Journal of Neonatal Surgery
ISSN(Online): 2226-0439
Vol. 14, Issue 29s (2025)
https://www.jneonatalsurg.com

OPEN ACCESS

Management of Extensive Dermatophytosis: A Comprehensive Review

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Cite this paper as: Dr. M. Harshitha, Dr. Manobalan Karunandhan, Dr. Srikanth. S, (2025) Management of Extensive Dermatophytosis: A Comprehensive Review. *Journal of Neonatal Surgery*, 14 (29s), 820-828

ABSTRACT

Dermatophytosis is a superficial fungal infection of the skin caused by keratinophilic fungi. Based on the extent of body surface area involved, it can be classified as mild, moderate and severe (extensive) infection. Topical antifungals can be used for treating mild to moderate infections whereas, for extensive involvement, systemic antifungal therapy is the mainstay of treatment. The most commonly used oral antifungals for treating dermatophytosis are fluconazole, terbinafine, itraconazole, griseofulvin, ketoconazole and rarely amphotericin-B, voriconazole and posaconazole. Presently, there is an adequate armamentarium of oral antifungal drugs but despite this, there is a rising trend of recalcitrant and recurrent dermatophyte infections. The reasons for this could be the emergence of resistance to the currently used antifungals, poor compliance of the patient to the treatment owing to the exorbitant cost of the newer oral antifungal drugs.

1. INTRODUCTION

Dermatophytosis, a superficial mycosis is an infection involving the skin, hair or nails affecting more than 20-25% of world population while the prevalence of dermatophytosis in India is around 13%.1,2 It is caused by keratinophilic fungi belonging to one of the following genera: Epidermophyton (infects skin and nails), Trichophyton (infects skin, hair and nails), and Microsporum (infects skin and hair).1 It is clinically characterised by the presence of annular (ring-like) lesions on the affected skin.3

Dermatophytes are classified based on the sites involved as tinea capitis (scalp), tinea barbae (beard and moustache area), tinea faciei (glabrous skin of face), tinea corporis (glabrous skin of the body), tinea cruris (groin), tinea manuum (hands), tinea pedis (feet) and tinea unguium (nails).4

During recent times, dermatophytosis has become a distressing issue to both the patient and the treating physician due to the emergence of resistance to the commonly used systemic antifungals. Systemic antifungals are preferred for the management of the extensive dermatophytosis (>10% body surface area.).5 This paper provides an overview on the management of extensive dermatophytosis.

2. LABORATORY DIAGNOSIS

KOH mount: Specimens like skin scrapping, hair root and nail are mounted on a slide with 10-20% KOH. Visualization of branching, rod-shaped septate hyphae in skin, hair or nail under direct microscope is the most effective way of diagnosing a fungal infection. hair shaft coated with dermatophyte spores may be noted in tinea capitis.6

Fungal culture

It is a gold standard for diagnosis of dermatophyte infections and also helps in species identification. Skin, nail, or hair scrapings are inoculated on Sabouraud's dextrose agar. It's quite time consuming as the culture usually takes 7 to 14 days to be declared positive and 21 days to be declared negative.6

3. TREATMENT OF DERMATOPHYTOSIS

Antifungal drugs:

Antifungals are classified into topical and systemic drugs. Topical agents are used for superficial fungal infections of limited extent (<10% BSA).5 Systemic agents are used to treat superficial fungal infections involving large body surface areas (>

10% BSA), onychomycosis and tinea capitis.7

There is no single drug or regimen effective against all manifestations of this disease because of the biological variability of the dermatophytes, different sites involved and varying extent of involvement.[8]

Ideal antifungal drug:

Broad spectrum of activity (yeasts and filamentous fungi)

Rapidly acting and highly fungicidal

Low toxicity and minimal drug interactions

Good pharmacokinetics

Good penetration into all tissue compartments

Cost effective

Table 1: Structural classification of antifungal drugs[1]

