

Review Article

Generating evidences on rational management of dermatophytic infections

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ABSTRACT

Superficial fungal infections are globally responsible for 25% of the skin mycoses cases. Dermatophytosis is a type of superficial fungal infection of skin, a significant cause of morbidity in the world. This pilot study includes most recent literatures with highest ratings and published work which has been submitted in last fifteen years. The literature review is completely oriented in reviewing evidence which includes the type of dermatophytic infection, diagnostic tools, therapeutic and non-therapeutic management of dermatophytic infection having highest level of evidences. Clinical diagnosis of dermatophytic infection and laboratory-based tests are vital in management of dermatophytic infections, considering conventional methods and incorporation of advanced techniques like preparation of skin specimens for microscopic examination by 10% to 20% mount microscopy, polymerase chain reaction, fungal culture, and spectroscopy. Over-use of corticosteroid is strictly discouraged as they carry multiple cutaneous adverse effects. A vast gap is evident in the management of dermatophytic infection with available reviews. Steroid abuse, in dermatophytic infection has led to many adverse effects and chronic skin conditions. Prevention and cure needs support of awareness about the disease and its severity.

Keywords: Dermatophytotic infection, Corticosteroids, Therapeutic combinations, Antifungal agents

INTRODUCTION

Dermatophytes are liable for 25% of the planet wide, skin mycoses cases and making dermatophytic infections one among the foremost common sorts of infective diseases on global basis. Cutaneous dermatophytosis results in differing types of clinical manifestations, like athlete's foot, tinea, jock itch, majocchi's granuloma. The dermatophytic fungal infection penetrates the stratum corneum and infects the keratinized layer of skin. There is evidence of host's factors which incorporate age, sex, ethnicity and genetic predisposition.¹ There is evidence of familial or genetic predisposition which may be mediated

by specific defects in innate and adaptive immunity. *Tinea imbricata* possess genetic predisposition which belongs to one of the primary fungal disease-causing agent. Dermatophytic infection have a great impact on quality of life. The prevalence and incidence of dermatophytic infection occurring in variable climatic, geographic and therapeutic conditions can affect the quality of life among individuals.²

Rising trends of dermatophytic infection

Environmental conditions are found to have great impact, on global basis in the incidence and prevalence of

dermatophytic infection. The humid climate of tropical and subtropical regions of the planet are the best suitable for the expansion of dermatophytes.³ The prevalence and endemicity of dermatophytic species within a particular area or region depends on the precise pattern of disease and can't depend upon one factor. Thus, region wise analysis of mycosis could help find the pattern of the disease within the locality. Preventive and treatment measures specific to the actual area might be outlined.⁴ In an observational study, about 100 symptomatic patients, were examined for risk factors, epidemiology and clinical profile of superficial fungal infections and reviewed that age, gender, occupation, tight clothing, lack of education, fomites sharing, use of over the counter drugs, were the risk factors responsible for dermatophytic infections. Case history of fomites sharing is the most useful markers, among the patients who attended the OPD.¹

Role of diagnostic tests

M38-A2, a reference method to work out the Minimum inhibitory concentration (MIC) of several antifungal agents against filamentous fungi. During a test performed to seek out the antifungal activity of fluconazole, itraconazole, ketoconazole, terbinafine and griseofulvin using broth microdilution technique with samples recovered from nails and skin. Itraconazole, ketoconazole and terbinafine isolates were found to carry low MIC values.⁵ Recent reviews have made the pathophysiology of dermatophytic infections easy to know and ensure the central role of cell-mediated immunity in controlling the spread of infection, clinical and laboratory based examination are essential for diagnosis, with newer techniques as direct microscopic examination.⁶

Efficacy of drugs and treatment: The efficacy of antifungal agents, itraconazole and terbinafine were found to be effective more than compared to other antifungal therapeutics. Fluconazole was found least effective during this study.⁷ Clinical isolates of dermatophytic infections are often determined of their susceptibility, by using antifungal disks of griseofulvin, miconazole, terbinafine, clotrimazole, fluconazole and ketoconazole with disk diffusion method. Clotrimazole was considered the simplest antifungal against dermatophytes followed by miconazole and ketoconazole.⁸ The disk diffusion method for the determination of dermatophytic isolates susceptibility against eight antifungal agents, incorporated, might be simple for the assessment of antifungal susceptibility of dermatophytes.⁹ The detection of biochemical characteristics of proteolysis degradation product, which may be a result of activity of mycological infections or non-infectious diseases, can identify upto 64 dermatophytic strains, obtain results within 24 hrs.¹⁰ The use of antifungal agents, both topical and systemic therapeutic agents, evaluated for efficacy when used as monotherapy, combination therapy or sequential therapy has been considered in management of the dermatophytic infection.¹¹ Anti-dermatophytic activity of clove volatile oil and its volatile vapours are found to be strongly active

against i.e. *T. rubrum* and *T. mentagrophytes*. These vapours completely inhibited spore germination of the two dermatophytic strains. The volatility of oil of cloves vapour also can strongly inhibit the mycelial growth of *Epidermophyton floccosum* and *Microsporum audouinii*. Oil of cloves has more fungicidal activity, therefore, the vapours have the fungistatic activity. Essential oils have traditionally been used since centuries for his or her antifungal property.¹²

Table 1: Interactions of itraconazole with other drugs.

