BJD
British Journal of Dermatology

British Association of Dermatologists' guidelines for the management of onychomycosis 2014

M. Ameen,[1] J.T. Lear,[2,3] V. Madan,[2,3] M.F. Mohd Mustapa[4] and M. Richardson[2,5]

[1]Royal Free London NHS Foundation Trust, Pond Street, London NW3 2QG, U.K.
[2]Manchester Academic Health Science Centre (MAHSC), University of Manchester, 46 Grafton Street, Manchester M13 9NT, U.K.
[3]Salford Royal NHS Foundation Hospital, Stott Lane, Salford M6 8HD, U.K.
[4]British Association of Dermatologists, Willan House, 4 Fitzroy Square, London W1T 5HQ, U.K.
[5]Mycology Reference Centre Manchester, University Hospital of South Manchester, Southmoor Road, Manchester M23 9LT, U.K.

Correspondence
Mahreen Ameen.
E-mail: m.ameen@nhs.net

Accepted for publication
21 July 2014

Funding sources
None.

Conflicts of interest
J.T.L. has acted as a consultant for Novartis (nonspecific); M.R. has acted as a consultant for Reckitt Benckiser (specific).

The authors are listed in alphabetical order.

M.A., J.T.L., V.M. and M.R. are members of the guideline development group, with technical support provided by M.F.M.M.

This is an updated guideline prepared for the British Association of Dermatologists (BAD) Clinical Standards Unit, which includes the Therapy & Guidelines (T&G) Subcommittee. Members of the Clinical Standards Unit who have been involved are J.R. Hughes (Chairman T&G), A. Sahota, M. Griffiths, A.J. McDonagh, S. Punjabi, D.A. Buckley, I. Nasr, V.J. Swale, C.E. Duarte Williamson, P.M. McHenry, N.J. Levell, T. Leslie, E. Mallon, K. Towers (British National Formulary), R. Davis (British Dermatological Nursing Group), C. Saunders (British Dermatological Nursing Group), S.E. Haveron (BAD Scientific Administrator), L.S. Exton (BAD Information Scientist) and M.F. Mohd Mustapa (BAD Clinical Standards Manager).

Produced in 2003 by the British Association of Dermatologists; reviewed and updated 2014

DOI 10.1111/bjd.13358

1.0 Purpose and scope

The overall objective of the guideline is to provide up-to-date, evidence-based recommendations for the management of onychomycosis. The document aims to (i) offer an appraisal of all relevant literature since January 2002, focusing on any key developments; (ii) address important, practical clinical questions relating to the primary guideline objective, for example accurate diagnosis and identification of cases, and suitable treatment to minimize the duration of disease and discomfort; (iii) provide guideline recommendations and, where appropriate, with some health economic implications; and (iv) discuss potential developments and future directions.

The guideline is presented as a detailed review with highlighted recommendations for practical use in the clinic, in addition to an updated patient information leaflet [available on the British Association of Dermatologists' (BAD) website, www.bad.org.uk].

2.0 Stakeholder involvement and peer review

The guideline development group consisted of consultant dermatologists and a consultant mycologist. The draft document was circulated to the BAD membership, the British Dermatological Nursing Group, the Primary Care Dermatological Society and the North West Region Kidney Patient Association for comments, and was peer reviewed by the Clinical Standards Unit of the BAD (made up of the Therapy & Guidelines Subcommittee) prior to publication.

3.0 Methodology

This set of guidelines has been developed using the BAD's recommended methodology[1] and with reference to the Appraisal of Guidelines Research and Evaluation (AGREE II) instrument (www.agreetrust.org).[2] Recommendations were developed for implementation in the National Health Service using a process of considered judgement based on the evidence. The PubMed, Medline and Embase databases were searched for meta-analyses, randomized and nonrandomized controlled clinical trials, case series, case reports and open studies involving onychomycosis published in the English language from January 2002

to February 2014; search terms and strategies are detailed in Data S1 (see Supporting Information). Additional relevant references were also isolated from citations in the reviewed literature, as well as from additional, independent targeted literature searches carried out by the coauthors. The preliminary results were split into four, with each consultant coauthor screening the identified titles; those relevant for first-round inclusion were selected for further scrutiny. The abstracts for the shortlisted references were then reviewed and the full papers of relevant material were obtained. The structure of the guidelines was then discussed and different coauthors were allocated separate subsections. Each coauthor then performed a detailed appraisal of the relevant literature, and all subsections were subsequently collated and edited to produce the final guidelines.

