e-ISSN : 2455-5258

Research in Pharmacy and Health Sciences

Review Article

Management of Superficial Mycotic Infections: A Review

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Abstract:

Superficial mycotic infections of skin and nails are the most common diseases seen in our daily practice and the main causative groups are dermatophytes, yeasts and moulds. The degree of immunosuppression and the number of immunosuppressed patients are increasing at an unprecendented pace, hence the management of dermatophytoses will be a challenge to mankind in the years to come.The increasing number of antifungal agents, reformulations of existing agents and novel treatment strategies have all improved the management of fungal infections, but still the infections are associated with high mortality. Currently, topical azoles and allylamines are used for the treatment of Cutaneous mycoses with disadvantages like long duration of therapy, which leads to poor compliance and a high relapse rate. Assessment of efficacy, Quality of life (QOL) and Medication adherence are important issues in all areas of clinical medicine, including dermatology. Here the clinical efficacy was assessed based on signs and symptoms severity score and global clinical response, Dermatology life quality by Finlay and Khan's 10 question Dermatology Life Quality Index (DLQI) and adherence by medication adherence questionnnaire. Both Terbinafine (250–500 mg/day for 2–6 weeks) and Itraconazole (100–200 mg/day for 2–4 weeks) appear to be effective for limited disease (tinea corporis/cruris/pedis). However, an appropriate dose and duration of administration which can produce mycologic cure and prevent recurrence remains elusive. This review also highlights the huge research gaps in the management of cutaneous dermatophytosis which need to be plugged to provide better and effective care to the patients.

Received: 10-05- 2016

Revised: 21-05-2016

Accepted: 06-06-2016

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Funding: Nil

Competing Interests: Nil

Keywords: *Superficial mycotic infection, Dermatophytes, Cutaneous mycoses, Efficacy, QOL, Adherence*

INTRODUCTION:

Superficial mycotic infections of skin and nails are the most common diseases seen in our daily practice. The main causative groups are dermatophytes, yeasts and moulds.[1] The dermatophytes that usually cause are : *Microsporum, Trichophyton, and Epidermophyton.* Dermatophytes grow on keratin and therefore cause diseases in body sites wherein keratin is present which include the skin surface, hair and nail. The skin surface is the habitat of most of these fungi and is liable to environmental contamination. According to the sites of skin involved dermatophyte infections are subclassified as Tinea faciei: face; Tinea manuum: hands; Tinea corporis: glabrous skin, Tinea cruris: crural folds; Tinea pedis: feet; Tinea capitis: scalp and Tinea unguium: nails.Although dermatophytoses cause morbidity and posses major health problem , it does not cause mortality [1]. No race in any geographical location is totally free from dermatophytoses [1]. Given that, the degree of immunosuppression and the number of immunosuppresed patients are increasing at an unprecendented pace, the management of dermatophytoses will be a challenge to mankind in the years to come. The choice of an antifungal agent should be based on an accurate diagnosis [2].Currently, topical azoles and allylamines are used for the treatment of Cutaneous mycoses with disadvantages like long duration of therapy, which leads to poor compliance and a high relapse rate. Some of the newer agents require only once-daily application and shorter courses of treatment, and are associated with lower relapse rates [2]. According to World Health Organization (WHO), the prevalence rate of superficial mycotic infection worldwide has been found to be 20-25%. It is more prevalent in tropical and subtropical countries like India where the heat and humidity is high for most part of the year[4].The causative species vary with geographic region and some species are distributed worldwide such as Trichophyton rubrum, T. mentagrophytes var. interdigitale, Microsporum canis, and Epidermophyton floccosum. Others have partial geographic restriction, such as T schoenleinii (Eurasia, Africa), T soudanense (Africa), T violaceum (Africa, Asia, and Europe), and T concentricum (Pacific Islands, Far East, and India). Most cases of tinea unguium, tinea cruris, tinea corporis, and tinea pedis are caused by T rubrum, which is the commonest dermatophyte in most developed countries as well as in urban areas of some developing countries**.** Dermatophyte infections can be acquired most commonly from another person , from animals such as puppies or kittens and least commonly from soil. Recent development in understanding the pathophysiology of dermatophytosis have confirmed the central role of cell-mediated immunity in countering these infections. Hence, a lack of delayed hypersensitivity reaction in presence of a positive immediate hypersensitivity (IH) response to

trichophytin antigen points toward the chronicity of disease. The laboratory diagnostic approach will involve
1) wet mount KOH examination that can be performed rapidly at the "bed-side" with or without staining (e.g. by Parker's blue black ink, chlorazole black), 2) culture for proper species identification. The scales from active lesions produced by skin scraping can be collected. Repeated sampling is sometimes required to isolate the causative fungi

