Residency Review

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Tinea: Unsightly and Uncomfortable, But Not Untreatable

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Tinea, the most common superficial fungal infection, is caused by fungi collectively called dermatophytes.[1] Specifically, three fungi genera, including *Microsporum*, *Trichophyton*, and *Epidermophyton*, generally lead to tinea infections. These dermatophytes infect the skin anywhere on the body and are classified by the affected area. Tinea corporis, seen on the body truncal area, is often referred to as "ringworm" due to the ring-shaped patches that can develop at the infected site. Tinea pedis of the foot, tinea capitis of the scalp, tinea cruris of the groin, tinea unguium of the nail, and tinea of the palms and beard do not have the characteristic ring-shaped patches upon presentation.

Most fungal infections are a result of skin or nail barrier breakdown or an associated comorbidity affecting the host's defense, such as diabetes, obesity, or immunodeficiency.[2] Impaired circulation, poor nutrition and hygiene, and occlusion of the skin can also lead to tinea infection. Those who spend time in hot, humid weather or those who sweat heavily are particularly susceptible to tinea infections.[3] In addition to these risk factors, other concerns for tinea transmission include close and shared contact to one another, such as with contact sports, close housing situations, and shared towels, clothes, and razors. Fungal transmission can occur via contact with an infected individual, animals, soil, or fomites. It is estimated that 10-20% of the United States population has tinea at any given time.[2]

Presentation of tinea infections ranges from mild itching and scaling to severe inflammatory responses characterized by denudation, fissuring, crusting, and discoloration. Usually, greater inflammation occurs with tinea infections transmitted from animals and in those experiencing their first tinea infection. Because tinea presentation varies widely, it is important to critically distinguish the underlying cause of the infection from other skin conditions that may have similar presentations, such as contact dermatitis and bacterial skin infections.

The most prevalent type of tinea infection is tinea pedis; commonly referred to as 'Athlete's Foot,' tinea pedis affects about 26.5 million people in the U.S. per year.[4] Of those who have tinea pedis infections, 70% are male. Infections may develop from moisture due to sweating feet or transmission in communal showers or pools. High-impact sports that cause foot trauma, such as with runners, can predispose individuals to tinea infections as fungi have the opportunity to invade the outer layers of the skin. Additionally, socks and shoes, worn together, exacerbate tinea pedis infections; heat and moisture cannot escape from the foot and fungal growth is facilitated. Footwear that allows the foot to remain cool and dry, such as sandals, are less likely to lead to tinea infections.

Early symptoms of tinea pedis include itching and burning between the toes and soles of the feet. Erythema, scaling, and dryness can develop at the site over time as well. Treatment includes both topical and oral agents. The area must be thoroughly washed and dried before using topical treatments as moisture reduction is a critical step in any tinea treatment plan. Despite appropriate treatment, recurrence is a concern and duration of therapy may need to be prolonged. Approximately 45% of those with tinea pedis infections will experience reoccurrence episodically for more than ten years.[2]

Tinea corporis, also called 'ringworm,' affects smooth and bare skin and is most common in prepubescent individuals.[2] It is prevalent among those who live in warm, humid climates and those who share close contact with one another, such as with wrestlers and day-care center attendees.[5] Additionally, individuals who have significant stress or who are overweight are at an increased risk of developing tinea corporis. Tinea corporis may be transmitted from an infected animal and can result in intense inflammation. Extensive tinea corporis could signal an underlying immune disorder, such as human immunodeficiency virus (HIV) or diabetes.

