

Review Article

Expert consensus on management of dermatophytosis in elderly patients, patients with comorbidities, and immunocompromised status: an Indian perspective

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ABSTRACT

Dermatophytosis is a common fungal infection of skin contributing to increasing disease burden worldwide. Increasing age, presence of comorbid conditions and immunity have a profound impact on the manifestation of dermatophyte infections. Treatment of dermatophytosis includes monotherapy, combination therapy, or sequential therapy of antifungal drugs. However, specific patient populations such as the elderly, people with comorbid conditions, immunocompromised patients, etc. are subjected to inappropriate adverse events due to highly interacting host and drug factors. Thus, the management of dermatophytosis in special populations is a challenge, and it demands a change in the regular treatment plan. A group of Indian experts reviewed the evidence available on different antifungal agents for the management of dermatophytosis and provided their expert opinion on safe and effective management of the condition in special clinical scenarios. This article summarizes the consensus clinical viewpoint of the entire expert panel for a choice of the antifungal drug, factors to be assessed, and treatment considerations in special populations with dermatophytosis. The panel emphasized that complete knowledge of patient's clinical history, presence of comorbid conditions, and pharmacokinetic and pharmacodynamic characteristics of antifungal agents and associated potential drug interactions are essential for the successful management of dermatophytosis in these patients. Also, regular monitoring of drug toxicity is important during antifungal therapy in special population.

Keywords: Dermatophytosis, Treatment, Elderly, Comorbidity, Immunocompromised, Polypharmacy

INTRODUCTION

Dermatophytosis is a common superficial fungal infection with an estimated prevalence of 36.6–78.4% in India.¹ It

causes a range of pathologic clinical presentations, including tinea pedis, tinea corporis, tinea cruris, etc.¹ Dermatophytosis constitutes about 16% of the total cutaneous diseases in elderly patients. These infections are

also common in up to 23% of elderly diabetic patients.² The prevalence of onychomycosis increases with age, and more than 20% of patients above 60 years of age are affected.² One of the major reasons of treatment failure in dermatophytosis is attributed to host factors such as low immunity, polypharmacy, age, comorbid conditions, etc.³ Other associated concerning factors include concomitant systemic diseases triggering immunosuppression, hepatic and renal dysfunction affecting the pharmacokinetics of the drugs and a high likelihood of drug interactions in presence of polytherapy.³ Thus, the management of dermatophytosis in special patient populations including the elderly and patients with concurrent diseases and immunocompromised state is challenging.^{2,4,5} Old age, comorbid diseases and their associated treatment medications influence the manifestation of dermatophytic infections and predispose individuals to recurrent infections and significant drug-drug interactions.² In such special clinical cases, the goal of the treatment is to achieve an effective mycological and clinical cure as well as less adverse effects. In addition, modified treatment methods are adopted and regular laboratory investigations of patients need to be performed.³ Currently, there is no Indian consensus statement for management of dermatophytosis in special clinical scenarios like the elderly patients, people on polypharmacy, immunocompromised patients, and patients with comorbid clinical conditions like liver disease, kidney disease or diabetes. This article presents clinical viewpoint of Indian dermatology experts in managing dermatophytosis in the above-mentioned clinical scenarios.

METHODS

Expert panel meetings involving 96 dermatologists were conducted across nine major cities in India – Delhi, Chandigarh, Lucknow, Mumbai, Nagpur, Kolkata, Bhubaneswar, Hyderabad, and Chennai in March 2019-April 2019. The main purpose of the panel discussion was to review the evidence available on different antifungal agents for the management of dermatophytosis and to gain an expert opinion on safe and effective management of the condition in special clinical scenarios like elderly patients, people on polypharmacy, immunocompromised patients, and patients with comorbid clinical conditions like liver disease, kidney disease or diabetes.

A literature search was also conducted using PubMed and Google to identify relevant articles using Boolean operators and/or search terms/keywords like dermatophytosis, fungal infections, treatment, special population, elderly, liver disease, renal disease, immunocompromised, diabetes, interaction and polypharmacy. Literature data were accessed from 28 published research articles, systematic reviews or meta-analysis performed on humans. This article outlines consensus experts' opinion on safe and effective management of dermatophytosis in special clinical scenarios highlighting the choice of the antifungal drug, factors to be assessed, and treatment considerations.

