The menace of dermatophytosis in India: The evidence that we need

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A spectre is haunting Indian dermatology – the spectre of dermatophytosis. Dermatophytoses have always been among the commonest infective dermatoses in India. However, the current perception among practicing Indian dermatologists based on their daily experience in the outpatients' clinics is that there is a huge change in clinical profile, both qualitative and quantitative, in the patients presenting with dermatophytosis. It is impossible to tell how much of this widely perceived change is the product of primarily the host, agent, environmental or pharmacological factors and how much of it is secondary to a change in the health-seeking behavior of the Indian patient. The latter is primarily governed by the ease with which a plethora of drugs, including many irrational combinations containing topical steroids, are available. The infection is apparently much more resilient, having a tendency to recur more frequently and the overall number of patients presenting with chronic/recurrent/recalcitrant dermatophytosis is much more. A disease that was taken for granted and hence treated with predictable results is now becoming a cause of anxiety and trepidation for the dermatologist. In such a scenario, the need of the hour for the practitioner is an evidence-based management guideline that will account for the changes in epidemiology and pathogenetic behavior of the fungi, if any.

The stumbling block for such guidelines is the glaring lack of evidence regarding the changing clinical patterns of the infection. Whatever information we have on epidemiology of dermatophytosis in India has been based on, almost without exception, hospital-based single-center studies. There are inherent drawbacks of such studies. Patients coming to these centers are not completely representative of the epidemiology of the infection in the population because these patients typically constitute a skewed sample of disproportionately more complicated infections. Moreover, they represent the patient population to whom the health-care facilities are more easily accessible. Hence, the baseline data give at best a fragmented idea about the situation at hand. Based on such studies, albeit those with a larger sample than most others, *Trichophyton rubrum* is considered to be the most common dermatophyte in India.[1] However, studies carried out in different geographic locations have found the preponderance of isolates of *Trichophyton mentagrophytes* and *Microsporum audouinii*.[2,3] To complicate matters further, small studies carried out in the same site in a gap of a few years have led to the reporting of two different predominant isolates.[4,5] Therefore, as far as evidence is concerned, the need of the hour is to have a multicentric large epidemiologic survey that can effectively establish the prevalence of fungal isolates present in all the corners of this large country of subcontinental dimensions with huge demographic, topographic and climatic variations. This, in our opinion, should be the starting point in developing the evidence base of dermatophytosis in India. Further elucidation of the complex problem will have to be led by two sets of research that may be broadly classified as upstream and downstream.

Although the prevalence of superficial mycotic infection is 20%–25% of the world population, with dermatophytes being the leading microorganism responsible, research in various aspects of the problem is lacking. The current upsurge of complicated dermatophytosis in India has also been noted in other parts of the world, particularly the tropics.[6] Due to the fact that dermatophytosis is a predominantly tropical dermatosis, despite its huge prevalence it probably does not get the attention it deserves as far as scientific research is concerned. This is manifested by the lack of definitions of even standard terminologies such as "chronic dermatophytosis" and "recurrent dermatophytosis." Such absence of clearly defined terms impedes our ability to accurately delineate the contours of the current problem: Is it simply an epidemic of chronic dermatophytosis? Or, is it relapsing or recurrent tinea? Or, does it signify bonafide resistance to multiple topical or systemic antifungal agents? Chronic dermatophytosis has been sought to be defined arbitrarily as disease continuing for more than 6 months to 1 year with or without recurrence in spite of being treated.[7] Similarly, recurrent dermatophytosis has been defined, without validation,

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as "cutaneous dermatophytosis in which the infection reoccurred within 6 weeks of stopping the adequate antifungal treatment with at least two such episodes in last 6 months."[8] We simply do not know whether the spectre that we are viewing with such alarm is chronic, relapsing or resistant tinea. Theoretically, it may well be relapse since the fungus may not have been eradicated due to an unnoticed nail involvement or the rarely documented tinea of vellus hair. It may, on the other hand, be a reinfection because of untreated family members, infected clothing and other fomites harboring the fungi. It is difficult to discount the possibility of secondary or primary resistance too without adequate studies. In the absence of such characterization, we have to simply term these as unresponsive dermatophytosis.

