

Original Article

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Antifungal Drug Resistance of Dermatophytes Causing Superficial Fungal Infections

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Abstract

Background: Superficial fungal infections (SFI) are common skin diseases that were largely simple to treat. However, due to increasing antimicrobial resistance (AMR) of dermatophytes to antifungal drugs, treatment of SFI has become difficult. This study aims to analyze the AMR of dermatophytes and to correlate with the clinical response of antifungal drugs.

Methods: A cross-sectional evaluation was undertaken of 570 consecutive patients with SFI such as tinea corporis, tinea cruris, tinea faciei, and tinea pedis, who were treated with any of the oral antifungal drugs fluconazole, itraconazole and terbinafine. Clinical response was taken within 1 month of stopping the therapy. Microscopic as well as culture and antimicrobial sensitivity analysis were done to characterize and determine the susceptibility of dermatophytes to antifungal drugs aforementioned.

Results: Among the 570 patients with SFI, the ratio of male (n=360, 63.16%) to female (n=210, 36.84%) was 1.7:1. The common age group affected by SFI was 31-40 years (27.71%, n=158). The tinea corporis was the most predominant (51.05%) followed by tinea cruris (13.68%). Clinical response analysis showed that the percentage of relapse of SFI after completion of treatment with fluconazole, itraconazole and terbinafine was about 55, 45 and 19, respectively. Culture and antimicrobial sensitivity analysis revealed that the percentage of resistance of dermatophytes from patients of SFI to fluconazole, itraconazole and terbinafine was approximately 70, 55 and 20, respectively.

Conclusion: Results reported herein support the notion that the antifungal resistance is evolving in dermatophytes causing SFI, and about 20% dermatophytes are multidrug resistant.

Keywords: Antifungal drugs, antimicrobial resistance, dermatophytes, superficial fungal infections, tinea.

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Introduction

Superficial fungal infections (SFI) also known as dermatomycosis or dermatophytosis is one of the most important infections which affect skin, nails and hairs of about 40% of the global population.¹

Keratinophilic filamentous fungi termed as dermatophytes comprising three genera called *Trichophyton*, *Microsporum* and *Epidermophyton* cause cutaneous dermatomycosis, and to date, thirty species of these three genera have been reported as human pathogens.^{2,3} Several social, environmental and predisposing factors influence the prevalence of SFI.¹ The occupational and climatic condition of a region are considered as important factors for SFI. The predisposing factors for SFI include dry skin, immune compromised conditions, obesity, diabetes, HIV infection, certain athletic activities and possibly smoking.⁴ Antifungal drugs are frequently prescribed as the treatment of SFI. However, treatments of SFI with the antifungal drugs have become difficult due to antimicrobial resistance (AMR) which is one of the greatest challenges for the global health.^{5,6}

The hot and humid tropical nature of Bangladesh has been phenomenal upsurge for SFI leading to tinea infection being endemic in our country.

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Consequently, there is not only an increase in SFI cases but also a large number of patients are experiencing a great degree of relapses and recurrences. The dermatologists in Bangladesh are facing drug resistance, poor drug compliance, inappropriate treatment and misuse of topical steroid as the potential causes for such a trend. In addition, other predisposing factors such as diabetes mellitus (DM), poor personal hygiene, immune suppression, atopy and corticosteroid abuse are also contributing to this trend. All these factors collectively contribute to the antifungal drug resistance of dermatophytes causing SFI. Therefore, it is necessary to find comparatively more active antifungal drug to treat the SFI. However, very few studies have been done in Bangladesh to compare the efficacy of systematic antifungal drugs applied on patients of SFI for finding the most effective drug. This study was done with the view to make a comparison of the outcome of systematic administration of fluconazole, itraconazole and terbinafine in different groups of SFI patients under close clinical examination at regular follow-up intervals and to find out the most effective drug in terms of clinical remission and absence of relapse. Furthermore, the culture and antimicrobial sensitivity of dermatophytes from patients of SFI has been done to associate with the clinical response of these three antifungal drugs usually prescribed by the physicians to treat SFI.