Tinea cruris or 'jock itch', is commonly caused by *Trichophyton rubrum* or *Trichophyton mentagrophytes*.[6] As with the other tinea infections, the primary risk factor is associated with a moist environment and as such, flare-ups most commonly occur in the summer months. Men are affected more often than women because of scrotum and thigh apposition. Typical presentations have pruritic, ringed lesions extending from the crural fold to the adjacent inner thigh. These ringed lesions can occur bilaterally and may be complicated by concurrent maceration, miliaria, candida infections, treatment reactions, scratch dermatitis, and lichenification. Pain is often reported during periods of sweating or with maceration of the area. Recurrence is a consideration as the dermatophytes may repeatedly infect people who are susceptible or have tinea pedis and onychomycosis, as those can serve as reservoirs for dermatophytes.[7] Those with tinea cruris should be advised to wear breathable underwear, made from cotton, and to keep the groin area clean and dry.

Overall, fungal infections do not have significant impact on mortality in an individual. However, tinea infections can reoccur,

even with appropriate treatment, and negatively affect quality of life. As such, treatment for tinea infections should be carefully considered. Goals of treatment are to eradicate existing infection, prevent reoccurrence, and provide symptomatic relief. Comprehensive treatment should include nonpharmacologic and pharmacologic measures and be patient-specific.

Nonpharmacologic measures are intended to complement pharmacologic approaches to treatment. Nonpharmacological measures should be followed during and after treatment of the tinea infection to ensure full eradication and prevention of recurrence. Patient counseling on nonpharmacologic measures should include cleansing the affected area with soap and water daily and using a separate towel to dry the area thoroughly, wearing clothes and shoes that do not occlude the skin, and avoiding contact with infected individuals and animals.[8] Additionally, patients should be encouraged to wear protective footwear in communal areas, such as pools and showers.

Tinea pedis, tinea corporis, and tinea cruris may be effectively self-treated with non-prescription topical antifungal agents in addition to nonpharmacologic measures, in many instances. Exclusions to self-care include unclear causative factor, unsuccessful initial treatment, worsening of condition, nail, scalp, face, mucous membranes, or genitalia involvement, signs of possible secondary bacterial infection, excessive and continuous exudation, extensive or debilitating condition, concurrent diabetes, immunodeficiency, or systemic infection, and concomitant fever or malaise.[2] Nail involvement is an exclusion to selfcare as topicals are not effective and systemic pharmacotherapy is required for appropriate treatment.

If self-care is deemed appropriate, there are numerous topical antifungal agents available in a variety of dosage forms and may be selected based on infection type and patient preferences. Clotrimazole, miconazole nitrate, terbinafine hydrochlorate, butenafine hydrochloride, tolnaftate, clioquinol, undecylenic acid, and imidazoles are considered safe and effective based on past well-designed clinical trials.[9] These agents are FDA approved for antifungal use in self-treated tinea pedis, tinea corporis, and tinea cruris.

A critical consideration to appropriate therapy outcomes is patient adherence as some of the treatment options are recommended up to four weeks to resolve the infection completely. Adherence to recommended pharmacologic and nonpharmacologic therapy is crucial as tinea recurrence is highly probable, in some circumstances. With chronic or significant tinea infections, prescription antifungal therapy may be more appropriate. Careful consideration of all patient characteristics, including comorbidities, potential adherence barriers, and risk of recurrence must be weighed when choosing therapy regimens.

Selected Nonprescription Topical Antifungal Products[2]

Tinea Pedis

Active Ingredient	Indications for Use	Directions for Use
Miconazole 2%	Those over 2 years old	Apply BID x 4 weeks
Clotrimazole 1%	Those over 3 years old	Apply BID x 4 weeks
Butenafine 1%	Those over 18 years old	Apply BID x 1 week or Apply once daily x 4 weeks
Tolnaftate 1%	Those over 2 years old	Apply once daily x 4 weeks
Undecylenic acid 10%, 22%, 25%	Those over 18 years old	Apply BID x 4 weeks

Tinea Corporis

Active Ingredient	Indications for Use	Directions for Use
Miconazole 2%	Those over 2 years old	Apply BID x 4 weeks
Clotrimazole 1%	Those over 3 years old	Apply BID x 4 weeks
Butenafine 1%	Those over 18 years old	Apply once daily x 2 weeks
Tolnaftate 1%	Those over 2 years old	Apply once daily x 4 weeks
Undecylenic acid 10%, 22%, 25%	Those over 18 years old	Apply BID x 4 weeks

