Combination therapy of systemic antifungals

There has been an increasing trend of combining oral antifungals with an expectation of achieving better treatment outcome. A recent article by Rengasamy *et al.* recommends combining two oral antifungal agents of different classes in patients with irregular treatment/recurrent episodes within 6 months. Besides, they recommend the use of combinations like fluconazole/itraconazole + terbinafine, griseofulvin + terbinafine or griseofulvin + fluconazole/itraconazole

Table 3: Adverse effects, contraindications and drug interactions of systemic antifungals

Drug	Adverse effects	Contraindications	Drug interactions
Griseofulvin	Headache and nausea Leukopenia, neutropenia and punctate basophilia LE, lupus-like syndromes Albuminuria Neurological symptoms Serum sickness Angioedema	Hypersensitivity Porphyria Liver failure Renal failure Lupus erythematosus Pregnancy	Griseofulvin reduces levels of warfarin, oral contraceptives, cyclosporine It potentiates the action of alcohol Barbiturates reduce the levels of griseofulvin
Fluconazole	Nausea, vomiting, diarrhea Fixed drug eruption, Stevens-Johnson syndrome/TEN Elevated liver enzymes Leukopenia, neutropenia, thrombocytopenia Anaphylaxis and angioedema	Hypersensitivity Pregnancy	Fluconazole increases levels of sulfonylurea, nifedepine, losartan, omeprazole, NSAIDs, theophylline, phenytoin, carbamazepine, warfarin, statins Fluconazole decreases levels of oral contraceptives Fluconazole level is decreased by rifampin Fluconazole level is increased by thiazide diuretics
Itraconazole	Nausea, vomiting, diarrhea Skin rash and urticaria Fixed drug rash[77] Symmetrical drug-related Intertriginous and flexural exanthem[78] Raised liver enzymes Leukopenia, neutropenia, thrombocytopenia Congestive cardiac failure Peripheral edema Pulmonary edema Hypertension Hypertriglyceridemia Uncommon side effects are - peripheral edema, pulmonary edema, taste disturbance, transient or permanent hearing loss, anaphylaxis, oliguria, hypokalemia, myalgiam arthralgia, menstrual disorders, erectile dysfunction	Hypersensitivity Ventricular dysfunction Cardiac failure pregnancy Metabolic syndrome since can cause hypertriglyceridemia, pedal edema and can trigger hypertension	Itraconazole increases levels of sulfonylurea, nifedepine, verapamil, omeprazole, phenytoin, warfarin, digoxin, atorvastatin, and so on. Itraconazole decreases levels of oral contraceptives Itraconazole level is decreased by antacids, H2 receptor antagonists, proton pump inhibitors rifampicin, phenytoin, phenobarbitone, carbamazepine and so on.
Terbinafine	Raised liver enzymes Nausea, vomiting, diarrhea Skin rash and urticaria Severe neutropenia, thrombocytopenia, agranulocytosis, pancytopenia Vasculitis Reduced visual acuity	Hypersensitivity Chronic active liver disease Lupus erythematosus First trimester of pregnancy	Terbinafine increases levels of tricyclic antidepressants, selective serotonin reuptake inhibitors, beta-blockers, warfarin Terbinafine level is decreased by rifampicin
Ketoconazole	Nausea, vomiting Severe hepatitis Adrenal insufficiency Gynaecomastia Reduced libido	Hypersensitivity Liver failure Pregnancy	Ketoconazole increases levels of sulfonylurea phenytoin, carbamazepine, warfarin Ketoconazole decreases levels of oral contraceptives Ketoconazole level is decreased by rifampin, isoniazid, H2 blockers, antacids

NSAIDs: Nonsteroidal anti-inflammatory drugs, TEN: Toxic epidermal necrolysis, LE: Lupus erythematosus

in patients with chronic dermatophytosis or recalcitrant dermatophytosis, when there is an unsatisfactory response at the end of three weeks of conventional therapy. It is advised to perform a baseline complete hemogram and liver and renal function tests, whenever updosing or when combination therapy is contemplated due to the issues of cumulative toxicity.[82]

In a recently published article, authors found that a combination of systemic terbinafine 250 mg/day and itraconazole 200 mg/day is an effective and safe therapeutic strategy in the management of dermatophytosis.[83] Conflicting opinions have been published by Sardana *et al.*[84] who have highlighted the flaws in the methodology of the study which include poor sample size and questionable statistical analysis.

Though it may be rational to combine two or more drugs with different mechanisms of action, in an attempt to reduce the chances of resistance and improve the therapeutic outcome, there are currently no large scale trial reports demonstrating

Table 4: Summary of antifungal agents useful in special situations

Condition	Topical agent	Systemic agent
Pregnancy	Clotrimazole and miconazole (safe but questionable efficacy in the current situation) Amorolfine and ciclopiroxolamine are category B drugs Second line: Terbinafine Luliconazole and sertraconazole are category C drugs	Terbinafine is a category B drug may be given in extensive cases, except in 1st trimester; but data is limited
Lactation	Any agent	Fluconazole safer (Risk III L2) Than itraconazole (Risk IV L2) Terbinafine and griseofulvin should be avoided
Liver dysfunction	Any agent	Fluconazole with dose adjustment and close monitoring of liver enzymes Terbinafine, griseofulvin and itraconzaole should be avoided
Renal dysfunction	Any agent	Fluconazole is safe and terbinafine can be given with dose adjustment and close monitoring of liver enzymes. Terbinafine should not be administered if CrCl<50 ml/min There is limited data available for itraconazole use and griseofulvin should be completely avoided
Cardiac problem	Any agent	Fluconazole is safest
Elderly population	Any agent	Terbinafine is the safest A close watch on drug interactions
Pediatric population	Any agent	All drugs may be given with dose adjustment

safety or efficacy of combination of oral antifungals in dermatophytosis, and those are, thus, not recommended.

