Continuing Professional Development

An update on the management of fungal foot infection: The present and the future

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INTRODUCTION

Fungal foot infection (FFI) continues to be the most commonly encountered infection on the foot. Rarely a threat to life, it still remains a cause of morbidity and quality of life, particularly when affecting the nails.[1-3] Around 34% of the European population is thought to have FFI (as tinea pedis, onychomycosis or both).[4] Regional variation is apparent, with rates generally higher in Northern areas, probably because of longer winters, necessitating the wearing of occlusive footwear for longer periods of the year, promoting fungal growth. Infection rates are also higher in males and increase with age.[5]

The main causative agents are a group of fungi adapted to living on the keratin of skin – the dermatophytes. The most frequent agents responsible for fungal foot infection remain *Trichophyton rubrum* and, to a lesser extent, *T. mentagrophytes var. interdigitale*, which between them made up around 90% of fungal foot infections in the UK in 2005.[6]

Fungal elements are acquired from the ground, where they may lie dormant for long periods. Fungal spores then may attach and adhere to the stratum corneum,[7] and begin to germinate within 24 hours if optimum conditions are present.[8] For many patients the typical dermatophyte infection with *T. rubrum* remains silent and is often unnoticed by the sufferer,[9] leading to chronicity of the condition.

Fungal infection can reside on the plantar surface before spreading to the interdigital areas and eventually into the nails, where it can act as a protected source for further infection to other parts of the body.[10] Fungal nail infection rates are estimated to be around 8%.[11] However, like tinea pedis, infection rates increase with age[12] and are seen most frequently in the over 50s.[13] Nails that have been damaged are particularly susceptible to fungal invasion.

DIAGNOSIS OF FUNGAL FOOT INFECTION

Establishing a diagnosis remains an important step in the management of FFI, particularly if an oral drug is to be prescribed.

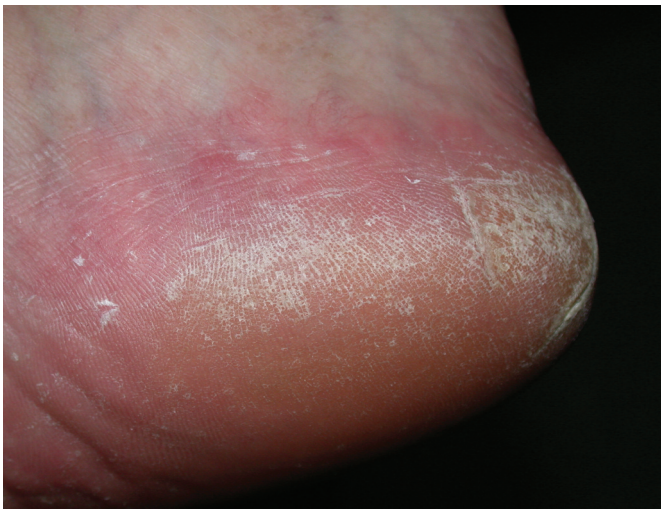

Figure 1. Plantar *T. rubrum* infection

Mycological evaluation is the most commonly used approach to establish the presence and identification of a pathogen in a sample of skin or nail. Practitioners are often frustrated by negative mycological results returned from the laboratory despite the clinical appearance of mycotic disease. In part, the success of the mycology relies on the skill of the practitioner taking the specimen and of the laboratory technician being able to process and visualise any viable fungal elements.

Firstly, studies have shown that, with typical distal and lateral onychomycosis, successful retrieval of fungus and ultimately a mycologically positive result is established by taking a nail sample as proximal as possible to the advancing fungal edge. In the studies conducted by Shemer and colleagues,[14] the more proximal the sample, the higher the yield rate, particularly if vertical drilling of

GENERIC NAME	PROPRIETARY NAME
Imidazoles	
Miconazole	Daktarin® *
Clotrimazole	Canesten®*
Econazole	Pevaryl®
Ketoconazole	Nizoral®, Daktarin Gold®
Allylamines	
Terbinafine	Lamisil® AT*
Others	
Griseofulvin	Grisol AF®
Undecenoates	Mycota® *
Tolnaftate	Scholl Athletes Foot Treatment®, Mycil*

** may also be available as non-proprietary (generic) products*

Table 1. Topical preparations available for the treatment of tinea pedis in the UK

the nail plate was incorporated[15] to help access and extract sub-ungual debris when compared with a distal nail clipping.

KEY POINT

When taking a nail sample for mycology testing, the more proximal the sample, the higher the chance of a positive diagnosis in distal fungal nail infection.

When a sample is being taken, adequate amounts must be sent to the laboratory to maximise the chances of a correct, positive diagnosis. Unlike bacterial swabs, fungal clippings do not need to be sent to the laboratory the same day. Delay causes drying in the sample, which does not affect the viability of the fungus but does kill any contaminant bacteria present. Once under the microscope and treated with potassium hydroxide (KOH), the skill of the operator is important to be able to locate and visualise fungal elements on the sample to give the diagnosis. These results can be available rapidly but the culturing of a sample on a Petri-dish can take up to several weeks.