Dermatophytosis in special clinical scenarios

Among dermatophytoses, tinea pedis and onychomycosis are more common in elderly patients.² Dermatophytosis and onychomycosis have been also identified in patients with liver and hepatic diseases.^{6,7} Moreover, liver cirrhosis has been regarded as an important risk factor for disseminated fungal infections with high mortality.⁶ Clinical studies suggest that patients with chronic kidney disease are more susceptible to dermatophytosis; especially onychomycosis. Patients with chronic kidney disease have been observed to be more susceptible to dermatophytosis, particularly onychomycosis and 42% of renal transplant patients were reported to have tinea cruris and corporis as the most common dermatophytic infections.^{2,8} It is well-known that diabetic patients are at an increased risk of foot infections, and the development of the infection is attributed to chronic hyperglycemia affecting cellular immunity and polymorph nuclear leukocytes, and impairing phagocytic functions.⁹ Although dermatophytes are generally limited to the stratum corneum or keratinized adnexal structures, they may cause extensive dermatophytosis (unusual extension of lesions or an unusual number of affected sites) or invasive infections such as deep dermatophytosis and Majocchi's granuloma in immunocompromised hosts.¹⁰

It is important to note that the patient's physical and physiological factors highly affect the clinical outcome of dermatophytic infection and its management. Comorbid conditions and associated medications affect the pharmacological properties of antifungal agents, thus influencing the choice of treatment and overall management of dermatophytosis in special population.²

Consensus point 1

The experts stated that the management of dermatophytosis in special clinical scenarios like the elderly, patients with the concomitant disease, etc. is challenging. They highlighted that the major concerns associated with the treatment of dermatophytosis in such cases include age-related physiological changes, reduction in glomerular filtration rate, ongoing concomitant medications, drug interaction potential of antifungal agents and systemic comorbidities like diabetes, hypertension, and liver or kidney diseases. Other common factors influencing the treatment of dermatophytosis include treatment adherence and non-compliance, self-medication, drug resistance, reinfection or recalcitrance, etc. The group of experts advised the use of topical antifungal agents in special clinical scenarios; however, the oral antifungal agents need to be employed in case of severe symptoms. The panel recommended using full dose of topical antifungal agents (e.g. cyclopirox olamine, luliconazole) with proper monitoring in these patients. They emphasized on the importance of selection of right antifungal agent based on patient profile and clinical need. In addition, they advised dose titration and clinical monitoring wherever indicated based on patient's

clinical condition and presence of comorbidity. The usual recommended dosages of commonly used antifungal drugs are shown in Table 1.^{11,12}

Elderly patients

Tinea pedis and onychomycosis are common in elderly patients. They are susceptible to recurrent infections and drug-drug interactions due to the presence of comorbidities and polypharmacy. Thus, treatment in the elderly is challenging with limited treatment options available.² Generally, a healthy elderly patient can be treated in the same way as a young adult.⁵ However, it is necessary to consider the patient's need, site and extent of involvement, the presence of comorbidities, the involvement of underlying vascular impairment, and the possibility of drug interactions before starting the treatment in elderly patients.^{1,5} Thus, individualized treatment is generally advocated for the elderly.^{5,13} A range of clinical factors such as physiological changes, comorbidities, polypharmacy, limitations in personal care, and type and extent of infection should be considered before deciding appropriate treatment for dermatophytosis in older people (Figure 1).²

In elderly patients, topical therapy is preferred for the treatment of dermatophytosis. Systemic therapy is indicated only in case of failure of topical therapy, extensive lesions and recalcitrant cases.¹ In addition, shorter treatment duration and fewer daily applications seem ideal in elderly patients.^{2,13} Among oral drugs, terbinafine is preferred over azole antifungal agents due to its low propensity for drug-drug interactions, thus making it suitable treatment agent in elderly patients with comorbid medical conditions and on polytherapy.^{1,2} Evidence suggest low potential use of griseofulvin in the elderly patient due to its low cure rates and high relapse rates.² It is also associated with prolonged duration of treatment, especially in onychomycosis, since it persists for only a short duration (~2 weeks) after the treatment is discontinued.¹⁴

