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Management of Onychomycoses

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Abstract

Onychomycoses, infections of the nail caused by fungi, are amongst the most common illnesses. Because of the high incidence of these infections and problems involved in their therapy, they have received much attention, particularly as concerns a better characterisation of the causative micro-organisms. Onychomycosis caused by dermatophytes (tinea unguium) is most common and is found more frequently on the feet than on the hands. The clinical presentation of onychomycosis is at best indicative of fungal infection, and the growth of a credible pathogen is an indispensable prerequisite for definite diagnosis. The clinical appearance is variable. Four major types of manifestation have been characterised, depending on localisation and spread.

New antifungal agents for systemic or topical application based on novel active substances or vehicles are available, and cure is feasible for the majority of cases. Therapy can and should be individualised, depending on the characteristics of the particular case.

Currently, continuous or intermittent oral treatment with itraconazole or terbinafine exhibit a particularly favourable risk : benefit ratio. Fluconazole might become an alternative in the near future. With respect to topical treatment, ciclopirox or amorolfine lacquer and the bifonazole/urea combination deserve particular interest. However, cure cannot be expected for every case.

1. Definition and Epidemiology

Onychomycosis is defined as an infection of the nail with fungi, whether dermatophytes, yeasts or moulds.

It seems that the frequency of infections of the nail due to fungi has increased in recent decades. Although there are no comparative world-wide statistics on infections, there is an increasing number of studies examining the frequency and causative organisms of onychomycoses from particular countries and groups of patients. In Europe, there seems to be an average prevalence of about 2 to 5%,[1,2] with the prevalence particularly increasing in older people. Important factors that influence the epidemiology comprise climatic conditions, geographical location, degree of urbanisation and social standards, in particular conditions of work and current footwear habits (onychomycosis of the feet is by and large restricted to populations wearing shoes).[3]

Moreover, there are some individual risk factors promoting the manifestation of onychomycosis. These include mechanical alteration, for example onycholysis or onychodystrophy, respectively, caused by frequent recurrent trauma in athletes or a single injury of the nail organ resulting in lifelong damage.[4] Even the application of cosmetic acrylic nail extensions can affect *Candida* nail bed infections and thus promote onychomycosis.[5]

2. Quality of Life

Onychomycosis is not merely an aesthetic problem, although this aspect must not be underemphasised. For many patients it is a major problem that interferes with their lifestyle. It has been proven repeatedly that this infection leads to psychological stress as well as to physical pain.[6-9] Affected patients experience a decrease of self-confidence, reduction of leisure activities and, particularly, a limitation of sports activities. Onychomycosis consequently compromises quality of life to a remarkable extent.

3. Clinical Types of Onychomycosis

The clinical spectrum of onychomycosis is generally represented by 4 different types of manifestation. According to localisation and spread, the classification differentiates between:[10]

- distal subungual onychomycosis
- white superficial onychomycosis
- proximal subungual onychomycosis
- onychomycosis associated with chronic mucocutaneous candidiasis.

These clinical types can involve either toenails and/or fingernails. Recently, a new classification of onychomycosis has been published, differentiating between distal and lateral subungual onychomycosis, superficial onychomycosis, proximal subungual onychomycosis, endonyx onychomycosis and total dystrophic onychomycosis.[11]

4. Aetiology and Pathogenesis

Fungal infections of the nail involve toenails more often than fingernails, in a ratio of about 5 : 1. With toenail onychomycosis, tinea pedis, especially of the intertriginous type, is responsible in most instances for the infection of the nail organ.[12]

Onychomycoses can be caused by dermatophytes, yeasts or moulds. However, dermatophytes are responsible for about 90 to 95% of infections. Among the dermatophytes, *Trichophyton rubrum* plays a major role as a pathogen.[13] In addition, *Trichophyton mentagrophytes* and *Epidermophyton floccosum* are regularly found as causative micro-organisms. Among the yeasts, *Candida albicans* plays the major, if not exclusive, role as a causative organism. Yeast infections of the nail organ are frequently associated with chronic paronychia or chronic mucocutaneous candidiasis, but yeast infection of the nail organ and chronic paronychia must clearly be differentiated. It is a matter of debate whether *C. albicans* is a primary pathogen of nails or whether it can only directly invade nail tissue that is already abnormal.[14] Nevertheless, onychomycoses due to *C. albicans* can show the same clinical picture as dermatophyte

onychomycoses. Among the moulds, *Scopulariopsis brevicaulis* is currently considered to be the major pathogen. In some countries, infections due to *Fusarium* and *Scytalidium* spp. are also not infrequent.[15-17] In overtly dystrophic nails, the relative proportion of mould infections is clearly increased.[18]

This distribution pattern applies to countries in climatically temperate zones. Under other conditions, other distributions of the frequency of pathogens can be found. In tropical zones, for example, there is a higher proportion of yeast infections.

In children, onychomycosis is seen at a lower frequency than in adults. The prevalence according to most studies world-wide is between 0% and 6%. The majority of these infections are due to *T. rubrum*.[19,20] The lower frequency may be explained by the faster growth of nails, a smaller surface to attack and structural differences.