New developments in the diagnosis of fungal foot infection

The shortcomings of these standard techniques have been noted, and alternative methods are now slowly being introduced. The Periodic-Acid Schiff (PAS) stain is a staining method that detects the presence of glycogen and other polysaccharides (glycoproteins and glycolipids) in tissues and can be rapidly performed. It has a range of applications in medicine but as fungal elements have a concentration of these products in their membrane, it has diagnostic potential in fungal infection.

Studies to confirm the effectiveness of the PAS technique have been undertaken. Compared with mycology, PAS consistently had a higher sensitivity in visualising fungal elements in samples than KOH and microscopy techniques.[16,17] Lawry[18] found PAS to be 85% sensitive compared with 57% for KOH microscopy, whilst a 2010 study found PAS 88% sensitive versus 50% for microscopy.[19] This may appear to be a future gold standard, as PAS is able to improve significantly the detection of fungal elements. However, it does not allow for identification of the specific species and occasionally false positives can be yielded when starch is present in the sample, such as with psoriatic nails,[20] and so culture still remains an important step in the process. In addition, a PAS stain costs around three times as much as fungal microscopy and culture.

Polymerase Chain Reaction techniques

Recognising the advantages of the PAS stain and its shortcomings, research has sought to develop a new technique that can demonstrate the presence of fungus consistently and identify the species, all in a timeframe much lower than the three weeks for culture. Polymerase Chain Reaction (PCR) is a molecular biological technology that can amplify sample fragments of DNA into many thousands of exact copies, permitting identification. The technique has been employed since the early 1980s and is used in paternity testing, forensic sciences and infectious diseases. Research to date in mycology has demonstrated this technique to have high sensitivities and specificities compared with traditional microscopy and cultures – in essence, showing itself to be a more rapid and reliable technique.[21] Most recently, a method has been reported giving a rapidly reliable turnaround directed at identifying the presence of dermatophyte species only.[22] Further developments are occurring and in the future, this may become a laboratory standard test.

DRUG TREATMENTS IN FUNGAL FOOT INFECTION

Topical agents for tinea pedis

Tinea pedis is a condition that is generally amenable to topical antifungal agents. In the UK today, most topical skin preparations are available from pharmacies without a prescription. A summary of the common preparations is presented in Table 1. These may be available in a range of vehicles depending on the individual products such as creams, gels, sprays etc. Some (marked with an asterisk) may also be available as non-proprietary (generic) brands and so may be cheaper for the patient to purchase.

The differences in the efficacy of topical treatments for tinea pedis have been explored. In a Cochrane review of 67 trials of topical treatments for tinea pedis, it was concluded that allylamines (terbinafine) and the azole group (miconazole, clotrimazole, etc) were much more effective than placebo. Head-to-head, allylamines (terbinafine) produced a slightly higher cure rate than the azoles[23] with a faster time to cure. In a more recent meta-analysis, a similar conclusion was reached but the superiority of terbinafine over the azoles was emphasised.[24] Topical terbinafine preparations remain more expensive than topical azole drugs, though the recent introduction of generic terbinafine products may reduce the over-the-counter costs.

In recent years, a single topical treatment for tinea pedis has been developed and introduced (as Lamisil Once®). A number of studies have concluded this to be comparable in efficacy to the traditional terbinafine cream, when used as directed.[25,26] A large scale review of terbinafine in its various forms and preparations was undertaken and concluded that the drug is equally effective in the various formulations in the topical treatment of tinea pedis.[27]

KEY POINT

Topical terbinafine has been shown to be equally effective for treating tinea pedis in all its forms, such as a spray, cream and film-forming solution.

Based on the available evidence to date, other treatments such as tolnaftate, undecenoates and older preparations such as Whitfield's ointment (benzoic and salicylic acid) are probably less effective than azoles and terbinafine. Tea tree oil (Melaleuca) remains a popular over-the-counter treatment based on its

antifungal properties. Although it has shown potential for use in interdigital tinea pedis, its propensity to cause irritancy and allergy remains an issue.[28,29] In the original study for the treatment of tinea pedis using the oil, 3.8% of subjects developed dermatitis.[30] Whilst it is appreciated that tea tree oil represents a heterogeneous group of formulations with differing properties, the available licensed topical antifungal preparations hold a significantly lower risk of irritancy and so the practitioner should consider this with the along with the needs of the patient before recommending.

KEY POINT

The use of tea tree oil in the treatment of onychomycosis is not recommended by National Institute for Health and Care Excellence (NICE) guidelines.

