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REVIEW

Common cutaneous dermatophyte infections of the skin and nails

Andre Marais,[1] Elzbieta Osuch[2]

[1]*Department of Pharmacology, School of Medicine, Faculty of Health Sciences, University of Pretoria, South Africa*
[2]*Department of Pharmacology& Therapeutics, School of Medicine, Sefako Makghato Health Sciences University, South Africa*
Corresponding author, email: dramarais@gmail.com / andre.marais@up.ac.za

Abstract

Superficial fungal infections occur in approximately 20% of the population. Dermatophyte infections are mainly caused by organisms from the *Trichophyton, Epidermophyton,* and *Microsporum* genera, and should not be confused with infections caused by *Candida sp.* since management may differ. The diagnosis of cutaneous dermatophyte infections are confirmed with potassium hydroxide (KOH) preparations as clinical diagnosis is not always accurate, and may result in inappropriate treatment. Most dermatophyte infections are successfully managed with topical antifungal preparations; however, systemic therapy provides an increased cure rate and reduces re-occurrence. This review focuses on the most common dermatophyte infections seen by South African health-care providers and briefly describes the available treatment options, which may differ from agents used elsewhere in the world.

Keywords: Tinea pedis, Tinea corporis, Tinea capitis, Tinea crusis, Tinea unguium, pharmacotherapy

Introduction

It is estimated that 10 – 20% of the global population is affected by fungal skin infections (mycosis) at any given time.[1] The lifetime incidence of contracting a superficial fungal disease is nearly 70%, rendering it one of the most contagious and prevalent disease groups encountered in the healthcare system. Mycosis is classified according to the tissue layer of the skin where initial colonization is established. Superficial mycosis is limited to the outermost parts of the skin (stratum corneum). Pityriasis versicolor and pityriasis capitis (dandruff) caused by yeasts in the genus *Malassezia* are some of the well-known examples. Cutaneous mycosis extends deeper into the epidermal structures including the keratinized layers of the skin, hair and nails. Subcutaneous mycosis involves the infection of deeper structures of the dermis, subcutaneous tissues, muscle and fascia by a variety of fungal yeasts, molds and spores. This short review will focus on cutaneous mycosis caused by the dermatophytes. Infections caused by Candida species are excluded in this review.

Clinically important dermatophyte infections are engendered by about forty different fungal species from the genera *Trichophyton, Microsporum and Epidermophyton*. These organisms metabolize keratin and cause various skin and nail infections which are described by the term "Tinea", meaning "fungus", followed by the Latin description depicting the site of infection. Familiar dermatophyte infections include Tinea pedis (athlete's foot), Tinea corporis (ringworm of the body), Tinea cruris (jock itch), Tinea capitis (ringworm of the scalp), and Tinea unguium (onychomycosis).[2] Tinea corporis and Tinea capitis are trivial in pre-pubertal children, whereas adolescents and adults are more likely to develop Tinea cruris, Tinea pedis, and Tinea unguium. Epidemiologically, tinea infections diversify significantly according to geographic location, climate, socioeconomic status and environmental exposure. Although these infections are seldom life threatening, chronic dermatophyte contagion carries a considerable morbidity. Predisposing factors are similar for many dermatophyte infections. Infection with one type is often associated with co-infection of another type. Atypical, generalized, or invasive dermatophyte infections are routinely observed in patients with depressed cellular immunity, diabetes mellitus, malignancy, HIV/AIDS, glucocorticosteroid- or immunosuppressant therapy.

The general diagnosis of tinea involves the preparation of skin scrapings from the affected areas with a drop of 10–20% potassium hydroxide (KOH) on a microscope slide. KOH dissolves keratin, leaving the fungal cell intact. The presence of hyphae or spores confirms the infection, but identification of the specific organism requires dermoscopy, mycological culture evaluation, or polymerase chain reaction (PCR) screening. Candida infection will show an absence of these hyphae during microscopy. With the exception of *Microsporum canis* and *Microsporum andouinii*, dermatophytes do not fluoresce, and light examination is therefore of limited use.