Drugs with increased plasma concentration	Drugs that reduce Itraconazole plasma concentration.	Drugs that increase Itraconazole plasma concentration
Alprazolam, Bromperidol, Cerivastatin, Cyclosporine, Calcium channel blockers, Buspirone, Cerivastatin, Cyclosporine.	H2 receptor blockers, Proton pump blockers, Simultaneous antacids, Carbamezapine, Phenytoin, Phenobarbital, Rifampin, Isoniazid.	Clarithromycin, Indinavir, Ritonavir

Table 2: Interactions of fluconazole with other drugs.

Increased plasma level	Adverse events	Indications
Alprazolam, amphotericin B, anticoagulants, atorvastin, clopidogrel, erythromycin, midazolam, nevirapine, phenobarbital, phenytoin, pimecrolimus, propranolol, sulfonyleurea, triamcinolone, warfarin, zidovudine.	Dizziness, diarrhoea, dyspepsia, headache, nausea, prolonged QT with/without arrhythmia. Rarely anaphylaxis / anaphylactoid reaction (AIDS). Fixed pigmented rash, neutropenia, eye haemorrhage and teratogenicity.	Superficial mycoses dermatophytic infection; tinea pedis, tinea corporis, tinea capitis and tinea cruris.

Oral therapy is advised among patients displaying vast area of infection or constant infection with itraconazole, fluconazole, griseofulvin and ketoconazole and has proved to give good results.¹³ Medications when applied topically often show mild skin reactions, at the site of application.¹⁴ Dermatophytic infection treatment and its success not only depend upon the knowledge about the disease, also on other factors as; clinical pattern of disease, strictness of infection, causative agent, and possible drug interaction.¹⁵

Table 3: Classification antifungal agents used in treatment of dermatophytic infections.

Antifungal class	Examples
Antibiotics polyenes	Amphotericin B, nystatin, natamycin
Hetrocyclic benzofuran	Griseofulvin
Antimetabolite	Flucytosine
Azoles Imidazoles	Topical therapy: oxiconazole, eberconazole, clotimazole, miconazole, sertaconazole, fenticonazole, bifonazole, luliconazole systemic therapy: ketaconazole.
Triazoles	Systemic therapy: albaconazole, fluconazole, itraconazole, posaconazole, pramiconazole, voriconazole.
Allylamines	Terbinafine, butenafine, naftifine.
Echinocandins	Caspofungin, anidulafungin, micafungin.
Cell wall derivatives	Caspofungin, micafungin.
Other agents	Amorolfine , ciclopirox , tolnafetate, Whitefield's ointment.
Newer and potential therapies	Demcidine, macrocarpel C.

Role of patient education

About hygiene and therefore, the role of fomites within the spread of mycosis might be crucial in endemic tropical and subtropical regions. Educating the affected individual and its community the methods to take care of hygiene by keeping the moist area of the body clean and dry. Continued or prolonged wearing of wet clothes or bathing suits should be avoided. Wearing of undergarments for several days without washing, and therefore, the undergarments made up of nylon clothing material or thick and non-ventilating materials must be avoided. Easy and lightweight to wear clothing the material should be used for undergarments. Body hygiene plays an extremely important role in preventing superficial fungal infections.

METHODS

With the aim to review available literatures with regard to management of dermatophytic infections and finding insufficient evidence that would be suggested for evidence generation and objectives to review available Randomized controlled trials (RCTs) associated with management of dermatophytic infections done by different researchers available on PubMed/Index medicus or on other search engine/ database of research papers and abstracts. To research Cochrane reviews/systematic reviews with regard to management of dermatophytic infections. To seek out

grade/level of evidence in reference to already generate evidence within the field of dermatophytic infections and management. Inspect and scrutinize the offered guidelines by study-groups and apex bodies in various types of dermatophytic infections. To delineate areas of evidence generation needed with regard to different setups and times problem of drug resistance. To offer and suggest evidence generation and practice solutions. After approval of this pilot study by the Ethical procedure, Faculty of Life Sciences University of South Wales United Kingdom, all the recent published literature reviews, evidence based with the highest ratings were reviewed to get a rational management of dermatophytic infections. The study methodology includes most up-to-date reviews published and are submitted in last fifteen years. The literature review is totally oriented in generating a rational management, which incorporates sorts of dermatophytes, diagnostic tools, and therapeutic, non-therapeutic and natural methods of management of dermatophytic infections. The safety and efficacy of topical and systemic antifungal in children, elderly and pregnant women are included during this study. Considering the research related question, whether the available literature are sufficient to "generate evidence" in reference to rational management of dermatophytic infections in several setup or more research is required for generating high grade evidence?