Azoles: Imidazoles: Topical - Sertaconazole, Eberconazole, Clotrimazole, Luliconazole, Econazole, Miconazole, Bifonazole, Fenticonazole, Oxiconazole, Tioconazole, Berconazole Systemic - Ketoconazole Triazoles: Fluconazole, Itraconazole, Voriconazole, Posaconazole, Ravuconazole Isavuconazole
Antimetabolite: Flucytosine
Antibiotics: Heterocyclic benzofuran: Griseofulvin Polyenes: Amphotericin B, Nystatin, Natamycin
Allylamines: Terbinafine, Butenafine, Micafungin, Naftifine
Echinocandins: Caspofungin, Anidulafungin, Micafungin, Aminocandin
Other agents: Tolnaftate, Ciclopirox, Amorolfine, Undecylenic acid, buclosamine, Whitfield's ointment, Benzoyl peroxide, Zinc pyrithione, Selenium sulphide
Newer and potential therapies: Demcidin, Macrocarpal C

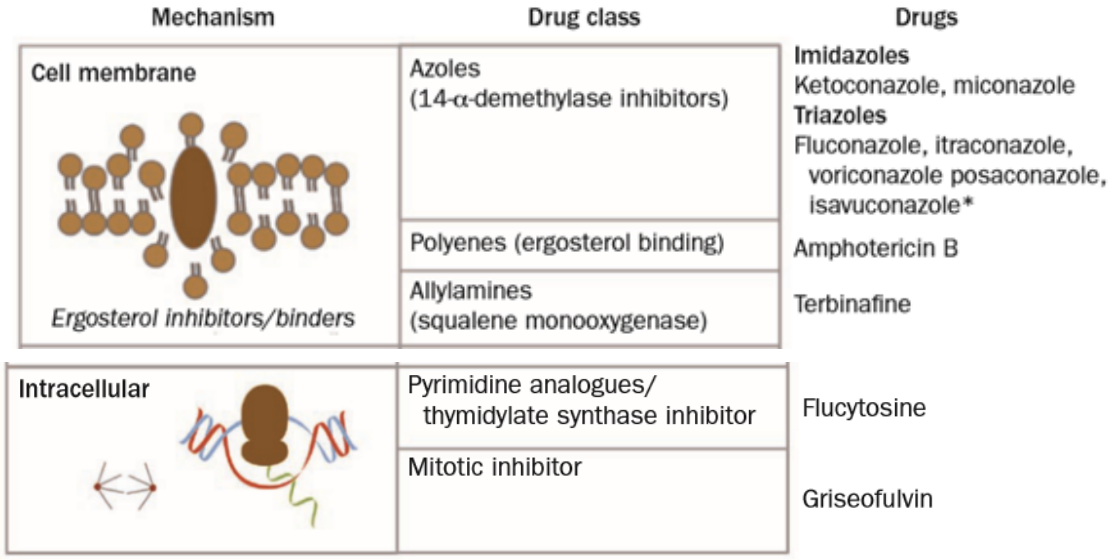

Figure 1: Sites and mechanism of action of systemic antifungal drugs[8]

Oral antifungal drugs:

Griseofulvin:

Griseofulvin is a metabolic derivative from *Penicillium griseofulvum.* It is a fungistatic drug which binds to tubulin and microtubule- associated proteins (MAP) and inhibits the formation of mitotic spindle. It is preferred for the treatment of dermatophytes while it is ineffective against yeast and molds since they lack prolonged energy-dependent transport system that facilitates its entry into the fungus.[7,9]

Bioavailability of the drug is better with dietary fat intake and with smaller (micronized/ultramicronised) particle size of the drug.

It is the first line of treatment for tinea capitis caused by *Microsporum sp* on par with other systemic antifungals like terbinafine, fluconazole and itraconazole for the treatment of dermatophytosis.