Tinea pedis

Tinea pedis, also known as "athlete's foot", has been pestering humanity for centuries, dating back to its first description in medical literature by Pellizzari in 1888. Clinical prevalence patterns may vary, but it is estimated that approximately 25% of the global population is infected by the two most common causative pathogens namely *Trichophyton rubum* and *Trichophyton interdigitale*.[2] South African epidemiological studies report a 41% prevalence rate, although non-symptomatic and occult infections contribute 10–15% of positive culture results.[3, 4] Predisposing factors are dependent on geographical location (customary in tropical countries), socioeconomic status (commonplace in crowded living conditions and close proximity to animals), environmental exposure (mundane in warm, humid conditions, people wearing occlusive shoes, the use of public swimming pools), cultural norms (double the infection rate in Muslim communities), and co-morbid diseases (typical in diabetics, HIV/AIDS and hyperhidrosis). Success in identifying genetic predisposition relating to athlete's foot, including potential protective polymorphisms, remains elusive. There is no association in regard to race or ethnicity, although the incidence increases with age from adolescence, being uncommon prior to puberty.[5] Athlete's foot is frequently accompanied by various other cutaneous dermatophyte infections.

Tinea pedis generally presents in the interdigital web spaces between the third and fourth toes, where it invades the epidermal layer of the skin covering the sides and plantar surfaces of the feet (Figure 1).

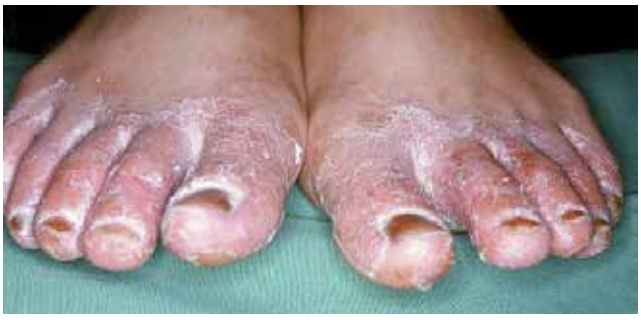

Figure 1. Tinea pedis

(Image available from http://www.fungalguide.ca/basics/images/fungal_4.html)

The lesions typically cause hyperkeratosis and thickening of the stratum corneum. In rare instances it may be accompanied by an increase in the glandular layer with vesiculobullous eruptions. Superficial Tinea pedis infections are outlined by varying degrees of pruritus, interdigital scaling and erythematous erosions. The disease is not painful, with the exception of vesicular eruptions and ulcerations where secondary bacterial infection is typical. Clinical diagnosis has an accuracy of approximately 37%, and therefore requires segmented hyphae confirmation with a KOH preparation, or culture from skin scrapings for identification.[6] Tinea pedis may be mistaken for interdigital candidiasis, atopic dermatitis, psoriasis or eczema.

Treatment aims to reduce pruritus, limit the spread, and prevent secondary bacterial infection. First line topical therapy with 1.5% ciclopirox olamine applied two to three times per week, or 1% tolnaftate applied twice daily for a period of 4 weeks are recommended. Systemic therapy with terbinafine 250 mg per day for two weeks, itraconazole 200 mg twice daily for one week, or fluconazole 150 mg once weekly for two to six weeks are used in adults when topical agents fail to elicit a clinical response after four weeks.[7] Griseofulvin may be prescribed as an alternative, but requires prolonged treatment and is less effective compared to the azoles.

Tinea corporis

"Ringworm" is a cutaneous dermatophyte infection occurring on the legs and trunk, but repeatedly involve exposed areas such as the face, arms, hands and shoulders. The majority of infections are caused by *Trichophyton rubrum*. Other responsible organisms include *Trichophyton tonsurans, Microsporum canis, Trichophyton violaceum, Microsporum gypseum*, and *Microsporum audouinii*.[2] The prevalence is higher in rural African countries with a warm climate.[8] South African epidemiological data suggests a prevalence of approximately 7%, but might be higher due to under reporting as a result of the HIV/AIDS pandemic.[9] More children are affected than adults, and transmission occurs by direct skin contact with an infected individual or animal. Infection may also be the result of secondary spread from other colonized sites such as the scalp or feet. Tinea corporis gladiatorum is a variant observed in wrestlers, and also transmitted by direct skin contact.[10]