Table 1: ANTIFUNGAL TREATMENTS

ROUTE	CONDITION	DRUG TREATMENT
TOPICAL	T.pedis, T.cruris, T.corporis, T.manuum	Imidazole e.g. miconazole BD or Terbinafine BD
	Pityriasis versicolor	Selenium sulphide 2.5% lotion
	Candidiasis	Imidazole BD or Polyene e.g. Nystatin BD / QDS
ORAL	Onychomycosis	Terbinafine 250mg OD or "pulse" Itraconazole 200mg BD
	T.cruris, T.corporis	Terbinafine 250mg OD or Itraconazole 100mg OD
	T.capitis	Griseofulvin 500mg OD
	Pityriasis versicolor	Itraconazole 200mg OD
	Candidiasis	Itraconazole 100mg OD

Pharmacological treatments for superficial fungal infections can be grouped into two; topical and systemic. Generally, imidazoles (isoconazole, tioconazole, clotrimazole) and triazoles (itraconazole, fluconazole) are active against yeast and dermatophytes. Topical allylamines (terbinafine, naftifine) and amorolfine may be fungicidal and polyenes (nystatin, amphotericin B) are active against *Candida* species but not dermatophytes. Systemic treatment may also be considered in cases with extensive disease or significant hyperkeratosis. The treatment course for topical treatment is from 1 week to 4-6 weeks. In the real life situation, a longer course is not uncommonly required. Systemic regimes are summarised in the following table.[1]

EFFICACY OF ANTIFUNGAL TREATMENT

Assessment of efficacy of antifungal treatment is essential in the present scenario.The main aim of the study[2] is to compare the efficacy of newer antifungals like Luliconazole, Amorolfine, eberconazole, sertaconazole and terbinafine cutaneous mycoses (commonest presentation- tinea corporis).[2] Here the clinical efficacy was assessed on signs and symptoms severity score of the target lesion. These signs and symptoms were scored as: 0=absent (none), 1= mild (barely perceptible), 2=moderate (distinctive presence), and 3= severe (marked, intense). The signs and symptoms that were evaluated were erythema, desquamation, pruritis, vesicles, and encrustation. Global clinical response was also evaluated by the investigator using the following 6 point scale: -1= exacerbation (flareup at the site of treatment), 0=unchanged, 1= mild improvement (<50% clearance), 2= moderate improvement (50% to 75% clearance), 3= excellent improvement (75% to 100% clearance), 4= cleared (100% clearance). The efficacy is assessed based on the parameters: 1) KOH test: A negative KOH preparation at the end of the study period was considered as mycological cure. 2) Change in the signs and symptoms score .Thereby the efficacy is assessed by the number of patients who has maximum improvement in signs and symptoms and those who has complete cure.[2]

QUALITY OF LIFE OF PATIENTS WITH MYCOTIC INFECTIONS

Measures of quality of life (QOL) have particular significance for dermatological conditions as, although not generally life-threatening, they frequently have a major impact on patient's psychosocial state, social relationships and everyday activities. Finlay and Khan's 10 question Dermatology Life Quality Index (DLQI), which is designed as a simple, compact uniform measure, for use as an assessment tool in routine daily clinical practice, and includes two questions relating to symptoms and feelings. It can be quickly self-completed and provide information that complements traditional clinical indicators. These scales should assist in informing treatment decisions by identifying impacts of different skin conditions and variations in responses among social and cultural groups, as well as guiding priorities for services within the specialty. The DQOLS are based on a greater number of items, comprising psychosocial, physical activities and symptom scales, and place considerable emphasis on the psychosocial impact of skin conditions.[3]

ADHERENCE OF PATIENTS TO ANTIFUNGAL REGIMEN:

Medication adherence is an important issue in all areas of clinical medicine, including dermatology. In dermatology, medication adherence for dermatomycosis is known to decrease with the duration of treatment and the frequency of applications required each day, particularly once symptoms have disappeared. Simpler dosing regimens are sought for the treatment of cutaneous fungal infections. It is hypothesized that its prolonged dermal retention may translate into the need for less frequent application for successful treatment in clinical practice. Possible consequences of nonadherence in clinical practice include death, reduced treatment benefits, biased assessments of treatment efficacy, and increased healthcare costs; 33 to 69 percent of medication-related hospital admissions in the United States are the result of poor adherence. Multiple possible causes for patient nonadherence have been postulated.[5] They include the following problems with the therapy, such as side effects; poor instructions given to the patient by the prescriber; poor physician-patient relationship; poor memory on the part of patients; and

patients' inability to pay for medications. With short-term treatment, adherence can usually be enhanced with patient education and followup by telephone or e-mail, but interventions capable of increasing adherence in patients with chronic health problems tend to be complex, involving combinations of patient education, reminders, family therapy, psychological therapy, crisis intervention, and close followup. As one report has noted, even the most effective interventions in patient's habits do not lead to large improvements in adherence or treatment outcome.

