Emerging Recalcitrant Tinea Pedis and Management Using Antifungal Susceptibility Testing: A Pilot Study

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Abstract- Tinea pedis (TP) is a common fungal infection that has become increasingly prevalent with the rise of drug-resistant strains. Traditional antifungal treatments are increasingly less effective, prompting a need for new therapeutic approaches. This pilot study aimed to explore the role of antifungal susceptibility testing (AST) in the management of recalcitrant TP. In this exploratory pilot study, TP Skin specimens were collected and examined microscopically and via culture, with PCR used for species differentiation. Antifungal susceptibility testing (AST) determined MICs for various antifungals, categorizing patients into sensitive, resistant, tolerant, or recalcitrant groups. All patients received clotrimazole 1% cream, with individualized oral antifungal treatments based on AST results and a standard 4-week treatment duration. The study involved 38 patients, with 28 diagnosed with TP. Isolates included *T. mentagrophytes* complex (67.85%), *T. rubrum* (25%), *E. floccosum* (3.57%), *M. canis* (3.57%). Antifungal susceptibility testing revealed high resistance rates, particularly to terbinafine (43%) and itraconazole (17%). Treatment responses varied, with 64.28% of terbinafine-resistant patients improving, while itraconazole-resistant cases often required a switch to voriconazole. Findings from this pilot study suggest that AST may be a valuable tool in the management of recalcitrant tinea pedis when performed by experienced laboratories in accordance with standardized guidelines. An MIC cut-off value of 2 µg/mL for defining terbinafine resistance is proposed; however, larger studies are required to establish definitive clinical breakpoints. Voriconazole appears to be a promising alternative treatment option in cases resistant to both terbinafine and itraconazole.

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Introduction

Tinea pedis (TP), commonly manifesting in interdigital and plantaris forms, is a superficial fungal infection of the feet, which manifests between the toes and on the underside of the foot. Around 59% of individuals with onychomycosis also suffer from a concurrent TP infection (1). Infected shoes, diabetes, inadequate blood flow to the extremities, nail injuries, and professions like swimming all play a role in causing a combination of symptoms (2). The simultaneous presence of onychomycosis and TP is of clinical importance and could result in additional bacterial infections like cellulitis (3). Simultaneous management of onychomycosis and TP infection may lead to decreased relapse and re-infection occurrences (4).

In Europe, TP and onychomycosis were not common before the 1950s, but have shown a significant increase since the end of World War II (5). Trichophyton rubrum is the main causative agent in Tinea unguium (TU), Tinea cruris (TCR), Tinea corporis (TCO), TP, and Tinea manuum (TM), followed by *Trichophyton*

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mentagrophytes (5-8). The predominant pathogen for superficial fungal infections was *T. rubrum* (32-82.9%), and an increase in its occurrence was seen in infections on glabrous skin (onychomycosis, TCO and TCR, TM, and TP) (9). The prevalence of TP and TU only emerged in recent times because of changes in modern living, like the popularity of leather footwear and sneakers, along with the utilization of communal bathing and sports amenities. Indeed, this species has emerged as a major human pathogen relatively recently compared with other dermatophytes.

Traditional available treatments for dermatophytosis include: terbinafine, imidazoles (e.g., clotrimazole, miconazole) and triazoles (e.g., fluconazole, itraconazole); administered either as monotherapy or in combination (10).

Currently, antifungal resistance is an escalating global health concern, since the recent reports present and warn the higher rates of treatment failure and the need for change in protocols of therapy; whether longer durations of treatment or choosing alternative medications. Moreover, the available treatment options remain limited and there has not been any approved new antifungal drug classes in the past two decades. Only one new agent, isavuconazole from a known antifungal class, azoles, has been clinically approved over the last ten years; while other novel agents remain under clinical trial evaluation and are not yet commercially available (11). The emergence of this resistance has been traditionally contributed to selective pressures from increased consumptions of antifungals for prophylaxis (such as in cancer settings and among immune-deficient patients), empiric therapy approaches and agriculture. Additionally, recent manifestations of fungal infections during the coronavirus pandemic in the past 5 years, such as COVID-19 associated aspergillosis and mucormycosis, demanded broad implication of antifungals, which may have had a role to do with further aggravation of resistance; possibly due the extensive exposure of the susceptible fungi to these chemicals (11). These limitations are challenged even more by drug-drug interactions, adverse toxicities, and impediments in administration routes (11). Subsequently, it is no surprise to mention that dermatophyte species have also been influenced by these alterations. Terbinafine-resistant dermatophytes isolates have been recently described globally (12-14), meanwhile, azole formulation resistance rates have been reported to become as frequent as 19% worldwide (15). These epidemiological changes have even highlighted the need for new terminologies to better describe the recent observations .

