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Conflict of interest

None.

Mycology – an update. Part 1: Dermatomycoses: Causative agents, epidemiology and pathogenesis

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Summary

Dermatomycoses are caused most commonly by dermatophytes. The anthropophilic dermatophyte *Trichophyton rubrum* is still the most frequent causative agent worldwide. Keratinolytic enzymes, e.g. hydrolases and keratinases, are important virulence factors of *T. rubrum*. Recently, the cysteine dioxygenase was found as new virulence factor. Predisposing host factors play a similarly important role for the development of dermatophytosis of the skin and nails. Chronic venous insufficiency, diabetes mellitus, disorders of cellular immunity, and genetic predisposition should be considered as risk factors for onychomycosis. A new alarming trend is the increasing number of cases of onychomycosis – mostly due to *T. rubrum* – in infancy.

In Germany, tinea capitis is mostly caused by zoophilic dermatophytes, in particular *Microsporum canis*. New zoophilic fungi, primarily *Trichophyton* species of *Arthroderma benhamiae*, should be taken into differential diagnostic considerations of tinea capitis, tinea faciei, and tinea corporis. Source of infection are small household pets, particularly rodents, like guinea pigs. Anthropophilic dermatophytes may be introduced by families which immigrate from Africa or Asia to Europe. The anthropophilic dermatophytes *T. violaceum*, *T. tonsurans* (infections occurring in fighting sports clubs as “tinea gladiatorum capitis et corporis”) and *M. audouinii* are causing outbreaks of small epidemics of tinea corporis and tinea capitis in kindergartens and schools.

Superficial infections of the skin and mucous membranes due to yeasts are caused by *Candida* species. Also common are infections due to the lipophilic yeast fungus *Malassezia*. Today, within the genus *Malassezia* more than 10 different species are known. *Malassezia globosa* seems to play the crucial role in pityriasis versicolor.

Molds (also designated non-dermatophyte molds, NDM) are increasingly found as causative agents in onychomycosis. Besides *Scopulariopsis brevicaulis*, several species of *Fusarium* and *Aspergillus* are found.

Introduction

Dermatomycoses may be divided according to the responsible pathogen into dermatophyte, yeast, and mold infections. Fungi on the skin, or dermatophytes,

Trichophyton rubrum is the most common dermatophyte in Germany and worldwide. The prevalence of fungal nail infections in certain risk groups, e.g., diabetics and psoriasis patients, is higher than in the general population.

Yeasts – primarily *Candida albicans* – cause candidiasis affecting the skin and mucous membranes. *Malassezia*-related superficial skin infections, primarily pityriasis versicolor, are very common.

Non-dermatophyte molds (NDM) are increasingly found to be the cause of onychomycosis of the toenails.

The most common pathogens identified in children and adolescents are zoophilic dermatophytes.

are the cause of dermatophytosis, also referred to as tinea (ringworm). The most common dermatophyte in Germany, and probably the world, is *Trichophyton rubrum*. Fungal nail infections, or onychomycosis, are very common disorders in industrialized nations [1]. The prevalence of fungal nail infections among certain risk groups, e.g., diabetics, is higher than in the general population; it is also higher in patients with disorders of keratinization affecting the skin and nails, e.g., psoriasis patients. The clinical diagnosis is often difficult, given that nail disorders due to other causes must be ruled out. A new epidemiological development is the increase in onychomycoses, usually due to *T. rubrum*, in children [2].

Yeasts – primarily *Candida albicans* – cause candidiasis of the skin and mucous membranes, also known as thrush. Although the term “thrush” (sponge) is still frequently used, it is considered obsolete. *Malassezia*-related superficial skin infections, primarily pityriasis versicolor, are very common; *Malassezia* folliculitis is less so. The lipophilic yeasts belonging to the *Malassezia* species are also associated with seborrheic and atopic eczema. Molds rarely cause cutaneous infections. Occasionally, secondary (hematogenic) skin infections can occur in immunosuppressed patients, e.g., with leukemia and after stem cell transplantation; primary skin infections due to molds are even rarer (e.g., due to *Aspergillus fumigatus*). Yet, non-dermatophyte molds (NDM) are considered *emerging pathogens* in onychomycosis of the toenails.

The most common pathogens among children and adolescents are zoophilic dermatophytes. The sources of infection are house pets and, less often farm animals. In Germany – probably due to immigration and greater urban densities compared to Austria – anthropophilic dermatophytes are becoming more common. Anthropophilic dermatophytes which are isolated in pediatric patients include *T. tonsurans* (associated with wrestling mats) and – becoming more common in kindergartens and schools – *Microsporum audouinii*. The latter fungus is from Africa and is transmitted, directly or indirectly, by immigrating families. A problem is chronic hyperkeratotic infections, which often involve pus and abscesses formation, on the scalp (e.g., tinea capitis profunda). These may be caused by well-known (*M. canis*) and “new” (*T. species von Arthroderma benhamiae*) zoophilic pathogens. Only rapid mycological diagnosis, also with molecular biological techniques for dermatophyte DNA detection, and immediate systemic antifungal treatment can prevent scarring of the scalp or pseudopelade of Brocq.