Materials and Methods

Study period and population

This randomized controlled study was conducted in the skin and VD OPD in Sylhet Women's Medical College Hospital, Sylhet, Bangladesh for one year from July 2020 to June 2021 in hot and humid weather. A total of 570 (male & female) patients diagnosed to have SFI were included, and were examined clinically and mycologically before the start and at the end of treatment, and after one month of treatment completion. The detailed clinical record of the selected patients was prepared including age, sex, address, occupation, family history, duration of the disease, size and extent of lesions, and history of previous treatments. Then the patients subjected to local and systemic examination, were investigated for Hb, CBC,

blood sugar, SGPT, SGOT, serum creatinine, blood urea, urine R/M/E. The investigations were repeated following 2 weeks of treatment and after the end of treatment. All patients gave consent for being volunteer participants in the study. The patients or their attendants were briefed about the aim of the study. Adult patients (18 years old or above) gave their written consents. However, the parents or the attendants of infants and children were interviewed. The study protocol was approved by the Institutional Ethical Committee of Sylhet Women's Medical College Hospital, Sylhet.

Inclusion and exclusion criteria

Patients of all ages giving consents and having different types of SFI such as tinea corporis (general skin / trunk), tinea cruris (groin), tinea faciei (face), and tinea pedis (legs) were included in the study. Patients having experience of first time SFI and who were diagnosed relapse and recurrent cases of SFI were considered for the study. This study excluded pregnant and lactating mothers, patients with immunosuppression, hepatic or renal disease, hypersensitivity or intolerance to treatment, and patients unwilling to visit for a regular follow-up.

Study design

All the enrolled patients were clustered into three groups- patients taking oral fluconazole (Group I), itraconazole (Group II), and terbinafine (Group III). Patients of each group were treated with a single oral antifungal drug: patients of Group I with capsule fluconazole (50 mg) once daily for six weeks, patients of Group II with capsule itraconazole (100 mg) twice daily for 1 month, and those of Group III with tablet terbinafine (250 mg) once daily for one month. The treatment duration for each group was selected based on the studies which reported that the terbinafine and itraconazole can persist in the epidermis for 3 weeks following the treatment.^{7,8} The patients showing no response completely to the therapy or had a recurrent lesion within 1 month of stopping the therapy were considered as the antifungal drug resistant. Patients were advised to keep the skin clean and dry, and not to use any other creams, lotions, or ointments on the lesions during the course of

treatment. Every patient of each group was advised to come to a follow-up after 2 weeks, and during the follow-up, the improvement of lesion was recorded as the response of the antifungal drug.

Mycological examination

Skin scrapings were taken from the patients during the first and follow-up visits for microscopic observation and culture of dermatophytes. For microscopy, the skin scrapings taken on slides were treated with 15 % KOH plus Blue-Black Ink Solution at the ratio of 9:1.⁹ Specimens were examined immediately under the light microscope for the presence of hyphae and spores. For culture of dermatophytes, specimens were inoculated on a selective and differential medium known as the dermatophytes testing media (DTM) (1% peptone, 1% glucose, 0.05% cyclohexamide, 0.01% gentamycin sulfate, 0.01% chlortetracycline, 0.02% phenol red and 1.7% agar, pH 5.6±0.2). Dermatophytes with white hyphae produce basic metabolites that bring about an alkalization to the DTM media causing the phenol red to change its color from yellow to red.¹⁰ Clinical response was categorized as either effective or ineffective treatment. The negative result of culture and microscopy at the end of the therapy was considered as the effective antifungal treatment. However, the outcome that did not meet this criterion was considered as the ineffective antifungal treatment. The severity of clinical signs and symptoms were assessed based on erythema, scaling, vesiculation, pruritis, pustules, exudation and crusting, and scored as four scales: absent (0 scale), mild (scale 1), moderate (scale 2) and severe (scale 3).

Antifungal susceptibility analysis

The antifungal susceptibility of dermatophytes was investigated by using the agar well diffusion method as described previously.⁵ In brief, spores were obtained from the freshly sub-cultured dermatophytes on DTM for 7 days, which were suspended in a solution of 0.85% NaCl with 0.025% Tween 20 and adjusted to 0.5 McFarland standards. The final inoculum was confirmed to be composed of spore without hyphae as described by Petrikkou et al. (2001).¹¹ The spore (100 µL) was spread evenly with a sterile cotton swab on potato dextrose

agar (PDA, 2% glucose, 20% potato infusion, 1.8% agar, pH 5.6 ± 0.2) media and 5 mm wells were created onto the PDA plate using sterile 1 mL micropipette tips. A 30 µL of the antifungal drug was loaded in each well and the plates were incubated at 30°C for 5 days. The amount of fluconazole (FCA, 25 µg), itraconazole (ITC, 20 µg) and terbinafine hydrochloride (THCL, 30 µg) was maintained during antifungal susceptibility testing.¹² In accordance with manufacturers' recommendation, the dissolution and dilution of ITC were done in dimethyl sulfoxide (DMSO), and those of FCA and THCL were done in distilled water. For investigation of susceptibility, freshly prepared solutions of antifungal agents were used. The susceptibility of dermatophytes was evaluated by measuring the diameter of the clear zone of inhibition produced by the antifungal agent in repeated experiments (n=3).