A broad range of manifestations are observed. Lesions present with wavering degrees of inflammation, depth of involvement, and varying sizes. These lesions may be single or multiple, and the size generally ranges from 1 to 5 cm, but larger lesions may occur.[11] Clinically it presents as a pruritic, round often erythematous, scaling patch that heals centrally with a remaining raised red active border around the hypopigmented central area (Figure 2). This process results in the ring-shaped plaque from which the disease derives its common name. Brown hyperpigmentation and scarring of the lesions may occur in the presence of a secondary bacterial infection. Tinea of the palm periodically occurs with Tinea pedis, whereas onychomycosis intermittently accompanies tinea of the palm and tinea of the

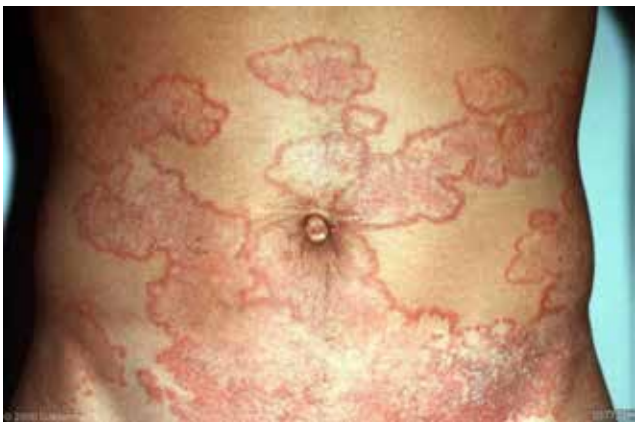

Figure 2. Tinea corporis of the trunk

(Image available from https://www.dermquest.com/image-library/image/5044bfcfc97267166cd62a2d?_id=5044bfcfc97267166cd62a2d

dorsum of the hand. As with athlete's foot, Tinea corporis require differentiation from eczema, psoriasis, seborrheic dermatitis, or other annular skin eruptions.

Tinea corporis responds well to topical antifungal agents from the imidazole (clotrimazole, econazole, ketoconazole) and allylamine (terbinafine, tolnaftate) groups, where it is administered once or twice per day for one to three weeks. Treatment is continued for at least one week after clinical resolution has been achieved. Systemic treatment with terbinafine 250 mg daily for one to two weeks, or itraconazole 200 mg daily for one week is usually effective in patients with extensive skin involvement, or those who fail on topical therapy. Griseofulvin 500 mg to 1000 mg per day for two to four weeks, or fluconazole 150 mg once weekly for two to four weeks may be used as an alternative. The recurrence rate with these agents is high in patients with extensive superficial infections and may require prolonged treatment. Deep inflammatory lesions require one to three (or more) months of oral therapy. Inflammation is reduced with wet compresses of Burow's solution, and appropriate oral antibiotic therapy if secondary bacterial infection is present.[12-14]

Tinea capitis

Fungal infection of the scalp most often presents in pre-pubertal children between the age of 3–7 years, living in poverty-stricken areas and low socioeconomic status characterized by crowded living conditions. Tinea capitis is more prevalent in boys than girls, although the occurrence in post-menopausal women has been described.[15] Local epidemiological data suggest *Trichophyton violaceumin* being responsible for almost 90% of all infections.[9] Different clinical variants are seen: the most common being the "black dot" type accounting for 50% of all cases. "Black dot tinea capitis" is caused by *Trichophyton tonsurans*, *Trichophyton violaceumin*, and *Trichophyton verrucosum* (from cattle). It is portrayed by multiple black dots, which represent the hair cortex being replaced by fungal spores impeding further exit of the growing hair. This results in a weakened hair to coil inside the infundibulum, appearing as a black dot with well-demarcated areas of hair loss ranging from a few millimeters to several centimeters in diameter (Figure 3). It is the most contagious form of Tinea capitis, and transmission occurs from contact with infected individuals, fallen hairs, animals, or contaminated objects such as clothing, bedding, hairbrushes, combs, hats and furniture. Red hairs will present a "red dot" pattern.