Furthermore, the treatment of onychomycosis in a diabetic elderly patient should be targeted at preventing bacterial infections and associated complications.¹⁵ Moreover, consideration is needed for predisposing clinical and patient factors for poor response to therapy or recurrence of onychomycosis in an elderly patient. These factors are nail plate abnormalities, slow rate of growth of the nail, involvement of nail matrix, the involvement of >75% of the nail, underlying diseases (peripheral vascular disease, diabetes, immunosuppression), physical trauma, poor hygiene, poor compliance, and choice of footwear.^{2,15}

Consensus point 2

The panel agreed that topical antifungal agents should be the preferred treatment option. If required, oral antifungal drugs for short duration is advisable. The experts highlighted that terbinafine is less likely to cause drug

interactions compared to azole antifungal drugs; hence, it is a preferred oral antifungal agent in elderly patients in their clinical practice. The panel emphasized the significance of history taking in elderly patients considering the presence of comorbidities and ongoing multiple drugs in them. The panel also suggested that lower dose itraconazole with a good topical agent can also be a good treatment option in elderly patients. However, baseline complete blood count, liver function and renal function tests, cardiac examination, and blood sugar levels may be considered in elderly patients (>80 years) before starting itraconazole therapy. In addition, better glycaemic control in elderly patients is advised.

Significance of drug-drug interactions

It is necessary to assess the benefits and risks of drug interaction potential to prevent toxicity or chance of therapy failure due to reduced efficacy.¹⁶ Major drug interactions of griseofulvin are noted with phenobarbital, anticoagulants, and oral contraceptives. It is contraindicated in people with porphyria and hepatocellular failure.¹⁶ Azole antifungal drugs are metabolized in the liver by the most common metabolizing enzyme, cytochrome 3A4 (CYP3A4). Among azoles, ketoconazole is the strongest and itraconazole is a potent inhibitor of CYP3A4. Fluconazole is the weakest inhibitor of CYP3A4 unless present in high doses.² Azole drugs have significant potential of drug-drug interactions with a wide range of medications for various clinical indications (Table 1).^{2,14,16-18} Azoles are known to interact with anti-epileptic drugs like phenytoin, carbamazepine, and phenobarbital which leads to reduction in the efficacy of azole drugs due to stimulation of CYP3A4.² They are contraindicated with most of the drugs including quinidine (antimalarial and antiarrhythmic drug), benzodiazepines (alprazolam, chlordiazepoxide, clonazepam, diazepam, estazolam, flurazepam, halazepam, quazepam, and triazolam for anxiety), and statins (lovastatin, simvastatin, atorvastatin for hypertension, heart disease).¹⁶

Terbinafine is metabolized by less than 5% of the total liver CYP450 capacity. It has a low potential for drug-drug interaction since it does not interact with CYP3A4. Thus, most of the side effects associated with concomitant administration of azoles and other drugs metabolized by CYP3A4 are not observed with terbinafine. However, terbinafine inhibits CYP2D6 and therefore caution is advised when coadministered with drugs metabolized by CYP2D6 such as nortriptyline, desipramine, metoprolol, etc.¹⁶

It is suspected that terbinafine may decrease the metabolism of carbamazepine (an anti-epileptic drug) and lead to its increased levels.¹⁹ In elderly patients and people with comorbid conditions, proper precaution and monitoring of drug levels are important when administering azoles with drugs metabolized by CYP3A4.²

Consensus point 3

The experts emphasized that history taking of concomitant medications is an important part of the clinical investigation because drug-drug interactions are known to affect the therapeutic outcomes. The panel provided administration instructions for griseofulvin and itraconazole to ensure their therapeutic efficacy; griseofulvin tablet has to be consumed after a fatty meal and capsule of itraconazole should be swallowed immediately after full meals. Regarding drug-drug interaction, experts agreed that terbinafine is less likely to cause drug interactions compared to azoles, hence it is preferred in people with polypharmacy. Among azoles, fluconazole is the weakest CYP450 inhibitor, thus may have less drug interaction potential and should be given more preference than other azole drugs.