Tinea Cruris

Active Ingredient	Indications for Use	Directions for Use
Miconazole 2%	Those over 2 years old	Apply BID x 2 weeks
Clotrimazole 1%	Those over 3 years old	Apply once daily x 2 weeks
Butenafine 1%	Those over 18 years old	Apply once daily x 2 weeks
Tolnaftate 1%	Those over 2 years old	Apply once daily x 2 weeks

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Oh my, Onychomycosis!

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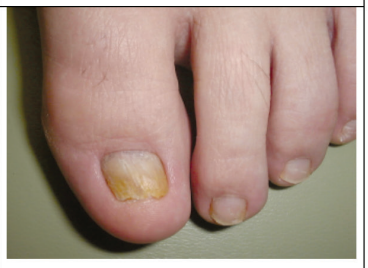
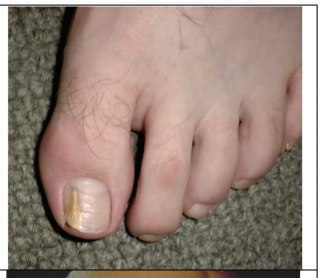
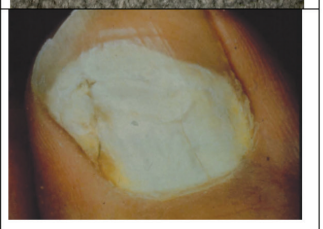
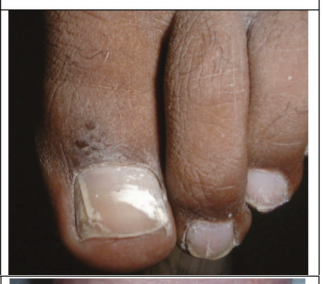
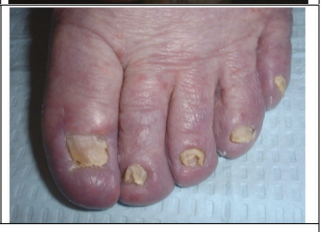
Onychomycosis is a fungal infection of the nails, more commonly the toenails than the fingernails. Onychomycosis is most commonly caused by dermatophytes (usually *Trichophyton rubrum*) and less frequently by non-dermatophyte molds and yeasts (typically *Candida* spp.). It is a common dermatologic condition that affects around 4.3% of people in Europe and North America.[1] It occurs more frequently in males compared to females and in adult patients compared to pediatric patients.[1,2] Risk factors that have been identified include increasing age, peripheral vascular disease, trauma, and occlusive footwear. Fungal nail disease is also more prevalent in patients with other nail problems such as psoriasis, in persons with immunosuppressive conditions such as diabetes mellitus or HIV infection, and in those taking immunosuppressive medications.[3]

Many misconceive onychomycosis to be a cosmetic issue that does not require treatment, but the condition is known to have a significant impact on patients' quality of life. It can also cause patients discomfort, embarrassment, and lowered self-esteem. Infected nails can also serve as a reservoir, with the risk of spreading fungi to the feet, hands, and groin, as well as to other close contacts. The goal of treatment is to eradicate the infecting organism. However, it is important to note that onychomycosis is known to be a difficult infection to treat. Recurrences also occur in as many as 40-70% of patients.[3] Many of the treatment recommendations lack concrete evidence, the available literature however follows.