The disease may progress to cause a widespread hypersensitivity reaction outlined by a diffuse pustular pattern, severe inflammation, alopecia, and scaling of the scalp, known as kerion. Painful cervical and post-auricular lymphadenopathy, including the development of an inflammatory plaque with thick crusting or draining pustules, are often present[11] (Figure 4). Other zoophilic organisms responsible for inflammatory Tinea capitis include *Microsporum canis* (transmitted by infected puppies or kittens), and *Microsporum gypseum*. The non-inflammatory types of Tinea capitis are less virulent and causative organisms include *Microsporum andouinii or Microsporum ferrugineum*

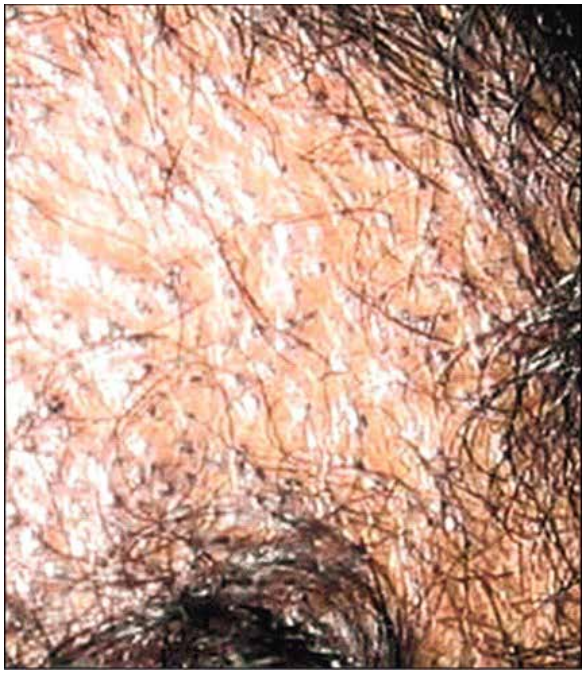

Figure 3: "Black dot tinea capitis"

(Image available from http://pedsinreview.aappublications.org/content/33/4/e22)

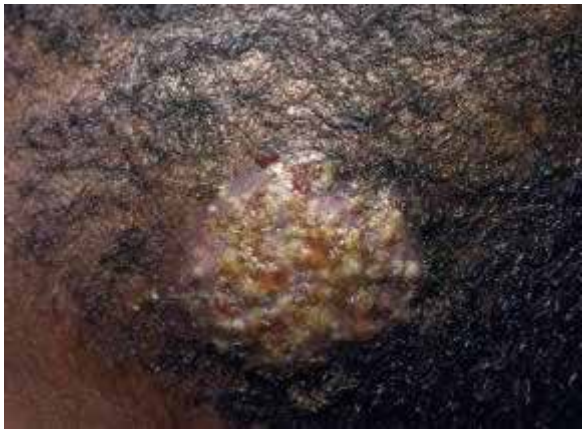

Figure 4. Tinea capitis kerion

(Image available from http://doctorv.ca/medical-conditions/hair/tinea-capitis-ringworm-fungal-scalp-infection-kerion/)

Tinea capitis has a clinical diagnostic accuracy of approximately 67% during physical examination.[16] Laboratory confirmation is accomplished by dermoscopy, PCR screening, and culture obtained from scalp scale samples. The most costeffective collection methods include the toothbrush technique (scalp brush scrapings) and cotton-tip applicator technique (cotton-tip moistened with water).[17] *Microsporum canis* and *Microsporum andouinii* are the only dermatophytes that allow for diagnosis with Wood's light examination, where they will fluoresce blue-green.

Systemic therapy with griseofulvin was the drug of choice in treating Tinea capitis for many years, and is still used in poor countries due to its safety, efficacy and low cost. Griseofulvin has remarkable activity against *Microsporum* species, but requires prolonged treatment and therefore reduces compliance. It

is administered at a dose of 10 mg/kg/day for 8–10 weeks, including Tinea capitis with *Microsporum* kerion. Shorter courses increase the relapse rate. Randomized clinical trials however confirmed the newer agents (terbinafine, itraconazole and fluconazole) having equal effectiveness, safety, and require much shorter duration of treatment.[18] Terbinafine is given at a dose of 3–6 mg/kg/day for a period of 4 weeks in *Trichophyton* infections and 8–12 weeks for *Microsporum* infections. Itraconazole is considered a second line agent if terbinafine and griseofulvin are ineffective. It is administered at a dose of 2-–4 mg/kg for 4–6 weeks.[17] Fluconazole is equally effective but also reserved as a second line option in children older than 6 months. It is administered at a dose of 3–5 mg/kg/day for 4 weeks.