Scope of review

To satisfy above aims and objectives: Need for evidence generation on this topic? Is it due to commonness of the problem? Is it due various views and differing protocols available or is it due to changing environmental scenario? The importance of hygiene and its role in management of dermatophytic infection? Epidemiological determinants? Role of lifestyle? Relation with occupation? Common myths associated with, irrational treatment, poly-pharmacy insufficient evidence associated with topic. Are different oral and topical drugs available? Are available drugs having sufficient evidence for its rational use? Are the recommended dose, route of drug administration and therapy duration evidence based? What's problem of use of topical, oral, and parenteral use of steroids in dermatophytic infections? What Evidence based Medicine and Evidence based practice describes in reference to dermatophytic infections.

RESULTS

The dermatophytic infections have a tendency to become chronic with drug abuse and recurrent with inadequate therapy as well as improper hygiene. Topical terbinafine for 4 weeks, treatment of choice for tinea corporis, tinea cruris and tinea pedis. For more extensive disease, the selection is a smaller amount clear. Terbinafine and Itraconazole have been found effective with appropriate dose and duration of administration, obtain complete cure and prevention recurrence of infection. Due to cutaneous adverse effects, topical corticosteroid utilized in the

clinical practice of tinea management has been strongly discouraged. Terbinafine, Itraconazole, and Fluconazole are oral antifungal which are effective in treatment of superficial mycoses. Athlete's foot, an infection of the feet and toes, is one among the foremost common sorts of dermatophytosis. Terbinafine, Itraconazole, and fluconazole are oral antifungal that are effective in the treatment of superficial mycoses. Itraconazole is the best antifungal active against the three dermatophytes: a) *T. mentagrophytes*, b) *T. rubrum* and c) *T. interdigitale*. Fluconazole was moderately effective and Griseofulvin was less active among all the species tested.

Table 4: Clinical types of tinea (ringworm infections) and associated causative organisms.

Clinical types	Site of infection	Causative dermatophytes
<i>Tinea capitis</i>	Head, scalp, eyebrows, eyelashes	<i>T. mentagrophyte</i> , <i>M. canis</i>
<i>Tinea favosa</i>	Scalp (crusty hair)	<i>T. schoenleinii</i> , <i>M. gypseum</i> .
<i>Tinea corporis</i>	Body (smooth skin)	<i>T. rubrum</i> , <i>T. tonsurans</i>
<i>Tinea cruris</i>	Groin region	<i>T. rubrum</i> , <i>E. floccosum</i>
<i>Tinea unguium</i>	Nails	<i>T. rubrum</i> , <i>T. mentagrophytes</i>
<i>Tinea barbae</i>	Beard in the face	<i>M. canis</i> , <i>T. rubrum</i>
<i>Tinea manuum</i>	Palmar region of hand	<i>T. rubrum</i> , <i>T. mentagrophytes</i>
<i>Tinea pedis</i>	Feet (athlete's foot)	<i>T. rubrum</i> , <i>T. mentagrophytes</i>
<i>Tinea imbricate</i>	Back, arms and abdomen	<i>T. concentricum</i>
<i>Tinea faciei</i>	Region of face without beard	<i>T. rubrum</i> , <i>T. tonsurans</i>
<i>Tinea gladiatorum</i>	Arms, neck and hands	<i>T. tonsurans</i>

Clinical diagnosis of dermatophytic infection and laboratory-based tests are vital in management of dermatophytic infections, considering conventional methods and incorporation of advanced techniques like preparation of skin specimens for microscopic examination by 10% to 20% mount microscopy, polymerase chain reaction, fungal culture, and spectroscopy. Fungal culture technique holds a robust proof in cases of relapsing dermatophytic infections involving multiple sites. Often topical monotherapy for jock itch and corporis in a controlled case is suggested and provides good results. The mixture therapy of systemic

and topical antifungal is found a simpler in new and recalcitrant athlete's foot, extensive lesions of corporis and recalcitrant cases of cruris and corporis.