In the context of this pilot study, recalcitrant TP was operationally defined as an infection that fails to respond to appropriately selected antifungal therapy despite adequate dosing and treatment duration, based on mycological identification. Recalcitrant cases were further categorized as tolerant or resistant according to antifungal susceptibility testing (AST) results and corresponding minimum inhibitory concentrations (MICs).

Materials and Methods

Sample collection and ethical statement

This prospective cross-sectional pilot study was conducted among patients with clinically suspected TP infection, who were referred to the dermatology clinic of Center for Research and Training in Skin Diseases and Leprosy (CRTSDL), Tehran, Iran, and medical mycology laboratory of Immunology, Asthma and Allergy Research Institute, Tehran University of Medical Sciences, Tehran, Iran.

The present study was approved by the Research Ethics Committee of Tehran University of Medical Sciences (Code: IR.TUMS.VCR.REC.1401.587). The authors attest that the process of this study followed the ethical standards of the Helsinki Declaration. All patients had been informed about the different treatment plans for their disease and were part of the decision-making process. All the patients signed a written consent form prior to participating in this study. Patients were informed about the photo documentation and gave their consent for the photos to be used in case their identities remain sealed. Also, Informed consent has been obtained from the patient for the publication of identifiable details, which may include photographs, case history and textual details, in journals and articles. To ensure diagnostic accuracy, patients were required to discontinue topical and systemic antifungal therapies for at least 2 weeks prior to sampling

Laboratory examination

Confirmation of infection was done via clinical evaluation by a dermatologist and mycological testing.

Skin specimens were collected from the active peripheral edge of lesion or closed vesicle by use of sterile scalpel. Each specimen was examined with Potassium Hydroxide (KOH) 10% microscopically for presence of hyphae and arthroconidia.

Skin scrapings and crusts were directly inoculated onto Mycosel™ Agar (Merck, Germany) and remained at room temperature for at most 14 days. Every species was

identified based on colony color and its microscopic features. Culture reports were collected in the data registry. For species from T. mentagrophytes complex, additional Polymerase Chain Reaction (PCR) assay using the internal transcript spacer (ITS1-2 region) gene and genomic sequencing were performed in order to differentiate the precise sub-species (16).

Antifungal susceptibility test

AST was performed in order to distinguish species antifungal susceptibility profile using the broth microdilution protocol according to the Clinical and Laboratory Standards Institute (CLSI) M38, third edition. The MIC of terbinafine, fluconazole, itraconazole, and voriconazole were assessed for all the isolates tested. All antifungal agents were purchased from Sigma® (USA). The results were interpreted as follows: Susceptibility was defined as an MIC <0.5 µg/mL, tolerance as an MIC of 0.5-1 µg/mL, and resistance as an MIC ≥2 µg/mL.

AST based management of TP infection

Patients were divided into three major groups of a) antifungal sensitive, b) antifungal resistant, and c) antifungal tolerant, based on the report of the AST. All patients received clotrimazole 1% cream twice daily as the base topical treatment. Individualized oral treatment protocol was chosen for each of the patients regarding the causative dermatophyte, and MIC level. The standard treatment duration for TP is usually considered 4 weeks. Drug doses were as follows: terbinafine (250 mg once daily), itraconazole (100 mg twice daily, up to 400 mg/day), and voriconazole (200 mg twice daily).

Results

Demographics data analyses

In this pilot study, a total of suspected 38 patients (25 males and 13 females) were included in this study, out of which 28 participants had TP. The mean age of subjects was 33.42 years old. 82.14 percent (23/28) of the patients had the infection for more than 6 months .

Laboratory findings

Consistent with macroscopic and microscopic features, the isolates were identified as *T. mentagrophytes* complex (n=19 [67.85%]), *T. rubrum* (n=7 [25%]), and *Epidermophyton floccosum* (n=1 [3.57%]), *Microsporum canis* (n=1 [3.57]) .

All of 19 isolates phenotypically known as *T. mentagrophytes* complex, were identified as *T. indotineae*, using the ITS1-2 region amplification.

AST results interpretation

Among the 28 dermatophyte spp., the MIC results were within±1 dilution according to the CLSI guide. Notably, 9 *T. indotineae* had the highest MIC value for terbinafine (MICs≥2 µg/mL), followed by 2 *T. rubrum* (MICs≥2 µg/mL), 1 *E. floccosum* (MICs=2 µg/mL). A total of 4 isolates out of 28 isolates (14.29%) including 3 *T. indotineae* and 1 *T. rubrum* were able to grow on the high dose itraconazole containing well (MICs≥ 2 µg/mL). *M. canis* was sensitive to all antifungal agents.