Monotherapy with topical antifungal agents is ineffective, and only used as an adjunct to oral therapy. Topical therapy reduces the risk of spread to uninfected individuals. Current guidelines recommend washing the hair with shampoos containing 2.5% selenium sulfide or 2% ketoconazole two to three times per week for a period of 4–8 weeks.[17] Daily application was encouraged in the past. Family members (or close contacts) need careful inspection to exclude infection. It is advisable to shave the hair at the start of treatment and 3–4 weeks later.[19]

Tinea cruris

Tinea cruris, ordinarily known as jock itch, is a dermatophyte infection involving the crural fold. It is more common in adult men and is caused by *Trichophyton rubrum, Trichophyton interdigitale* and *Epidermophyton floccosum*.[20] Warm and humid conditions such as wearing occlusive clothing, excessive sweating, tropical geographic location and a compromised immune system are predisposing factors. Jock itch presents unilaterally or bilaterally, starting with a red patch on the proximal medial thigh. It most often spares the scrotum and penis, but may spread to the perineum and perianal area. The infection progresses with incomplete central clearing, leaving an erythematous elevated and clearly demarcated border containing small itching vesicles (Figure 5).

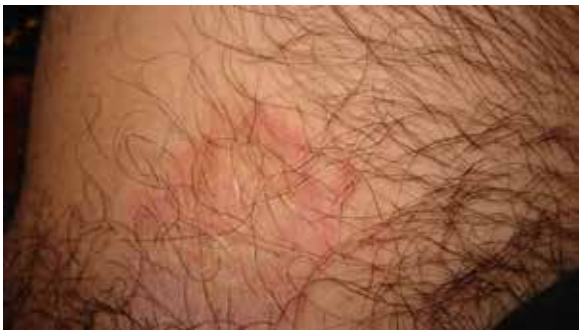

Figure 5. Tinea cruris

(Image available from http://forums.menshealth.com/topic/63643898177459471)

Diagnosis is similar to other dermatophyte infections, using KOH solution to confirm segmented hyphae from skin scrapings collected from the active border. Fungal culture will confirm the diagnosis. Differential diagnosis includes psoriasis, erythrasma, seborrheic dermatitis and candidiasis.[11]

The treatment is similar to Tinea corporis described above.

Tinea unguium

Yeasts (*Candida* sp.) or molds cause onychomycosis (nail infections), but dermatophyte infections from *Trichophyton rubrum* and *Trichophyton interdigitale* are responsible for the majority (85%) of cases. Tinea unguium affects about 10% of the worldwide population and accounts for a third of all mycotic infections of the skin. It is more prevalent in adults living in urban areas. Infection rates increase with age and males are affected more than females.[21] Other predisposing factors include diabetes mellitus, HIV/AIDS, peripheral vascular impairment, sporting activities and injury to the nails. The clinical presentation may vary according to the manner in which the fungus colonizes the nail. The distal hyponychium and lateral side edges of the first toe nail are typically affected (Figure 6). Nail thickening, brittleness and nail plate discoloration extending proximal with progression as the nail grows are common features.

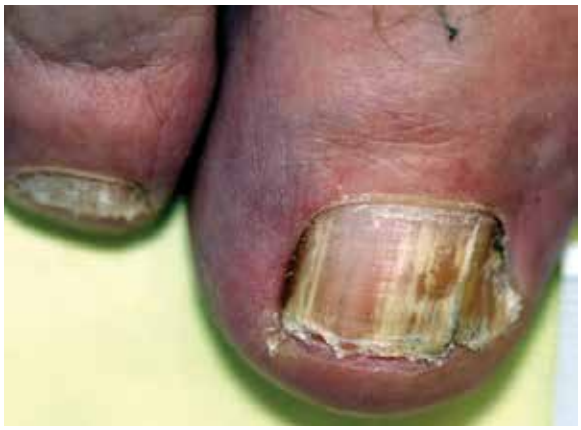

Figure 6: Tinea unguium

(Image available from http://lermagazine.com/article/onychomycosis-remains-a-major-clinical-challenge)

The disease is not life-threatening but secondary bacterial infections, cellulitis, foot ulcers, nail disfigurement and self-esteem issues are frequently encountered.[22] Clinical diagnosis is reliable in 50% of cases and successful identification requires laboratory analysis of nail clippings and debris from the affected nails. Differential diagnosis includes chronic paronychia, viral warts, dermatitis, psoriasis, lichen planus or nail dystrophy.[23]