In immunosuppressed patients, particularly those with AIDS, onychomycosis is not an overwhelming problem. Although the prevalence in this group of patients seems to be slightly higher, severe manifestations of the disease, as seen for example with oral candidiasis, are uncommon.[21] There are indications, however, of a shift of frequency of the clinical types towards proximal subungual onychomycosis.[22]

5. Diagnosis

In patients with nail disease indicative of onychomycosis, diagnostic proof of infection and identification of the pathogen is required before therapy starts. The first step in diagnosis is normally microscopic examination of native material. The infected part of the nail must first be cleansed with a disinfectant such as 70% isopropanol to remove contaminants such as bacteria.[23] The outermost parts of the nail-plate to be examined should be removed as far as possible, and specimens should be taken from deeper layers. For this purpose, high speed abrasion using a special type of frais has proven particularly beneficial.[24] The material should be soaked in 15 to 20% potassium hydroxide solution and be examined by microscopy after incubation for 1 hour in a wet chamber. In a positive case, mycelial material can be seen. Efforts can be made to differentiate between dermatophytes, yeast and moulds; however, this will not generally be rewarding.[25] Potassium hydroxide preparations can be false-negative. If potassium hydroxide preparations are repeatedly negative but onychomycosis is still considered, a nail biopsy can be done. This approach is more sensitive but also more invasive, and for that reason it does not belong in the standard diagnostic procedures.[26,27]

In addition to the native preparation, a proof of fungal nail disease by culture should be performed in every case. For this culture, media such as Kimmig's agar or Sabouraud glucose agar can be used. For each specimen at least 2 cultures should be performed: one without any additive and the other with cycloheximide and/or chloramphenicol to prevent overgrowth by airborne bacteria or moulds present in the environment. The culture is time-consuming, taking at least 2 weeks and up to 4 weeks. A clear differentiation of the pathogen at the species level can be made by growth form, surface and colour, and the microscopic appearance of macro- and microconidia, as well as further parameters based on subcultures.[28] As yet, molecular approaches to diagnostics have not reached clinical practice.[29]

6. Treatment

6.1 Nail Removal

Previously, nail removal by extraction was employed not infrequently. Because of the high efficacy of the newer antifungal agents, surgical treatment by and large belongs to history. Surgery causes temporary disablement for work, intra- and postoperative complications, and in particular traumatisation of the nail matrix with possible permanent deformation. Therefore, its use must be approached very critically. A more recent alternative is represented by atraumatic chemomechanical maceration of the diseased nail with urea ointment under occlusion, an option systematically developed in the context of the characterisation of

Table I. Chemistry and route of administration of the most important antimycotics

Drug	Structural class	Administration
Amorolfine	Morpholine	Topical
Bifonazole	Imidazole	Topical
Ciclopirox	Hydroxypyridone	Topical
Clotrimazole	Imidazole	Topical
Econazole	Imidazole	Topical
Fluconazole	Triazole	Oral/intravenous
Griseofulvin	Dimethoxycoumarin derivative	Oral
Itraconazole	Triazole	Oral
Ketoconazole	Imidazole	Oral/topical
Terbinafine	Allylamine	Oral/topical
Tioconazole	Imidazole	Topical

bifonazole/urea ointment which is commercially available in several countries.[30-33]

6.2 Drug Treatment

6.2.1 General Considerations

For drug treatment of onychomycoses, the topical and systemic routes of application of antifungal agents are considered relevant (table I). Topical therapy might seem to be the treatment of choice, since it does not lead to systemic adverse effects or to any interactions with other systemic drugs taken by the patient. Unfortunately, at present topical treatment alone does not provide cure for more than a significant subgroup of patients.

The reasons for the failure of topical treatment may be multiple. Apart from other factors, success depends on the type of infection. Success is considered unlikely in the context of the most common type, pedal distal subungual onychomycosis, if more than 30 to 50% of the nail plate is affected.[34] Moreover, cure seems to be particularly difficult if the lateral part of the nail plate is involved with the lesion reaching from the free margin to the nail matrix.[35] Additionally, the probability of cure depends on the number of infected nails. With more than 5 infected nails, cure is unlikely. A shorter period of therapy is commonly required for the treatment of fingernail onychomycosis and cure rates are slightly higher than with toenail onychomycosis. As topical antimycotics must, in most cases, diffuse through the horny material of the nail plate into deeper layers to reach the causative organisms, the chance of cure seems to be particularly low with thickly keratinised, dystrophic, predamaged nails. Finally, a significant number of patients have problems with the application of the antifungal agent on toenails because of additional movement disorders.

Topical therapy is particularly justified when less than 30% of the nail plate is affected and with white superficial onychomycosis.[34] With more extensive infections, or even in total dystrophic onychomycosis, topical treatment does not generally lead to success and systemic therapy is necessary (table II). However, use of systemic therapy is limited by several factors, including possible severe adverse effects caused by the active compound itself or by its interaction with concomitant medication.