Emerging topical drugs in the treatment of fungal foot infection

As there is a desire to reduce risk to patients undergoing antifungal therapy, much development work has focused on new topical agents, to avoid the risks associated with systemic drugs. Traditionally, the difficulty for topical products applied to the nail has been the nail thickness and the fact that nail keratin binds many drugs, reducing the amount of free drug reaching the deeper areas of the nail plate. Pharmacological research has focussed on agents that can penetrate the nail plate more effectively. To this end, two new products have recently been developed, licensed and marketed in the USA and Japan. Luliconazole (Luzu 1% cream® and a topical nail solution) is a newer topical antifungal agent that has been licensed as a cream and solution. Although an imidazole, studies have shown its activity and potency against the common dermatophytes to be similar or superior to terbinafine, with improved drug delivery as it does not bind so readily to keratin compared with other imidazoles.[31]

Efinaconazole has also been recently licensed in the USA and Japan. A triazole agent, similar to itraconazole, this is currently marketed as a solution for the topical treatment of onychomycosis, and, like Luliconazole, it has a broad spectrum against a range of dermatophyte and non-dermatophyte moulds and does not bind to keratin, making more of the drug available for delivery through the nail.[32] Further work is ongoing to investigate these new products. These drugs are not currently available in the UK at the time of writing.

Topical agents for onychomycosis

When onychomycosis is considered to be mild to moderate (essentially sparing the lunula), topical agents can be considered although treatment requires good compliance as it can continue for 6-12 months. In the UK, there are two drugs available. Amorolfine 5% is a nail lacquer applied to the affected nails once or twice a week. It is available as a prescription only medicine (POM; Loceryl® Lacquer – 5 ml) and as a generic drug. Smaller quantities can be purchased by patients at pharmacies under the brand name Curanail® (3 ml). Tioconazole 28% is also a POM nail paint (Trosyl®) applied daily to the affected nails. Recommendations published on the use on topical antifungals suggest amorolfine to be a superior agent with cure rates of around 50%,[33] and so should be considered as the first-line choice of treatment in mild-to-moderate nail disease.

Studies have proven that the delivery of topical drugs to the infected nail can be enhanced by reducing the nail.[34-36] This should be considered as standard practice before commencing antifungal therapy. However, drilling nails has raised concerns about the hazards of nail dust.[37] Alternative techniques using a chemical

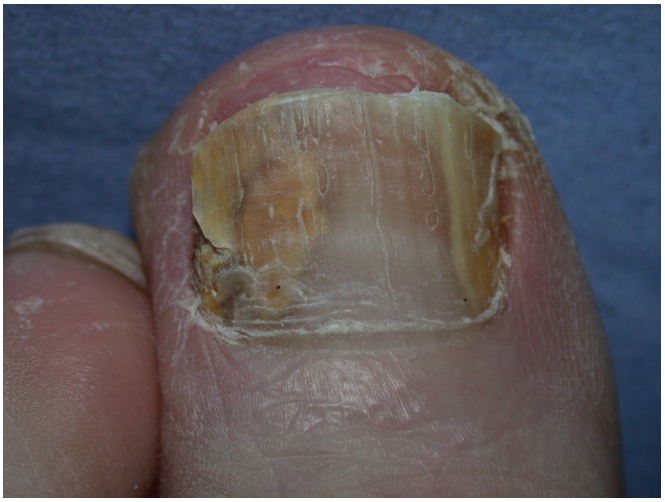

Figure 2. Onycomycosis

avulsion consisting of 40% urea applied to the nail have shown success when compared with topical treatment without urea avulsion.[38] A proprietary formulation of 40% urea fungal treatment is now available in the UK as an over-the-counter product for home use by patients (Canespro®). The cost is around £30. As the product only contains urea, an additional topical antifungal will need to be used with it, increasing the cost to the patient. Moreover, it is important to note that a 40% urea ointment will only dissolve nail that is infected and leave healthy nail intact. Therefore, the product should only be used where the nail is dystrophic through the whole thickness of the nail plate (ventral to dorsal), as sub-ungual infection underneath a relatively healthy nail will not respond to this therapy.

KEY POINT

Nail reduction prior to antifungal treatment in onychomycosis improves the cure rate.

A range of non-pharmacological treatments is available to patients such as Phytex® Paint (Borotannic complex 8%), Excilor® (Ethyllactate and acetic acid) and generic antifungal nail solutions, although published studies on these agents remain limited. Current guidelines from NICE do not recommend tea tree oil for the treatment of onychomycosis.[39]

Systemic drugs

Systemic antifungal agents are indicated in the treatment of both tinea pedis and onychomycosis, although rarely are they prescribed for the former, as topical agents are generally sufficient in most patients. The decision to treat toenail onychomycosis with a systemic agent should be considered carefully, and the following criteria are suggested as a guide to proceed with treatment:[39]

- Walking is uncomfortable.
- Abnormal-looking nails are causing significant psychological distress.
- The person has diabetes, vascular disease, or a connective tissue disorder (because of a higher risk for secondary bacterial infections and cellulitis).
- The nail infection is thought to be the source of fungal skin infection.
- The person is, or likely to become, severely immunocompromised (for example with haematological malignancy or its treatment).