4.0 Limitations of the guideline

This document has been prepared on behalf of the BAD and is based on the best data available when the document was prepared. It is recognized that under certain conditions it may be necessary to deviate from the guidelines and that the results of future studies may require some of the recommendations herein to be changed. Failure to adhere to these guidelines should not necessarily be considered negligent, nor should adherence to these recommendations constitute a defence against a claim of negligence. Limiting the review to English language references was a pragmatic decision but the authors recognize that this may exclude some important information published in other languages.

5.0 Plans for guideline revision

The proposed revision for this set of recommendations is scheduled for 2019; where necessary, important interim changes will be updated on the BAD website.

6.0 Background

6.1 Definition

The term tinea unguium is used to describe dermatophyte infections of the fingernails or toenails.[3–5] Onychomycosis is a less specific term used to describe fungal disease of the nails. The condition is worldwide in distribution. In addition to dermatophytes, it can be caused by a number of other moulds and by *Candida* species. Some of the contributing factors causing this disease are occlusive footwear, repeated nail trauma, genetic predisposition and concurrent disease, such as diabetes, poor peripheral circulation and HIV infection, as well as other forms of immunosuppression.

There is wide geographical and racial variation in the aetiological agents of onychomycosis, but in the U.K. 85–90% of nail infections are due to dermatophytes and about 5% are due to nondermatophyte moulds.[4–6] The most commonly implicated dermatophyte is the anthropophilic species *Trichophyton rubrum*, followed by *Trichophyton interdigitale*. Zoophilic species are seldom involved, and usually only in fingernail infections.

6.2 Epidemiology

Onychomycosis is among the most common nail disorders in adults, accounting for 15–40% of all nail diseases.[7] Onychomycosis is most prevalent in older adults but, because of the limited number of large-scale studies, the actual incidence of the condition is difficult to assess. Moreover, many reports do not distinguish between dermatophytosis and other forms of onychomycosis, or between infections of the fingernails and toenails. It has been estimated that onychomycosis occurs in about 3% of the adult population in the U.K.[8]

6.3 Aetiology

Many risk factors for onychomycosis have been identified. They include increasing age, peripheral vascular disease, trauma and hyperhidrosis. Fungal nail disease is more prevalent in men and in individuals with other nail problems such as psoriasis, in persons with immunosuppressive conditions such as diabetes mellitus or HIV infection, and in those taking immunosuppressive medications. Tinea unguium is associated with tinea pedis in up to one-third of cases. The difference between the incidence of onychomycosis in men and women might be a reflection of the degree to which individuals are concerned about the appearance of their nails. Likewise, the higher incidence of onychomycosis in older individuals could be due to the greater likelihood of younger patients seeking treatment at an earlier stage. Although infrequent, onychomycosis can affect children and is most likely due to the wearing of occlusive footwear.

6.3.1 Onychomycosis in children

There are few reports studying the aetiology of onychomycosis in children. A recent study from Spain illustrates the spectrum of causal agents and disease patterns.[9] To study childhood dermatophyte onychomycosis, a retrospective study was carried out of children < 16 years of age, with dermatophyte onychomycosis diagnosed between 1987 and 2007. Of 4622 nail samples from 3550 patients, 218 came from 181 children up to 16 years old. Onychomycosis caused by dermatophytes was demonstrated in 28 cases (15·5%). *T. rubrum* (18 cases) was the most prevalent species, followed by *T. tonsurans* (five cases), *T. mentagrophytes* var. *interdigitale* (four cases) and *T. mentagrophytes* var. *mentagrophytes* (one case). Concomitant dermatophytosis at other locations was confirmed in seven cases (25%). Toenail onychomycosis was associated with tinea pedis in five cases. Distal and lateral subungual onychomycosis was the most common clinical pattern. The superficial white type was found in two cases of toenail onychomycosis caused by *T. rubrum* and *T. tonsurans*. During the period of study, only 5·1% of all investigated people were children aged up to