Statistical analysis

Data were analyzed by using SPSS for Windows version 22. Student's T-test or one-way ANOVA were used for assessment of differences between arithmetic means. A *p*-value of ≤0.05 was considered to be statistically significant. Data were presented as the means ± standard error of the mean of repeated experiments having at least three replicas, or as noted in the figure legends.

Results

Demographic data

Among the 570 patients, the ratio of male (n=360, 63.16%) to female (n=210, 36.84%) was 1.7:1. This result indicates that males are more susceptible to SFI compared to females. All the patients included in the study were clustered into different age groups (Table 1). People at the age of 21-50 years were more susceptible to SFI (Table 1). However, the most prevalence of SFI was observed among the people at the age of 31-40 years, and the average of the patients was 32.33± 6.5 years. Nevertheless, the prevalence of SFI was also very high among the people at the age of 41-50 and 21-30 years. Most of the predisposing factors of SFI such as dry skin, diabetes, obesity, immunosuppression, and smoking are age and gender-dependent and prevalent in males compared to females.^{1,13}

Clinical presentation of SFI

The SFI may occur in any site of the body. The SFI in the whole body is termed as the tinea. Tinea localized only to the trunk, groin, face, foot, nail, hand and scalp is called as tinea corporis, tinea cruris, tinea faciei, tinea pedis, onychomycosis, tinea manum and tinea capitis, respectively. In the present study, the former four SFI were observed. The tinea corporis was

predominant (51.05%) followed by tinea cruris (13.68%) (Table 1). However, tinea faciei and tinea pedis were observed only in 3% and 6% patients. Interestingly, a large number of patients presented mixed SFI. About 15% patients had tinea corporis plus tinea cruris, and ~11% patients presented tinea corporis plus tinea cruris associated with tinea faciei.

Table 1: Clinical presentation of SFI*

Age group (Year)	T.corporis (n=291, 51.05%)	T. cruris (n=78, 13.68%)	T. faciei (n=17, 2.98 %)	T. pedis (n=33, 5.78 %)	T.corporis + T. cruris (n=86, 15.08 %)	T. corporis + T. cruris + T. faciei (n=65, 11.40%)
0-10	18	3	4	1	2	2
11-20	27	4	3	1	4	2
21-30	45	17	3	5	12	14
31-40	89	21	2	6	25	15
41-50	75	19	2	8	20	17
51-60	22	7	2	5	15	9
>60	15	7	1	7	8	6

*Data in all age groups are shown as number of patients

Clinical response of patients to different antifungal drugs

According to the study design aforementioned, male and female patients were clustered into three groups to investigate the clinical response

of fluconazole, itraconazole and terbinafine. Male and female patients of each group having the same number of patients were treated with fluconazole, itraconazole and terbinafine (Table 2).

Table 2: Patients treated with antifungal drugs

Antifungal drugs	Male	Female	Ratio
Fluconazole	120	70	1.71:1
Itraconazole	120	70	
Terbinafine	120	70	
Total	360	210	

Clinical response revealed that approximately 55% patients treated with fluconazole relapsed SFI (Table 3). The clinical response of itraconazole was relatively better compared to that of fluconazole showing recurrence of SFI in about 45% patients. However, the clinical

response of terbinafine was the best among the three antifungal drugs although about 19% patients relapsed SFI. Interestingly, no significant deviation was observed in clinical response of the three antifungal drugs in male and female patients.

Table 3: Clinical response of patients with SFI to the three antifungal drugs

Antifungal drugs	Dose	Duration	No. of patients (n)	Cured %	Relapse %	Adverse effect
Fluconazole	50 mg daily	1 ½ month	190	45.26 (n=86)	54.73 (n=104)	Nausea, vomiting
Itraconazole	100 mg twice daily	1 month	190	55.78 (n=106)	44.21 (n=84)	Nausea, headache and abdominal pain
Terbinafine	250 mg daily	1 month	190	81.57 (n=155)	18.42 (n=35)	Gastric upset, headache, altered taste, hypokalemia, rash