Use of systemic antifungals in special situations

Topical antifungals are preferred in elderly patients. Terbinafine is a safe option when it comes to oral drugs. In the pediatric age group, topical antifungals are preferred considering thinner skin and better penetrability. In cases where lesions are nonresponsive to topical antifungals, extensive or in cases of steroid abuse, use of systemic antifungals becomes imperative. Considering the growing resistance to terbinafine, itraconazole can be considered as the second line systemic agent in infants one month and above. A study by Gupta *et al.* reported the effectiveness of itraconazole 5 mg/kg/day for one week in tinea corporis and tinea cruris and two weeks in tinea pedis and mannum) in children.[85] The duration of treatment in this scenario, however, seems to be short and it is prudent to have a trial with extended duration. Another review published by Chen *et al.* found itraconazole to be a safe and effective second-line therapy for infants with superficial dermatophytosis (5 mg/kg/day) and systemic mycoses (10 mg/kg/day)[86] It is interesting to note that the bioavailability of itraconazole oral solution is 30% greater than itraconazole capsules because of the cyclodextrin vehicle, and in contrast to itraconazole capsules, maximal absorption is obtained when taken on an empty stomach.[87] This formulation has been used to overcome the problem of treating children who have reduced absorption of itraconazole capsules because of nausea or vomiting or reduced stomach acidity. It has also been used for children who have difficulty in swallowing itraconazole capsules.[88]

In pregnancy, it is prudent to treat with topical antifungals. Recent studies conclude terbinafine as a safe oral drug in pregnancy.[89]

Choice of drugs in special situations is summarized as in Table 4.

Treatment recommendations in major textbooks written by authors in the Western world are found to be irrelevant and inadequate in the current scenario of dermatophytosis in India. Higher doses of oral antifungal agents for longer duration along with topical antifungals are needed to overcome the infection. There is a need for many more large-scale studies in Indian patients and, therefore, we consider it premature to recommend therapeutic guidelines on treatment of superficial dermatophytosis despite the prevailing epidemic-like situation in India.

Conclusion

Resistance to griseofulvin, azoles and allylamines have been reported in several studies during the current outbreak. However, there appears to be some discordance between *in vivo* and *in vitro* resistance. The major problem in interpretation of antifungal susceptibility testing is the absence of clinical breakpoints and epidemiological cut off values. In their absence, evaluation of the upper limit of minimal inhibitory concentrations of wild type isolates may be beneficial for managing dermatophytosis and monitoring the emergence of isolates with reduced susceptibility. High resistance rates of *Trichophyton mentagrophytes* genotype VIII, and *Trichophyton rubrum* to terbinafine were found first in studies conducted in India. *Trichophyton mentagrophytes* VIII strains show high frequency of single point mutations in the squalene epoxidase gene leading to terbinafine resistance.[90] Terbinafine antifungal susceptibility testing by breakpoint method or minimal inhibitory concentration determination and genetic point mutation analysis of the squalene epoxidase gene for epidemiological surveys should be established in India.

Recommendations for treatment of superficial dermatophytoses found in Western textbooks of dermatology are often found to be inadequate in both dosage and duration. Treatment recommendations in the current epidemic like scenario of dermatophytoses in India are more experience-based than evidence-based. It is an irony that there is a relative dearth of studies related to the therapeutic aspects of dermatophytoses considering such a high prevalence of the disease and the plethora of drugs available to us. Itraconazole rules the roost in the oral treatment and is used in higher doses for a longer period of time, sometimes as long as 6–8 weeks, despite lack of evidence of increased effectiveness. Increasing the dose beyond 200 mg per day should not be encouraged. The high minimum inhibitory concentration of terbinafine and the squalene epoxidase gene mutation are responsible for the drug falling out of favor steadily. There is a resurgence of older antifungal drugs. Azoles like fluconazole, despite their high minimal inhibitory concentrations, are being used because of their high absorption and cheaper prices. Recent randomized controlled trial evidence suggests that the four major oral antifungal agents, namely, itraconazole, fluconazole, terbinafine and griseofulvin, have varying degrees of disappointing effectiveness in chronic and chronic relapsing tinea corporis, tinea cruris and tinea faciei patients in India. Among topical agents, luliconazole and sertaconazole are the most popular. Other topical drugs like terbinafine, amorolfine, ciclopiroxolamine and so on are being used too but unfortunately there is a paucity of comparative studies except for head to head studies of just two molecules and those too are sparse. There seems to be a dire need for more systematic comparative studies. To summarize, treatment of dermatophytoses shall continue to remain a challenge for the treating physicians, and the role of non-pharmacological measures (general measures and counseling) cannot be over-emphasized.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

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