16 years. Onychomycosis tended to increase in prevalence over the years and represented 15·5% of all nail dystrophies in children. The findings emphasized that dermatologists must consider onychomycosis in the differential diagnosis of nail alterations in children and always perform a mycological study to confirm the diagnosis.

6.3.2 Onychomycosis in athletes

Specific aspects of athletics lead to a higher prevalence of onychomycosis in athletes, such as trauma, previous tinea pedis infection, increased sweating and increased exposure to infectious dermatophytes.[10] A study of Icelandic swimmers observed a threefold increase in the occurrence of onychomycosis in swimmers (23%) compared with the general population (8%),[11] and the Achilles survey demonstrated a 1·5 times higher prevalence of onychomycosis in athletes compared with nonathletes.[12] Fungus invading the nail can spread to the foot to cause tinea pedis when activated by periods of increased warmth and humidity or impaired immunity. Moreover, the presence of one infection may increase the risk of the other occurring. The key predisposing factors that contribute to infection in sports persons are the speed/intensity involved with sport (runners), the sudden starting and stopping nature of the sport (e.g. tennis, squash, football, cricket and ice skating), practising sports without protective footwear (e.g. gymnasts, ballet dancers), frequency of nail injuries, prevalent use of synthetic clothing and shoes that retain sweat, water sports and communal bathing.[10]

6.3.3 Onychomycosis in diabetics

Diabetics are almost three times more likely to develop onychomycosis than nondiabetics.[13] Diabetics may have increased difficulty in doing regular foot check-ups due to obesity or complications of diabetes such as retinopathy and/or cataracts. This may contribute to diabetics (typically with poor circulation of the lower extremities, neuropathy and impaired wound healing) having a generally higher risk of developing complications from onychomycosis. Diseased nails, with thick sharp edges, can injure the surrounding skin tissue and result in pressure erosion of the nail bed, injuries that may go unnoticed in diabetics due to sensory neuropathy. The injury may act as an entry point for bacteria, fungi or other pathogens, leading to limb-threatening complications or even possible amputation of the lower extremities. Approximately 34% of all diabetics have onychomycosis, as the worldwide diabetic population displays many of the risk factors associated with increased prevalence of the disease.[14]

Studies investigating the dermatophyte species in diabetic individuals are limited.[13] In agreement with the majority of previous studies, recent reports have found that the most common causative agent for tinea pedis and onychomycosis was *T. rubrum*, followed by *T. mentagrophytes* in diabetic patients.[15] The types and frequency patterns of dermatophyte species in diabetic patients were similar to those in the immunocompetent group.

6.3.4 Age and sex

Onychomycosis is reported to be more prevalent in the elderly and appears to occur more frequently in men.[5,16] Approximately 20% of the population aged over 60 years, and up to 50% of subjects aged over 70 years are reported to have onychomycosis.[5] The correlation between increasing age and onychomycosis may be attributed to reduced peripheral circulation, inactivity, suboptimal immune status, diabetes, larger and distorted nail surfaces, slower-growing nails, difficulty in grooming the nails and maintaining foot hygiene, frequent nail injury and increased exposure to disease-causing fungi.