The panel highlighted the significant drug interactions of various antifungal drugs. Griseofulvin should be administered with caution with warfarin type anticoagulant and barbiturates; it enhances their metabolism and decreases their therapeutic activity. Azole drugs like itraconazole and fluconazole significantly interacts with H2 receptor antagonists, H1 antihistamines, didanosine, rifampicin, phenytoin, phenobarbitone, carbamazepine, benzodiazepines, isoniazid, oral hypoglycemic drugs, statins, anti-retroviral drugs, digoxin, warfarin, etc. Terbinafine has shown significant interactions with metoprolol, antidepressants, warfarin, and antiarrhythmic agents.

Comorbid conditions and dermatophytosis

Patients with hepatic disease

Wu et al reported a case of an extensive deep dermatophytosis with hematogenous dissemination involving hair follicles and dermis caused by *T. rubrum* in a patient with liver cirrhosis. The spreading of infection was attributed to the infection of hair follicles and predisposed by the host's immune deficiency.⁶ Onychomycosis was the most common nail change (18%) in patients with liver disease or hepatic failure.⁷

Liver diseases alter the pharmacokinetics of drug by affecting hepatic blood flow, protein binding, and enzyme activity. Only mild changes in hepatic drug clearance are observed with liver diseases except in liver cirrhosis cases.² Griseofulvin is associated with dosage-dependent hepatic toxicity in patients with prior liver damage.¹⁶ In patients without prior liver disease, the relative risks of liver injury were found to be highest with ketoconazole (RR: 228.0) followed by itraconazole (RR: 17.7). Terbinafine was associated with a low incidence of liver injury (RR: 4.2) than azole drugs.¹⁶ In addition, the incidence of terbinafine-related hepatobiliary dysfunction is as low as 1 in 45 000–120 000 patients.¹⁶ A study by Lo et al demonstrated that rates of acute liver injury were comparable and low for fluconazole, ketoconazole, and

itraconazole. The incidence rates were more common for voriconazole and posaconazole users. In addition, preexisting chronic liver disease was observed to increase the risk of azole-induced liver injury.²⁰

The risk for drug-induced hepatotoxicity increases with concomitant alcohol intake, old age, drugs with significant hepatic metabolism and a daily dosage of antifungal drug exceeding 50 mg.²

Consensus point 4

The experts highlighted that pre-existing chronic liver disease is a strong risk factor for the development of acute liver injury among azole users. They suggested that azole antifungal drugs and griseofulvin should be avoided in patients with liver failure since they are associated with liver injury and hepatotoxicity. In such cases, terbinafine can be a safer alternative along with proper usage of topical antifungal treatment. It is also necessary to perform liver function tests after four weeks of antifungal therapy. The experts mentioned that a transient asymptomatic elevation of liver enzymes can be observed, however, it is not known why some patients develop significant drug-induced liver injury while others seem to adapt to it. Nevertheless, all patients should be made aware of symptoms of liver toxicity. The experts advised that routine monitoring is not recommended for patients unless patients are symptomatic or have a background history of the liver. Liver function test monitoring is recommended for patients who receive multiple medications, who are elderly, who are on long-term treatment, or who have a previous history of liver cell damage.

Patients with renal disease

Irimie et al reported a higher frequency of dermatophyte infections in patients with ESRD undergoing haemodialysis compared with controls (32.2% versus 29.5%, $p > 0.05$). The study also observed that *T. rubrum* was the common causative agent for dermatophyte infection in patients with end-stage renal disease (ESRD), similar to the immunocompetent population.⁸ It has been noted that increased susceptibility to skin infections are caused by immunological and histological skin changes induced by uraemia in patients with advanced chronic kidney disease.⁸

In patients with renal disease, treatment depends on the presence of comorbidities, polypharmacy, and type and extent of dermatophytic infection.² Besides the degree of renal insufficiency, consideration is required for the causative dermatophyte strain and pharmacokinetic properties of antifungal drugs.^{2,8}

Out of all antifungal drugs, fluconazole and flucytosine are excreted via kidneys as unchanged drug or active metabolite. Only fluconazole and terbinafine require dose reduction by 50% in patients with creatinine clearance < 50 ml/min.⁸