There are five clinical patterns associated with onychomycosis (Table 1).[2,3]

Table 1:

Classification	Clinical Manifestations	Comments	Photos
Distal and lateral subungual onychomycosis (DLSO)	• Nails thicken and become discolored (yellow-white or brown-black) • Onycholysis* occurs at varying degrees • Toenails are more commonly affected	• Most common presentation of dermatophyte nail infection • Toenails are more commonly affected • Most commonly caused by *T. rubrum*	
Superficial white onychomycosis (SWO)	• Crumbling, white lesions appear on the surface and extend to the entire nail plate • No onycholysis usually seen	• Most commonly seen in children • Usually caused by *T. interdigitale* • Does not respond well to topical therapies	
Proximal subungual onychomycosis (PSO)	• White coloring and onycholysis occur under the proximal portion of the nail and spread distally	• Most cases involve the toenails • Most commonly caused by *T. rubrum* • Least common presentation of dermatophyte nail infection, though can be common in persons with HIV/AIDS	
Endonyx onychomycosis	• White discoloration of the nail • No onycholysis	• Most commonly caused by *T. soudanense* and *T. violaceum*	
Total dystrophic onychomycosis (TDO)	• Nail plate is almost completely destroyed	• Primary TDO is rare and is usually caused by Candida species, typically affecting immunocompromised patients	

* Onycholysis is the separation of the nail and the nail bed

Treatments:

Topical Treatments:

Generally speaking, finger and toenails are hard, compact structure composed of protein. Specifically, the hard and the translucent portion of nails are composed of keratin and connective tissue makes up the nail plate. Given the anatomy of the nail, penetration of topical medication is low, limiting the use of these therapies. In fact, the concentration of topically applied medications can be reduced by 1,000 times from the outer to inner surface. For this reason, guidelines suggest that topical therapies be limited to very few subsets of patients. Specifically, topical antifungal use is limited to the following:

- SWO (except in transverse or striate infections);
- Early DLSO (except in the presence of longitudinal streaks) when <80% of the nail plate is affected and there is no involvement of the lunula;
- When systemic antifungals are contraindicated.[3]

Ciclopirox 8%

Ciclopirox is hydroxypyridone derivative with activity against *T. rubrum*, *S. brevicaulis* and Candida species. Through metal-dependent enzymatic processes, ciclopirox inhibits fungal nutrient uptake and interrupts intracellular energy production and toxic peroxide degradation. It is the only prescription agent in the US, approved as a component of a comprehensive management program for the treatment of immunocompetent patients with mild to moderate onychomycosis of fingernails and toenails (without lunula involvement), due to *T. rubrum*. It is important to note that the comprehensive management program also includes removal of the unattached, infected nails by a health care professional as frequently as monthly. Ciclopirox is applied to the nails daily for a duration of 24 weeks in fingernail infections and 48 weeks in toenail infections. Adverse effects include burning, itching, and stinging at the application site. When used alone, ciclopirox has a mycotic cure rate of 29% to 36%, and a clinical cure rate of 6% to 9%.[4]

Over-the-counter Topical Agents

Nonprescription topical agents have only been evaluated in a small number of studies including few patients and therefore are not recommended for the treatment of onychomycosis. However, these agents include topical mentholated ointment, tea tree oil, and *Ageratina pichinchensis* (snakeroot) extract.

Systemic Therapies:

The main systemic drugs approved and widely used for the treatment of onychomycosis are terbinafine and triazoles, such as itraconazole and fluconazole. Griseofulvin is also approved for the treatment of dermatophyte infections, including onychomycosis.[3]