DISCUSSION

Dermatophytosis is a cutaneous dermatophytic infection and is caused by fungal species known as Trichophyton, Microsporum and Epidermophyton species. It invades the keratin layer but does not reach the epidermal layer. Dermatophytic infection affect various sites in individuals with respective to age, gender, type of work and life style like type of cloths and environment.¹⁶ Non-dermatophytes can also be a cause of superficial or cutaneous fungal infections example: *Aspergellus*, *candida*, *mucor* and *Acremenium* spp.¹ Wearing tight fitting garments was found to be a reason for crural fold involvement. Use of over the counter medications, particularly topical corticosteroid, and their chronic use produce reduction in the local cell mediated immunity leading to the proliferation of superficial fungal infections. Patient may have atypical manifestation of superficial skin fungal infection or exacerbated by application of topical steroids.^{17,18} There is evidence of practice of frequent sharing of towel, foot wears and cloths are contributing factors in spreading of infection among close inmates, and sometimes community as well. Transmission of fungal pathogens is very common among family members and inmates due direct exposure with beddings, clothing, daily use linen and other house hold fomites.¹⁹ Recurrence of fungal infection is very common if any family member is asymptomatic. Unwashed, unhygienic clothes worn for a longer duration, tight fitting clothes, woollen garments during winter season often create moist and favourable environment for growth of dermatophytes.²⁰ Topical application of corticosteroids indiscriminately to suppress the unbearable pruritus in dermatophytic infections, especially corticosteroid combination products are a definite cause of flare up of infection. Recognition, on global and regional basis, registries of all diseases, including fungal diseases is not maintained. Dermatophytosis management has become a menace with over the counter use of topical steroids and inadequate therapy leading to more of resistant cases. There is a close relationship between education and living standards with prevalence of this infection. Those individuals who are educated often come up with problems earlier than those who are uneducated and with poor living standards, basis lack of awareness about the disease and its effects. The present scenario of prevalence of dermatophytic infections all over the world have been possibly a complex interplay between host, fungus, drug and environment, a contribution by multiple factors as; humid and warmer climatic conditions, topical corticosteroids-based combination, abuse. Increased use of broad-spectrum antibiotics, doubtful role of antifungal drug resistance.^{21,22}

Table 5: Summary of use of topical antifungal in the treatment of *Tinea corporis*, *Tinea cruris* and *Tinea pedis*.

Topical antifungal	Preparations	Site	Frequency of application	Duration of use
Azoles (imidazoles) clotrimazole 1%	Cream, lotion	T. corporis/cruris/pedis.	BD	4-6 weeks
Econazole 1%	Cream	T. corporis/cruris/pedis.	OD-BD	4-6 weeks
Miconazole 1%	Cream, lotion	T. corporis/cruris/pedis.	BD	4-6 weeks
Oxiconazole 2%	Cream, lotion	T.corporis/cruris/pedis.	OD-BD	4 weeks
Sertaconazole 2%	Cream	T.corporis/cruris / pedis.	BD	4 weeks
Luliconazole 1%	Cream, lotion	T.corporis/cruris/ pedis.	OD	2 weeks
Eberconazole 1%	Cream	T.corporis/cruris/pedis.	OD	2-4 weeks
Trizoles efinaconazole	Solution	T. pedis.	OD	Upto 52 weeks in co-existing <i>Tinea unguium</i>
Allylamines terbinafine	Cream, powder	T.corporis/cruris/pedis/ mannum	BD	2-4 weeks
Naftifine	Cream	T. corporis/cruris/pedis.	OD-BD	Use 2 weeks beyond resolution of symptoms.
Butenafine	Cream	T.corporis/cruris/pedis.	OD-BD	2-4 weeks
Others amolorfine (0.25%)	Cream	T.corporis	BD	4 weeks
Amphotericine B (0.1%)	Liquid based gel	T.corporis	BD	2 weeks

Table 6: The efficacy of antifungal agents and their assessment in treatment of dermatophytic infection.¹

Antifungal agent	Method	Results
Griseofulvin, Terbinafine, Itraconazole Ketaconazole, Fluconazole, Voriconazole Clotrimazole Ciclopirox Amorolfine and naftifine.	Broth microdilution method (M38-A) CLSI standards.	Itraconazole and Terbinafine lowest (MIC) Fluconazole greatest (MIC).

CONCLUSION

In this study of the generation of evidence on rational management of dermatophytic infections, the reviews available highlight the vast gap in the management of cutaneous dermatophytosis. Steroid abuse, in dermatophytic infection has led to many adverse effects and chronic condition of disease. Steroid misuse leads to the development of steroid modified dermatophytosis, involving multiple sites. The gap between existing recommendations for the treatment of dermatophytic infections needs future maintenance of registry, the measurement of herd immunity, measuring skin levels and blood levels of drug and response to therapy. Skin reactions or dermatophytic reactions are secondary to dermatic eruptions, have an immunologic origin and a response to dermatophytic infection which may show good

response with topical steroid and anti-pruritic agents in relieving the symptoms. Use of desiccating powders and avoidance of occlusive clothing can prove beneficial in prevention and recurrence of tinea infection in the groin region. Hygiene maintenance on a daily basis is very important.

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