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Onychomycosis – a review of its presentation and treatment

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ABSTRACT
Dermatophyte onychomycosis is a common condition, particularly in the elderly and immunosuppressed. As these sections of the population are set to increase, it is likely that the prevalence of dermatophytic nail infection will also increase. Advances in antifungal therapy, with the introduction of newer and safer drugs such as terbinafine and itraconazole, have improved outcomes significantly. However, around a quarter of patients will suffer reinfection or recurrence in the subsequent months. The possible reasons for this are considered. Data from recently published studies have demonstrated an increased mycological and clinical cure rate using a combination of topical and oral antifungal agents. This approach may be a cost-effective means of improving outcomes for patients with more resistant nail disease.

INTRODUCTION

Onychomycosis is defined as a fungal infection of any part of the nail unit.[1] The disease predominantly affects the toenails[2] and accounts for almost 50% of all nail dystrophy.[3] Fungal nail infection may be caused by non-dermatophyte moulds (NDMs), yeasts or dermatophytes. NDMs rarely infect the toenails[4] and in European studies account for around only 1.6–6% of cases of onychomycosis.[5] More frequently they are found to co-exist with a dermatophyte and are thus labelled as a 'mixed' infection.[6] Yeast infections of the toenails are also rarely observed, usually being associated with severe immunosuppression.

In clinical practice, 90% of toenail mycosis is caused by dermatophyte infection,[7] where the condition is referred to as tinea unguium.[8] In the more temperate climates of Europe, the causative dermatophytes are almost exclusively *Trichophyton* spp; *Trichophyton rubrum, Trichophyton mentagrophytes* (var. *interdigitale*) and, to a lesser extent, *Epidermophyton floccosum*.[3]

Tinea unguium is almost invariably associated with skin invasion.[9] Skin infection arises as fungal elements are disseminated by infected individuals in areas such as swimming pools and communal changing areas. The dermatophyte population in these areas has been found to be high, particularly in the more humid, tropical-type swimming pools.[1]. Fungal elements adhere to the soles of the feet[11] and then invade the outer most layer of the epidermis, the stratum corneum. Experimentally, penetration has been shown to be enhanced in high humidity climates.[12] The number of patients with skin infection who go on to develop nail infection is unknown. In one study involving patients attending a Japanese dermatology department, 59% of those diagnosed with skin infection (tinea pedis) also had associated nail changes.[13] In a similar type of study of European subjects, 23% of patients with fungal skin infection of the foot also showed nail involvement.[14]

Nail invasion by dermatophytes typically occurs through a distal-lateral subungual route. Subungual invasion causes nail-bed inflammation with the production of subungual hyperkeratosis, which leads to onycholysis. Superficial invasion of the dorsal surface of the nail plate is less common, but is almost exclusive to toenails.[15] As the infection spreads, chronic nail infection may lead to eventual total nail dystrophy.

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PREVALENCE

The true prevalence of the disease is difficult to ascertain. Studies have looked at specific occupational groups, geographical areas and selected age groups. Furthermore, studies vary greatly between the diagnostic criteria and methodologies employed. Hay[16] has suggested the true prevalence lies somewhere between 3% and 22%. However, from most reported data it would appear consistent that tinea unguium is a disease predominantly affecting males[14] and has a prevalence that rises with age.[17]

Fungal nail infection is rarely seen in children under the age of ten. Studies on young populations suggest a prevalence of 0.19-2.1%.[18,19] The reason for this is unknown but it has been suggested that a faster rate of nail growth in children and a lack of cumulative trauma renders the nail more resistant to invading fungi.[20] In adolescence the prevalence rises, steadily increasing to a peak in those aged 55 and over.[2] As this section of the population is likely to expand in numbers with increased longevity, it can be assumed that the prevalence of onychomycosis will continue to rise in parallel.