Terbinafine

Terbinafine is an allylamine derivative that inhibits squalene epoxidase, a key enzyme in ergosterol synthesis. With a deficiency in ergosterol, the fungal cell membrane is disrupted, leading to fungal cell death. Terbinafine has broad activity against Trichophyton, but is less effective against Candida species as compared to triazole antifungals. Terbinafine is generally well tolerated with few adverse drug reactions or drug-drug interactions; however, it is contraindicated in patients with chronic or active hepatic disease. Labeled dosing of terbinafine involves 250 mg orally once daily for 6 weeks in fingernail infections and 12 weeks in toenail infections. However, this agent is sometimes used in a pulsed regimen using 250 mg twice daily for 1 week, followed by 3 weeks off. A recent systematic review and meta-analysis found that compared to placebo, continuous terbinafine significantly impacted mycological cures (OR 16.41, 95% CI 6.49-41.47). Researchers also found that continuous terbinafine was almost 2 times more likely to achieve mycological cure compared to pulse itraconazole (OR 1.95, 95% CI 1.04-3.65) or pulse terbinafine (1.80, 95% CI 1.13-2.87). Continuous terbinafine was also found to be statistically superior to topical regimens, though this difference was not seen with pulse regimens. A meta-analysis from 2004 evaluated oral therapies for the treatments of toenail onychomycosis and demonstrated a 76% mycotic cure and 66% clinical cure rate with terbinafine.[3,5,6,7]

Itraconazole and Fluconazole

Itraconazole and fluconazole are triazole antifungals that inhibit fungal cytochrome P450 synthesis of ergosterol, preventing formation of the fungal cell membrane. Itraconazole is a broad-spectrum agent with activity against Candida and other non-dermatophyte yeasts and molds, as well as against some dermatophytes. However, it is less effective against dermatophytes compared to terbinafine. Fluconazole also has some activity against dermatophytes and some Candida species, but it is not currently licensed for treatment of onychomycosis. Both agents have similar adverse reactions, including headache and gastrointestinal upset, as well as similar serious warnings, such as hepatotoxicity and arrhythmias. With their mechanism of action targeting the cytochrome P450 system, both agents are implicated in many drug-drug interactions. The labeled dosing regimen for itraconazole is 200 mg once daily for 12 consecutive weeks. Similarly to terbinafine, pulse dosing is sometimes utilized (though off-label in the US), most commonly with 200 mg twice daily for 1 week, followed by 3 weeks off. Fluconazole, which has a longer half-life than itraconazole, is typically given at a dose of 450mg weekly when used off-label for this indication. Lower doses have also been studied (150-450mg), but have shown less success compared to the 450 mg dosing strategy. In the 2019 meta-analysis, when compared to placebo, continuous itraconazole was found to be an effective regimen for achieving mycological cure (OR 18.61, 95% CI 7.40-46.81). Continuous itraconazole was found to be significantly greater compared to topical treatments, however fluconazole, and itraconazole pulse regimens were not significantly different from topical treatments. In the 2004 meta-analysis that evaluated oral therapies for the treatments of toenail onychomycosis, mycotic cure rates were 63% for itraconazole with pulse dosing, 59% for itraconazole with continuous dosing, and 48% for fluconazole. Clinical cure rates were 70% for itraconazole with pulse dosing, 70% for itraconazole with continuous dosing, and 41% for fluconazole.[3,6,7,8,9]

Griseofulvin

Griseofulvin inhibits fungal cell mitosis at metaphase and binds to human keratin making it resistant to fungal invasion. Griseofulvin is dosed at 500-1000 mg per day for varying durations depending on the site of infection. Duration of treatment with this agent is much longer than with terbinafine or the azole antifungals, however, sometimes necessitating more than 12 months of therapy. Adverse effects including nausea and rashes are frequent, occurring in up to 15% of patients. It is contraindicated in pregnancy and its use is not advised in men fathering a child within 6 months of therapy. Drug-drug interactions are frequent and disulfiram-like reactions can occur with concomitant use of alcohol. Studies that have compared griseofulvin to previously mentioned treatments including terbinafine and itraconazole have shown lower cure rates at only 30-40%. For these reasons, it is not recommended as a first-line treatment regimen for onychomycosis.[3,10]

Conclusion

Due to the nail's structural nature onychomycosis is a difficult infection to treat with varying rates of success among various different treatment strategies. Despite treatment with lengthy regimens, onychomycosis is associated with subpar cure rates and high rates of recurrence.

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