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GUIDELINES

Guidelines for treatment of onychomycosis

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Summary These guidelines for management of onychomycosis have been prepared for dermatologists on behalf of the British Association of Dermatologists. They present evidence-based guidance for treatment, with identification of the strength of evidence available at the time of preparation of the guidelines, and a brief overview of epidemiological aspects, diagnosis and investigation.

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Introduction

Onychomycosis is one of the commonest dermatological conditions. A large questionnaire survey of 10 000 people suggested a prevalence of 2·71% in the U.K.[1,2] More recent mycologically controlled surveys in Finland[3] and in the U.S.A.[4] indicate a prevalence of between 7 and 10%. Increasing publicity about disease prevalence, and the advent of new and more effective antifungal drugs, has led to a greater enthusiasm among sufferers to seek treatment and among medical practitioners to institute therapy. However, treatment is often prescribed without mycological confirmation of infection, there may be confusion as to whether fungi isolated on culture are primary or secondary pathogens, the relative efficacy of different antifungal agents against different fungi is not completely understood and drugs are often prescribed for inappropriate treatment durations.

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These guidelines were commissioned by the British Association of Dermatologists Therapy Guidelines and Audit subcommittee. Members of the committee are N.H.Cox (Chairman), A.V.Anstey, C.B.Bunker, M.J.D.Goodfield, A.S.Highet, D.Mehta, R.H.Meyrick Thomas, A.D.Ormerod, J.K.Schofield and C.H.Smith.

Definition

Onychomycosis is an infection of the nail apparatus by fungi that include dermatophytes, nondermatophyte moulds and yeasts (mainly *Candida* species). The toenails are affected in 80% of all cases of onychomycosis; dermatophyte infection, mostly due to *Trichophyton rubrum*, is the cause in over 90% of cases.[5]

Onychomycosis is classified clinically as distal and lateral subungual onychomycosis (DLSO), superficial white onychomycosis (SWO), proximal subungual onychomycosis (PSO), candidal onychomycosis and total dystrophic onychomycosis.

Distal and lateral subungual onychomycosis

DLSO accounts for the majority of cases and is almost always due to dermatophyte infection. It affects the hyponychium, often at the lateral edges initially, and spreads proximally al[illegible] subungual hyperkerat[illegible] the nail plate is not i[illegible]

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Distal and lateral subungual onychomycosis

DLSO accounts for the majority of cases and is almost always due to dermatophyte infection. It affects the hyponychium, often at the lateral edges initially, and spreads proximally along the nail bed resulting in subungual hyperkeratosis and onycholysis although the nail plate is not initially affected. DLSO may be

confined to one side of the nail or spread sideways to involve the whole of the nail bed, and progresses relentlessly until it reaches the posterior nail fold. Eventually the nail plate becomes friable and may break up, often due to trauma, although nail destruction may be related to invasion of the plate by dermatophytes that have keratolytic properties. Examination of the surrounding skin will nearly always reveal evidence of tinea pedis. Toenail infection is an almost inevitable precursor of fingernail dermatophytosis, which has a similar clinical appearance although nail thickening is not as common.

Superficial white onychomycosis

SWO is also nearly always due to a dermatophyte infection, most commonly *T. mentagrophytes*. It is much less common than DLSO and affects the surface of the nail plate rather than the nail bed. Discoloration is white rather than cream and the surface of the nail plate is noticeably flaky. Onycholysis is not a common feature of SWO and intercurrent foot infection is not as frequent as in DLSO.

Proximal subungual onychomycosis

PSO, without evidence of paronychia, is an uncommon variety of dermatophyte infection often related to intercurrent disease. Immunosuppressed patients, notably those who are human immunodeficiency virus-positive, may present with this variety of dermatophyte infection; conditions such as peripheral vascular disease and diabetes also may present in this way. Evidence of intercurrent disease should therefore be considered in a patient with PSO.

Candidal onychomycosis

Infection of the nail apparatus with *Candida* yeasts may present in one of four ways: (i) chronic paronychia with secondary nail dystrophy; (ii) distal nail infection; (iii) chronic mucocutaneous candidiasis; and (iv) secondary candidiasis.

Chronic paronychia of the fingernails generally only occurs in patients with wet occupations. Swelling of the posterior nail fold occurs secondary to chronic immersion in water or possibly due to allergic reactions to some foods, and the cuticle becomes detached from the nail plate thus losing its water-tight properties. Microorganisms, both yeasts and bacteria, enter the subcuticular space causing further swelling of the posterior nail fold and further cuticular detachment, i.e. a vicious circle. Infection and inflammation in the area of the nail matrix eventually lead to a proximal nail dystrophy.