Their terminal half-lives increase in patients with renal impairment.² There is lack of pharmacokinetic data for terbinafine in patients with creatinine clearance values <20 ml/min. Itraconazole needs dose adjustment only in the case of glomerular filtration rate (GFR) <10 ml/min. Other antifungal drugs, ketoconazole and voriconazole, do not need dose adjustments in patients with renal insufficiency.⁸

Terbinafine demonstrated lowest mean minimum inhibitory concentration values against all dermatophytes isolated from patients with ESRD. It was suggested to be the most active antidermatophytic agent in patients with chronic kidney disease. However, its dose would need adjustments based on creatinine clearance; and frequent monitoring for side effects is not ruled out.⁸

Overall, studies suggest prompt recognition and identification of fungal lesions for early and judicious management to improve quality of life in these patients.²¹

Consensus point 5

The experts advised that oral antifungal agents should be cautiously used in patients with kidney disease or failure. Itraconazole is predominantly metabolised by the liver, thus dose adjustment (dose reduction by half) is required only in cases of advanced renal failure. In patients with decreased creatinine clearance (<50 ml/min), fluconazole and terbinafine require dose reduction by half. According to the experts, proper usage of topical antifungals along with oral terbinafine therapy should be undertaken in these patients.

Patients with cardiovascular disease

Azole antifungal drugs (fluconazole and voriconazole) have been associated with prolongation of QT interval and cause torsade de pointes through inhibition of cardiac human ether receptor a go-go (hERG) potassium channels.^{22,23}

A case report by Okuyan et al showed that itraconazole led to the signs and symptoms of heart failure in a patient who did not have hypertension or cardiomyopathy or coronary artery disease before itraconazole administration.²⁴ The mechanism of congestive heart failure due to itraconazole is not known, however, it may cause decreased cardiac contractility indicating a direct negative inotropic effect on the heart. Besides decreasing heart rate, itraconazole decreases coronary flow and prolongs PR and QRS intervals.²⁴ Itraconazole has also been associated with serious cardiovascular effects such as torsade de pointes when co-administered with terfenadine (anti-histamine).²⁵ It has also been associated with acute systolic failure in healthy people and cardiac arrest on co-administration with amiodarone.¹³ Itraconazole treatment requires evaluation of the history of cardiac issues/heart failure and baseline serum electrolytes and cardiac evaluation are advised for long-term itraconazole treatment.^{25,27}

Salem et al reported post-marketing pharmacovigilance data regarding systemic azole antifungal agents and the development of torsade de pointes. Out of 191 cases, torsade de pointes occurred within one week of starting azole drug in approximately half of the cases. In addition, more than half of the cases were on concomitant interacting drugs.²³ It is necessary to be aware of azole-induced torsade de pointes and assess concomitant drugs taken by the patients to prevent serious consequences.²³ Thus, azole drugs are to be used very cautiously with regular monitoring of at-risk patients for the development of serious cardiovascular effects.^{22,23} Terbinafine has a low potential for drug-drug interactions and is not associated with cardiac complications, even in elderly patients.¹³

Consensus point 6

The panel agreed that azole drugs including are associated with serious cardiovascular adverse events. It is necessary to assess patient's medical history for any cardiovascular conditions like heart failure and evaluate ongoing medications before initiating treatment with oral antifungal drugs. They advised that it would be better to consider oral terbinafine in these patients given its low drug interaction potential. The experts highlighted that cardiac examination should be done especially with long-term treatment i.e. >6 weeks.

