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UPDATE ON ONYCHOMYCOSIS

- **Onychomycosis, a fungal disease of the nails, accounts for 50% of all nail problems and can adversely affect a person's emotional, social and occupational functioning**
- **Onychomycosis rarely occurs in a healthy nail; predisposing factors are normally present**
- **Pharmacotherapy includes topical and systemic options which normally require long-term usage, over several months**
- **Adherence to therapy and lifestyle management are vital to ensure successful treatment**

INTRODUCTION

Onychomycosis is a term used to describe fungal disease of the nails.[1] The condition is found worldwide and accounts for approximately 50% of all nail problems.[2] The prevalence is governed by lifestyle factors and the presence of concomitant diseases such as diabetes mellitus (DM) and other skin conditions e.g. psoriasis;[2,3] prevalence is also reported to increase with increasing age and male gender.[1,4] Previously, onychomycosis was often regarded as merely a cosmetic problem, however it is now known that it can have significant negative effects on patients' emotional, social and occupational functioning.[4] Studies have shown that persons without the infection tend to report negative perceptions towards patients with onychomycosis;[5] while patients with onychomycosis report that the infection has had a negative impact on their quality of life in terms of psychological, social and occupational outcomes.[5,6]

Many patients with onychomycosis are not symptomatic and may not require or seek treatment.[3] **However, for some patients, especially in those with concomitant disease or impaired immunity (such as DM or immunosuppression) there is a risk of more serious infection and complications, if onychomycosis is left untreated**;[2,3] neglecting onychomycosis in these groups of patients can result in significant costs to the health budget. Therefore there is a need for early diagnosis and effective management in order to prevent serious complications or recurrence.

The National Medicine Information Centre's clinical enquiry answering service frequently receives questions in relation to the management of onychomycosis, therefore this bulletin will outline the diagnosis and contemporary management of onychomycosis.

CAUSES OF ONYCHOMYCOSIS

The mature nail organ is composed of several structures: the nail matrix, the nail bed, the nail plate and the nail folds.[7] The nail plate is composed of translucent keratin and is the part that people identify as the nail. Fingernails grow at a rate of 2 to 3 mm / month and toenails at a rate of 1 mm / month; therefore it takes about 6 months to replace a fingernail and 12 to 18 months to replace a toenail.[4] As a rule, a healthy nail is not susceptible to fungal infection.[6] Table 1 outlines factors which predispose to fungal nail infection.

Table 1: Predisposing factors for fungal nail infection[4,6]

Nail and nail bed microtrauma due to sporting activities (e.g. running, soccer, track and field)
Toe or toenail deformities (e.g. onychodystrophy, hallux valgus, hammer toe)
Tinea pedis ("athlete's foot")
Psoriasis vulgaris and psoriasis of the nail
Diabetes mellitus
Ichthyosis vulgaris
Circulatory disorders (e.g. chronic venous insufficiency, peripheral arterial disease)
Lymphoedema in the lower extremities
Reduced cellular immunity
Positive family history (genetic and environmental factors)

Onychomycosis is also noted to occur more frequently with advanced age (possibly due to co-morbidities such as DM, poor circulation, problems with maintaining care of thickened nails and slower rate of nail growth), and in males (possibly due to lifestyle factors, including involvement in sporting activities and/or presence of tinea pedis).[8]

Dermatophytes are the most frequently implicated **causative agents** in onychomycosis;[7,9] up to 90% of dermatophyte infections (also referred to as tinea unguium) are reportedly caused by two pathogens: *Trichophyton (T) rubrum* (accounting for up to 70%) and *T interdigitale* (10-20%).[2,7,9] Some studies have suggested a genetic component to susceptibility of infection with *T rubrum* in some families.[6,7] Yeasts (*Candida* species) and non-dermatophyte moulds (NDM, e.g. *Scopulariopsis breviacaulis*, *Aspergillus* species) may also cause onychomycosis; yeast or mould infections are more commonly seen in the elderly, in patients with skin diseases that affect the nails and in immunocompromised patients (e.g. HIV patients).[2,9]