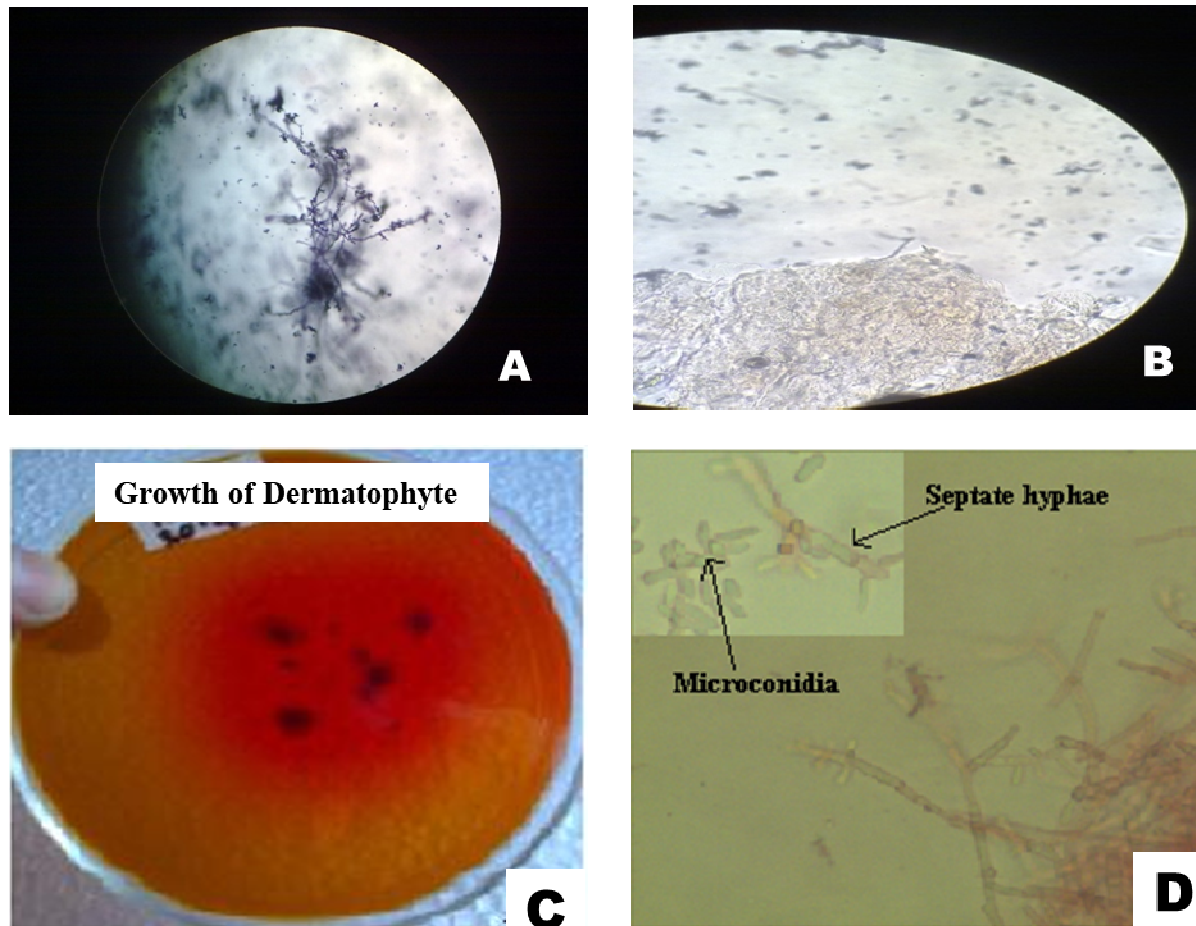


Figure 1: Microscopic observation, cultural and morphological characteristics of dermatophytes causing SFI.

The positive (A) and the negative (B) results of fungal elements observed by direct microscopy are shown. The dermatophyte turned the yellow color of the DTM media to red (C). Microscopic study of the dermatophyte grown in panel C revealed the septate hyphae and microconidia (D). Only the representative picture of repeated experiments (n=3) are shown.

Antifungal susceptibility pattern of dermatophytes causing SFI

The presence of fungal hyphae and spores in the SFI investigated preliminary by microscopic examination was confirmed by culture on the DTM media (**Figure 1**). The growth of dermatophytes having different cultural morphologies was observed in the samples of SFI collected from patients. This result indicated

that different species of dermatophytes were associated with the SFI.