Distal nail infection with *Candida* yeasts is uncommon and virtually all patients have Raynaud's phenomenon or some other form of vascular insufficiency. It is unclear whether the underlying vascular problem gives rise to onycholysis as the initial event or whether yeast infection causes the onycholysis. Although candidal onychomycosis cannot be clinically differentiated from DLSO with certainty, the absence of toenail involvement and typically a lesser degree of subungual hyperkeratosis are helpful diagnostic features.

Chronic mucocutaneous candidiasis has multifactorial aetiology leading to diminished cell-mediated immunity. Clinical signs vary with the severity of immunosuppression, but in more severe cases gross thickening of the nails occurs, amounting to a *Candida* granuloma. The mucous membranes are almost always involved in such cases.

Secondary candidal onychomycosis occurs in other diseases of the nail apparatus, most notably psoriasis.

Total dystrophic onychomycosis

Any of the above varieties of onychomycosis may eventually progress to total nail dystrophy where the nail plate is almost completely destroyed.

Diagnosis

This section follows the criteria set out by Evans and Gentles.[6] Treatment should not be instituted on clinical grounds alone. Although 50% of all cases of nail dystrophy are fungal in origin it is not always possible to identify such cases accurately. Treatment needs to be administered long-term and enough time must elapse for the nail to grow out completely before such treatment can be designated as successful. Toenails take around 12 months to grow out and fingernails about 6 months. This is far too long to await the results of therapeutic trial and, in any case, treatment is not always successful. If the diagnosis is not confirmed, and improvement does not occur, it is impossible to tell whether this represents treatment failure or an initial incorrect diagnosis. Although the cost of diagnostic tests may be deemed high at times of budgetary constraint, the cost is always small relative to inappropriate and unnecessary treatment.

Laboratory diagnosis consists of microscopy to visualize fungal elements in the nail sample and

culture to identify the species concerned. The success or otherwise of such tests depends upon the quality of the sample, the experience of the microscopist and the ability of the laboratory to discriminate between organisms that are likely pathogens, organisms growing in the nail as saprophytes, and contamination of the culture plate.

Given that dermatophyte onychomycosis is primarily a disease of the nail bed rather than of the nail plate, subungual debris taken from the most proximal part of the infection is likely to yield the best results. In DLSO material can be obtained from beneath the nail: a small dental scraper is most useful for this purpose. If the nail is onycholytic then this can be cut back and material can be scraped off the underside of the nail as well as from the nail bed. As much material as possible should be submitted to the laboratory because of the relative paucity of fungal elements within the specimen. In SWO the surface of the infected nail plate can be scraped and material examined directly. PSO is rare and again should be scraped with a scalpel blade. However, punch biopsy to obtain a sample of the full thickness of nail together with the nail bed may be necessary. Some of the material obtained is placed on a glass slide and 20% potassium hydroxide added. Fifteen to 20 min should be allowed to elapse before examining the sample by direct microscopy. The addition of Parker's blue/black ink may enhance visualization of the hyphae. An inexperienced observer may very well misdiagnose cell walls as hyphae and care should be taken to examine all of the specimen as fungal elements within the material may be very scanty.

The remaining material should be cultured on Saboraud's glucose agar, usually with the addition of an antibiotic. The culture plate is incubated at 28 °C for at least 3 weeks before it is declared negative, as dermatophytes tend to grow slowly.

Direct microscopy can be carried out by the clinician, and higher specialist training includes teaching of this technique. However, nail microscopy is difficult and should only be carried out by those who do it on a regular basis. Fungal culture should always be carried out in a laboratory experienced in handling mycology specimens, because of potential pitfalls in interpretation of cultures. It must be remembered that the most common cause of treatment failure in the U.K. is incorrect diagnosis, which is usually made on clinical grounds alone. This should not be further compounded by incorrect laboratory interpretation of results.

Histology is almost never required and its use is usually confined to other causes of nail dystrophy. Such dystrophies, notably psoriasis, regularly yield *Candida* yeasts on culture but they are rarely causal in aetiology of fungal nail infection.

Reasons for treatment

Although dermatophyte onychomycosis is relentlessly progressive there remains a view among some practitioners that it is a trivial cosmetic problem that does not merit treatment. In the elderly the disease can give rise to complications such as cellulitis and therefore further compromise the limb in those with diabetes or peripheral vascular disease. While these complications may not be common they are certainly serious. The high prevalence of the disease is the result of heavy contamination of communal bathing places[7] by infected users; disinfecting the floors of such facilities is very difficult because fungal elements are protected in small pieces of keratin. It is therefore logical to try to reduce the number of infected users by effective treatment and thus reduce disease prevalence. Finally, onychomycosis is a surprisingly significant cause of medical consultation and of absence from work.[8]

Onychomycosis should not therefore be considered a trivial disease, and there is a sound case for treatment on the grounds of complications, public health considerations and effect on quality of life.