Patients with diabetes

Fungal infections are more commonly observed in patients with poor glycemic control and peripheral circulatory failure in diabetic patients.⁹ The risk of foot infections is 2-3 fold higher in people with diabetes than non-diabetics.²⁸ Also, diabetic patients with tinea pedis/onychomycosis are at increased risk of foot ulceration and gangrene.^{28,29}

Systemic therapy is usually employed for dermatophyte infections in diabetic patients, especially with onychomycosis. Clinical studies have demonstrated acceptable cure rates with terbinafine, itraconazole and fluconazole in patients with diabetes.²⁸ However, azole drugs are known to potentiate the hypoglycemic effects of antidiabetic drugs such as sulphonylureas, thiazolidinediones, etc.^{28,30} Terbinafine has demonstrated efficacy and good tolerability with mycological cure rates of 62%-78% in patients with diabetes mellitus, which is comparable to non-diabetic patients.³¹

Studies also demonstrate that terbinafine was not associated with hypoglycemic side effects.³² There is good evidence (level II) suggesting that oral terbinafine is as safe effective as itraconazole therapy for the treatment of onychomycosis in people with diabetes.²⁹ Griseofulvin and terbinafine have not shown any drug-drug interaction with anti-diabetic drugs. Besides, topical treatment of the nail with 8% ciclopirox nail lacquer, bifonazole with urea and amorolfine have been reported to be successful in patients with diabetes.²⁸ Figure 1 shows clinical factors deciding treatment in elderly people. In elderly patients

with dermatophytosis, clinical factors that influence the choice of treatment include type and extent of the infections, physiological changes, presence of

comorbidities, and drug interactions. In addition, limitations in personal care in old age affect medication adherence and compliance.