As the recurrence of the SFI was observed in a large number of patients following treatment with fluconazole, itraconazole and terbinafine (Table 3), antifungal susceptibility of the dermatophytes isolated from the patients of SFI was investigated (Figure 2). The antifungal susceptibility of the dermatophyte isolates was assessed by measuring the diameter of zone of inhibition produced by the antifungal agents aforementioned. Diameters of the zone of inhibition considered for the assessment of sensitive, intermediate sensitive and resistance were ≥ 20 , 12-19 and ≤ 12 mm, respectively.¹² The antifungal resistance pattern of dermatophytes to fluconazole, itraconazole and terbinafine was approximately 70%, 55% and 20%, respectively (Figure 3).

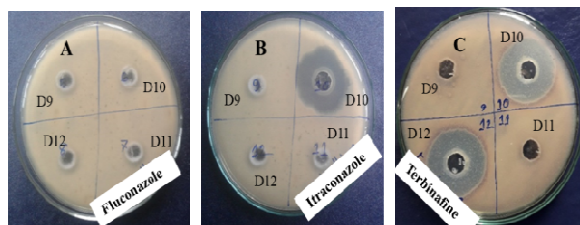


Figure 2: Culture and sensitivity of dermatophyte isolates to fluconazole, itraconazole and terbinafine. Representative plates of antibiogram of fluconazole (A), itraconazole (B) and terbinafine (C) against dermatophytes isolated from the patients of SFI are shown. The representative results of repeated (n=3) experiments are shown.

However, the sensitivity levels of dermatophytes to fluconazole, itraconazole and terbinafine were about 20%, 30% and 70%, respectively, indicating terbinafine as a comparatively active antifungal agent in the treatment of SFI. Nevertheless, approximately 10-15% of dermatophytes isolated from the patients of SFI showed intermediate sensitivity to the three antifungal drugs (Figure 3). It is mentionable that more than 55% dermatophytes were resistant to fluconazole and itraconazole. Interestingly, all the dermatophyte isolates showing resistance to terbinafine were resistant to fluconazole and itraconazole (Figure 3). This result revealed that about 20% dermatophytes were resistant to all of the three drugs, indicating them as multidrug resistant (MDR).

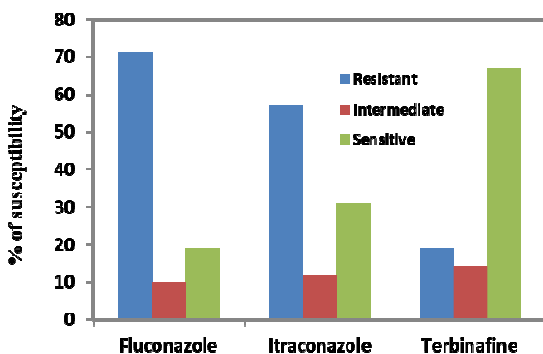


Figure 3: Susceptibility of dermatophyte isolates to fluconazole, itraconazole and terbinafine.

The percentage of susceptibility (expressed as sensitive, intermediate sensitive and resistant) of dermatophytes to fluconazole, itraconazole and

terbinafine is delineated. The representative results of repeated (n=3) experiments are shown.

Discussion

Dermatophytes, the filamentous fungi, can obtain nutrients by digesting keratin present as a principal component in skin, hair and nails. The dermatophytes can affect different sites on the skin surface and produce a variety of clinical manifestations. Although dermatophytes usually infect the upper layers of the skin, these fungi can be invasive to generate deep and disseminated infection in immunocompromised patients. However, AMR that is inherently generated in dermatophytes due to several reasons has become a great challenge to treat the SFI with antifungal drugs.^{6,14,15} Furthermore, some risk factors such as poor hygiene and association of some diseases such as DM, and immunodeficiency negatively contribute to the healing process of antifungal drugs.¹⁶ In Bangladesh, the SFI is a common fungal infection due to the hot and humid climate.¹⁷ Therefore, it is essential to elucidate the clinical response of antifungal drugs such as fluconazole, itraconazole and terbinafine commonly used in SFI, and the susceptibility of dermatophytes causing the SFI to these antifungal drugs.