A number of risk factors have been suggested for the development of onychomycosis including running,[21] swimming,[22] occupation,[23] immunosuppression[24,25] smoking and arterial disease[26] and psoriasis.[27] A review of the literature suggests that there is conflict between authors in determining whether people with diabetes are more prone to onychomycosis. Romano *et al*,[28] in a survey of 171 diabetic subjects and 276 controls concluded there was no difference in infection rates.

However Gupta[29] examined 550 diabetic subjects and found that diabetic individuals had a prevalence 2.77 times greater than non-diabetics. Significant risk factors for development of onychomycosis in people with diabetes included immunosuppressive therapy, a family history and the presence of peripheral vascular disease.

Complications of chronic fungal infection

The nature of dermatomycosis is such that fungal skin infection typically leads to fissuring of the epidermis. Dystrophic fungal nails may harbour fungi and cause damage to adjacent soft tissues rendering the foot susceptible to secondary invasion by pathogenic bacteria such as Streptococci and Staphylococci. The link between erysipelas and fungal foot infection has not been firmly established but implied. A review of 30 patients with erysipelas of the leg and foot found that 13 had concurrent fungal foot infection.[30] Dupuy in a case-control study found that web space intertrigo was strongly associated with a risk of developing erysipelas.[31] Tissue damage of this extent can be a limb-threatening event for patients with risk factors such as diabetes and peripheral ischaemia.

Quality of life

Not all patients with fungal foot infection seek treatment for the condition, possibly due to reasons such as unawareness of the condition or embarrassment. Maruyama and colleagues compared a cohort of 41 individuals who were discovered by medical examination to have mycologically proven foot infection but not seeking treatment with a group of diagnosed patients who were actively seeking treatment. The main difference between the groups was the level of symptoms suffered. Those seeking treatment had significantly higher scores for erythema and itching.[32]

Until recently, it was not known how nail disease impacted on a patient's life. In 1993, the first quality-of-life study was undertaken examining sufferers' mental and general health using adapted generic instruments. Lubeck[33] compared patients with onychomycosis with controls and concluded that sufferers experienced embarrassment and discomfort, thus reducing their quality of life. Drake,[34] adapting the Lubeck questionnaire, interviewed 258 patients by telephone and highlighted that three-quarters of sufferers had difficulty with nail care, suffered embarrassment and nearly half had associated pain. More recently a specific onychomycosis measure (ODSQ) has been developed, which has shown greater sensitivity than generic measures such as the SF-36,[35] but so far no studies have been published documenting its use.

THERAPY

Traditionally the treatment of fungal nail infection has required the use of a topical or systemic antifungal agent. In discussing the effectiveness of various drugs it is important to highlight the wide variation of reported cure rates between studies comparing antifungal agents. The term 'cure' can be expressed as a clinical cure in which visible improvement is the main outcome measure, mycological cure where there are no fungal elements identified upon microscopy and culture or a combination of both (global cure). Furthermore, populations are studied using differing methodologies and may have varying levels of nail disease.

Topical

Topical agents rely on sufficient penetration of the agent through the affected nail plate. Owing to their limited penetration capacity topical agents are only indicated for use in distal nail disease when the nail matrix is spared.

Amorolfine is an antifungal of the morpholine class exhibiting both fungistatic and fungicidal properties at low concentrations. Its main effect is against dermatophytes and some yeasts, and works by inhibiting the formation of ergosterol, a component of the fungal cell membrane.[36] A study of its nail penetration abilities was undertaken and it was concluded that amorolfine penetrates through the nail within 24 hours following application, the degree of penetration being influenced by the nails' consistency and thickness.[37] Available data suggest that topical amorolfine 5% (Loceryl® nail lacquer) applied to the toenails once weekly for six months will lead to mycological and clinical cure rates of up to 66%.[38]

Tioconazole is an imidazole derivative. Imidazoles have a similar spectrum of activity to that of amorolfine. Their full mode of action is not fully understood, however it is known that they work by increasing fungal cell membrane permeability causing cellular leakage and interference with cell division.[39] At lower concentrations imidazoles have been shown to be primarily fungistatic rather than fungicidal,[40] which may explain their lower cure rates compared with the more modern topical agents. Tioconazole is available as a nail paint (Trosyl®) applied daily for six months. Cure rates are around 22%.[41]

