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In Vitro Antifungal Susceptibility Profiles of 12 Antifungal Drugs against 55 *Trichophyton schoenleinii* Isolates from Tinea Capitis Favosa Patients in Iran, Turkey, and China

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ABSTRACT *Trichophyton schoenleinii* is an anthropophilic dermatophyte mainly causing tinea favosa of the scalp in certain regions of the world, especially Africa and Asia. We investigated the *in vitro* susceptibilities of 55 *T. schoenleinii* isolates collected over the last 30 years from Iran, Turkey, and China to 12 antifungals using the CLSI broth microdilution method. Our results revealed that terbinafine and ketoconazole were the most potent antifungal agents among those tested, independently of the geographic regions where strains were isolated.

KEYWORDS *Trichophyton schoenleinii*, tinea capitis favosa, antifungal susceptibility testing

Favus, or tinea capitis favosa, is a chronic inflammatory dermatophytosis of the scalp, particularly diagnosed in children aged 4 to 14 years and occasionally in adults (1–3). Favus is characterized by scutulum formation and scarring atrophy (cicatricial alopecia), which can be differentiated from other clinical forms of tinea capitis, e.g., tinea capitis superficialis and kerion celsi (1, 4).

Anthropophilic *Trichophyton schoenleinii* is responsible for over 95% of favus cases (5). However, in rare instances, several anthropophilic (*Trichophyton violaceum*), zoophilic (*Trichophyton quinckeanum* and *Trichophyton verrucosum*), and geophilic (*Microsporum gypseum*) dermatophytes are reported as etiological agents of favus (1, 6).

With the introduction of griseofulvin in 1958, the anthropophilic agents of tinea capitis, *T. schoenleinii* and *Microsporum audouinii*, were almost eradicated in most parts of the world (5–7). Currently, favus is common mainly in African countries—Nigeria (8) and Ethiopia (9)—and western China (5, 10) and geographic regions where lifestyles are associated with malnutrition and poverty (11, 12). The disease has also been reported sporadically in Iran (13), Turkey (14, 15), Western Europe (3), and South America (11).

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Importantly, the efficacy of griseofulvin has decreased over the years, and now the drug requires larger doses and longer treatment durations (16, 17). This suggests that griseofulvin is no longer the treatment of choice in superficial cutaneous fungal infections (18, 19). In contrast, the newer antifungal drugs, such as allylamine terbinafine, triazoles, and echinocandins, have the advantage of shorter treatment durations than griseofulvin and may remain present in fungicidal concentrations for several weeks after the course of treatment has been completed, which allows short treatment durations with fewer side effects and also prevents reinfection (17, 18).

Although the infections caused by *T. schoenleinii* are of considerable medical importance, little is known about the utility of the newer antifungal agents for the management of tinea capitis caused by *T. schoenleinii* from different geographic regions. Therefore, we investigated the *in vitro* susceptibilities of a large collection of clinical isolates of *T. schoenleinii* strains to 12 antifungal drugs by using the Clinical and Laboratory Standards Institute (CLSI) broth microdilution method (20).

(Parts of these results were presented at the 26th European Congress of Clinical Microbiology and Infectious Diseases 2016, 9 to 12 April 2016, Amsterdam, the Netherlands [21].)

A total of 55 *T. schoenleinii* isolates obtained from patients with tinea capitis from Iran, Turkey, and western China were used. All isolates were cultured on Sabouraud glucose agar (Merck, Darmstadt, Germany) at 25°C for 5 to 7 days. For identification, morphological identifications were confirmed using sequence-based analysis of the ribosomal DNA (rDNA) internal transcribed spacer (ITS) regions, as described previously (22).

Conidial suspensions were harvested after isolates were subcultured on Sabouraud dextrose agar (SDA) for 5 to 7 days at 25°C and were suspended in normal saline containing 0.025% Tween 20. The inocula were then prepared spectrophotometrically and further diluted in normal saline in order to obtain a final inoculum concentration of 0.5×10^6 to 2.5×10^6 CFU/ml.

We tested the *in vitro* susceptibilities of the isolates to 12 antifungals by using a broth microdilution format according to CLSI guidelines (20). Final concentrations of the following antifungal agents ranged from 0.016 to 16 μg/ml: amphotericin B, ketoconazole, miconazole, itraconazole, voriconazole, posaconazole, caspofungin, anidulafungin, and terbinafine. Flucytosine, fluconazole, and griseofulvin were assessed over a 2-fold concentration range, from 0.064 to 64 μg/ml. The MICs of amphotericin B, flucytosine, ketoconazole, miconazole, fluconazole, itraconazole, voriconazole, posaconazole, griseofulvin, and terbinafine were determined visually: an inverted mirror was used for comparing the growth in wells containing the drugs with that in the drug-free control well. The results were also read using a microtitration plate spectrophotometric reader (Anthos htIII; Anthos Labtec Instruments, Salzburg, Austria). The minimum effective concentrations (MECs) of caspofungin and anidulafungin were read using a plate microscope (Olympus SZX9; Olympus Nederland, Zoeterwoude, the Netherlands), at $\times$25 to $\times$50 magnifications.