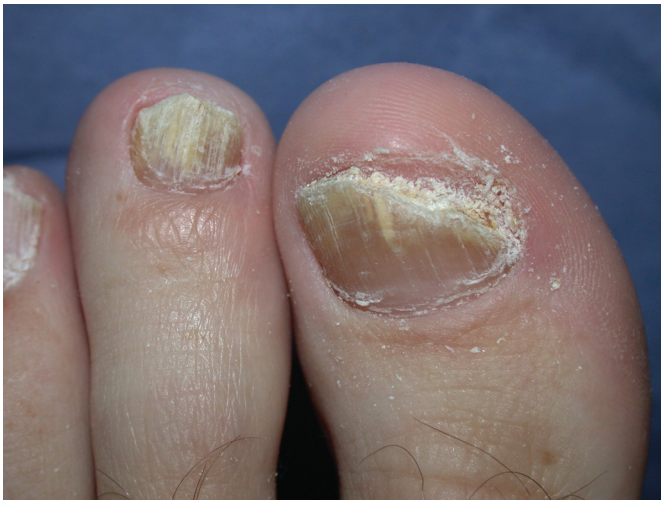

Figure 3. Nail resected to advancing edge of the fungal infection

Every patient receiving an oral antifungal agent should have a positive confirmation of the diagnosis prior to commencement to prevent inappropriate therapy. Terbinafine is recommended as the first-line drug of choice for onychomycosis, particularly when the infection is considered severe (where infection has spread to the lunula and deeper into the nail matrix). The drug is given as a 250mg dose (3-6 months with a visible improvement normally expected after three months in new nail growth). As an alternative, itraconazole can also be used (usually as pulse treatment - 200mg b.d. for one week then repeated after 21 days). At least three pulses in toenail infections are normally recommended. Meta-analysis of published studies has shown terbinafine to be more effective than itraconazole,[40,41] with fewer side-effects and interactions.

KEY POINT

Any patient receiving systemic antifungal agents should first have the infection confirmed in the laboratory to prevent prescribing errors.

When discussing systemic antifungal agents, safety is often a concern. Shortly after the launch of terbinafine, a case of liver toxicity was reported, raising concerns about its safety. Subsequent studies have consistently shown the drug to have a low incidence of adverse effects.[42-44] Typically, these have been mild and transient such as taste disturbance, nausea, abdominal pain and diarrhoea. However, systemic agents should generally be avoided in those with known liver disorders.

Griseofulvin is an older oral antifungal drug that has shown to be effective in dermatophyte nail infections. As its effectiveness is less than half that of the newer agents such as terbinafine, its use should be reserved for those who cannot take the first-line drugs, although outcomes with griseofulvin are likely to be significantly poorer.[45] It should not be used to treat onychomycosis caused by non-dermatophyte moulds due to its limited spectrum of activity. Other systemic agents such as fluconazole and ketoconazole, although unlicensed for the treatment of onychomycosis, have been used. However, oral ketoconazole (Nizoral®) has been suspended by the European Medicines Agency due to the high risks of liver toxicity associated with this drug and the availability of safer alternatives in the management of fungal nail infection.[46]

Although onychomycosis is uncommon in children, those with confirmed disease requiring systemic antifungal therapy should be referred to a dermatologist for specialist treatment.

KEY POINT

Children with onychomycosis who may require systemic treatment should be referred to a dermatologist.

LASER TREATMENTS IN ONYCHOMYCOSIS

In the last five years, laser systems have been developed and introduced into the UK and the global market as a treatment for onychomycosis. The potential effect of the laser on the invading dermatophyte has not been fully investigated. Although it has long been known that near-UV light frequencies have inactivated and destroyed microbes, the effects of the various wavelengths and energies of laser light energy have not been fully explored. Some authors have suggested photothermal effects (light energy heats water within tissues) destroying the fungus.[47] Alternate suggestions have been photomechanical effects – laser energy affecting mitochondrial membranes affecting the production of redox species, leading to the demise of the fungal cells,[48] or immune-modifying effects that ultimately inhibit or destroy fungal elements within the nail unit.

It is often assumed that approval of laser systems in Europe requires detailed, robust evidence of efficacy to allow them to proceed to market. However, this is not the case. Laser systems are licensed as medical devices, and primarily to reach market only need to demonstrate safety whilst performance can be evaluated on similar previously approved devices (termed 'substantial equivalence'). Hence, robust clinical data on their effectiveness are not required for market approval and the vast majority of cleared products reach the market without any supporting scientific data and adequate evaluation.[49] For lasers licensed as medical devices to treat onychomycosis this has been the case, with clinical reports only filtering through after they have entered the marketplace.

As a practitioner, one can often be faced with a bewildering choice of systems and suggested capabilities. Much of the literature available on the internet is of mixed quality, with many company commissioned or sponsored papers that have not undergone independent review, making the choice even more difficult. With significant sums of investment required for a practice adopting this technology, it is important for the practitioner to assess the potential benefits. In addition, in offering this service to patients, it would seem paramount to be able to give patients the best advice on the costs and likely outcomes.