Ciclopirox is a hydroxypyridone derivative, which differs from other antifungal agents. It is thought to exert its effect by the chelation of polyvalent cations rather than interfering with fungal cell wall formation. It has been shown to be an effective topical treatment for onychomycosis with a broad spectrum of activity against dermatophytes, *Candida albicans* and some non-dermatophyte moulds.[42] Reported mycological cure rates have varied widely from study to study, ranging from 47% to 86%.[43] It is available as a nail lacquer in the US and some European countries, but it is not currently licensed for use in the UK.

Systemic

Currently in the UK there are a number of systemic agents available for the treatment of fungal toenail infection. Griseofulvin has been available for over 30 years. It is active against dermatophytes only as a fungistatic, and as a result requires a long course of treatment (around 12-24 months). Comparisons with more modern systemic antifungal agents have found it to have inferior cure rates of around 40%[44] and a higher rate of side-effects when compared with newer agents.[45]

Ketoconazole and fluconazole are members of the azole group. Ketoconazole was the first significant broad-spectrum, orally administered imidazole. Its fungistatic activity has limited success on toenail mycosis.[46] Moreover, its use has declined owing to its hepatotoxicity.[15,47] Both ketoconazole and fluconazole are not currently licensed for fungal nail infection in the UK.[48]

Itraconazole, a triazole, is a recent addition to the azole group of drugs and is an effective treatment for fungal skin and nail infection, persisting in these areas for some weeks after administration.[49] It exerts its broad-spectrum effect on fungi by depleting ergosterol, which is necessary for cell wall formation. Therapy for nail infection is normally a 12-week course, 200mg daily. Cure rates for onychomycosis are around 75%.[44] The drug has a slightly superior effect over yeasts such as *Candida albicans* when compared with terbinafine, as the latter has been found to be fungistatic rather than fungicidal against this particular pathogen.[50] Itraconazole, however, has a higher number of drug interactions with commonly used drugs such as oral hypoglycaemics, warfarin and oral contraceptives, than terbinafine.[51]

Terbinafine is an allylamine which like the azoles blocks fungal cell wall development by inhibiting the formation of ergosterol. In contrast to the azoles it acts at a more proximal point in the biochemical pathway – inhibiting the enzyme squalene epoxidase. The drug is rapidly absorbed and is well suited for the treatment of superficial mycoses as it is rapidly distributed to the skin and sebum.[52]

The drug is typically taken for 12 weeks (250mg daily) for control of toenail infection. In onychomycosis, studies have indicated a mycological cure rate of around 75%. A meta-analysis undertaken to evaluate and compare terbinafine with griseofulvin, itraconazole and placebo in nail mycosis found that terbinafine had a significant

Nail Factors:
- Presence of large amounts of subungual debris (>2mm)
- Lateral nail infection
- Total nail involvement (including the matrix)
- More than 50% of the nail involved
- No or little nail growth
- Subungual fungal mass 'Dermatophytoma'

Pathogen Factors:
- 'Mixed' infection profile
- Resistant organisms

Patient Factors:
- Poor absorption
- Poor compliance
- Immunosuppression
- Diabetes mellitus
- Peripheral vascular disease
- Elderly

Table 1. Typical characteristics of non-responders to anti-fungal therapy. Adapted from Scher & Baran[60] and Roberts *et al*.[48]

advantage over these other treatments in terms of negative microscopy and culture. Oral terbinafine is well tolerated,[53] with minimal side-effects, the majority being transient in nature.[47] Costing studies have been undertaken comparing the main systemic agents and it would appear terbinafine is the most cost-effective.[47,54-56] The results from studies have established the superiority of this drug over itraconazole in its mycological cure rate[57,58] and it is suggested as the first-line oral therapy for tinea unguium.[44,48,59]