Transmission of infection may occur within the family (e.g. via the bath), either horizontally (from one spouse to the other) or vertically (across generations); the latter type of transmission may be associated with genetic

susceptibility within the family.[6,7] Other sources of infection include public swimming pools, saunas, sporting facilities, nail salons or hotel bedrooms.[1,7]

CLINICAL FEATURES OF ONYCHOMYCOSIS

Several classification systems have been used to define the various types of onychomycosis.[1,4,7,10] Table 2 outlines the 5 main clinical patterns of infection, as described by the British Association of Dermatology.[1]

Table 2: Clinical patterns of onychomycosis[1]

Clinical description	Clinical Features
Distal + lateral subungual onychomycosis (DLSO)	Commonest presentation. Toenails > fingernails. *T rubrum* is the commonest causative organism. Fungus invades the nail + nail bed by penetrating the distal or lateral margins → thickened and discoloured nails (+/- onycholysis).
Superficial white onychomycosis (SWO)	Less common than DLSO. Mostly affects toenails. *T interdigitale* is the usual causative organism. Fungus invades the nail plate directly → well-delineated opaque spots on the external nail plate with rough, soft, crumbly nails and minimal inflammation.
Proximal subungual onychomycosis (PSO)	Uncommon in general population but common in immunocompromised patients. Mostly affects toenails. *T rubrum* is the commonest causative organism. Infection starts either in the proximal nail fold or beneath the proximal nail plate. Distal portion of nail is normal until late in course of infection.
Endonyx onychomycosis	Uncommon presentation. *T sudanese / T violaceum* are causative organisms (these organisms originate in tropical regions, especially Sub-Saharan Africa →infection is primarily identified in immigrant populations). Fungus penetrates the nail plate keratin directly →lamellar splitting of nail, discolouration (milky patches) of nail plate and minimal inflammation.
Total dystrophic onychomycosis (TDO)	Rare presentation. Any of the above presentation types may progress to total nail dystrophy, with almost total destruction of nail plate. May be seen in immunocompromised patients (possibly in association with *Candida* infection).

Candidal onychomycosis may present in several ways: (1) as **chronic paronychia** with secondary nail dystrophy (in patients with wet occupations or in thumb-sucking children) (2) as **distal nail infection** (in patients with vascular insufficiency such as Raynaud's phenomenon or in those on corticosteroids) (3) as chronic **mucocutaneous candidosis** (where patients have infection of mucous membranes in addition to nail thickening) or (4) as **secondary candidosis** in patients who have existing nail disease such as psoriasis.[4]
Non-dermatophyte mould (NDM) infections occur most commonly in individuals with existing nail problems, or immunosuppression (due to existing disease such as HIV or DM or in patients on immunosuppressive therapy).[1,3]

DIAGNOSIS OF ONYCHOMYCOSIS

The clinical signs of onychomycosis are often difficult to distinguish from other conditions (infectious and non-infectious) which are responsible for 50% of nail dystrophic damage.[1,7] Differential diagnoses of nail dystrophy are outlined in Table 3.

Table 3: Differential diagnoses of nail dystrophy [1,4,7,11,12]

Cause	Types	Comment
Infectious	Dermatophyte infection Yeast infection NDM infection Bacterial infection	These fungal infections are responsible for 50% of dystrophic nail conditions. NDM infections may be difficult to diagnose. Bacterial infections may occur alone (e.g. *Pseudomonas aeruginosa*) leading to green / black discolouration of nail) or in conjunction with a fungal infection.
Non- infectious	Psoriasis Lichen planus Traumatic onycholysis Subungual tumours (e.g. melanoma) Eczema / contact dermatitis	Psoriasis is the commonest non-infectious cause and is usually (but not always) seen in conjunction with psoriasis at other skin sites. 10% of lichen planus patients have nail dystrophy. Nail bed looks normal with dystrophy due to trauma. Tumours are very rare.