Evidence to date on the efficacy of lasers in the treatment of onychomycosis has been reviewed (see suggested reading below). So far, the evidence presented has been of poor methodological quality, consisting predominantly of case series with significant variations in equipment used, treatment regimes, laser settings and follow-up, making basic comparisons difficult. Moreover, results from these studies have been conflicting. More recent papers published with longer follow-up times have discussed relapse or deterioration of the infection at the latter stages of the study, suggesting the effect of the laser may be temporary.[50,51] To date, no comparative trials have been published with large patient populations, so evidence of effectiveness is still not clear.

KEY POINT

Current evidence has not shown to date any significant benefits of laser therapies in the treatment of onychomycosis.

Of additional concern is the safe use of the devices. Training in their use is essential to ensure patient and practitioner safety - a

recent survey published a review of 50 patients who suffered treatment errors made with laser devices in non-medical practitioners.[52] Lasers are based on the principle that they deliver pulses of light energy through the nail that heat tissues to a high enough temperature that can destroy pathogens, ultimately heating the surrounding tissue and producing a plume of smoke.[53] A temperature of 55 degrees centigrade has been suggested as lethal for fungal pathogens – heating the nail unit to this temperature does risk severe pain for the patient and the additional risk of tissue burns.[54] Although this can be mitigated in some laser systems by adjusting the energy dose, length of pulse, or use of cooling sprays, the safety aspect has not been widely investigated or addressed in current studies.

Recently, a report has been published of tissue necrosis occurring in a diabetic patient undergoing laser treatment for onychomycosis.[55] Moreover, laser systems, as they produce smoke, should be used with a suitable vacuum extraction system to reduce the likelihood of inhalation of the smoke, which can contain viable fungal elements and other pathogens that may be present in the treatment area.[56]

OUTCOMES IN THE TREATMENT OF FUNGAL FOOT INFECTION

Technical success versus aesthetic failure

At the conclusion of this review, which has covered the diagnosis and treatment of fungal foot infection, it is important to appreciate the current issues around treatment outcomes with the disease. Tinea pedis remains a disease that is relatively straightforward to diagnose and, for the most part, has an effective treatment. However, onychomycosis presents more of a challenge to the practitioner and the sufferer alike.

The desired outcome for a patient presenting with onychomycosis may be subtly different for the patient and practitioner. The practitioner can see a fungal nail and can offer an intervention that can potentially destroy the fungus causing the infection (a 'mycological cure'), whilst the patient is relatively uninterested in this, and is purely seeking to restore a dystrophic nail to its former, normal appearance (the 'clinical cure'). Research into the effectiveness of the treatment of onychomycosis shows a great variability in the results, as the higher mycological cure rates are more frequently headlined in studies over the significantly lower clinical cure rate, giving an illusion that these interventions are effective, albeit not to restore a normal looking nail, but to just remove the invading fungus.

Clinical experience tells us that fungal nail infection does not occur in healthy nails, but in nails previously traumatised – confirming the clinical observation that most onychomycosis occurs in the hallux and fifth nails, due to footwear trauma. Therefore, these nails are frequently dystrophic before the infection occurs. Successful administration of any onychomycosis treatment will merely serve to remove the infection but leave a nail that is fungal free but looks onychauxic. Although a mycological cure (the fungus has gone), the patient may feel the treatment has not worked as there is very little difference in the nail appearance afterwards (a clinical cure failure).

The conclusion to this is that patients should be advised of the potential outcomes of onychomycosis before undertaking any intervention to avoid disappointment at the end of a course of treatment.

Fungal foot infection usually returns

Despite the availability of effective antifungal agents and successful mycological cures, studies have shown that fungal foot infection is very likely to return.[57,58] Re-exposure to fungal fomites is inevitable from the environment, the patient's hosiery and footwear, causing reinfection. Therefore any intervention should include detailed advice about preventing recurrence. Providing a foot is clear of fungus, normally the only route to re-infection is through the skin and, if unchecked, eventually into the nails. Therefore, prophylactic use of anti-fungal agents should be encouraged on a regular basis for those suffering persistent infections.

Figure 4. Adequate amounts of nail debris and skin must be collected to improve mycological results

Footwear and hosiery decontamination remains an option as the footwear can act as a fungal reservoir, and research proving the effectiveness of decontamination has been limited but informative. One such study demonstrated that terbinafine as a powder spray or solution can have rapid antifungal effects (within 48h) following a single application on infected insoles, lasting up to 3-6 weeks.[59] The use of copper oxide impregnated socks has been shown to be effective in a single case report but remains to be fully tested.[60]

KEY POINT

Whatever therapy is being implemented, fungal foot infection virtually always returns and so measures should be taken to prevent its recurrence.

CONCLUSION

Fungal foot infection continues to be a common problem, particularly in older adults, showing no reduction in its prevalence. Confirmation of the diagnosis is required for any patient, particularly if treatment is being considered for onychomycosis. A range of treatment options is available to patients with tinea pedis that, when used appropriately, are usually effective.

Onychomycosis remains a more significant challenge, with topical and systemic drug agents being popular. Laser therapy hailed as a step forward for the condition remains to produce convincing evidence of its safety, effectiveness or cost-effectiveness to date. Careful consideration with the patient is required before deciding on any particular treatment. Clarity in conveying the likely outcomes is important and it must be appreciated that, for many patients, despite the chance of successful treatment by any modality, reinfection over the subsequent months is a common occurrence, so measures should be taken to prevent this from occurring.