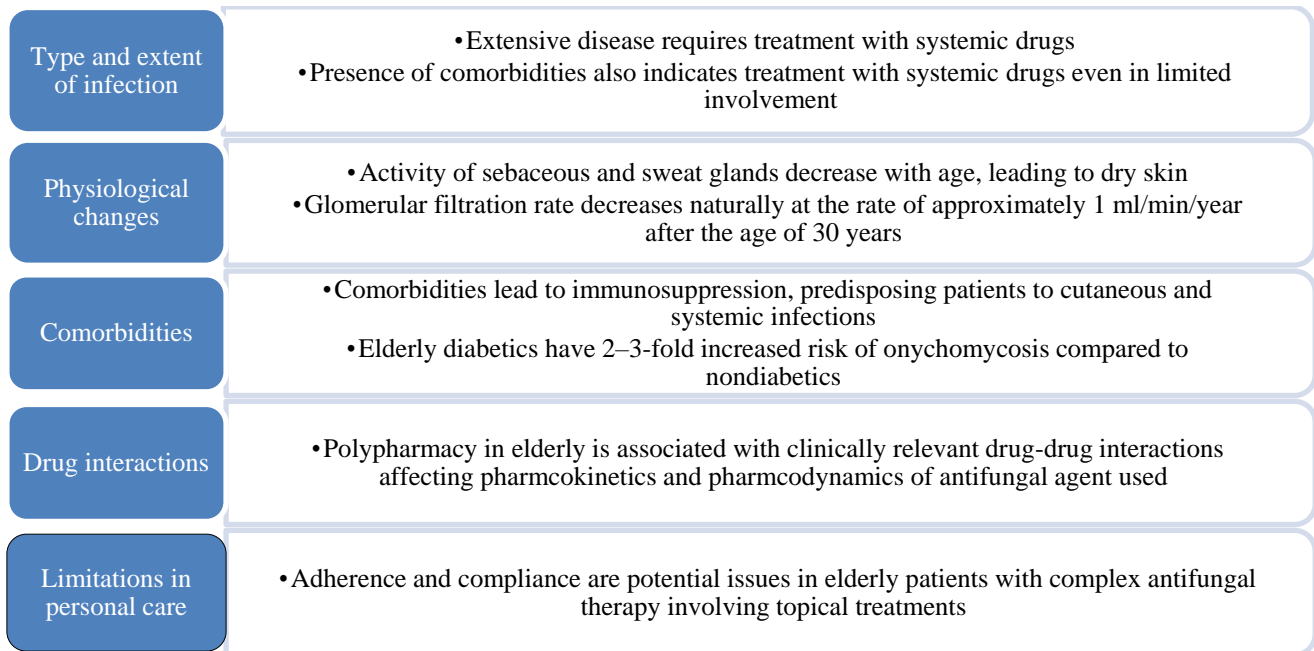


Figure 1: Clinical factors deciding treatment in elderly people.²

Table 1: Dosage of oral antifungal drugs.^{11,12}

Antifungal drug	Dermatophytic infection	Recommended dosage and treatment duration	
		Naive case	Other cases*
Terbinafine	Glabrous tinea ¹¹	250 mg/day (4 weeks)	250 mg BD/day (4 weeks)
	Onychomycosis ¹²	250 mg daily (6 weeks for finger nail and 12 weeks for toenail)	-
Itraconazole	Glabrous tinea ¹¹	100 mg 1 or 2 capsules OD (3 weeks)	100mg BD/100 mg 2 OD (4 weeks)
	Onychomycosis ¹²	200 mg once daily (3 months) or pulse regime with 200 mg twice daily for a week every month	-
Fluconazole	Glabrous tinea ¹¹	50-100 mg/day (4 weeks) or 150-300 once weekly (8 weeks)	100 mg/day (6 weeks) or 150 mg/thrice weekly [#] (8 weeks)
	Onychomycosis ¹²	100 mg daily or alternate day regimen	
Griseofulvin	Glabrous tinea ¹¹	500 mg/day (8 weeks)	750-1000 mg/day (8 weeks)
	Onychomycosis ¹²	500 mg-1g/day	-

Glabrous tinea - tinea corporis, tinea cruris and tinea faciei, *chronic cases, steroid modified tinea cases, recalcitrant cases, #dosage in current practice and not evidence based

Table 2: Drug interaction potential of oral antifungal drugs.^{2,14,16,17,18}

Antifungal agent	Drugs	Indication	Observations
Benzofuran (griseofulvin)	Phenobarbital	Epilepsy	Barbiturates may alter the metabolism of griseofulvin and possibly lead to its impaired absorption or enhanced metabolism ¹⁷
	Warfarin	Anticoagulation for heart disease, stroke	Enhances metabolism of warfarin and decreases its concentration ^{14,17}
	Oral contraceptives	Contraception	Enhances metabolism of oral contraceptives and decreases its concentration ^{14,17}

Continued.

Azoles (Ketoconazole, itraconazole, fluconazole)	Phenytoin, carbamazepine, phenobarbital	Epilepsy	These anti-epileptic drugs reduce the efficacy of azole drugs ²
	Astemizole, terfenadine	Allergy	Azoles increase concentration of these drugs which may lead to life-threatening torsade de pointes ^{2,14}
	Midazolam	Anxiety	Increased blood concentrations of midazolam ^{2,14}
	Oral hypoglycemic drugs	Diabetes	Risk of hypoglycemia. Blood glucose needs to be monitored ^{2,16}
	Statins*	High cholesterol, heart disease	Increase in blood concentration of statins ^{2,14}
	Methylprednisolone*	Arthritis, allergic conditions	Increase in methyl prednisolone levels ²
	Cisapride*	Gastrointestinal motility	Azoles increase concentration of cisapride which may lead to life-threatening torsade de pointes ^{2,14}
	Ritonavir, saquinavir, indinavir, zidovudine, nevirapine	HIV	Ritonavir, indinavir increases antifungal levels. Concomitant use of itraconazole and nevirapine should be avoided. Only fluconazole interacts with zidovudine at doses >400 mg ²
	Rifabutin	Tuberculosis	Rifabutin reduces the efficacy of azole drugs. Fluconazole increases its levels. No significant effect on metabolism of fluconazole is observed ²
	Digoxin	Congestive heart failure	Increase in blood concentrations of digoxin. Monitoring of drug levels needed ^{2,14}
	Rifampicin	Tuberculosis	Rifampicin reduce the efficacy of azoles ²
	Tacrolimus	Immunocompromised patients (transplant recipients)	Increase in blood concentrations of tacrolimus. Its toxicity needs to be monitored ^{2,14}
Warfarin	Anticoagulation for heart disease, stroke	Azoles increase concentration of warfarin. INR should be monitored closely ^{2,16}	
Allylamine (terbinafine)	Nortriptyline, amitriptyline, desipramine	Depression	Increase in serum concentrations of nortriptyline, amitriptyline, and desipramine ¹⁸
	Perphenazine	Psychosis	Increase in serum concentrations of perphenazine ¹⁸
	Cimetidine	Dyspepsia	Cimetidine increases blood concentrations of terbinafine and decreases its rate of plasma clearance ¹⁶
	Rifampicin	Bacterial infections	Rifampicin decreases blood concentration and increases its rate of plasma clearance of terbinafine ¹⁶
	Metoprolol	Angina, hypertension	Terbinafine can alter metoprolol metabolism. Close monitoring of heart rate and blood pressure should be considered ¹⁸
	Warfarin	Anticoagulation for heart disease, stroke	Concentrations of warfarin may be altered ¹⁶