The types of tinea according to major body site involvement among Indians have also been documented in a fragmentary manner as described above. As informed by most single-center studies, including the relatively larger ones, tinea corporis and cruris are the commonest clinical presentations in this country. These studies also almost invariably found *T. rubrum* to be the most common isolate; however, there are some small studies that have reported tinea unguium as the commonest presentation.[9,10] The predominant clinical distribution must also be the subject of a pan-Indian study as that has a direct bearing on the problem at hand. About 90% of cases of chronic dermatophytosis have been attributed to *T. rubrum* and the major subtypes were tinea cruris and corporis.[11] Among the current crop of atypical dermatophytosis in the Indian scenario, a large number of tinea faciei cases in adults, a location that has been hitherto described among pediatric patients in the majority, is a significant finding, and almost invariably these are topical steroid-modified tinea. The phenomenon does not seem to respect any gender; however, there are some unpublished observations that women seem to be more affected and almost always they are secondarily infected by a primary case of steroid-modified tinea afflicting a male member of the family. Likewise, there are unconfirmed reports of children getting tinea more frequently now than ever before. It involves the glabrous areas (like forehead) at will and is as unlike the classical morphology in adult men (aka tinea barbae) as it can be. These variations have not been recorded in a formal study and provide more reason why an all-encompassing epidemiologic study is urgently needed.

In the informal discussions on steroid-modified tinea, some of our colleagues have also reported that there is a widespread tinea, somewhat akin to the *T. rubrum*-related tinea corporis generalisata, sometimes with pustular borders, among close members of the family of the index patient with a history of applying steroids, though these secondary cases do not apparently have any history of having applied steroids themselves. In addition, there are several notable clinical observations such as involvement of multiple sites, larger-sized lesions, eczematous change in the center of the lesions, pustular borders, bizarre shapes, multiple annular lesions at times showing clustering and increased frequency of male genital involvement. These undocumented observations have raised the question whether the pattern of virulence and infectivity of the dermatophytoses have changed. The "ring-within-a-ring" appearance, named tinea pseudoimbricata, for its resemblance with tinea imbricata caused by *Trichophyton concentricum* and caused by *T. mentagrophytes* or even *T. rubrum*, has already been established as a clinical marker of topical steroid abuse.[12,13]

For answering our questions on infectivity and virulence, the importance of the so-called upstream research comes to the fore. The resilience of *T. rubrum*, and the mechanisms by which it can subvert our immune system, have been well researched.[14] Further questions need to be answered whether *T. rubrum* or any other dermatophyte (e.g., *T. mentagrophytes*) have equipped themselves with hitherto unknown armaments to evade or modify our immunity. To fully unravel the role of host factors, genetic mutation analysis of the cases with severe, resistant and atypical presentations will also be necessary as single gene mutation (viz., CARD9) has been found to be associated with regulation of multiple downstream pathways having antifungal response.[15] Other issues, such as biofilms (described in both *T. rubrum* and *T. mentagrophytes*) and role of mannans, have hardly been addressed in mycological studies in India.[16] The question of encountering fungi other than dermatophytosis is also moot, in view of the findings of a study carried out in North India where the predominant entities in cases of dermatomycosis were not dermatophytes but nondermatophyte molds.[17]

Whether the putative role of topical steroid misuse behind the sudden outbreak of the complicated, atypical, chronic and recalcitrant dermatophytosis is only a convenient hypothesis is also open to question. It is gladdening to note that various centers and individuals are involved in questionnaire-based studies and all of them so far uniformly show shocking abuse of irrational combination creams containing topical steroids that are available "over the counter" in India. However, close examination of the issue creates more conundrums. Topical steroid-antifungal combinations have been used for a long time and the range of evidence in favor of short- or ultrashort-term use of such products is huge though more recent well-controlled studies reveal that the combination products offer equal or lower mycologic or clinical cure rates compared with antifungal agents alone in the management of dermatophytosis.[18] Corticosteroids have been demonstrated to stimulate fungal metabolism in low concentrations while inhibiting fungal metabolism in high concentrations by their cytostatic effects.[19] However, in practice, all corticosteroid preparations might be considered as working at low concentrations since absorbed concentrations of corticosteroids are expected to decrease after penetration through the skin layers.[18] Having said so, we must not miss the fact that new evidence in favor of such combinations is still being unearthed. A recent report of successful treatment of tinea corporis with combination of topical isoconazole (one of the relatively newer azoles) with diflucortolone (a potent topical steroid) is a case in point.[20] Our nuanced observation in this regard must not be misconstrued. Use of steroid-antifungal combination is certainly not to be recommended in view of the newer well-controlled studies that fail to show its superiority to antifungal alone other than the numerous obvious complications that will ensue following its long-term use. Furthermore, whatever we have stated here pertains to the use of the two-drug (steroid-antifungal) combinations. We vehemently oppose the use or even the existence in the Indian market of the patently irrational triple and quadruple combination creams (steroid-antifungal-antibacterial, etc.) that are the highest selling creams in India and are unfortunately grossly abused and often the first creams used by the patient with tinea who buys them over the counter from the pharmacist or are prescribed by general practitioners.[21,22] However, it may be considered presumptuous to ascribe all our current problems with unresponsive dermatophytosis to the use of steroid-antifungal combinations alone since we lack the evidence justifying such a position.

