Fungal skin infections: current approaches to management

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The dermatophyte skin infections tinea capitis, tinea pedis and onychomycosis are common and challenging to treat. This review focuses on key points and recent guidelines on the diagnosis and management of fungal skin infections.

Superficial fungal infections (SFI) are common diseases worldwide with a wide array of systemic and topical treatment options. They can affect a variety of body locations and are named accordingly. It is estimated that 20–25 per cent of the world population may suffer with fungal infections.[1]

Fungal infections may encompass dermatophyte, non-dermatophyte and candidal infections. This article will focus on dermatophyte infections causing tinea capitis, tinea pedis and tinea unguium (also known as onychomycosis), which are common and challenging to treat.

The warm, humid condition of human skin allows dermatophytes to thrive, as surface temperatures of 25–28°C are ideal for growth. Tropical climates, and occlusive clothing, overcrowding, increased urbanisation, community showers, and participation in sports are other contributing factors. Risk factors include bodily spread of dermatophyte and non-dermatophyte tinea pedis, close quarter living environments, peripheral vascular disease, damaged nails via sports and trauma, older age, genetics, immunodeficiency and diabetes.[2] Superficial fungal infections tend not to be self-limiting, thus contributing to further spread in the absence of treatment.

The organisms causing superficial dermatophyte infections can be characterised according to their ecological niche and their asexual genera. The three genera include *Microsporum*, *Trichophyton* and *Epidermophyton*. Geophilic, zoophilic and anthropophilic describe their ecological origins, namely the soil, animals and humans accordingly, although these groups are not always sharply demarcated. Disease severity correlates the ecological niche of the infecting dermatophyte. Anthropophiles (*eg Trichophyton rubrum*) present as a chronic disease with mild inflammation. Geophilic or zoophilic organisms present as a severe disease with acute inflammation and can be self-limiting.

Dermatophytes are flourishing with increased tourism, migration and international sports, which are facilitating dissemination of less common or well-recognised species. Rarely, dermatophytes can cause invasive or disseminated infection,

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Figure 1. Tinea capitis requires systemic antifungal treatment

and cases in immunocompromised patients have been reported.[3] This article will review some of the key points and recent developments in the diagnosis and treatment of these infections.

Clinical features and mycology

To ensure appropriate treatment of a dermatophyte infection, mycology samples should be taken prior to and after completion of treatment to ensure resolution of the infection.

Tinea capitis (see Figure 1)
Tinea capitis refers to a dermatophyte infection of the scalp usually involving the scalp hair and occurs predominantly in children. Atypical presentations may be seen in the immunocompromised. In the UK *Trichophyton tonsurans* is thought to be responsible for 50–90 per cent of cases. Unlike most superficial skin infections, tinea capitis does not resolve with topical treatments and requires systemic antifungal therapy. Success of treatment is also species dependent, thus reinforcing the importance of species identification.

Clinical signs are variable and can range from mild scaling to a kerion. There is often associated occipital lymphadenopathy, and pustular lesions and alopecia can also fall within the spectrum of infection (see Table 1). Multiple methods of skin sampling such as skin scraping and scalp brushing are best undertaken to avoid false negatives and increase sensitivity.[4]

Due to the transmissional nature of this condition it is wise to test siblings, who may not have as florid a presentation.

Tinea pedis (see Figure 2)
Tinea pedis affects the soles of the feet and the interdigital spaces. It may be confused with plantar eczema or psoriasis, although unilateral involvement is more suggestive of infection. Risk factors include occlusive footwear and increasing age.

There are four main recognised patterns of presentation. These include interdigital, moccasin or dry type pattern of infection, vesicular or inflammatory, and ulcerative.