Although there have been some important advances in topical therapy in recent years, the most significant advances have been made in systemic therapy. This is particularly reflected by cure rates. A larger number of effective drugs are available today for drug therapy of onychomycosis than ever before. However, with this relative abundance of options, an informed choice of the correct anti-

Table II. Therapeutic procedures for culture-proven onychomycoses[34]

Clinical type	Degree of severity[a]	Therapy
White superficial onychomycosis	I-III	Topical, possibly tangential removal
Distal subungual onychomycosis	I-II	Topical, possibly with nail plate removal
Distal subungual onychomycosis	III	Systemic
Proximal subungual onychomycosis	II-III	Systemic
Onychomycosis associated with chronic mucocutaneous candidiasis	I-III	Systemic
Total dystrophic onychomycosis		Systemic

a I = <30% of the nail affected; II = 30 to 60% of the nail affected; III = >60% of the nail affected.

mycotic agent for a given patient is even more important. The different classes of agents have different targets (fig. 1) and thus differ considerably with respect to their therapeutic and adverse effect profiles. Special consideration should be given to the risk : benefit ratio as well as to the cost : benefit ratio.

It has become clear that griseofulvin as a therapeutic agent has ceased to be the gold standard, and today it is rarely used in the therapy of onychomycosis in highly industrialised countries. Occasionally it still is used in studies as a comparative antifungal drug, because its action and effectiveness are well established. Another antifungal agent that has been removed from the therapeutic armamentarium is ketoconazole. Instead, the newer agents itraconazole, terbinafine and fluconazole are considered for first-line systemic treatment; numerous studies of the effectiveness, optimal dosage, adverse effects and cost of these agents have been, and currently still are being, performed.

6.2.2 Former Standard Antimycotics

Griseofulvin is a compound synthesised by some species of *Penicillium*. It has been used for systemic treatment of dermal mycoses, including onychomycoses, since 1959. Its efficacy is limited to dermatophytes. The mechanism of action is fungistatic, due to interactions with microtubule-associated proteins and the ensuing inhibition of fungal cell mitosis. The gastrointestinal absorption of griseofulvin shows remarkable interindividual differences, and depends also on the drug formulation. The highest rates of absorption are found with the ultramicrosize preparation.[37] The route by which griseofulvin gets to the site of infection has not yet been fully elucidated; it is probably incorporated into newly formed keratinocytes.

Griseofulvin undergoes hepatic metabolism to 6-demethyl-griseofulvin, which is excreted in the urine.[38] In onychomycosis of the toenails, the rates of success of griseofulvin treatment are lower than 40% despite treatment periods of a year or more.[39]

For some time at the beginning of the 1980s ketoconazole was used as an oral antifungal agent

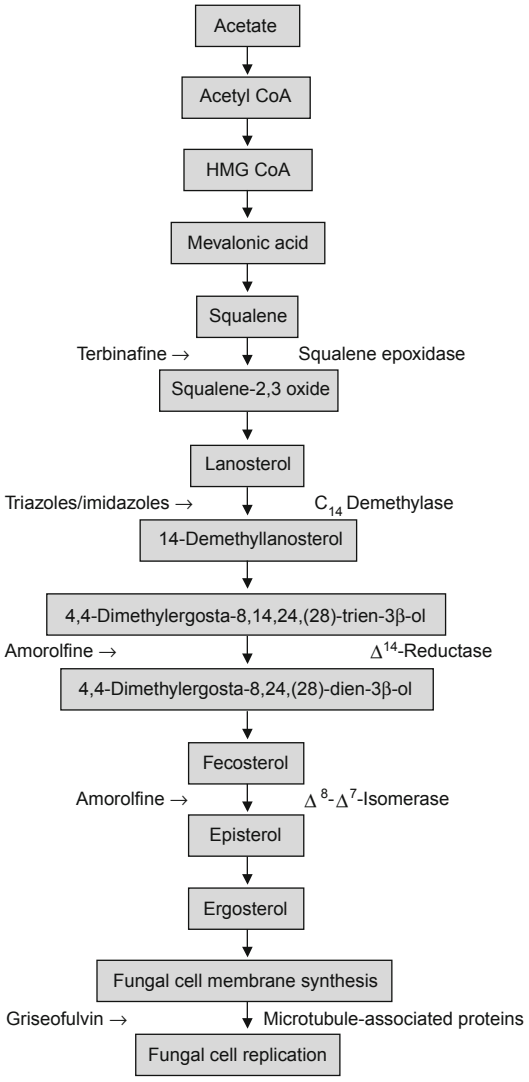

Fig. 1. Molecular targets of relevant antimycotics (modified from Gupta et al.,[36] with permission).

for systemic therapy of onychomycoses and severe tinea of glabrous skin, with cure rates similar to those seen with griseofulvin. It was the forerunner of the more modern azoles itraconazole and fluconazole. After some fatal cases of idiosyncratic drug-induced hepatitis, systemic ketoconazole is no longer generally approved for the treatment of onychomycoses. Nevertheless, it may be used with

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