6.3.5 Genetics

Some recent studies suggest a genetic basis for susceptibility to onychomycosis.[17] Familial patterns of distal lateral onychomycosis were caused by *T. rubrum* infection that appeared to be unrelated to interfamilial transmission. Several studies have reported the autosomal dominant pattern of inheritance associated with *T. rubrum* infection and highlighted the increased risk of developing onychomycosis in subjects where at least one parent had onychomycosis.[17]

6.3.6 Immunodeficiency

Individuals infected with HIV have an increased risk of developing onychomycosis when their T-lymphocyte count is as low as 400 cells mm^{-3} (normal range 1200–1400), and their onychomycoses tend to be more widespread, usually affecting all fingernails and toenails.[5] Proximal subungual onychomycosis has been considered as an indication of HIV infection. However, transplant recipients, individuals on immunosuppressive treatments and individuals with defective polymorphonuclear chemotaxis may exhibit a similar type of infection. *T. rubrum* is the causative fungus in most cases, except for cases of superficial white onychomycosis (SWO), which are usually caused by *T. mentagrophytes*.

Experimental human infection has been developed using different morphological forms of dermatophytes on different tissue substrates.[18] Infection of the nail plate has been induced with macroconidia, microcondia, arthrospores from natural infection, fragments of agar cultures, and dermatophyte-infected skin scales. From these studies it can be concluded that all of the different morphological forms of dermatophytes have the potential to cause human infection, but arthroconidia, because of their *in vivo* formation and shedding from the skin and nail, are likely to be the forms involved in the spread of infection.[18,19] In the direct mode of dermatophyte spread – contact with exfoliated infected material – the role of arthrospores is substantiated by the fact that besides being spores, i.e. nonvegetative and thus having no exogenous nutritional requirements, they are resistant to adverse conditions. They can also be produced in large numbers. As arthrospores are produced by fragmentation of hyphae, it is

suggested that these fungal cells are the most suitable of the dermatophyte spores for the growth of dermatophytes in the nail plate.

7.0 Rationale for treating onychomycosis

It is a common misconception among physicians that as onychomycosis is a cosmetic problem it need not be treated. However, it is clear that onychomycosis can have a significant impact on the quality of life of patients.[20] Problems associated with onychomycosis include discomfort, difficulty in wearing footwear and walking, cosmetic embarrassment and lowered self-esteem.[4] Infected nails may serve as a reservoir of fungi with a potential for spread to the feet, hands and groin. Fungal diseases are contagious and may spread to other family members, if not treated. Onychomycosis can result in disruption of integrity of the skin, providing an entry point for bacteria leading to the development of foot ulcers, osteomyelitis, cellulitis and gangrene in diabetic patients.[21] Furthermore, there can be huge financial implications of neglecting onychomycosis in this group of patients.[4] In addition, the presence of sensitizing fungal/dermatophytic antigens in the nail plate may predispose to other clinical conditions in subjects with onychomycosis. These include asthma/sensitization of the respiratory tract, and skin conditions, such as atopic dermatitis, urticaria and erythema nodosum.

Nail changes are an important medical concern for patients and, therefore, nail diseases should raise attention and receive proper care from both physicians and other healthcare providers.[22] Approximately half of all patients with onychomycosis experience pain or discomfort. About 30% of the patient population have difficulty in wearing footwear. Although onychomycosis is not a life-threatening condition, many important functional purposes of the nails may be severely compromised. Difficulty in walking, emotional embarrassment and work-related difficulties are the most commonly reported issues. However, severe cases appear even to have a negative influence on patients' sex lives. Socks and stockings may frequently be damaged, due to the constant friction with sharp, dystrophic diseased nails in patients with onychomycosis.

8.0 Classification/clinical manifestations

Onychomycosis is a fungal infection caused by various pathogens, which can adopt any of several clinical patterns. The five main clinical patterns are (i) distal and lateral subungual onychomycosis (DLSO), (ii) SWO, (iii) proximal subungual onychomycosis (PSO), (iv) endonyx onychomycosis and (v) total dystrophic onychomycosis (TDO).

8.1 Distal and lateral subungual onychomycosis

DLSO is the most common presentation of dermatophyte nail infection. Toenails are more commonly affected than fingernails. The fungus invades the nail and nail bed by penetrating the distal or lateral margins. The affected nail becomes thickened and discoloured, with a varying degree of onycholysis (separation of the nail plate from the nail bed), although the nail plate is not initially affected. The infection may be confined to one side of the nail or spread to involve the whole of the nail bed. In time the nail plate becomes friable and may break up.