Interdigital is the most common type and presents with maceration, typically of the last two lateral spaces, but may comprise of erythema, scaling and fissuring. Moccasin type presents with hyperkeratosis of the plantar and lateral aspects of the foot. Vesicular or inflammatory is less frequent and presents with vesicles or bullae on the medial foot. This needs to be differentiated from pompholyx. The Cochrane review[5] found the most prevalent infecting dermatophyte in tinea pedis to be *T. rubrum*. *Trichophyton interdigitale* (mentagrophytes) and *Epidermophyton floccosum* were also reported.

Examination of the remainder of the skin will help to differentiate whether this is part of an inflammatory dermatosis such as psoriasis or eczema. Other areas, however, may reveal concomitant fungal infections and these should be routinely screened for.

Onychomycosis (see Figure 3)
Onychomycosis is an infection of the nail apparatus. The toenails are more commonly affected than the fingernails and the most common dermatophyte infection is reported as *T. rubrum*.[6] It is commonly associated with tinea pedis.

Dermatophytic onychomycosis may be categorised into several distinct forms: distal-lateral subungal, proximal subungal, superficial white, endonyx, total dystrophic and mixed-type onychomycosis.[7] Distal-lateral subungal is the most common and presents with onycholysis and subungal hyperkeratosis.[3] Other types are presented in Table 2.

Onychomycosis is relentlessly progressive and, untreated, can give rise to cellulitis. The sharp shards of the dystrophic

Occipital lymphadenopathy
Pustular lesions
Kerion
Diffuse scale
Grey patches with alopecia

Table 1. Clinical features of tinea capitis

Figure 2. Topical azoles are recommended in tinea pedis; allylamines are more effective but also more expensive

Figure 3. Nail clippings, including subungal debris, should be taken in onychomycosis

nail may pierce the skin on neighbouring toes leading to potential entry sites for infection. This is of special clinical significance in patients with diabetes or peripheral vascular disease and may result in multiple medical consultations and absence from work.[8]

A recent new dermatophyte reportedly causing onychomycosis is *Chaetomium globosum*.[9] This was in an immune-competent patient who developed striking brown discolouration after a traumatic haematoma to the nail. The infection was cured with a three-month course of terbinafine. This is an uncommon dermatophyte that should be considered in the correct clinical setting and highlights the need for culturing suspected onychomycosis to establish the organism and thus direct treatment more effectively.

Diagnosis of a fungal infection
History
A thorough history is of vital importance with attention to location affected, duration of symptoms, previous treatments and possible contacts.

Current techniques of identification of dermatophytes are slow and time consuming. Direct microscopy can be performed immediately and is able to report the absence or presence of fungal elements, namely yeast or hyphae. This can be performed by the clinician with 10 per cent potassium hydroxide (KOH) or at the laboratory within 24 hours. Although this can confirm the diagnosis, culture is still required to identify the precise organism.

Samples are then cultured on agar for identification, which usually takes at least two weeks, although a negative culture requires incubation for six weeks for confirmation. These techniques are known to have a low sensitivity so it is not uncommon to need to take second samples, especially in onychomycosis.

Diagnostic tools
A Wood's lamp is still a useful tool in helping to diagnose fungal infections. Bright green fluorescence is typically seen in

Microsporum species (*M. canis*, *M. distortum*, *M. ferrugineum*, *M. gypseum*). Similarly *Trichophyton schoenleinii* fluoresces a faint blue colour. *Trichophyton tonsurans* and *Trichophyton verrucosum* do not fluoresce at all.

Methods of collection (see Table 3)
Scrapings This is the traditional method used for sampling affected skin or scalp. It involves using a blunt instrument, such as a surgical U or banana blade or the back of a scalpel blade, to scrape the active edge of the suspected infection for scales. This is then transported in dark paper to the laboratory for mycological microscopy and culture.

Brushings Scalp brushings, using a "travelling toothbrush", are an alternative way of collecting samples for suspected tinea capitis.[10] It appears to have equal efficacy in diagnosis but is more expedient.