Formulations and dosage: 250 mg and 500 mg microsize and 125 mg, 165 mg, and 250 mg ultramicrosize tablets, and 125-mg/5ml oral suspensions.[10] It is given at a dosage of 1 gram per day (micronized) and 660 mg or 750 mg per day (ultramicronised) for a duration of 4-8 weeks in the treatment of tinea mannum and pedis while half of the dose is preferred for the management of tinea corporis and other types. In children preferred dosage schedule is 20-25mg/kg/day for micronized and 10-15mg/kg/day for ultramicronised for the management of dermatophytosis.[7,11]

Griseofulvin is generally well tolerated, with the most common side effects being hypersensitivity in the form of skin rashes, urticaria, angioneurotic oedema and epidermal necrolysis has been reported. Headache, nausea and photosensitivity are also observed. Serious adverse effects such as hepatotoxicity, leukopenia, thrombocytopenia, or anaemia are rarely reported. This drug should not be taken along with phenobarbitone, alcohol (disulfiram like reaction), cyclosporine, oral contraceptives, aspirin, warfarin.[12]

Pregnancy category: C[13]

Amphotericin-B

It is a polyene isolated from *Streptomyces nodosus*. Amphotericin B binds to ergosterol in the fungal cell membrane, resulting in the formation of pores, ion leakage and finally fungal cell death. It has a significant place in the treatment of invasive fungal infections like systemic aspergillosis, candidiasis and cryptococcal meningitis. The mode of administration in above conditions is parenteral.[14] It is rarely used in the treatment of dermatophytosis. It is available in topical lipid-based formulations for proper penetration through the stratum corneum. This topical formulation has been used for perceived "clinical" resistance in recalcitrant cases of dermatophytosis.[15]

Pregnancy category: B[13]

Allylamines:

Terbinafine:

Terbinafine, an allylamine antifungal, exerts its fungicidal action by inhibiting squalene epoxidase that is required for fungal cell membrane biosynthesis.16 [16]

It is a lipophilic drug, not influenced by food intake and, tends to rapidly distribute and accumulate in hair follicles, nails, and skin with minimal concentrations in plasma. The half-life of the drug is 17 hours. A dose adjustment is necessary in patients with advanced renal or liver diseases.[10,17,18]

Formulations and dosage: 250 mg, 500 mg tablets and 125 mg, 187.5 mg oral granules.[7] In adults the dosage is 250 mg/day for 2 to 4 weeks for tinea corporis, pedis and cruris, while a duration of 6 weeks for finger nail infection and 9 to 12 weeks for toe nail infections. Pulsed regimen of 500 mg/day/ week in a month for the same duration as mentioned above for tinea unguium has also been tried with reasonable success. In children older than 4 years of age it is given at a dose of 5mg/kg/day.[7,19]

The side effects reported are dysgeusia (altered taste), loss of smell, tongue discoloration, hepatotoxicity, hematologic disorders including pancytopenia which is usually reversible after drug stoppage, GIT upset, aggravates psoriasis, lupus erythematosus. Terbinafine should not be administered concomitantly with nortriptyline, amitriptyline, venlafaxine, and desipramine, rifampicin or cimetidine.[19]

Terbinafine is a pregnancy category B.[13] When indicated, this is the only systemic antifungal given in pregnancy.

Azole derivatives:

Azoles are classified into imidazoles (have 2 nitrogen atoms in the azole ring) and triazoles (have 3 nitrogen atoms). They are fungistatic but exerts fungicidal effects in higher concentrations. All azoles have similar mechanism of action and the action is executed by inhibition of demethylation of carbon-14 of sterol which is a component of fungal cell wall. So, there is inhibition of synthesis of normal ergosterol which results in arrest of growth and replication of fungi. Triazoles like

fluconazole, itraconazole, voriconazole, posaconazole and ravuconazole are used in systemic treatment of fungal infections.[20,21]

Ketoconazole:

Ketoconazole was the first marketed oral azole derivative. The absorption of oral ketoconazole is increased by acidic beverages and decreased with increase in gastric pH.[17]

Ketoconazole tablets are available at a strength of 200 mg and can be given once daily for 7 to 10 days in dermatophytosis. Oral suspension of 100mg/5ml is also available. This drug has been noted to be significantly associated with the incidence of hepatic toxicity so it has been largely removed from the market.[22] The other side effects are GIT disturbance like nausea, vomiting, diarrhoea, abdominal pain, headache, sleeping disturbances, dizziness, pancytopenia. It also has minimal anti-androgen effect resulting in impotence, gynecomastia, and decreased libido.[7]

