Clinical Implications of Antifungal Drug Susceptibility Testing of Dermatophytes

Dear Editor,

We read with interest the editorial by Dogra *et al.* titled "Antifungal Drug Susceptibility Testing of Dermatophytes: Laboratory Findings to Clinical Implications" and congratulate the authors for an explicit review on the methodology of antifungal susceptibility testing (AFST) in dermatophytes and problems thereof.[1] We reiterate that in routine microbiology laboratories; the complexity of susceptibility testing procedure in dermatophytes hampers the determination of actual burden of antifungal resistance. Further, as the authors point out, the lack of epidemiological cutoffs (ECV) and clinical break points (CBP) hinders clinical application of AFST data on dermatophytes. We agree with the authors that as with many other pathogenic molds, in dermatophytes too the availability of clinical outcome for determining the CBPs is by and large lacking. Nonetheless, some significant papers on outcome data on dermatophytoses including individual reports, case series and clinical trials are available that will benefit the readers interested in dermatohytoses research, specifically pertaining to AFST and its clinical implications, and are summarized below.

The earliest attempt at correlating minimum inhibitory concentrations (MIC) with *in vivo* response was possibly by Artis *et al.* (1981).[2] The study came after a few individual reports of lack of response to Griseofulvin (GRI) in infections by *Trichophyton tonsurans*[3] and *Epidermophyton flocossum*[4] with reported MICs of 10-20 μg/ml and 1.6-1.8 μg/ml (increased to 6.8-7.0 μg/ml later) respectively. Artis *et al.* described 43 patients with tinea corporis/pedis/manuum who had failed GRI therapy.[2] The failure was defined as absence of substantial improvement despite atleast 4 months of GRI 250 mg twice a day therapy. Specimens from all 43 patients grew *Trichophyton rubrum* on culture. The mean MIC of failures in the tinea corporis group was 6.3 μg/ml versus 1.6 μg/ml in the control group (responders). In the tinea pedis/manuum group the corresponding values were 3 μg/ml and 1 μg/ml. The authors suggested that an MIC of ≥3 μg/ml may be taken as indicative of relative GRI resistance. Notably, the reported MIC 90 of GRI in some recent Indian studies are 64,[5] 4[6] and 8 μg/ml.[7]

For terbinafine (TRB), there are a few reports of therapeutic failure correlated with *in vitro* MICs. The earliest report was described in a patient of onychomycosis who failed treatment with TRB 250 mg/day for 24 weeks.[8] This was the first, and for a long time the only, report of *in vivo* TRB failure, confirmed with high MICs and presence of mutations of the target enzyme, squalene epoxidase (SQLE).[9] The MIC of TRB was reported as 4 μg/ml at the start of treatment. Interestingly, the subsequent MICs remain unchanged when measured by the broth micro-dilution method, but an increasing trend was observed when AFST was performed using the macro-dilution method.[9]

Over past 2 years, a few more cases and a clinical trial have been added to the existing literature on *in vivo* correlation of TRB MICs. Digby *et al.* from Denmark reported a patient with Darier's disease and extensive dermatophytoses, who failed to respond to two 30-day courses of TRB 250 mg/day.[10] The MIC of TRB was reported as >4 μg/ml.[10] Subsequently, another report from Denmark described a child with icthyosis who failed to respond to TRB.[11] The MIC of TRB was 4 μg/ml.[11] All of these three reports were with *T. rubrum* infections.[8-11] The most recent is a prospective study from India where 30 patients of tinea corporis/cruris were

treated with increasing durations and up-dosing (250 mg BD) of TRB as per a fixed protocol and the clinical outcomes compared with *in vitro* MICs and SQLE mutation data.[6] A significant finding of the study was that patients infected with a strain with TRB MIC of ≤1 μg/ml were 2.5 times more likely to respond to TRB than those infected with strains with higher MICs. Most of the non-responders had MIC of ≥32 μg/ml. The group which responded to OD dose with standard/prolonged treatment durations had a GM MIC of 1.515 μg/ml, while the group in which TRB was up-dosed to effect a response had a GM MIC of 5.039 μg/ml.[6] The study and the previous reports highlight that a MIC beyond 4-5 μg/ml may preclude therapeutic success with TRB. However, the interpretation has limitation of small patient numbers and warrants further research.

Unfortunately, to the best of our knowledge, no *in vivo* correlation of MIC data is as yet available for systemic azoles used in dermatophytoses. This is however highly needed in the present scenario, with itraconazole being increasingly used for the infection. To conclude, there are various factors which hinder the routine use of AFST for dermatophytes.[1] However, in the wake of the recalcitrance being seen in the country, there is an imminent need to conduct high-quality research encompassing AFST and its *in vivo* correlation to facilitate best utilization of the available antifungal drugs against dermatophytoses.

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Conflicts of interest

There are no conflicts of interest.

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