NDM=non-dermatophyte mould

Ideally laboratory confirmation of the diagnosis should be obtained before initiating treatment, if the clinical features of the dystrophic nails suggest the possibility of fungal infection (see Table 2), especially in the presence of predisposing factors (see Table 1).[3,4] It may be difficult to get a good nail specimen: material should be taken from any discoloured, dystrophic, brittle or crumbly part of the nail, using nail drills or scalpels.[1] The demonstration of fungus is made by microscopy (results within 24 hours, but with a high false negative rate) and/or by culture which may take up to 6 weeks but has the advantage of potentially identifying the causative organism.[3,4,7] Molecular diagnostic techniques may be available in some laboratories.[1,10] **No single method offers 100% sensitivity** therefore more than one method / serial specimens may be needed to confirm the diagnosis.[13] Initiation of therapy, based only on symptoms, may lead to inappropriate pharmacotherapy, unless there is firm evidence of a clinical diagnosis of onychomycosis; specialist opinion may be required.[1,13-15]

PHARMACOLOGICAL TREATMENTS FOR ONYCHOMYCOSIS

The decision on the optimal type of treatment for onychomycosis is based on the number of affected nails, the extent of individual nail involvement, the identified pathogen and the presence of co-morbid conditions.[1,3,7] Pharmacological options include topical and systemic therapies. Table 4 outlines the currently authorised medicines for management of onychomycosis.

Table 4: Pharmacotherapeutic options for adults with onychomycosis [1,7,16-24]

Treatment	Mode of Action [CYP effects]	Directions for use*	Duration of Therapy	Undesirable effects / Precautions*
Amorolfine nail lacquer (T)	Fungicidal	Apply once weekly	6 mths (fingernails) 9-12 mths (toenails)	Local irritation symptoms may occur.
Ciclopirox nail lacquer¥ (T)	Fungicidal, fungistatic, sporocidal	Apply once daily	6 mths (fingernails) 9-12 mths (toenails)	Local irritation symptoms may occur.
Tioconazole nail solution (T)	Fungicidal	Apply twice daily	6-12 mths	Local irritation symptoms may occur.
Terbinafine (O)	Fungicidal and fungistatic activities [moderate-potent CYP 2D6 inhibitor]	250mg daily (Baseline LFTs required and then every 4-6 weeks during treatment)	6 wks - 3 mths (toe-nails may need up to 6 mths).	C/I in active or chronic liver disease. GI upset; taste disturbance; skin rash / urti-caria. Use with caution in renal impairment. Risk of DDIs.
Itraconazole (O)	Primarily fungistatic activity [potent CYP3A4 inhibitor]	200mg daily (continuous) *or* [400mg daily X 1 week per mth = pulse therapy] ** (Regular LFTs recommended with usage longer >one month)	3 mths (continuous) 2 pulses (fingernails) 3 pulses (toenails)	GI upset. Risk of congestive heart failure with use. **Risk of DDIs** including drug-induced QT prolongation
Griseofulvin***¥ (O)	Fungistatic (against dermatophytes only) [CYP 3A4 inducer]	500mg – 1gram daily (take after high fat meal to ↑ absorption) (Regular LFTs required)	6-12 mths	C/I in active or chronic liver disease. GI upset++; teratogenic. **Risk of DDIs**.
Fluconazole*** (O)	Fungistatic [potent CYP2C9 inhibi-tor, moderate CYP3A4 inhibitor]	150mg weekly (Regular LFTs recommended with longer use (e.g.> one month or with high dosage))	3-6 mths (fingernails) 6-12 mths (toenails)	GI upset; skin rash; insomnia. Use with caution in ↓ liver / ↓ renal function; adjust dosage with ↓ renal function. **Risk of DDIs**.

* Full prescribing information for each medicine is available in the Summary of Product Characteristics [SmPC] (www.hpra.ie)
**Details on "pulse therapy" currently not included in the SmPC
***Only to be used when other agents are not considered appropriate / not tolerated.
¥ Currently not marketed in Ireland
T=topical; O=oral; C/I=contraindicated; CYP=cytochrome P450; LFTs=liver function tests; GI=gastrointestinal; DDIs=drug-drug interactions.