Pregnancy category: C[13]

Itraconazole:

Itraconazole is a broad- spectrum fungistatic triazole, synthetically derived from ketoconazole.[9]

Formulations and dosage: It is available as 100 mg capsule, 200 mg tablet 10 mg/ml of intravenous and oral suspension. The bioavailability of the drug varies with the formulation: capsule is better absorbed after a full meal or fasting with a cola beverage whereas suspension is to be taken without food.[7] It accumulates slowly in skin and persists for one month even after the discontinuation of the drug contributing to a residual effect of the drug even after it is stopped. Sebum excretion of itraconazole has also been reported[23] The recommended dose for tinea infections is 100 mg twice daily for 7 days, tinea capitis is treated with 200 mg/day for 2 to 8 weeks For the treatment of onychomycosis, itraconazole is given as a continuous regimen in a dose of 200 mg for 6 weeks or a monthly pulse dose of 400 mg/d for 1 week. In children the dose is 5 mg/kg/day.[7]

The most common side effects are nausea, vomiting, unpleasant taste. Triad of edema, hypertension and hyperkalemia has been reported in elderly patients. The other side effects are heart failure, hepatitis, Stevens-Johnson syndrome, anaphylaxis.[7] H2 receptor blockers and proton pump blockers when used concomitantly will reduce the efficacy of itraconazole.[10]

Pregnancy category: C[13]

Fluconazole:

Fluconazole is a water- soluble bis-triazole.[10] The absorption is very good orally and has high bioavailability, without being affected by concurrent food intake. The protein binding of the drug is very minimal so the possibility of drug-drug interactions is less. The drug is mainly eliminated through kidney and hence dose adjustment is required in renal insufficiency conditions.[8,24]

Formulations available: Fluconazole is available as 50, 100, 150, 200 mg tablets, 2 mg/ml intravenous infusion, 50 mg/5ml and 200mg/5ml oral suspension.[9] In tinea corporis, cruris, pedis, barbae 150 mg/week tablet for 2 to 6 weeks is given while in onychomycosis, 150-300 mg/week is given for 6 to 9 months for finger nail and 9 to 15 months for toe nail. In children it is given at a dose of 3 to 6 mg/kg/day.

The most common adverse effects are nausea, vomiting and elevations in level of liver function tests. Rarely cardiac abnormalities like prolonged QT intervals, torsades des pointes, Stevens-Johnson syndrome and toxic epidermal necrolysis have been reported.[10] Fatal arrhythmias can happen when fluconazole is administered with astemizole, cisapride, terfenadine or pimozide.[9,10,24]

Pregnancy category: C[13]

Voriconazole:

Voriconazole was discovered in the late 1980s. It also belongs to the triazole class of drugs. Voriconazole has a broad spectrum of activity against *Candida glabrata*, *C. krusei* and *Candida lusitaniae*, *Aspergillus*, *Cryptococcus neoformans* and other emerging organisms including species of *Fusarium*, *Acremonium*, *Scedosporium*, *Trichosporon* and *S. apiospermum* also respond well to therapy with voriconazole.

The oral bioavailability of voriconazole is around 96%, which allows switching between intravenous (IV) and oral formulations if necessary. As the presence of high-fat food affects voriconazole absorption, oral voriconazole should not be taken within 1 hour of a meal. The drug is available as 50, 200 mg tablet, 200 mg/vial intravenous infusion and 200mg/5ml oral suspension.[25]

From a dermatological point of view, it is interesting to note that voriconazole is active in-vitro against dermatophytes and *Malassezia* with a minimum inhibitory concentration of 0.002 to 0.06 microgram/ml[26]

Pregnancy category: D[13]

Posaconazole:

