**Nail anatomy and growth**

Nails are plates of tightly packed, keratinised epidermal cells. The nail is made up of three parts (see Figure 1):

- **The nail body** (the visible part of the nail)
- **The free edge** (the part extending past the end of the digit)
- **The nail root** (the portion buried at the base in a fold of skin)

Most of the nail appears pink due to blood in the capillaries beneath. The free edge appears whitish because there are no underlying capillaries. The lunula, the half-moon shaped area at the base of the nail also has a whitish appearance because the vascular tissue does not show through the thickened stratum basale, the deepest layer of the epidermis.

At the tip of the finger beneath the free edge is a thickened region of stratum corneum, called the hyponychium. This band of tissue is made up of layers of flattened, dead keratinocytes, and secures the nail to the fingertip. The cuticle (eponychium) is a narrower band of stratum corneum that attaches the sides and base of the nail to the skin.

Nail growth occurs from the nail matrix, the epithelium beneath the nail root, through the transformation of superficial cells into nail cells. Growth rate is determined by the rate of mitosis in matrix cells, which, in turn, is influenced by age, health and nutritional status.

Growth rate also varies according to season, time of day and temperature. The rate of growth increases with the length of the digit and the amount of use it has — the fastest growing nail is that of the middle finger on the dominant hand. Fingernails grow at a rate of 2 to 3 mm per month and toenails grow at around 1 mm per month. It takes about six months for a cell at the base of a fingernail to reach the tip (12–18 months for toenails).

**Figure 1: Nail anatomy**

### Fungal nail infection

(onychomycosis) is a more common condition than is sometimes realised. Prevalence in adults is estimated at between 3.8 per cent and there are more than one million sufferers in the UK.¹

Onychomycosis is often considered to be a trivial disease with only cosmetic implications but it can cause and undermine self esteem. Moreover, if left it can lead to pain and discomfort and spread to surrounding tissues. Onychomycosis presents as a discoloured nail (white, yellow or brown), which is thick or brittle, or both. It is important to recognize that the appearance of fungal nail infections can vary.

### Onychomycosis

Nails can be infected by a dermatophyte (a fungus that obtains nutrients from keratin), a yeast (e.g. *Candida* spp), or a mould. Dermatophytes are responsible for 90 per cent of toenail and more than 50 per cent of fingernail infections. “Tinea unguium” is the term used specifically to describe dermatophytic onychomycosis. The dermatophytes comprise three genera that can cause pathogenic infections of the skin and nails in humans and animals: *Epidermophyton*, *Trichophyton* and *Microsporum*. The most common cause...
of tinea unguium (and tinea pedis - athlete’s foot) is *Trichophyton rubrum*, followed by *T mentagrophytes* and *Epidemophyton floccosum*.

Onychomycosis accounts for one-third of all fungal skin infections. Infection rates in children are about 30 times lower than in adults, and in patients with diabetes about three times higher. Immuno-suppressed individuals (e.g. as a result of disease or drug therapy) have a high susceptibility to infection. Predisposing factors for onychomycosis include: increasing age, male gender, diabetes, nail trauma, excessive sweating, peripheral vascular disease, poor hygiene, athlete’s foot, immunodeficiency and chronic exposure of the nails to water (this presents a particular risk of candidal onychomycosis).

There are several types of onychomycosis, differentiated by clinical presentation and route of invasion. Panel 1 presents four main types. "Total dystrophic onychomycosis" describes late-stage nail infection, where the entire nail has become thick and deformed as a result of any of the four types.

**Diagnosis**

It is important that pharmacists are able to distinguish distal or lateral subungual onychomycosis (DLSO) from other nail conditions because the over-the-counter amorolfine lacquer is only licensed for the treatment of mild (not more than two nails) DLSO.

Ideally, the diagnosis of onychomycosis should be confirmed by both microscopic analysis and culture of a specimen because only about 50 per cent of nail dystrophies are caused by fungal infections. There are, however, several difficulties in doing so in a community pharmacy:

- Pharmacist are not trained to take samples and it is, in any case, difficult to get a good sample of nail clippings and subungual scrapings (e.g. for suspected DLSO, samples must be taken from the nail bed and as close to the cuticle as possible).
- Microscopy and culture results can take up to six weeks (although this is not long in the context of the length of development of the condition and its treatment).
- There is also the question of who would pay for the microscopy and culture – patients are likely to be reluctant to.

Indeed, many GPs depend on clinical features alone for diagnosis of onychomycosis and do not take samples. Moreover, if results of tests come back as negative (e.g. with direct microscopy there is a 5 to 15 per cent possibility of a false negative result), some doctors will still institute antifungal treatment if the clinical signs clearly point to an infection. In the case of OTC sale of amorolfine lacquer it is recognised that there could be occasional inappropriate use, but this is relatively harmless and the licensing conditions require regular monitoring and referral to a doctor if treatment does not improve the condition.