Topical therapies: The hard keratin and compact structure of the dorsal nail plate act as a barrier to topical drug diffusion into and through the nail plate; therefore the concentration of topically applied drug can drop 1,000 fold from the outer to inner surface.[1] However, **topical treatment may be useful when fungal infection is limited (e.g. where <80% of the nail is affected, ≤ 3 nails are affected, in the absence of matrix involvement (which is identifiable as yellow streaks)) or where systemic therapies are contraindicated or not tolerated**.[1,7] Types of onychomycosis suitable for topical therapy include (1) limited DLSO and (2) SWO (see Table 2). Detailed information on correct use, including nail preparation (and/or applicators), is supplied with topical preparation packs.[16-18] **Studies have reported response rates of up to 50% of patients, suitable for topical therapy, who have received any of the currently authorised therapies** (see Table 4); there may be a discrepancy between "clinical improvement" rates (i.e. how the nail looks) and "mycological cure" rates (which includes microscopy and/or culture) due to the slow rate of growth of the nail.[1,16-18] A study has reported that amorolfine may also have benefit in preventing recurrence of infection.[25] Side effects with use of topical treatments include local erythema, burning and irritation; systemic absorption has been shown to be minimal.[16-18]

Systemic therapies are recommended (1) for management of more widespread fungal infection including matrix infection (2) in the presence of co-morbidities or (3) where topical therapies have failed. Clinical studies have shown "cure" responses (negative mycology and normal nail) of up to 50% for both terbinafine and itraconazole; both persist in the nail for a considerable period after elimination from the plasma (Table 4).[1,19,20] Therefore terbinafine and itraconazole are regarded as first-line oral treatment options.[1] Guidelines **recommend terbinafine as the first choice agent in dermatophyte onychomycosis**, based on its higher efficacy (both in the acute treatment phase and in reduced frequency of clinical relapse) and favourable tolerability profile.[1,26] However, **itraconazole may be preferred in the management of infections caused by yeasts or NDMs, and in "mixed" (i.e. dermatophyte plus yeast/NDM) infections due to its broader antimicrobial coverage**.[1,20,27] Clinical studies have shown that **fluconazole** is less efficacious compared with terbinafine and itraconazole;[1,7,28] however its once weekly dosing (due to its long half-life) may be useful for patients who cannot tolerate the first-line options.[1,22] Doses of up to 450mg fluconazole weekly (unauthorised) have been associated with increased efficacy.[29-31] **Griseofulvin** is no longer considered as first-line treatment for adults due to its narrow antimicrobial spectrum and long duration of treatment.[1] **Adverse reactions** to oral therapies include GI upset and headache to varying degrees with all oral therapies, which may interfere with compliance over the long treatment period.[19-22] Regular evaluation of liver function is recommended during treatment with some antifungal medicines; there is also **a potential for drug-drug interactions, particularly with itraconazole, fluconazole and griseofulvin** (see Table 4).

Combination therapy involving concomitant use of both topical and oral antifungal agents may be considered (1) in the presence of more severe onychomycosis (especially of the toenail) (2) to reduce the duration of oral therapy and improve safety profile and reduce cost or (3) to provide a wider antifungal spectrum of activity (especially in the presence of infection due to yeasts or NDMs) in order to optimise treatment response rates.[3] Various combinations have been used with variable results.[1,3]

OTHER INTERVENTIONS FOR ONYCHOMYCOSIS

Nail removal, (either by surgical avulsion or by use of 20-40% urea ointment) with subsequent topical antifungal therapy, has been used for fungal infection of single nails, with variable success rates.[7,9] This may be an option for those who are intolerant of oral antifungal agents. Although some studies have reported success with use of **photodynamic therapy** and **laser therapy**,[3,32] further studies are required to enable a full evaluation of their role in the management of onychomycosis.[1,7]

Onychomycosis and tinea pedis are contagious therefore **lifestyle interventions are important to improve treatment efficacy and prevent relapse**.[3,4,33] Patients should be advised to keep their nails as short as possible, to wash feet daily and to wear absorbent socks (e.g. cotton socks). Family members may also need to be treated to prevent recontamination within the home; nail clippers should not be shared with others. In addition to pharmacological interventions, patients should be advised to ensure that they use protective footwear in areas such as hotel bedrooms, swimming pools, saunas or gyms (or other possible sources of infection). Shoes can harbour fungal infection and therefore should either be discarded or else treated to eliminate possible fungus (e.g. by use of naphthalene mothballs or antifungal powders). In addition, poorly fitting shoes should be avoided to reduce further nail trauma (a predisposing factor for fungal infection).