Trichophyton rubrum – the most common dermatophyte

T. rubrum continues to be the most common dermatophyte in the world with the highest incidence in Europe (Figure 1). *Trichophyton* is derived from the Greek words “θρίχός” “hair” and “φυτόν” “plant”; “*rubrum*” (Latin for red) refers to the red-brown pigmentation found in the fungal culture on the underside of the colony of the white thallus. Yet unlike most other dermatophytes, *T. rubrum* (“red hairy plant”), only rarely affects the hair and hair roots. Its target structures are the stratum corneum of the epidermis and the nail keratin. The percentage of the anthropophilic fungus *T. rubrum* among the dermatophytes causing tinea unguium is 91% in Germany [3]. *T. rubrum* and *T. interdigitale* (previously known as *T. mentagrophytes*) are also responsible for about 90% of all cases of dermatophytosis in Poland. The same figures have been reported in Great Britain

The target structures for *Trichophyton rubrum* are the stratum corneum of the epidermis and the nail keratin.



Figure 1 *Trichophyton rubrum*: Typical white thallus on Sabouraud's dextrose agar. The isolate originated from woman with tinea unguium.

The percentage of the anthropophilic fungus *T. rubrum* among the dermatophytes causing tinea unguium is more than 90%.

T. rubrum infections are increasingly occurring at other sites on the body than previously reported.

Tinea pedis and onychomycosis are caused by the anthropophilic dermatophytes *T. rubrum*, *T. interdigitale* and *Epidermophyton floccosum*.

and Sweden [4]. In Poland, the most common forms of fungal skin infections, irrespective of causative dermatophytes, are tinea unguium pedum (42.2%) and tinea pedis (41.4%); tinea corporis (5,6%), tinea manuum (4.1%), tinea unguium manuum (3.0%), tinea capitis (2.4%), and tinea cruris (1.3%) are much less common [5].

Along with tinea pedis and tinea unguium, *T. rubrum* infections are increasingly occurring at other sites on the body than previously reported [6]. An example is tinea faciei due to *T. rubrum* after autoinoculation with tinea pedis et unguium of the lower extremities [7]. Tinea capitis due to *T. rubrum* is unusual.

Dermatophyte transmission in the home

The pathogen reservoir for tinea pedis and onychomycosis are anthropophilic dermatophytes, i.e., *T. rubrum* and *T. interdigitale* (only anthropophilic strains) and *Epidermophyton floccosum* (Table 1). The most common source of infection is the bath; and transmission among family members is the most common route. Spread may be horizontal, e.g., between spouses, or vertical between the generations. The latter, for instance, between a father or grandfather and (grand-) child, is much more common than horizontal spread. Other sources of infection are showers in fitness studios, changing rooms at public pools, mats in sports facilities (wrestling or martial arts facilities, tropical baths, and hotels and mosques) [1].

Molecular epidemiology and transmission of *Trichophyton rubrum* in the home

The results of a recent study done in the United States confirmed the transmission of dermatophytes within homes in which individual family members had tinea

Table 1 Anthropophilic dermatophytes. The list is based on the current Centraalbureau Voor Schimmelcultures (Utrecht, The Netherlands) suggested and established taxonomy and nomenclature of fungi [8]. Species and subspecies or varieties that are no longer considered distinct have been omitted.

<i>Epidermophyton floccosum</i>	Increasingly rare in Germany, infections of feet, toenails, and groin
<i>Microsporum audouinii</i>	Mainly in Sub-Saharan African
<i>Microsporum ferrugineum</i>	Mainly found in Asia, rarely in Africa or Eastern Europe
<i>Trichophyton concentricum</i>	Limited to Southeast Asia, cause of tinea imbricata (“Tokelau”) as cockade-like fungal infection
<i>Trichophyton interdigitale</i> (anthropophilic strains)	Second most common dermatophyte in Germany
<i>Trichophyton megninii</i>	Very rare in Germany; tinea pedis, tinea manuum, tinea unguium, tinea barbae
<i>Trichophyton rubrum</i>	Most common dermatophyte in the world, tinea unguium, tinea pedis et corporis, rarely invades hair and hair roots
<i>Trichophyton rubrum</i> var. <i>raubischekii</i>	Variant of <i>T. rubrum</i> , found nearly only in Africa; recent isolated reports in Germany, Turkey, Spain, and Asia (Japan)
<i>Trichophyton schoenleinii</i>	Favus pathogen, rare in Europe
<i>Trichophyton tonsurans</i>	Tinea capitis pathogen in America; in Germany tinea gladiatorum occurs in martial arts participants
<i>Trichophyton violaceum</i>	Most important dermatophyte in Africa
<i>Trichophyton soudanense</i>	Found in Africa; genotypically, but not phenotypically, identical to <i>T. violaceum</i>
<i>Trichophyton vanbreuseghemii</i>	Very rarely isolated from humans (skin) or soil