REFERENCES

1. Elewski B: The effect of toenail onychomycosis on patient quality of life. *Int J Dermatol* 1997; **36**:754-756.
2. Lubeck D, Patrick D, McNulty P, Fifer K, Birnbaum J: Quality of life of persons with onychomycosis. *Qual Life Res* 1993; **2**:341-348.
3. Turner R, Testa M: Measuring the impact of onychomycosis on patient quality of life. *Qual Life Res* 2000; 9:39-53.
4. Burzykowski G, Molenberghs D, Abeck E, Haneke E, Hay RJ, Katsambas D, Roseeuw D, van der Kerkof P, van Aelst R, Marynissen G: High prevalence of foot diseases in Europe: results of the Achilles project. *Mycoses* 2003; **46**:496-505.
5. Faergemann J, Baran R: Epidemiology, clinical presentation and diagnosis of onychomycosis. *Br J Dermatol* 2003; **149** Suppl 65:1-4.
6. Borman AM, Campbell CK, Fraser M, Johnson EM: Analysis of the dermatophyte species isolated in the British Isles between 1980 and 2005 and review of worldwide dermatophyte trends over the last three decades. *Med Mycol* 2007; **45**:131-141.
7. Zurita J, Hay RJ: Adherence of dermatophyte microconidia and arthroconidia to human keratinocytes in vitro. *J Invest Dermatol* 1987; **89**:529-534.
8. Duek L, Kaufman G, Ulman Y, Berdicevsky I: The pathogenesis of dermatophyte infections in human skin sections. *J Infect* 2004; **48**:175-180.
9. Ogasawara Y: Prevalence and patients consciousness of tinea pedis and onychomycosis. *Nippon Hifuka Gakkai Zasshi* 2003; **44**:253-260.
10. Szepietowski JC, Reich A, Garlowska E, Kulig M, Baran E: Factors influencing coexistence of toenail onychomycosis with tinea pedis and other dermatomycoses: a survey of 2761 patients. *Arch Dermatol* 2006; **142**:1279-1284.
11. Ameen M: Epidemiology of superficial fungal infections. *Clin Dermatol* 2010; 28:197-201.
12. Gupta AK, Jain HC, Lynde CW, Watteel GN, Summerbell RC: Prevalence and epidemiology of unsuspected onychomycosis in patients visiting dermatologists' offices in Ontario, Canada - a multicenter survey of 2001 patients. *Int J Dermatol* 1997; **36**:783-787.
13. Tosti A, Hay R, Arenas-Guzman R: Patients at risk of onychomycosis—risk factor identification and active prevention. *J Eur Acad Dermatol Venereol* 2005; **19** Suppl 1:13-16.
14. Shemer A, Trau H, Davidovici B, Grunwald MH, Amichai B: Nail sampling in onychomycosis: comparative study of curettage from three sites of the infected nail. In *Book Nail Sampling in Onychomycosis: Comparative Study of Curettage from Three Sites of the Infected Nail*, vol 5. pp. 1108-1111. City; 2007:1108-1111.
15. Shemer A, Davidovici B, Grunwald MH, Trau H, Amichai B: Comparative study of nail sampling techniques in onychomycosis. *J Dermatol* 2009; **36**:410-414.
16. Lilly KK, Koshnick RL, Grill JP, Khalil ZM, Nelson DB, Warshaw EM: Cost-effectiveness of diagnostic tests for toenail onychomycosis: a repeated-measure, single-blinded, cross-sectional evaluation of 7 diagnostic tests. *J Am Acad Dermatol* 2006; **55**:620-626.
17. Shenoy M, Teerthanath S, Karnaker V, Girisha B, Krishna Prasad M, Pinto J: Comparison of potassium hydroxide mount and mycological culture with histopathologic examination using periodic acid-Schiff staining of the nail clippings in the diagnosis of onychomycosis. *Indian journal of dermatology, venereology and leprology* 2008; **74**:226-229.
18. Lawry M, Haneke E, Strobeck K, Martin S, Zimmer B, Romano P: Methods of diagnosing onychomycosis. A comparative study and review of the literature. *Arch Dermatol* 2000; **136**:1112-1116.
19. Wilsmann-Theis D, Sareika F, Bieber T, Schmid-Wendtner MH, Wenzel J: New reasons for histopathological nail-clipping examination in the diagnosis of onychomycosis. *J Eur Acad Dermatol Venereol* 2011; **25**:235-237.
20. Singh G, Lavanya M: *The Reliability of Periodic Acid-Schiff Staining in the Diagnosis of Onychomycosis,* 2009.
21. Luk NM, Hui M, Cheng TS, Tang LS, Ho KM: Evaluation of PCR for the diagnosis of dermatophytes in nail specimens from patients with suspected onychomycosis. *Clin Exp Dermatol* 2012; **37**:230-234.
22. Paugam A, L'Ollivier C, Viguié C, Anaya L, Mary C, de Ponfilly G, Ranque S: Comparison of real-time PCR with conventional methods to detect dermatophytes in samples from patients with suspected dermatophytosis. *J Microbiol Methods* 2013; **95**:218-222.
23. Topical treatments for fungal infections of the skin and nails of the foot. [http://www.cochrane.org/reviews/en/ab001434.html]