The ranges and geometric means (GMs) of the MICs and MECs were determined for each species and drug after 48 and 72 h of incubation. If no growth was observed or growth was inadequate, incubation was extended to 120 h. *Paecilomyces variotii* (ATCC 22319), *Candida parapsilosis* (ATCC 22019), *Candida krusei* (ATCC 6258), and *Trichophyton mentagrophytes* (ATCC MYA 4439) were used for quality controls in all experiments. All experiments on each strain were performed using three independent replicates on different days.

Data were analyzed using GraphPad Prism, version 5.0, for Windows (GraphPad Software, San Diego, CA). MIC/MEC distributions between the groups and within distinct geographic areas were compared using Student's *t* test and the Mann-Whitney-Wilcoxon test; differences were considered statistically significant at *P* values of $\leq$0.05 (two-tailed).

The overall results obtained from visual and spectrophotometric readings were similar for the MIC and MEC endpoints. The geometric means (GMs) of MICs/MECs, the

TABLE 1 Geometric means of MICs/MECs, MIC/MEC ranges, and MIC_{50}/MEC_{50} and MIC_{90}/MEC_{90} values obtained by testing susceptibilities of 55 *Trichophyton schoenleinii* strains to 12 antifungal agents

Drug[a]	MIC/MEC (μg/ml)[b]			
	Range	MIC_{50}/MEC_{50}	MIC_{90}/MEC_{90}	Geometric mean
AmB	0.031 to 0.5	0.25	0.5	0.29
5-FC	64 to >64	64	64	64
FLC	4 to 64	16	64	25
ITC	0.063 to 4	0.25	2	0.81
VRC	0.063 to 4	0.25	2.00	0.89
POS	0.031 to 0.5	0.125	0.50	0.20
MCZ	0.125 to 1	0.50	1.00	0.57
KTZ	0.125 to 1	0.50	1.00	0.52
AFG	0.016 to 8	0.02	0.02	0.68
CAS	0.25 to 1.00	0.5	1.00	0.60
GRZ	0.05 to 2	0.63	2	0.92
TBF	0.016 to 0.125	0.031	0.125	0.05

[a]Abbreviations: AmB, amphotericin B; 5-FC, flucytosine; FLZ, fluconazole; ITC, itraconazole; VRC, voriconazole; POS, posaconazole; MCZ, miconazole; KTZ, ketoconazole; AFG, anidulafungin; CAS, caspofungin; GRZ, griseofulvin; TBF, terbinafine.

[b]MECs were used for caspofungin and anidulafungin. MICs were used for all other drugs.

MIC/MEC ranges, and the MIC_{50}/MEC_{50} and MIC_{90}/MEC_{90} distributions of the 12 antifungal agents and 55 *T. schoenleinii* isolates are listed in Table 1.

The geometric means of the MICs/MECs of the antifungals across all isolates were as follows (in increasing order): terbinafine, 0.05 μg/ml; posaconazole, 0.20/ml; amphotericin B, 0.29 μg/ml; ketoconazole, 0.52 μg/ml; miconazole, 0.57 μg/ml; caspofungin, 0.60 μg/ml; anidulafungin, 0.68 μg/ml; itraconazole, 0.81 μg/ml; voriconazole, 0.89 μg/ml; griseofulvin, 0.92 μg/ml; fluconazole, 25 μg/ml; and flucytosine, >64 μg/ml.

The MIC/MEC ranges across all isolates were as follows: terbinafine, 0.016 to 025 μg/ml; posaconazole, 0.031 to 0.5 μg/ml; amphotericin B, 0.031 to 0.5 μg/ml; ketoconazole, 0.125 to 1 μg/ml; miconazole, 0.125 to 1 μg/ml; caspofungin, 0.25 to 1 μg/ml; anidulafungin, 0.016 to 8 μg/ml; itraconazole, 0.063 to 4 μg/ml; voriconazole, 0.063 to 4 μg/ml; griseofulvin, 0.05 to 2 μg/ml; fluconazole, 4 to 64 μg/ml; and flucytosine, 64 to >64 μg/ml.