It is a triazole antifungal drug which is FDA approved for the treatment of oropharyngeal candidiasis and is effective against Candida and Cryptococcus species, many molds and some endemic fungi. Inhibition of the enzyme 14-α-demethylase results in inhibition of ergosterol which is essential for the fungal cell membrane. It is available as 40mg/ml oral suspension, so its main use is in antifungal prophylaxis. Posaconazole has less drug interactions in comparison with itraconazole.[27]

Pregnancy category: C[13]

Newer triazole antifungals:

Isavuconazole, ravuconazole and albaconazole are the latest additions to this group. These are extended spectrum triazoles that have shown promise in the treatment of fungal infections. These drugs are in various phases of clinical trials, hence a detailed report from these trials will help to shed light on the use of these drugs for dermatophyte infections. One of the major concerns with these newer triazoles is the possibility of developing cross-resistance as demonstrated by in-vitro studies.[28]

RESISTANCE TO ANTIFUNGALS

The evolution of antimicrobial drug resistance is an inexorable process in the microbial world. Although fungal resistance is not as rampant as bacterial resistance, the economic burden associated with fungal infections remains extremely high especially in a developing country such as ours. One of the major factors exacerbating antifungal drug resistance is the inappropriate use of antifungal and steroid combinations.[29,30]

Fungal resistance can be:

Microbiological resistance or in vitro resistance

Clinical resistance or in vivo resistance

Microbiological resistance refers to "non-susceptibility of a fungus to an antifungal agent by in vitro susceptibility testing, in which the MIC of the drug exceeds the susceptibility breakpoint for that organism."

Clinical resistance is defined as the "failure to eradicate a fungal infection despite the administration of an adequate dose of antifungal agent with in vitro activity against the organism." Host immune status, pharmacokinetics and pharmacodynamics of the drug, compliance of patient, persistent focus of infection are some of the factors important in determining a successful clinical outcome in addition to the susceptibility of the pathogenic organism to the antifungal drug".[31,32]

Factors responsible for antifungal drug resistance are many and range from fungal factors like reduced concentration of drug with the fungal cell wall, increased metabolism of the drug or due to biofilm production; host factors like decreased patient immunity or increased severity of infection may also play a role. Sometimes the nature of the drug can also predispose to antifungal resistance and is especially noted with fungistatic drugs.[32]

Table 2 Mechanisms of drug resistance in commonly used oral antifungals

Drugs	Presumed resistance mechanism
1.Terbinafine	Modification of target enzyme by mutation[33,34] Increased drug efflux[35] Stress adaptation[36]
2. Fluconazole	Increased drug efflux[35] Stress adaptation[36]
3. Itraconazole	Increased drug efflux[35]
4. Ketoconazole	Increased drug efflux[37]
5. Amphotericin B	Increased drug efflux[37] Stress adaptation[37]
6. Griseofulvin	Increased drug efflux[35,36] Stress adaptation[36]

In-vitro drug resistance of dermatophytes is not very well studied, but many recent reports suggest that resistance is on rise. In spite of a good armamentarium of agents effective against dermatophytes, the incidence of chronic infection, reinfection,

and treatment failures are on the rise.[38,39] This has led to the belief that the organisms are probably becoming resistant to the available antifungal drugs.

Since 1960's resistance/recurrence to griseofulvin therapy in patients has been recorded.[40,41] Allylamines became the preferred choice of treatment, with the advent of treatment failure with griseofulvin.[19] Primary resistance of terbinafine in *T. rubrum* was first reported by Mukherjee et al.[42] Following this Osborne et al conducted a study at the molecular level to find out the mechanism of resistance to terbinafine. From the same patient six *Trichophyton rubrum* isolates were found to be resistant to terbinafine and cross-resistant to some other squalene epoxidase (SE) inhibitors suggestive of a target-specific mechanism of resistance. Rudramurthy et al., recently conducted a study from India in which they observed increased terbinafine resistance in *T. interdigitale* followed by *T. rubrum* isolates.[39]