Table 2: Summary of systemic treatment of superficial fungal infections

Disease	Systemic	Duration		Remarks
T. corporis	Griseofulvin Terbinafine Itraconazole	500 – 1000 mg daily 250 mg daily 100 mg daily 200 mg daily	2-4 weeks 1-2 weeks 2 weeks 1 week	
T. cruris	Griseofulvin Terbinafine Itraconazole	500 -1000 mg daily 250 mg daily 100 mg daily 200 mg daily	2-4 weeks 2 weeks 2 weeks 1 week	
T. manuum	Terbinafine Itraconazole	250 mg daily 100 mg daily 200 mg bd 200 mg daily	2 weeks 30 days 1 week 1 week	
T. pedis	Griseofulvin Terbinafine Itraconazole	750-1000 mg daily 250 mg daily 200 mg daily 200 mg bd	4 - 8 weeks 2 weeks 2 weeks 1 week	
T. unguium	Griseofulvin Terbinafine Itraconazole Fluconazole Ketoconazole	750-1000 mg daily 250 mg daily 200 mg daily 200 mg bd (pulse dosing) 100 – 200 mg daily 150 – 400 mg/week 200 – 400 mg daily	6–12 months (fingernail) 12–18 months (toenail) 6weeks (fingernail) 12 – 16 weeks (toenail) 6weeks (fingernails) 12weeks (toenails) 1week,to repeat after 21 day interval, finger nails: 2 courses; toenails:3 courses ≥6-12 months	FDA approved; cure rate: ~30% FDA approved; cure rate: ~80%; most effective in dermatophyte infections; serious side effects in less than 1% of patients; monitor LFT at 4 to 6 weeks FDA approved; effective in infections caused by dermatophytes, yeasts and moulds; side effects diminished when taken as pulsed doses; monitor LFT if used more than 1 month Less effective in dermatophytes than in yeasts More effective for *Candida* than dermatophytes; highest incidence of LFT abnormalities
Pityriasis versisolor	Itraconazole Fluconazole Ketoconazole	400 mg stat 200 mg daily 400 mg stat 400 mg stat 200 mg daily	7 days 10 days	

CONCLUSION

The increasing number of antifungal agents, reformulations of existing agents and novel treatment strategies have all improved the management of fungal infections in recent years. Although high cure rates can be achieved in the treatment of many superficial infections, systemic fungal infections are still associated with high mortality. For several years, amphotericin-B was the most effective agent for the treatment and prevention of systemic fungal infections. However, the introduction of the triazoles – fluconazole and itraconazole – has challenged amphotericin-B as the gold standard. In particular, the triazoles have become the agents of choice in chemoprophylaxis; fluconazole has been widely used but the introduction of an itraconazole oral solution offers an agent with high bioavailability and a broader spectrum of activity than that of fluconazole.Treatment of cutaneous dermatophytosis has increasingly become difficult, and dermatologists have been forced to think beyond conventional wisdom to counter this menace. Although there is sufficient evidence to demonstrate the efficacy of topical antifungals in limited disease yet, there is scarce data on the frequency of relapse once topical monotherapy is discontinued. Allylamines are a new group of agents that are structurally distinct from any other group of antifungal drugs. Among various options, Allylamines such as Terbinafine for 4 weeks appears to be the treatment of choice for limited disease (tinea corporis/cruris/pedis). For more extensive disease, the choice is less clear. Both Terbinafine (250–500 mg/day for 2–6 weeks) and Itraconazole (100–200 mg/day for 2–4 weeks) appear to be effective. However, an appropriate dose and duration of administration which can produce mycologic cure and prevent recurrence remains elusive. This review also highlights the huge research gaps in the management of cutaneous dermatophytosis which need to be plugged to provide better and effective care to the patients. More stringent RCTs are the need of the hour comparing the various oral antifungal therapies to give a clear idea regarding the appropriate dose and duration of therapy.

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Cite this article as: Anto A, Bincy CM, Mincy C Das, Babitha M. Management of Superficial Mycotic Infections: A Review. Res Pharm Healt Sci. 2016;2(3):152-156.