Fluconazole, a synthetic triazole, is used as an azole antifungal drug. In the present study, resistance of dermatophytes against fluconazole was the most common followed by itraconazole (Figure 3). The resistance pattern of dermatophytes to the both antifungal drugs is higher in comparison with other studies.^{8,6} Although low level of resistance of dermatophytes to fluconazole was reported one decade before, the resistance pattern is unexpectedly increasing with the time.⁶ However, the percentage of recurrent SFI after treatment with fluconazole and itraconazole is not well-correlated with the resistance pattern of dermatophytes against these two drugs (Table 3 and Figure 3). The intrinsic immunity of the patients might have triggered the killing of intermediate sensitive dermatophytes resulting in enhanced clinical response. Itraconazole having lipophilic and keratophilic properties shows mode of action similar to that of other azole antifungal drugs. Itraconazole is a well-

tolerated drug with minor adverse effects of nausea, headache and abdominal pain.

Terbinafine is an allylamine synthetic antifungal drug. This antifungal drug inhibits squaleneepoxidase, a fungal enzyme that is essential for the biosynthesis of ergosterol. This mode of action differs from that of azoles. Terbinafine is strongly lipophilic and well absorbed in the dermis, epidermis and adipose tissue. Terbinafine is easily metabolised and excreted in the urine. The most common side effects of terbinafine include gastric upset, headache, altered taste, altered liver function tests and rash. Although resistance to terbinafine in SFI is not common in clinical practice, it has been reported in clinical dermatophyte isolates.¹⁸ The terbinafine resistance in dermatophytes was well described by Mukherjee et al.¹⁴ Recently, clinical failure and recurrence of SFI have been observed in patients treated with terbinafine.⁶ In the present study, among the three antifungal drugs, terbinafine showed the highest level of both clinical response and sensitivity of dermatophytes. It is still a choice of drug for treatment of SFI. However, it is really alarming that about 20% of clinical dermatophytes showed terbinafine resistance and the similar percentage of the patients demonstrated recurrence of SFI. As the terbinafine resistant dermatophyte isolates are also resistant to fluconazole and itraconazole, it can be inferred that about 20% dermatophytes are resistant to three drugs and termed as MDR.¹⁹

Association of other diseases with the SFI may contribute to the poor clinical response of antifungal drugs and thereby increase the recurrence of the SFI. The current study revealed that about 77.46% (n=71) of DM patients showed poor response or relapse of the SFI after completion of treatment even with the terbinafine. Therefore, good controlling of DM is essential for better clinical response of treatment of SFI with antifungal drugs. Presence of psoriasis also served as a factor for decreasing the clinical response of terbinafine or increasing the relapse of the SFI in approximately 83% (n=47) of patients who had SFI with psoriasis.

This study revealed that resistance to antifungal drugs is increasing, which is a threat for treatment of SFI. Many factors are contributing in increasing the AMR in pathogens.¹⁹ In

developing countries like Bangladesh, self-medication with easily available antifungal drugs in the pharmacy, misuse and abuse of antifungal agents, not fulfilling the prescribed antifungal regimens once the patient feels better, are the possible reasons of increasing AMR in dermatophytes. Furthermore, the over prescription of antifungal drugs by physicians without confirming the causing agent is contributing to increase the AMR in dermatophytes. Therefore, proper legislation formulated by the policy making body of the country should be applied for prescribing, selling and using antifungal drugs. Moreover, preventive measures should be addressed by the patients to keep fungal infections minimized. The preventive measures may include wearing cotton loose garments, avoiding of sharing bed linen, towels and clothes. Furthermore, regular washing of towels and bed linen in hot water, taking regular showers, wearing non-occlusive footwear might be recommended as preventive measures for SFI.²⁰ However, this study has some limitations. It was done with only three antifungal drugs depending on clinical ground. It was not possible to include socio-economic conditions, socio-demographic parameters such as rural and urban residence, sanitation, personal hygiene, education, comorbidities, and drug intake. Therefore, it is necessary to conduct epidemiological and surveillance studies to understand the perturbation in the pattern and widespread of AMR in dermatophytes against antifungal drugs.

Conclusions

The SFI relapsed in a large number of cases (at least 45%) following treatment with fluconazole and itraconazole. However, terbinafine is more effective compared to fluconazole and itraconazole as the percentage of recurrent SFI decreased to approximately 20 following treatment with it. The clinical response of the three antifungals followed the trend of resistance pattern of dermatophyte isolates. Interestingly, terbinafine resistant dermatophyte isolates are MDR showing resistance to fluconazole and itraconazole. Results reported herein support the notion that the AMR is expanding in dermatophytes, which will generate challenges for the treatment of SFI.

Contribution of Authors: Concept, design of the study, experiments, data collection, and manuscript editing: PAC and AKA, Critical review of the manuscript: MUS, SAS and KF.

Conflict of Interest: Authors declare no conflict of interest.

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