Reinterpreting minimum inhibitory concentration (MIC) data of itraconazole versus terbinafine for dermatophytosis – time to look beyond the MIC data?

Sir,

We read with interest the article by Mahajan *et al*. titled, "Clinico-mycological study of dermatophytic infections and their sensitivity to antifungal drugs in a tertiary care center."[1] It is a yet unsubstantiated notion that terbinafine, which has been used as a first-line drug against dermatophytic infections for years, has probably lost its clinical efficacy in India. This has been supported by two recent publications in Indian literature, though there is little clinico-mycological correlation in these.[2,3] Patient's immune response is crucial for elimination of dermatophytes and this, along with rampant steroid abuse, is also a potential cause of the recalcitrance.[4]

Nevertheless, mycological studies are important. The present study highlights two noteworthy points. Firstly, the epidemiological shift in the causative strains, with *T. mentagrophytes* being isolated from 75.9% of cases and *T. rubrum* from only 11.3%. This is contrasting to the reports prior to 2012, wherein *T. rubrum* was most commonly isolated. Secondly, this is probably the first documentation of high minimum inhibitory concentrations (MICs) of *T. mentagrophytes* to terbinafine. There are occasional reports of terbinafine resistance to *T. rubrum*, but none of *T. mentagrophytes*, to the best of authors' knowledge.

However, there are a few contradictions in this study, which we would like to highlight. Firstly, with reference to the MICs of terbinafine, the authors say that "Only two studies had similar minimum inhibitory concentration which ranged from 0.003 to 16 μg/ml." However, in the quoted study, the mentioned level is for *T. rubrum* and not for *T. mentagrophytes*, the strain which the authors have tested.[5] The MICs in the mentioned study (reference 39 in the article) were in fact lower for *T. mentagrophytes* (0.007–0.5 μg/ml) than *T. rubrum* (0.003–16 μg/ml).[5] Secondly, the authors mention that "There was a statistically significant difference in the sensitivity of itraconazole as compared to terbinafine, fluconazole and griseofulvin." However, the MIC values for terbinafine and itraconazole, mentioned in Table 1, are identical. Further, the *P* value mentioned is 0.12, not satisfying the criteria for statistical significance. Thirdly, with reference to itraconazole, the authors mention that sensitive strains have MIC between 0.01 and 8 μg/ml and that only three of their strains (6%) had MIC ≥8 μg/ml and hence were resistant to itraconazole. But, the quoted reference mentions this cutoff value in relation to *Aspergillus fumigatus* and not *T. mentagrophytes*.[6] MIC cutoffs are specific to a drug–species pair and cannot be generally applied to other strains/class of fungi. Also, instead of merging the data of MIC for all isolates, various levels with the number of isolates under each level would have been more informative. Lastly, it is erroneous to compare the MIC levels of fluconazole to terbinafine or itraconazole as it is intrinsically higher, without necessarily predicting failure.

Arthroconidia have been considered as the primary cause of infection by dermatophytes. However, the *in vitro* antifungal

testing evaluates the responses mainly of microconidia or hyphae, and dermatophytes *in vivo* often produce arthroconidia, a cellular structure presumably more resistant to antifungals. The difference in the susceptibility between microconidia and arthroconidia depends on the drug and on the strain, and may be one of the causes of therapeutic failure, but this is rarely the focus of mycological studies, including the present one.[7]

Most importantly, overuse of a drug leads to a high MIC and that does not mean treatment failure. A moot point is whether there is a clinical utility of standard antifungal susceptibility test methods. *In vitro* susceptibility of an organism to an antifungal agent does not predict a successful therapeutic outcome.[8] It must be remembered that the MIC is a construct that is largely defined by testing conditions, rather than a physical or chemical measurement. This measure might correlate with clinical outcome, but a multitude of factors related to the host (immune response, underlying illness, site of infection), the infecting organism (virulence) and the antifungal agent [dose, pharmacokinetics (PK), pharmacodynamics (PD), drug interactions] may be more important than susceptibility test results in determining clinical outcomes for infected patients. An important step toward establishing clinical utility of antifungal susceptibility test data is to determine clinical breakpoints for each drug. Clinical breakpoints categorize fungal isolates into (i) susceptible (the drug is an appropriate treatment); (ii) resistant (the drug is not recommended as a treatment) and (iii) intermediate (the drug may be an appropriate treatment, depending on certain conditions). Clinical breakpoints are established based on clinical trial data, global susceptibility surveillance, resistance mechanisms and PK/PD parameters from model systems. These may be easier to establish for dermatophytes (these infections being very prevalent) than other molds. But sadly, the same are available for other fungi *(accessible from http://www.eucast.org/clinical_breakpoints)* but none for dermatophytes. The focus of future research should be to generate quality clinically correlated susceptibility data and further clinical breakpoints for each species–drug pair.

In conclusion, the present study should not lead to an assumption that terbinafine has lost its clinical utility against dermatophytes. Also, projection of itraconazole as the most effective drug is speculative and dangerous. Azoles have an inherent ability to potentiate resistance. The suboptimal quality of many itraconazole brands in the country may further worsen the situation. In addition, it is important not to trivialize the various innate and/or adaptive immune responses that may affect the body's ability to clear fungi organisms.[9] We should abstain from an inordinate focus on isolated MIC data, which even in ideal circumstances cannot mirror the clinical response. This is evident in India where in spite of the use of supra-pharmacological and unapproved doses of itraconazole (200 and 400 mg), and in spite of the drug's low MICs, commensurate results are not consistently achieved. This is a clear signal that the answer to recalcitrant dermatophytoses lies elsewhere.

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Conflicts of interest
There are no conflicts of interest.

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