Cytobrushing has been proven to be a better technique. It involves using a sterile commercial brush, routinely used for cervicovaginal smears, to sample the affected skin of the scalp. Cytobrushing demonstrated increased sensitivity and expediency compared to traditional methods with a statistically significant positive rate of 97 per cent on the first isolate versus 85 per cent with skin scrapings. Addition benefits include that the cytobrush is available in a sterile state and is comprised of soft bristles, making it a gentle method of collection.[11]

Swabs Dampened swabs may be used for fungal culture.[12] Bacterial swabs may be utilised in suspected secondary infection, particularly in the context of kerions, pustules and maceration.[13]

Type	Clinical features	Most frequently found dermatophyte
Distal lateral subungal (DLSO)	Onycholysis Subungal hyperkeratosis	*T. rubrum*
Superficial white (SWO)	White chalky patches on the surface of the nail	*T. mentagrophytes*
Proximal subungal (PSO)	Leukonychia Onycholysis Starts at the proximal nail fold	*T. rubrum*
Endonyx (EO, rare)	Invasion via skin with direct invasion of the nail plate	*T. soudanense* or *T. violaceum*
Mixed types (MO)	DLSO + SWO DLSO + PSO	as above
Total dystrophic (TDO)	End result of all types of onychomycosis	as above

Table 2. Features of different types of onychomycosis

Site	Method of collection	Diagnostic tools
Tinea capitis	Scrapings Brushing (cytobrush or travelling toothbrush)	Microscopy Culture PCR
Tinea pedis	Swabs Scrapings	Microscopy Culture PCR
Onychomycosis	Nail clippings (including subungal debris)	Microscopy Culture PCR
PCR = polymerase chain reaction; not routinely available yet		

Table 3. Methods for collecting samples

Nail clipping Nail clippings must include subungal debris in the sample, as the yield is often unpredictable. More than one sample may be needed.

Current treatments
Systemic agents
Systemic treatments for superficial dermatophyte infections include griseofulvin and the newer systemic agents including azoles (itraconazole and fluconazole) and the allylamine terbinafine.

Terbinafine has a good safety profile. It is fungicidal compared to the azoles, which are fungistatic. Azoles are metabolised by the cytochrome P450, which can also result in drug interactions.

Studies have shown terbinafine to be more effective in treating dermatophytes than itraconazole; however, itraconazole has broader antimicrobial cover for non-dermatophyte moulds and *Candida* species.

The systemic agents are generally well tolerated and safe. The most commonly reported side-effects are gastrointestinal, such as diarrhoea and nausea, followed by headaches and skin complaints.[13]

Second-generation triazoles still in phase 2 and 3 trials include isavuconazole, ravuconazole, pramiconazole and albaconazole.

Tinea capitis
Griseofulvin is the only antifungal licensed for the treatment of tinea capitis in children. It is now difficult to obtain and expensive in the micronised formulation required for paediatric use. However, although unlicensed, terbinafine is widely used in the UK, supported by the British Association of Dermatologists (BAD) guidelines, and paediatric doses are quoted in the *BNF*.

Terbinafine (3.125–6.25mg per kg per day) has been shown to be more effective in the treatment of *Trichophyton* species, while griseofulvin (6.25–12.5mg per kg per day) is more effective in *Microsporum* species.[14] This was comparing

four and eight weeks' treatment respectively. Terbinafine is becoming more acceptable as it is effective and well tolerated.

Although itraconazole in not licensed for use in children in the UK, it is the preferred agent in Europe as it has activity against both *Microsporum* and *Trichophyton* species. It is well tolerated at doses of 50–100mg per day for four weeks or 5mg per kg per day for two to four weeks, is available as a liquid formulation and has been shown to be safe in the first year of life.[15]

Fluconazole is also used in the treatment of tinea capitis, although availability, side-effects and cost limit its use.

Tinea pedis
Topical treatment for tinea pedis is generally adequate with either allylamines or azoles, both being superior to placebo. In head-to-head studies, allylamines have been found to be more effective than azoles, particularly with increasing duration. Due to cost, however, topical azoles are recommended first line with allylamines being used for treatment failures.[16] For extensive infection, especially in immunosuppressed patients, oral therapy may be required. Severe maceration suggesting secondary infection may require concurrent antibiotic therapy.