24. Rotta I, Otuki MF, Sanches AC, Correr CJ: Efficacy of topical antifungal drugs in different dermatomycoses: a systematic review with meta-analysis. *Rev Assoc Med Bras* 2012; **58**:308-318.
25. Ortonne JP, Korting HC, Viguie-Vallanet C, Larnier C, Savaluny E: Efficacy and safety of a new single-dose terbinafine 1% formulation in patients with tinea pedis (athlete's foot): a randomized, double-blind, placebo-controlled study. *J Eur Acad Dermatol Venereol* 2006; **20**:1307-1313.
26. Li RY, Wang AP, Xu JH, Xi LY, Fu MH, Zhu M, Xu ML, Li XQ, Lai W, Liu WD, et al: Efficacy and safety of 1% terbinafine film-forming solution in chinese patients with tinea pedis: a randomized, double-blind, placebo-controlled, multicenter, parallel-group study. *Clin Drug Investig* 2014; **34**:223-230.
27. Korting HC, Kiencke P, Nelles S, Rychlik R: Comparable efficacy and safety of various topical formulations of terbinafine in tinea pedis irrespective of the treatment regimen: results of a meta-analysis. *American Journal of Clinical Dermatology* 2007; **8**:357-364.
28. Hammer KA, Carson CF, Riley TV, Nielsen JB: A review of the toxicity of *Melaleuca alternifolia* (tea tree) oil. *Food Chem Toxicol* 2006; **44**:616-625.
29. Rutherford T, Nixon R, Tam M, Tate B: Allergy to tea tree oil: Retrospective review of 41 cases with positive patch tests over 4.5 years. *Aust J Derm* 2007; **48**:83-87.
30. Satchell AC, Saurajen A, Bell C, Barnetson RS: Treatment of interdigital tinea pedis with 25% and 50% tea tree oil solution: A randomized, placebo-controlled, blinded study. *Australas J Dermatol* 2002; **43**:175-178.
31. Scher RK, Nakamura N, Tavakkol A: Luliconazole: a review of a new antifungal agent for the topical treatment of onychomycosis. *Mycoses* 2014:n/a-n/a.
32. Sugiura K, Sugimoto N, Hosaka S, Katafuchi-Nagashima M, Arakawa Y, Tatsumi Y, Jo Siu W, Pillai R: Efinaconazole: low keratin affinity contributes to nail penetration and fungicidal activity in topical onychomycosis treatment. *Antimicrob Agents Chemother* 2014; **58**(7):3837-3842.
33. Roberts DT, Taylor WD, Boyle J: Guidelines for treatment of onychomycosis. *Br J Dermatol* 2003; **148**:402-410.
34. Jennings MB, Pollak R, Harkless LB, Kianifard F, Tavakkol A: Treatment of Toenail Onychomycosis with Oral Terbinafine Plus Aggressive Debridement: IRON-CLAD, a Large, Randomized, Open-Label, Multicenter Trial. *J Am Pod Med Assn* 2006; **96**:465-473.
35. Malay DS, Yi S, Borowsky P, Downey MS, Mlodzienski AJ: Efficacy of debridement alone versus debridement combined with topical antifungal nail lacquer for the treatment of pedal onychomycosis: a randomized, controlled trial. *J Foot Ankle Surg* 2009; **48**:294-308.
36. Sumikawa M, Egawa T, Honda I, Yamamoto Y, Sumikawa Y, Kubota M: Effects of foot care intervention including nail drilling combined with topical antifungal application in diabetic patients with onychomycosis. *J Dermatol* 2007; **34**:456-464.
37. Tinley P, Eddy K, Collier P: Contaminants in human nail dust: an occupational hazard in podiatry? *J Foot Ankle Res* 2014; **7**:15.
38. Tietz H-J, Hay R, Querner S, Delcker A, Kurka P, Merk HF: Efficacy of 4 weeks topical bifonazole treatment for onychomycosis after nail ablation with 40% urea: a double-blind, randomized, placebo-controlled multicenter study. *Mycoses* 2013, **56**:414-421.
39. Clinical Knowledge Summaries: Fungal Nail Infection [http://cks.nice.org.uk/fungal-nail-infection#!scenariorecommendation]
40. Krob AH, Fleischer AB, Jr., D'Agostino R, Jr., Feldman SR: Terbinafine Is More Effective Than Itraconazole In Treating Toenail Onychomycosis: Results from a Meta-analysis of Randomized Controlled Trials. *JCMS* 2003; **7**:306-311.
41. Crawford F, Young P, Godfrey C, Bell-Syer S, Hart R, Brunt D: Oral treatments for toenail onychomycosis:a systematic review. *Arch Dermatol* 2002; **138**:829-830.
42. Tavakkol A, Fellman S, Kianifard F: Safety and efficacy of oral terbinafine in the treatment of onychomycosis: analysis of the elderly subgroup in Improving Results in ONychomycosis-Concomitant Lamisil and Debridement (IRON-CLAD), an open-label, randomized trial. *Am J Geriatr Pharmacother* 2006; **4**:1-13.
43. Hall M, Monka C, Krupp P, O'Sullivan D: Safety of oral terbinafine: Results of a postmarketing surveillance study in 25 884 patients. *Arch Dermatol* 1997; **133**:1213-1219.
44. Chang C-H, Young-Xu Y, Kurth T, Orav JE, Chan AK: The Safety of Oral Antifungal Treatments for Superficial Dermatophytosis and Onychomycosis: A Meta-analysis. *The American Journal of Medicine* 2007; **120**:791-798.e793.