On the other hand, lack of adherence to standard treatment regimen – an often underemphasized aspect with hardly any

systematic research – is certainly an indubitable factor in the development of *in vivo* resistance to antifungals. It is a common practice of our patients to stop treatment on their own as soon as the antifungal begins to show results within some days of the start of therapy. The symptomatic relief provided by various fixed drug combinations due to their steroid content translates into an even shorter duration of treatment which is often repeated *ad libitum*. This behavior will logically culminate in the growth of the most resistant strains. That, in turn, creates pressure on the clinicians to recommend for their patients longer treatment or higher dosages of antifungals than are otherwise mandated. However, the vicious cycle becomes complete when selective targeting mounted by such overuse of antifungals creates a favorable milieu for the selection of the most resistant strains that would eventually become predominant in the population even accounting for a low frequency of gene mutation. Whether we are witnessing such a phenomenon in our country today should become the focal point of a nationwide mycologic analysis that would isolate the most common strains and map their antifungal susceptibility. In this regard, a significant Polish study may be recalled that demonstrated the development of resistance in *T. rubrum* following prolonged exposure to itraconazole and fluconazole as also the development of cross-resistance between both the azoles.[23] Current initiatives taken by the Indian pharma industry promoting updosing of terbinafine and itraconazole, in the absence of studies that would take into cognizance the concerns mentioned above, must be viewed with circumspection. Are we deepening the crisis unwittingly by our incomplete and facile understanding of the current scenario?

It is also important to note that, just like complicated dermatophytosis which appears to be well-entrenched throughout the tropics, the increasing resistance to common antifungal agents used in dermatophytosis is also being reported from different corners of the globe.[24] Both clinical and microbiologic resistance, either occurring singly or in tandem, as well as primary and secondary resistance to antifungal agents have been reported.[25] However, in contradistinction to clinical resistance, proven microbiologic resistance to antifungals is a rarity.[26] Such a situation demands that we take a closer look at the unfolding events involving the few mycology laboratories in our country that are equipped to perform the requisite analysis.

The situation of dermatophytosis management in India is completely chaotic, largely based on ex cathedra pronouncements by self-proclaimed authorities and guided purely by empiricism in the absence of any evidence generated locally. Thus, we have peddling of hitherto unheard of concepts such as combining oral antifungals, multidrug treatment in dermatophytosis and regular use of oral antifungals such as voriconazole. The crisis in credible management options is further compounded by a drug market where formulations are introduced without any supportive evidence in the form of clinical research. Thus, we have itraconazole in unconventional forms such as tablets, compounded in beta cyclodextrin and sustained release preparations or topical antifungals such as amorolfine and luliconazole with penetration enhancers. Itraconazole is being marketed as powder. Topical amphotericin B gel is bandied about freely as a treatment of dermatophytosis. It is frightening to see such precious agents commonly used against deadly, invasive fungi being used in such a cavalier fashion, thus promoting their resistance in the community. Itraconazole, fluconazole and terbinafine are being used in varying dosage schedules and for varying durations without performing any dose-ranging studies. Isotretinoin is being used in combination with itraconazole on the basis of a single case report though questions have been raised regarding the pharmacokinetic rationale of the combination.[27,28]

One can fill pages writing about such instances of our current practice of treating tinea without a shred of evidence. It is a futile exercise in a country where most practitioners do not even have access to a most basic test as a potassium hydroxide mount; reliable fungal cultures are done only in few centers across the country; and strain isolation with current techniques and antifungal susceptibility studies may be carried out in only one or two elite institutions. Hence, we have no option but to start generating our own evidence as we spiral downward to a situation where tinea is added to the list of superbugs to which we have no answer. The research to be done, as detailed above, is long, and needless to say, cannot be addressed by means of a single study, however exhaustive it may be. Therefore, we have to prioritize the agenda of generating evidence that we need to formulate national guidelines, involving dermatologists and mycologists, within the framework of available financial and infrastructural resources. The time is now.

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