In the systemic treatment of tinea pedis, the Cochrane review[16] found oral terbinafine to be more effective than griseofulvin and itraconazole when given for a two-week period. However, reporting of trials showed lack of blinding of outcome assessors and potential bias.

Onychomycosis
In the treatment of onychomycosis, management may include systemic or topical antifungal agents and chemical or mechanical debridement, alone and in combination.[17]

Topical antifungals are not considered to be effective monotherapy in treating onychomycosis. Agents include amorolfine and tioconazole (Trosyl).

They are available in a solution or lacquer and can be painted directly onto the nail. They exhibit either antifungal or antimicrobial properties but tend to be ineffective with reported clinical cure rates ranging from 9 to 52 per cent.[5]

A recent meta-analysis of published studies of toenail onychomycosis found that in the majority of the studies, terbinafine treatment showed a higher cure ratio than the other drugs for dermatophyte onychomycosis.[18] Continuous oral terbinafine has been found to be more effective in the treatment of onychomycosis than pulsed or continuous itraconazole, griseofulvin or fluconazole with mycological cure rates of 70–76 per cent.[4] The acceptable dosage is currently 250mg daily for three to four months. At the end of this duration of therapy there may still be distal evidence of onychomycosis but the actively growing new nail will be unaffected and contain terbinafine, preventing the dermatophyte from invading the new nail growth.

Alternative treatments
Photodynamic therapy has been reported as being effective in several cases[5] and this may be a suitable alternative for

patients who are unable to tolerate systemic antifungals. However, further studies are needed.

The future of SFI diagnosis and treatment

Accurate and rapid diagnosis is essential for successful treatment of SFI. The future direction for laboratory diagnosis will likely be a molecular one.[3] Fifty percent of patients are presumed misdiagnosed by clinical diagnosis. Direct microscopic analysis lacks specificity and the time needed to grow a fungal culture is four to six weeks. Therefore in recent years, in house real time polymerase chain reaction (PCR) tests and PCR reverse-line blot assays have been developed as time-saving diagnostic techniques to identify dermatophytes directly from clinical specimens and they have performed well.[19] However, large scale comparative studies are needed to determine whether DNA detection of dermatophytes will improve the diagnosis of SFI.

Also in future, studies on epidemiology of SFI across Europe and the rest of world may change current recommendations. Emerging new treatments for onychomycosis include: efinaconazole 10 per cent nail solution and tavaborole topical solution 5 per cent.

Efinaconazole is a new triazole recently approved in the USA used for the treatment of distal and lateral subungual onychomycosis (DLSO) by inhibiting fungal lanosterol 14alpha-demethylase in the ergosterol biosynthesis pathway.[20] It has potent antifungal activity against dermatophytes, as well as activity against *Candida* species and non-dermatophyte moulds, and demonstrated promising results in clinical trials.

Tavaborole is a new boron-based antifungal agent that has also been approved by the US Food and Drug Administration (FDA) for the treatment of toenail onychomycosis.[21] Results from two randomised phase 3 studies demonstrate that once-daily tavaborole, without adjunctive debridement, effectively penetrated the nail plate and is safe, and well tolerated.

Other new treatment options include laser therapies, iontophoresis and ultrasound,[23] which would have the benefit of no systemic side-effects or problems of patient adherence. More studies are needed to determine their efficacy.[23]

Conclusion

Dermatophyte infections are a common problem worldwide. Identification of the infective organism is imperative prior to initiation of antifungals to tailor the correct treatment to the patient.

Likewise, review after completion of treatment is of value to ensure both clinical and mycological cure and prevention of relapse. Treatment is important to prevent continued spread of dermatophytes in untreated patients and to limit morbidity in affected patients.

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Declaration of interests

None to declare.

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