Treatment remains a major challenge, and depends on disease severity, causative organism and possible adverse drug effects. The relative ineffectiveness of the available pharmacological agents is a result of poor drug delivery to the non-vascular and impermeable keratin containing nails. Treatment includes topical and systemic antifungal agents, laser treatment, photodynamic therapy and surgery. Both topical and systemic antifungal agents are used to treat onychomycosis where less than 50% of the nail is infected. Topical treatment becomes ineffective if more than 50% of the nail (or involvement of the matrix/lunula) is infected. Children respond more favorably to topical treatment because of a thinner nail plate and a faster growth rate.[24] Oral terbinafine remains the first line agent for mild to moderate infections and dosages of 250 mg daily for adults and 62 mg for

children weighing more than 20 kg is recommended. Treatment is indicated for a period between 6 weeks and 3 months, with a maximum clinical response rate of approximately 80%. Itraconazole (200 mg daily for 3 months), provides an alternative in patients failing to respond, or those unable to tolerate the side effects associated with terbinafine. In addition, itraconazole may be administered as pulse therapy requiring 3 sessions. Each session involves a dose of 200 mg twice daily for one week, followed by a 21 day rest period after which the cycle is repeated. The clinical endpoint to this approach is slightly less (75%). Pulse therapy with fluconazole 150 mg per week for three months may achieve a clinical response of 78%.[25] The use of griseofulvine and ketoconazole is not recommended considering a high relapse rate and unfavorable side effects respectively.

Topical treatment is limited to specifically indicated agents and general topical antifungal agents, including tolnaftate, are of negligible use. The only currently available agent include 5% amorolfine nail lacquer. It is to be applied once weekly for six months. A cure rate of between 38% and 46% can be expected if nail involvement is less than 80%.[26]

Clinical pharmacology of available antifungal agents in South Africa

Various pharmacological agents, some briefly described above, are available in the treatment of Tinea infections. Considerable uncertainty and controversy surrounding their efficacy, the optimal treatment period, appropriate dosage and frequency of application remain.[13] Selective toxicity forms the basis of antifungal mechanistic action. Anti-fungal agents are broadly categorized according to their ability to disrupt fungal cell wall integrity and synthesis (β-glucan synthase inhibitors), ergosterol synthesis and cell membrane function ((lanosterol 14 alpha-demethylase inhibitors, ergosterol binding inhibitors, squalene monooxygenase inhibitors, sterol reductase inhibitors), and agents disrupting intracellular metabolism, DNA and RNA synthesis (Pyrimidine analogues/thymidylate synthase inhibitors, mitotic inhibitors, aminoacyl tRNA synthetase inhibitors).

Disruptors of fungal cell wall integrity and synthesis

Echinocandins (caspofungin, micafungin and anidulafungin) are the newest class of antifungal agents. They disrupt fungal cell wall synthesis by the inhibition of the enzyme 1,3-β glucan synthase, thereby preventing cross-linking of glucans necessary to maintain cell wall integrity. These agents are not used in the treatment of cutaneous dermatophyte infections.[27]

Inhibitors of ergosterol synthesis and cell membrane function

Azole antifungal agents [imidazoles – (bifonazole, clotrimazole, econazole, fenticonazole, isoconazole, ketoconazole and miconazole), and triazoles (fluconazole, itraconazole, posaconazole and voriconazole)] arrest fungal growth by inhibiting the cytochrome P450 enzyme 14-alpha-sterol-demethylase responsible for the conversion of lanosterol to ergosterol, an essential molecule of the cell membrane.[28] These agents have a broad spectrum of activity against candidiasis and dermatophytosis, however individual agents differ in their ability to elicit a favorable clinical response to the various types of tinea infections. With the exception of ketoconazole, imidazole antifungals are mostly available as topical preparations requiring treatment for at least 14 days after the lesion has healed. Side effects are minimal and limited to hypersensitivity reactions when applied locally. Systemic administration of ketoconazole may result in hepatotoxicity, cardiac rhythm disturbances, endocrine dysregulation, photosensitivity, dyspepsia, nausea and abdominal discomfort. In addition, it inhibits the CYP3A4 hepatic iso-enzyme, therefore being responsible for a myriad of drug interactions.[29] Triazole derivatives have a broader spectrum of uses and are superior to imidazoles in treating systemic or severe dermatophyte infections. First generation agents (itraconazole and fluconazole) are mostly used in severe tinea infections, whereas the second-generation drugs (voriconazole and posaconazole) are indicated for other invasive and systemic fungal infections not described here. Adverse effects include dizziness, nausea, headache, abdominal pain and skin rash.[30] Drug interactions with azoles are diverse. Co-administration may increase the toxicity of warfarin, benzodiazepines, digoxin, cisapride, cyclosporine and statins. The efficacy of the azoles is reduced by rifampicin phenytoin and cimetidine.[31]