MANAGEMENT OF ONYCHOMYCOSIS IN SPECIAL POPULATIONS

Diabetes mellitus: **Onychomycosis has been reported to affect up to one third of diabetic patients**;[34-36] the majority of cases are due to dermatophytes. The risk increases with age, male gender, poor blood glucose control, concomitant peripheral vascular disease or tinea pedis; onychomycosis of the toenails is also significantly more common if feet are not washed on a daily basis.[6] Diabetic patients are more likely to develop complications such as bacterial cellulitis, osteomyelitis or foot ulcers, therefore early diagnosis and treatment of onychomycosis in DM are important.[1,6,26] Because of the potential risk for drug-drug interactions with itraconazole and the fact that it is contraindicated in heart failure (see Table 4), **terbinafine is the recommended oral treatment** in diabetic patients.[1] Combination therapy may also be considered to reduce the risk of recurrence or to minimise oral dosage, while topical therapy alone may be sufficient in early stage disease.[1,37]

Immunosuppressed patients: **Onychomycosis may be present in up to 30% of patients with immunosuppression**, e.g. HIV, which is primarily caused by the dermatophyte *T rubrum*.[1,3] In addition, patients receiving immunosuppressive medications (e.g. post-organ transplant) are also at increased risk of onychomycosis. **Terbinafine is the oral treatment of choice** because of the lower risk of drug-drug interactions with anti-HIV or immunosuppressant medication.[1,19,38] Since fungal nail infections may be severe with immunosuppression, early diagnosis and treatment (which may be prolonged) is required. If there is no response to first-line treatment, the laboratory diagnostic tests should be repeated to ensure the accuracy of the diagnosis and appropriateness of the treatment.[38]

Onychomycosis in children: Onychomycosis is relatively uncommon in children less than 18 years of age.[39] Most infections are reported to affect toenails, primarily in adolescents and are caused by *T rubrum*; more rarely, cases of *Candida* infections may be identified in fingernails of younger children, due to thumb-sucking.[40] **Neither terbinafine, itraconazole nor fluconazole is authorised for management of onychomycosis in children** and there are few clinical studies evaluating the efficacy and safety of systemic antifungals in this population. A recent review of 26 publications (clinical trials, retrospective reviews and case reports, n=171 children with onychomycosis) suggested higher cure rates and faster response times in children compared with adults with use of oral antifungal agents.[39] Terbinafine and itraconazole appeared to show superior efficacy compared with griseofulvin and fluconazole with similar safety profiles to those noted in adults. Combination therapy (reported in 20 children only, all >8 years of age) was associated with increased efficacy compared with monotherapy. Current guidance from the **British Association of Dermatology states that terbinafine is recommended by consensus for the treatment of paediatric onychomycosis**, with itraconazole (or fluconazole) useful for *candida* infections.[1] These agents should be used under specialist advice in children.[41]

SUMMARY POINTS IN THE MANAGEMENT OF ONYCHOMYCOSIS

- Onychomycosis should be considered in the differential diagnosis of nail alterations, especially in the presence of predisposing factors
- Management requires correct mycological identification (where possible), assessment of the extent and susceptibility of the disease and evaluation of concomitant risk factors
- Patients, especially those considered to be high-risk, may require regular monitoring to assess efficacy of therapy and to evaluate liver and/or renal function
- The potential for drug-drug interactions should be considered in patients on oral therapy
- Patients should be informed of the importance of adherence to the optimal treatment regimen, which may last for several months, in order to achieve cure
- In addition to the pharmacotherapy regimen, patients should be advised of appropriate lifestyle interventions to optimise treatment efficacy and prevent reinfection or relapse

List of references available on request. Date of preparation: November 2016

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