Treatment

Introduction

Both topical and oral agents are available for the treatment of fungal nail infection. The primary aim of treatment is to eradicate the organism as demonstrated by microscopy and culture. This is defined as the primary end-point in almost all properly conducted studies. Clinical improvement and clinical cure are secondary end-points based on a strict scoring system of clinical abnormalities in the nail apparatus. It must be recognized that successful eradication of the fungus does not always render the nails normal as they may have been dystrophic prior to infection. Such dystrophy may be due to trauma or nonfungal nail disease; this is particularly likely in cases where yeasts or nondermatophyte moulds (secondary pathogens and saprophytes, respectively) are isolated.[9]

Invariably mycological cure rates are about 30% better than clinical cure rates in the majority of studies, the clinical cure rates often being below 50%. Publications of clinical trials in onychomycosis are often

criticized for quoting mycological cure rates and thus overemphasizing the efficacy of treatment. While it is understood that the patient is more concerned with improvement in the clinical appearance of the nail rather than eradication of the organism, questions regarding patients' satisfaction at the end of a study usually mirror very closely the mycological cure rate. This suggests that eradication of the organism does restore the nail to its previous state prior to infection even though that state may not be completely 'normal' as defined by a scoring system.

Systemic therapy is almost always more successful than topical treatment, which should only be used in SWO, possibly very early DLSO or when systemic therapy is contraindicated.

Topical therapy

There are several topical antifungal preparations available both as prescription-only medicines and on an over-the-counter basis. The active antifungal agent in these preparations is either an imidazole, an allylamine or a polyene, or a preparation that contains a chemical with antifungal, antiseptic and sometimes keratolytic properties such as benzoic acid, benzyl peroxide, salicylic acid or an undecenoate. Products that are specifically indicated for nail infection are available as a paint or lacquer that is applied topically. There are four such preparations (Table 1).

There are no published studies on the efficacy of salicylic acid (Phytex®; Pharmax, Bexley, U.K.) and methyl undecenoate (Monphytol®; LAB, London, U.K.) in fungal nail infection and their use cannot be recommended.

Amorolfine (Loceryl®; Galderma, Amersham, U.K.) nail lacquer has been shown to be effective in around 50% of cases of both fingernail and toenail infection in a large study where only cases with infections of the distal portion of the nail were treated.[10] There are several published studies examining the efficacy of tioconazole (Trosyl®; Pfizer, Sandwich, U.K.) nail solution, with very variable results ranging from cure rates of around 20% up to 70%.[11] While it is clearly possible to achieve clinical and mycological cure with topical nail preparations, these cure rates do not compare favourably with those obtained with systemic drugs. Currently, topical therapy can only be recommended for the treatment of SWO and in very early cases of DLSO where the infection is confined to the distal edge of the nail.

A combination of topical and systemic therapy may improve cure rates still further or possibly shorten the duration of therapy with the systemic agent. Thus far the results of such studies are inconclusive. A study comparing terbinafine and amorolfine with terbinafine alone produced somewhat idiosyncratic results[12] and was not properly blinded, so further evidence from well-controlled double-blind studies is required before combination therapy can be advocated.

Although there are no studies comparing one topical preparation with another in a properly controlled fashion, it is likely that amorolfine nail lacquer (Loceryl®) is the most effective preparation of those available.

Systemic therapy

The three drugs currently licensed for general use in onychomycosis are listed in Table 2. The two other systemic agents available for oral use, ketoconazole and fluconazole, are not licensed for nail infection. Ketoconazole may be used in some recalcitrant cases of yeast infection affecting the nails but cannot be prescribed for dermatophyte onychomycosis because of problems with hepatotoxicity. The use of fluconazole thus far has concentrated on vaginal candidiasis and systemic yeast infections although it is active against dermatophytes. There are some published studies of its use in nail infection but the dose and duration of treatment are not yet clear and it is not licensed for this indication in the U.K., nor does it appear likely to be so in the near future.

Griseofulvin. Griseofulvin (Fulcin®; Grisovin®; GlaxoSmithKline, Uxbridge, U.K.) is weakly fungistatic, and acts by inhibiting nucleic acid synthesis, arresting cell

Table 1. Topical agents for onychomycosis, with strength of recommendation and quality of evidence grading

Agent	Strength of recommendation and quality of evidence
Amorolfine (Loceryl®; Galderma, Amersham, U.K.) nail lacquer	*Strength of recommendation B, Quality of evidence II-ii*
Tioconazole (Trosyl®; Pfizer, Sandwich, U.K.) nail solution	*Strength of recommendation C, Quality of evidence II-iii*
Salicylic acid (Phytex®; Pharmax, Bexley, U.K.) paint	*Strength of recommendation E, Quality of evidence IV*
Undecenoates (Monphytol®; LAB, London, U.K.) paint	*Strength of recommendation E, Quality of evidence IV*

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