Due to the prescription of sub-inhibitory doses of azoles and allylamines by some of the non specialists, recalcitrant and chronic infections have become very rampant in the community.[43] Resistance to azole group of drugs has been observed to be 19% worldwide.[44] High MIC values for fluconazole and itraconazole (66.7% and 25% respectively) in 100 isolates of *T. rubrum* obtained from the patients with onychomycosis was found in a study conducted in Brazil which indicates that the possibility of itraconazole resistant strains is also on the rise.[45]

Itraconazole resistant strains also seem to be on the rise based on a study conducted by Azambuja et al, in patients with onychomycosis. This study showed that the MIC values of fluconazole and itraconazole were high in 100 isolates of *T. rubrum*.[45]

Whenever prolonged therapy is required or when the disease has failed to respond to a standard regimen,[46] especially in cases with treatment failure,[47] in-vitro antifungal drugs susceptibility testing of dermatophytes will be of great value in the management of such patients.

Definitions in dermatophytosis:[5]

"Dermatophytosis- Dermatophytosis (ringworm or tinea) is an infection of the skin or skin derivatives, caused by fungi known as dermatophytes leading to erythema, small papules, plaques, vesicles, fissures, and scaling having ring-like morphology. Dermatophytes are filamentous fungi prone to invade and multiply in keratinised tissue, i.e. skin, hair and nails."

"Naïve infection: A given subject is not previously exposed to a particular infection of a given disease or treatment for that disease."

"Chronic Dermatophytosis: Dermatophytosis is considered to be chronic when the patients who have suffered from the disease for more than 6 months to 1 year, with or without recurrence, in spite of being adequately treated."

"Recurrent Dermatophytosis: Dermatophytosis is considered to be recurrent when there is re-occurrence of the disease (lesions) within few weeks (< 6 weeks) after completion of the treatment."

"Relapse: Relapse denotes the occurrence of dermatophytosis (lesions), after a longer period of infection-free interval (6–8 weeks) in a patient who has been cured clinically."

"BSA: The area of outstretched palm from the wrist to the tip of the fingers can be considered roughly 1% of the body surface area. Less than 3% can be counted mild, 3–10% as moderate, and more than 10% as severe, in terms of the extent of involvement."

ECONOMIC BURDEN OF ANTIFUNGAL TREATMENT

The financial burden of the current epidemic of dermatophytoses in India, is understated and underemphasized. New antifungal drugs replace older ones contributing to significant financial burden to the patients.[48]

Nirmala et al conducted a study in Madras Medical College to compare the efficacy, safety and treatment cost of four oral antifungals, in which they observed that the cost of treatment with griseofulvin was Rs. 168 for an 8 week course, ketoconazole was Rs. 756 for 8 weeks, fluconazole was Rs. 459 given weekly once for 8 weeks and itraconazole was Rs. 989 for 2 weeks. According to the authors griseofulvin is the cheapest oral antifungal available and should still be considered as a treatment option for dermatophytosis, especially in a developing country like India.[49] The cost of drugs varies with the brand used.

To understand the economic burden of antifungal treatment Sil et al conducted a questionnaire based cross- sectional study of a state branch of Indian Association of Dermatologists, Venereologists, and Leprologists, to evaluate the price control of antifungal medicines. The authors observed that The Government of India had introduced price control on two antifungal drugs, namely griseofulvin and tolnaftate, in 1995 (Drug Price Control Order- DPCO). These two drugs are less commonly used by practitioners today. Most of the commonly prescribed anti-fungal drugs are outside price control thereby increasing the cost of treatment.[50]

Cost of treatment is an important factor which determines patient compliance in our country so cost-effective treatment

protocols should be devised for a country like ours.

CONCLUSION

From this review it is evident that there are considerable number of systemic antifungals that can be effectively used against dermatophytosis. Unfortunately, some of the available oral antifungal drugs have started showing varying degrees of resistance. This poses an alarming threat in clinical practice, necessitating proper and judicious use of systemic antifungals in the management of dermatophytosis. At present, there is a dire need to evolve national guidelines for cost-effective treatment of dermatophytosis specific to the Indian population.

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