pedis or onychomycosis. The dermatophytes were detected using molecular biological methods with polymerase chain reaction (PCR). The primer used was the *internal transcribed spacer* (ITS) region (ITS1 und ITS4). For stem cell differentiation, a ribosomal-DNA-specific probe (containing ITS1, 5.8S ribosomal DNA and ITS2) was used to detect restriction fragment length polymorphism (RFLP). In 50 households, 18 family members had multiple infections [9]. *T. rubrum* was the most common dermatophyte, followed by *T. mentagrophytes* (*T. interdigitale*) and *Epidermophyton floccosum*. Sixteen *T. rubrum* strains were found in 8 households with multiple infections. Certain *T. rubrum* strains had a significantly higher tendency toward spreading; there was also an association with a history of tinea pedis and onychomycosis, with plantar scaling, and nail plate discoloration.

Pathogenesis of dermatophytosis

As a rule, a healthy nail is not susceptible to fungal infection.

Predisposing factors for tinea pedis et unguium include circulatory disorders affecting the lower extremities as well as metabolic disorders such as diabetes mellitus.

In treatment-refractory onychomycosis, keratinization disorders affecting the skin and nails are more common than previously thought.

Predisposing host factors for dermatophyte infections

Predisposing host factors allow tinea pedis and onychomycosis to occur. As a rule, a healthy nail is not susceptible to fungal infection. Among predisposing factors for tinea pedis et unguium are circulatory disorders affecting the lower extremities as well as metabolic disorders such as diabetes mellitus (Table 2).

Psoriasis vulgaris and onychomycosis

In treatment-refractory onychomycosis, keratinization disorders affecting the skin and nails are more common than previously thought. Most patients have undetected

Table 2 Predisposition factors for athlete's foot and onychomycosis.

- ▶ Circulatory disorders (chronic venous insufficiency, peripheral arterial circulatory disorder)
- ▶ Lymphedema in the lower extremities
- ▶ Malalignment of the feet including hallux valgus, hammer toe
- ▶ Toenail deformities/onychodystrophy
- ▶ Psoriasis vulgaris and psoriasis unguium
- ▶ Ichthyosis vulgaris
- ▶ Diabetes mellitus
- ▶ Nail and nail bed microtrauma due to sporting activities (track and field, jogging, marathon running, soccer)
- ▶ Strong perspiration/hyperhidrosis pedum
- ▶ Immunosuppression (HIV/AIDS)
- ▶ Patients with trisomy 21

27% of psoriasis patients who have nail changes have onychomycosis involving the toenails.

psoriasis vulgaris and psoriasis unguium; atopic eczema and ichthyosis vulgaris are also related to more pronounced keratinization, which is a predisposing factor in dermatophyte infections. Twenty-seven percent of patients with psoriasis who have nail changes have onychomycosis involving the toenails [10]. The findings of in vitro studies show that scale taken from patients with psoriasis can promote the growth of dermatophytes, yeasts, and molds [11].

In patients with psoriasis vulgaris, there is a significantly higher rate of *Candida* colonization of the toenails [12]. Kaçar and colleagues [13] studied patients with onychomycosis, 168 of whom had concomitant psoriasis and 164 who did not. Using fungal tests, onychomycosis was diagnosed in 22 patients with psoriasis (13.1%) and in 13 controls (7.9%). In the psoriasis group, primarily dermatophytes were found to be the pathogens in onychomycosis; in the control group, it was mainly molds. Dermatophytes were isolated significantly more often in psoriasis patients than in the control group.

In one study with patients in Bulgaria and Greece on the prevalence of fungal nail infections in psoriasis vulgaris, out of 228 patients with nail changes and psoriasis vulgaris, 62% had a positive fungal culture [14]. In 67% of these patients, a dermatophyte was isolated; in 24% a yeast was found; and in 6%, a mold was identified. The incidence of onychomycosis in psoriatic patients was higher.

Ichthyosis as a predisposing disease for dermatophytosis due to *Trichophyton rubrum*

A 10-month old child with congenital lamellar ichthyosis had a treatment-refractory *T. rubrum* infection. Tests revealed a high total IgE and specific IgE to *T. rubrum* [15]. Ichthyosis, a keratinization disorder affecting the epidermis is a risk factor for chronic dermatophytosis; both the excessive amounts of keratin as well as the barrier defect are predisposing factors. A type IV immune response (delayed type of hypersensitivity) to *T. rubrum* promotes healing of tinea. Immediate hypersensitivity and IgE do not protect against tinea; chronic infection may be expected.

Cellular immunity as a predisposing factor for dermatophytosis

The host-specific side of dermatophyte infections, that is, the cellular immune response, has been studied in patients with severe dermatophytosis due to *T. rubrum* [16].

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