The highest MIC_{90} values were 64 μg/ml, for flucytosine and fluconazole, which were significantly different from those of the other 12 antifungal agents ($P < 0.01$). No statistically significant differences in the susceptibility profiles of *T. schoenleinii* were detected within the geographic regions investigated ($P > 0.05$).

Antifungal therapy is a central component of patient management for dermatophytosis, and depending on the strategy chosen, topical and/or systemic drugs can be used (23). Despite the increasing number of investigations on the utility of the newer antifungal agents for the management of dermatophytosis (17, 24), the *in vitro* antifungal susceptibility profiles of newer antifungal agents against *T. schoenleinii* remain poorly investigated. Most of the studies on the topic have investigated only a limited number of *T. schoenleinii* strains in the general context of testing the susceptibility of dermatophytes (25–31).

To the best of our knowledge, our study provides the first profiles of susceptibility to 12 antifungals using a large set of clinical *T. schoenleinii* strains isolated from tinea capitis favosa patients from a wide geographic range, worldwide. For all tested strains, terbinafine, posaconazole, amphotericin B, ketoconazole, miconazole, caspofungin, anidulafungin, itraconazole, voriconazole, and griseofulvin had low MICs, whereas fluconazole and flucytosine did not show inhibitory effects.

Our study confirms the findings of previous studies, in which terbinafine demonstrated potent antifungal activity against dermatophyte species obtained from tinea capitis patients, with MICs ranging from 0.02 to 0.13 μg/ml (25, 26, 28–30).

With the exception of fluconazole, all tested azoles showed potent *in vitro* activity against *T. schoenleinii*. The activity of posaconazole (GM, 0.20 μg/ml; MIC range, 0.031

to 0.5 μg/ml) was similar to that of terbinafine (GM, 0.05 μg/ml; MIC range, 0.016 to 0.13 μg/ml), and this was followed by the activity of ketoconazole (GM, 0.52 μg/ml; MIC range, 0.125 to 1 μg/ml), miconazole (GM, 0.57 μg/ml; MIC range, 0.125 to 1 μg/ml), itraconazole (GM, 0.81 μg/ml; MIC range, 0.063 to 4 μg/ml), and voriconazole (GM, 0.89 μg/ml; MIC range, 0.063 to 4 μg/ml). In agreement with our findings, Fernandez-Torres et al. also previously tested 2 *T. schoenleinii* strains and reported an itraconazole MIC range of 0.01 to 0.05 μg/ml, a voriconazole MIC range of 0.01 to 0.06 μg/ml, a miconazole MIC range of 0.031 to 0.063 μg/ml, a ketoconazole MIC range of 0.03 to 0.125 μg/ml, and a fluconazole MIC range of >16 μg/ml (25). In another study, by Indira (29), ketoconazole and itraconazole also demonstrated MIC ranges of 0.06 to 0.96 mg/ml and 0.12 to 0.96 mg/ml, respectively. Similarly, a few other studies also have reported potent *in vitro* activity of azoles against *T. schoenleinii* (26–28, 30, 31).

In the present study, amphotericin B was potently effective (MIC range of 0.031 to 0.5 μg/ml) against all 55 *T. schoenleinii* strains tested, which agrees with previous reports of an amphotericin B MIC of 0.25 μg/ml (25). In our study, we also observed that MEC values of caspofungin and anidulafungin were relatively low, with MEC ranges of 0.25 to 1 and 0.016 to 8 μg/ml, respectively.

Of all agents tested, fluconazole and flucytosine were the drugs for which the highest MIC values were measured, which is similar to the results of previous studies (25). No clinical investigation has been conducted using flucytosine and dermatophytes, but fluconazole has been used for treating tinea capitis. Previous studies have shown that high doses of fluconazole (≥4 to 8 mg/kg of body weight/week) applied for long durations (12 to 16 weeks) might be used for treatment of tinea capitis regardless of the fungus type (18).

Although for almost 4 decades griseofulvin was the standard treatment for tinea capitis worldwide (18), nowadays it is no longer the treatment of choice in superficial cutaneous fungal infections (18). The efficacy of griseofulvin has decreased over the years, resulting in griseofulvin-resistant isolates of dermatophytes (32). Griseofulvin now requires larger doses and longer treatment durations, which put the patient at higher risk of toxicity (16).

In conclusion, our results revealed that terbinafine and ketoconazole were the most potent antifungals against *T. schoenleinii* among systemic and topical antifungals tested, independently of geographic regions where strains were isolated. However, it will be necessary to obtain more clinical data to confirm if this potent *in vitro* efficacy is predictive of clinical outcome.

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