The main diagnostic features of DLSO are:

- The nail is thickened and has turned yellow or white
- These changes appear to have started at the top of the nail but may have spread down towards the nail base
- Debris (created as a result of the in-
fection) has accumulated under the nail (“subungual debris”)
- Scaling and distortion of the nail has occurred
- The nail may have become brittle and some or all of it may have broken off.

Other conditions that may be confused with DLSO are described in Panel 2. These require treatment by a podiatrist, GP or dermatologist.

**Treating onychomycosis**

Onychomycosis is one of the most difficult fungal infections to treat because of the time it takes for the nail to grow, the hardness of the nail plate and location of the infectious process (between the nail bed and plate). For many years, griseofulvin was the only oral antifungal agent available, but its effectiveness was restricted by its limited antifungal spectrum and poor pharmacokinetic profile. In addition, topical agents were generally ineffective due to their inability to penetrate the entire nail. In recent years, however, more effective agents have become available. Oral antifungals are recommended unless the infection is mild and limited to two nails.

**Oral therapies**

Terbinafine and itraconazole are now considered to be the treatments of choice for the systemic treatment of onychomycosis. Evidence from several trials supports the effectiveness of itraconazole in onychomycosis, but a systematic review has found good evidence that a continuous regimen of the allylamine terbinafine (250 mg daily for three months) is the most effective oral treatment for fungally infected toenails.

Terbinafine inhibits ergosterol formation earlier in the synthesis pathway than the azoles (see Figure 2), at the point where squalene is converted to squalene epoxide, the precursor of lanosterol. This step does not require cytochrome P450, so side effects associated with cytochrome P450-mediated actions do not occur (see below). The resulting intracellular accumulation of squalene exerts a disruptive effect on the fungal cell membrane, a step that is likely to be fungicidal, whereas the ergosterol deficiency caused by azole antifungals is probably fungistatic.

Azole antifungals inhibit cytochrome P450-dependent enzymes in the fungal cells, impairing the formation of ergosterol, an essential component of the fungal cell wall. High doses of the imidazoles, such as ketoconazole, are required to effect this inhibition, leading to an unacceptable level of adverse effects, which include gastrointestinal effects and, rarely, hepatotoxicity. Patients on long-term ketoconazole require regular liver function tests.

In addition, there are potentially serious drug interactions between the imidazoles and drugs metabolised by cytochrome P450. Triazole antifungals (e.g. fluconazole and itraconazole) bind less strongly to mammalian cytochrome P450 enzymes than the older imidazoles but retain a high affinity for fungal P450 enzyme sites, resulting in a decreased probability of side effects.

Itraconazole reaches the site of infection within 24 hours of administration. It can be detected in the nail plate within a month of beginning therapy and persists in the nail for longer than fluconazole or terbinafine. A 200 mg dose can be taken ond continuously for three months but, because of its rapid penetration into and prolonged presence in the nail, treatment can be reduced to one-week courses at intervals, with advantages in terms of cost and a greater likelihood of adherence. This is known as “pulse therapy”, where the itraconazole is taken for seven days, with subsequent courses after a 21-day interval. Two courses are prescribed for fingernails and three for toenails.
Topical treatments

Three preparations are licensed in the UK for topical treatment of onychomycosis: amorolfine 5 per cent nail lacquer, tioconazole 28 per cent cutaneous solution and a paint containing undecanoates. There is little clinical evidence for the effectiveness of tioconazole or undecanoates in onychomycosis and both products require twice daily application to the affected nail. Use of OTC amorolfine lacquer is covered in Panel 3.

Advice for patients

Although the newer antifungal treatments have considerably increased treatment success rates in recent years, one in five onychomycosis patients is still not cured. The reasons include inaccurate diagnosis, misidentification of the pathogen and the presence of a second disorder. It is important, therefore, for pharmacists to refer patients to a podiatrist or to their GP if they are in any doubt over the diagnosis or if there appears to be no improvement after treatment.

To assist treatment and prevent recurrence, pharmacists can provide the following additional advice:

• A cure cannot be achieved overnight. It is important that treatment is continued and directions are followed.
• Wash and thoroughly dry feet everyday.
• To try to prevent the infection spreading to other toes, avoid tight fitting or occlusive shoes.
• Rest shoes periodically to limit exposure to infectious fungi.
• Use antifungal powders once a week to help keep shoes free from pathogens.
• Exercise good nail care and be alert for infection recurrence.
• Visit a podiatrist regularly.

The infection can be passed to others through contamination of shared facilities so patients should be advised not to go barefoot in the family bathroom or public places.

Resources References


References