REINFECTION AND RECURRENCE

Despite the seemingly improved cure rates over recent years with new and more effective treatments with around a quarter of patients, the problem persists or relapse occurs.[16] Often studies of various interventions fail to follow up patients beyond a certain time and so relapse rates may not be fully reported. An Icelandic study followed up patients treated with oral therapy and found that after five years only 46% of patients treated with terbinafine remained disease free compared with just 13% of patients treated with itraconazole.[58] Relapse can be categorised as recurrence (where the infection reappears after an absence of a year or more) or reinfection (where the infection returns within a year). The latter typically suggests a poor response to antifungal therapy, thus not achieving a mycological cure at the cessation of treatment.

Reasons for poor response are multifactorial. Scher & Baran[60] summarised the characteristics of the typical poor responder in a recent paper (Table 1). Such patients may require longer courses of therapy or a combination of treatments to eradicate successfully long-standing fungal infections. Although resistance is mentioned within the table there is currently little evidence to suggest that drug resistance is a major problem in onychomycosis.[16]

Recurrence usually arises a year or more after an infection has been treated and eradicated. Infection may be re-acquired through exposure to fungal arthroconidia in old socks and shoes. Where possible, discarding infected hosiery and footwear at the time of mycological cure may reduce recurrence rate.[61] When this is not possible, disinfection of the footwear should be carried out with suitable antifungal powders or sprays.

A recent study tested the efficacies of various disinfectant agents against dermatophytes that could be used on personal belongings to eradicate fungal elements.[62] Terbinafine 1% spray was found to inactivate arthroconidia from five different strains of *Trichophyton* (including *T mentagrophytes* and *T rubrum*) As reinfection of the nails frequently follows from skin infection, it is important to educate the patient with regard to skin care and the regular use of topical agents on suspected skin lesions. Some authors advocate the use of nail lacquer as a preventative measure in susceptible individuals.[15, 63]

COMBINATION THERAPY

Even with the latest developments of more modern topical and systemic antifungal agents for onychomycosis, a relatively high relapse rate still exists. In 1971, Medoff and co-workers first discovered a synergistic effect in antifungal therapy when combining two systemic antifungal agents.[64] Drug synergism can be defined as a situation where a combination of two or more drugs has a greater effect than the individual effects of each drug alone. The potential advantages of combining antifungal agents include:
- Faster time to cure
- Increased curative effect
- Increased fungicidal activity
- Broader spectrum of activity
- Improved tolerability of the patient

Recent studies have focused on the idea of combination therapy for onychomycosis, combining an oral with a topical agent. Olaffsson and colleagues[63] reviewed work reporting the effects of various combinations of oral agents (griseofulvin, itraconazole and terbinafine) with topical agents (amorolfine nail lacquer and tioconazole paint). The greatest benefits have been reported by 12 weeks administration of oral terbinafine and 15 months of weekly applications of amorolfine nail lacquer.

Mycological and clinical cure was observed in 72.3% of patients using combination therapy compared with just 37.5% of those on 12 weeks of terbinafine alone.[65] Itraconazole (200mg once daily for 12 weeks) combined with once-daily amorolfine nail lacquer for 24 weeks versus itraconazole alone (200mg daily for 12 weeks) was also found to have a superior mycological cure rate.[66] At week 24, 93.9% of the patients on the combination therapy were mycologically cured compared with just 68.8% of patients on itraconazole alone.

Lambert[67] conducted a cost-effective analysis using the data from the two trials, and although the initial costs of prescribing two agents for therapy may seem expensive, the two regimes were found to be more cost-effective than monotherapy alone. As with all new developments, more research is required to verify these early reports and, in particular, longer term follow up of patients would be beneficial to assess recurrence rates in these patients.

CONCLUSION

Onychomycosis, although a common condition, can be effectively managed in most cases with minimal side-effects using modern antifungal agents. Newer topical and systemic agents have shown benefits over the more established drugs. Combination therapy in initial studies has shown great promise in improving cure rates. More time is required with follow-up studies to assess relapse rates in these patients.

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