Ergosterol binding polyene antifungals such as nystatin and amphotericin B are not used in the management of dermatophytosis. These agents are used for candida infections and severe systemic fungal infections caused by aspergilosis, cryptococcus, and blastomycosis.[32]

Allylamines (terbinafine and tolnaftate) arrest ergosterol biosynthesis my inhibiting the enzyme squalene monooxygenase. This results in ergosterol deficiency and squalene accumulation causing fungal cell death.[33] Terbinafine is one of the most frequently prescribed oral and topical antifungal agents in the management of various cutaneous dermatophyte infections due to its low incidence of side effects and drug interactions. Systemic side effects are rare, but may include gastro-intestinal disturbances, skin reactions and drug interactions with agents metabolized by the CYP2D6 iso-enzyme system. It should be used with caution in those with hepatobiliary dysfunction. Duration of treatment depends on clinical response but may be administered for periods up to six months.[34] Tolnaftate is only indicated for very superficial infections without hair follicle involvement. Topical application may cause skin irritation. Both terbinafine and tolnaftate remain inferior to the azoles.

Sterol reductase inhibitors (morpholines), such as amorolfine, deplete ergosterol availability due to the accumulation of inactive ignosterol in the fungal cytoplasmic cell membranes. This agent is exclusively used to treat onychomycosis, and is applied to infected nails in a 5% solution. The effectivity is increased if used in combination with a systemic anti-fungal agent and ranges between 60% to 70% if applied twice weekly for a period of up to six months.[35] Side effects are mild and may cause nail discoloration, separation from the nailbed or allergic reactions.

Disruptors of intracellular metabolism

The mechanism of action of ciclopirox is still largely elusive, but recent studies indicate that topical administration disrupts fungal DNA repair by inhibiting the ion transfer mechanism across fungal cell membranes. It is applied as a cream or shampoo twice daily for a period of four weeks. Ciclopirox is indicated in onychomycosis and the management of seborrheic scalp dermatitis, where application is done twice weekly. Mild local reactions characterized by redness, pruritus, pain and a burning sensation of the skin occurs in approximately 5% of patients.[36]

Griseofulvin has been used as an antifungal agent since the late 1930s. It binds to fungal tubulin thereby disrupting microtubule function and inhibiting cell mitosis at metaphase.[37] With the exception of Tinea versicolor, it displays a wide range of activity against dermatophyte infections of the skin, hair and nails not adequately responding to topical therapy. Griseofulvin is administered orally and relies on the presence of a fatty meal for increased absorption where it ultimately binds to keratinocytes, making it resistant to further fungal invasion. This mechanism ensures that newly formed keratin remains free of fungal elements. Metabolism is largely by the liver and acts as an inducer of CYP3A4 iso-enzymes.[38] Caution should therefore be taken in patients on warfarin therapy, or females taking oral contraceptives where the therapeutic effect may be reduced. Other common adverse effects include headache, gastrointestinal discomfort and skin rash. A few incidences of Steven-Johnson Syndrome, leucopenia and CNS symptoms have been reported. Griseofulvin is teratogenic and contra-indicated in pregnancy. It may damage sperm, and male patients are advised not to father children until six months after treatment.[39]

Selenium sulfide is indicated for the treatment of Tinea capitis and Tinea versicolor caused by *Trichophyton* and *Microsporum* species. It interferes with antimitotic action, resulting in a reduction in the turnover of epidermal cells by limiting the cross linkages within keratin molecules.[40] Side effects are rare but may include allergic skin reactions, rash, swelling of the tongue or face, dizziness or difficulty in breathing.

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