Among the 23 recalcitrant patients, AST demonstrated that 16 (69.56%) exhibited resistance to one or more antifungal agents; these included 4 itraconazole- resistant patients [patient IDs: 12, 23, 22, 26] and 12 terbinafine-resistant patients [patient IDs: 2, 3, 6, 9, 10 ,11, 13, 14, 16, 18, 21, 20]. 7/23 patients had antifungal tolerance (MIC of 0.5-1 µg/mL for one drug or more); these included five itraconazole-tolerant patients [patient IDs: 1, 5, 7, 8, 14] and two terbinafine- tolerant patients [patient IDs: 7, 8,]. There were three patients who had simultaneous resistance and tolerance to more than one medication [patient IDs: 7, 8, 14].

Follow up AST based management of recalcitrant patients

As part of this exploratory pilot assessment, treatment outcomes were descriptively evaluated following AST-guided therapeutic adjustments. Among patients who adhered to continuous therapy based on the study protocol, the duration to complete clinical and mycological cure ranged from 4 to 9 weeks. In the terbinafine-resistant or -tolerant group, a preliminary response rate of 64.28% (9/14) was observed. Eleven patients treated with itraconazole achieved complete cure within 6-7 weeks. Three patients who failed to respond to initial therapy were subsequently treated with voriconazole due to combined terbinafine and itraconazole resistance or tolerance, as indicated by AST results.

None of the itraconazole-resistant or -tolerant patients responded to prolonged treatment with standard-dose itraconazole (100 mg/BD). One itraconazole-tolerant patient (ID:8) achieved complete cure after four weeks of high-dose itraconazole (200 mg /BD). The remaining four itraconazole-tolerant patients required a switch to voriconazole based on AST findings. Patients with IDs 5, 7, and 14 responded to voriconazole within six weeks, whereas patients 1 and 8 achieved complete cure after nine weeks of voriconazole therapy.

Discussion

The rise of terbinafine-resistant species has placed it among the top concerns in the world. Thus, it is essential to propose appropriate treatment. In this pilot study, we explored the use of AST-guided therapy as a potential approach for managing recalcitrant TP.

So far there has not been any determined MIC cut-offs and epidemiological cutoffs (ECVs) for any drugs against dermatophytes by the two major guidelines CLSI (M38-3RD ED) and EUCAST. MIC results were presented descriptively. According to these observations, four isolates exhibited relatively higher MIC values for itraconazole, twelve isolates showed higher MIC values for terbinafine, and seven isolates demonstrated intermediate MICs (0.5-1 μg/mL) to one or more antifungal agents (were considered tolerant), in line with previous exploratory reports (17-21).

In present pilot cohort, all patients underwent a therapy using the AST-findings. We followed our patients' progress for a duration of at most 12 weeks. Among 14 patients with isolates showing higher or intermediate MICs to terbinafine, 11 patients responded to itraconazole treatment after discontinuation of steroid-based agents, resulting in an overall descriptive cure rate of 78.57%. For terbinafine-tolerant isolates, no additional evidence was observed to support benefit from higher doses or prolonged treatment.

Recent studies have also shown that itraconazole remains an effective treatment against terbinafine-resistant strains in many cases and its therapeutic capacity should not be overlooked (18,22,23).

In our cohort, one of five itraconazole-tolerant patients showed clinical improvement with an increased dose (400 mg/day) over an additional four weeks, while four other itraconazole-tolerant patients were treated with voriconazole for up to nine weeks.

This study has several limitations inherent to its pilot/exploratory design. First, the sample size was relatively small, which limits the statistical power and prevents generalization of the findings to broader populations. Second, the study was conducted at a single center, which may introduce selection bias and limit the external validity of the results. Third, the follow-up period was limited to a maximum of 12 weeks, which may not fully capture long-term relapse or reinfection rates.

Additionally, while AST provided valuable guidance for individualized therapy, standardized clinical breakpoints for dermatophytes are not yet established; therefore, MIC interpretations were descriptive and exploratory. The lack of a control group and randomization further limits the ability to draw definitive conclusions about the comparative efficacy of different antifungal regimens.

Finally, environmental and host factors, such as comorbidities, hygiene, or footwear habits, were not fully controlled and may have influenced treatment outcomes. Despite these limitations, this pilot study provides preliminary insights into the potential role of AST-guided therapy in managing recalcitrant tinea pedis and can serve as a foundation for larger, multicenter, controlled studies.

Findings from this pilot study suggest that AST can provide useful guidance in managing recalcitrant TP when performed by experienced mycologists in accordance with established protocols. MIC values should be interpreted descriptively, and further studies are needed to define clinical breakpoints with confidence. Our preliminary observations also indicate that voriconazole may be a valuable alternative for patients with isolates showing reduced susceptibility to both terbinafine and itraconazole.

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