*no significant interaction with fluconazole

Consensus point 7

The expert panel mentioned that the management protocol in patients with diabetes is the same as for non-diabetic patients. They highlighted that commonly used oral anti-fungal drugs like itraconazole, fluconazole, terbinafine have demonstrated good clinical response in diabetic patients with dermatophytosis. However azole drugs exhibit significant drug interactions with anti-diabetic medications like sulphonylureas. Thus, it is preferable to use oral terbinafine in people with diabetes.

Immunocompromised patients

There are no specific clinical features observed in severe dermatophytosis in immunocompromised patients, however, they may have involvement of lymph nodes and organs. Diagnosis can be difficult and require tissue biopsy and culture. In severe cases of dermatophytosis, no specific species is the causative pathogen, but *T. rubrum* is identified as the most common one. Other species such as *M. canis*, *T. tonsurans*, *T. mentagrophytes*, *T. violaceum* and *Epidermophyton floccosum* have also been reported.¹⁰

Non-dermatophyte infections such as aspergillosis, mucormycosis, fusariosis or phaeohiphomycosis can also develop in immunocompromised patients. Thus, it is necessary to confirm the causative pathogen for deep dermatophytosis by positive culture or immunohistochemistry or specific molecular diagnostic tools.¹⁰ Severe dermatophytosis (extensive or deep dermatophytosis) may affect a large group of people with innate immunodeficiency (CARD9 deficiency) or acquired immunodeficiency (solid organ transplantation, autoimmune diseases requiring immunosuppressive treatments, HIV infection, haematological malignancy, liver disease, diabetes mellitus, etc.).¹⁰

There is no consensus treatment advised for extensive or invasive dermatophytosis, but terbinafine and azoles (itraconazole or posaconazole) are found to be effective systemic antifungal agents.¹⁰ A case series by Kershenovich et al reported rapid resolution of lesions with oral terbinafine or fluconazole within 1-4 months with no relapse over a long follow-up period.³³ Terbinafine is preferred due to its low interaction with cytochrome P450 3A4 enzyme, however, triazoles can inhibit the clearance of immunosuppressive agents and cause accumulation of the immunosuppressive agent and thus prolonged immunosuppression.^{22,33} Besides terbinafine, fluconazole is the least toxic azole antifungal for immunocompromised patients.³³ On an additional note, prompt and adequate treatment of superficial dermatophytosis is required before or when starting immunosuppressive treatment to prevent the development of severe disease.^{10,33}

Consensus point 8

The experts highlighted that the drug interaction potential of antifungal agents should be highly considered before initiating treatment in immunocompromised individuals. Of all, terbinafine demonstrates low drug-drug interactions and may be preferred in this subset of patients. In addition, treatment monitoring is advised to follow to avoid severe consequences.

CONCLUSION

Treatment of dermatophytosis in special population groups such as elderly patients, patients with comorbid conditions, and patients on polypharmacy, immunocompromised patients, etc. needs a cautious treatment approach. In these patients, treatment adherence issues, self-medication, prescribed multiple medications, drug resistance, etc. are prevalent, thus treatment is often challenging. The experts emphasized that treatment plan in these special populations should be based on age-related physiological changes, ongoing concomitant medications, drug interaction potential of antifungal agents and systemic comorbidities. Topical antifungal drugs with lower dose oral antifungal agent should be used in these patients with proper monitoring. Among oral antifungal drugs, terbinafine is mostly preferred due to its low drug

interaction potential. However, the choice of treatment should be individualized based on patient characteristics, comorbidities, pharmacokinetic and pharmacodynamics properties of concomitant drugs, and potential drug interactions.

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