45. Faergemann J, Anderson C, Hersle K, Hradil E, Nordin P, Kaaman T, Molin L, Pettersson A: Double-blind, parallel-group comparison of terbinafine and griseofulvin in the treatment of toenail onychomycosis. *J Am Acad Dermatol* 1995; **32**:750-753.
46. European Medicines Agency recommends suspension of marketing authorisations for oral ketoconazole [http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/07/news_detail_001855.jsp&mid=WC0b01ac058004d5c1].
47. Kimura U, Takeuchi K, Kinoshita A, Takamori K, Hiruma M, Suga Y: Treating onychomycoses of the toenail: clinical efficacy of the sub-millisecond 1,064 nm Nd: YAG laser using a 5 mm spot diameter. *Journal of drugs in dermatology : JDD* 2012; **11**:496-504.
48. Bornstein E, Hermans W, Gridley S, Manni J: Near-infrared photoinactivation of bacteria and fungi at physiologic temperatures. *Photochem Photobiol* 2009; **85**:1364-1374.
49. Karsai S, Jünger M: Laser dermatology – beware the sharks! *Br J Dermatol* 2014; **170**:473-474.
50. Hees H, Jäger MW, Raulin C: Treatment of onychomycosis using the 1064 nm Nd:YAG laser: a clinical pilot study. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft* 2014; **12**:322-329.
51. Hollmig ST, Rahman Z, Henderson MT, Rotatori RM, Gladstone H, Tang JY: Lack of efficacy with 1064-nm neodymium:yttrium-aluminum-garnet laser for the treatment of onychomycosis: A randomized, controlled trial. *J Am Acad Dermatol* 2014; **70**:911-917.
52. Hammes S, Karsai S, Metelmann H-R, Pohl L, Kaiser K, Park B-H, Raulin C: Treatment errors resulting from use of lasers and IPL by medical laypersons: results of a nationwide survey. *JDDG: Journal der Deutschen Dermatologischen Gesellschaft* 2013; **11**:149-156.
53. Gupta AK, Simpson FC: Medical devices for the treatment of onychomycosis. *Dermatologic Therapy* 2012; **25**:574-581.
54. Carney C, Cantrell W, Warner J, Elewski B: Treatment of onychomycosis using a submillisecond 1064-nm neodymium:yttrium-aluminum-garnet laser. *J Am Acad Dermatol* 2013; **69**:578-582.
55. Moutran R, Maatouk I, Hélou J: Diabetic neuropathy and Nd-YAG (1064 nm) laser for onychomycosis: be careful. *J Eur Acad Dermatol Venereol* 2014:n/a-n/a.
56. Karsai S, Daschlein G: 'Smoking guns': Hazards generated by laser and electrocautery smoke. *Journal der Deutschen Dermatologischen Gesellschaft = Journal of the German Society of Dermatology : JDDG* 2012; **10**:633-636.
57. Piraccini BM, Sisti A, Tosti A: Long-term follow-up of toenail onychomycosis caused by dermatophytes after successful treatment with systemic antifungal agents. *J Am Acad Dermatol* 2010; **62**:411-414.
58. Sigurgeirsson B, Olafsson JH, Steinsson JB, Paul C, S B, Evans EGV: Long term effectiveness of treatment with terbinafine versus itraconazole in onychomycosis. *Arch Dermatol* 2002; **138**:353-357.
59. Feuilhade de Chauvin M: A study on the decontamination of insoles colonized by Trichophyton rubrum: effect of terbinafine spray powder 1% and terbinafine spray solution 1%. *J Eur Acad Dermatol Venereol* 2012; **26**:875-878.
60. Bristow I, Turner A: Antifungal socks as part of a regime to prevent recurrence of tinea pedis and onychomycosis. *Podiatry Now* 2009; **12**:27.

FURTHER READING

1. Bristow IR, The effectiveness of lasers in the treatment of onychomycosis: a systematic review. *Journal of Foot and Ankle Research* 2014, 7:34. Full text available (free) from: http://www.jfootankleres.com/content/7/1/34/about

Key points

Learning outcomes

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