The most common causative organism is *T. rubrum*. As DLSO has a similar clinical presentation whether caused by dermatophytes or nondermatophytes, it is important to obtain a nail sample for mycological examination so that the causative organism can be identified.

Tinea unguium of the toenails is usually secondary to tinea pedis, while fingernail infection often follows tinea manuum, tinea capitis or tinea corporis. Tinea unguium may involve a single nail, more than one nail, both fingernails and toenails, or, in exceptional circumstances, all of them. The first and fifth toenails are more frequently affected, probably because footwear causes more damage to these nails. Dermatophyte infection of the fingernails occurs in a similar pattern to that in the toenails, but is much less common. Fingernail infections are usually unilateral.

8.2 Superficial white onychomycosis

In SWO, the infection usually begins at the superficial layer of the nail plate and spreads to the deeper layers. Crumbling white lesions appear on the nail surface, particularly the toenails. These gradually spread until the entire nail plate is involved. Some forms of superficial infection emerge as linear bands from the proximal nail fold, but are superficial. Also some forms show deep penetration. Neither of these will respond well to topical therapy. This condition is most commonly seen in children and is usually due to *T. interdigitale* infection.

8.3 Proximal subungual onychomycosis

Most cases of PSO involve the toenails. This infection can originate either in the proximal nail fold, with subsequent penetration into the newly forming nail plate, or beneath the proximal nail plate. The distal portion of the nail remains normal until late in the course of the disease. *T. rubrum* is the usual cause. Although PSO is the least common presentation of dermatophyte nail infection in the general population, it is common in persons with AIDS, and has sometimes been considered a useful marker of HIV infection. In patients with AIDS, the infection often spreads rapidly from the proximal margin and upper surface of the nail to produce gross white discoloration of the plate without obvious thickening.

8.4 Endonyx onychomycosis

In endonyx onychomycosis, instead of invading the nail bed through the nail plate margin, the fungus immediately penetrates the nail plate keratin. The nail plate is discoloured white

in the absence of onycholysis and subungual hyperkeratosis. The most common causative organisms are *T. soudanense* and *T. violaceum*.

8.5 Total dystrophic onychomycosis

Any of the above varieties of onychomycosis may eventually progress to total nail dystrophy (TDO), where the nail plate is almost completely destroyed. Primary TDO is rare and is usually caused by *Candida* species, typically affecting immunocompromised patients.

8.6 Mixed pattern onychomycosis

Different patterns of nail plate infection may be seen in the same individual. The most common combinations include PSO with SWO, and DLSO with SWO.[23]

8.7 Candidal onychomycosis

Infection of the nail apparatus with *Candida* yeasts may present in one of four ways.

8.7.1 Chronic paronychia with secondary nail dystrophy

Chronic paronychia of the fingernails generally occurs only in patients with wet occupations and in children due to thumb sucking. 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 cuticular detachment, thus generating a vicious circle. Infection and inflammation in the area of the nail matrix eventually lead to a proximal nail dystrophy.

8.7.2 Distal nail infection

Distal nail infection with *Candida* yeasts is uncommon, and virtually all patients have Raynaud phenomenon or some other form of vascular insufficiency, or are on oral corticosteroids. 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.

8.7.3 Chronic mucocutaneous candidosis

Chronic mucocutaneous candidosis 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.

8.7.4 Secondary candidosis

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

8.8 Mould (nondermatophytic) infection of nails

Various filamentous fungi other than dermatophytes have been isolated from abnormal nails.[5,24,25] Often these are casual, transient contaminants, and direct microscopic examination of nail clippings and scrapings is negative. However, certain environmental moulds that are found in soil or plant material are capable of causing nail infection, and when this is so it is important that their significance is recognized. Unlike dermatophytes, these moulds, with the exception of *Neoscytalidium* species, are not keratinolytic and they are generally considered to be secondary invaders rather than primary pathogens of the nail plate.

There is wide geographical variation in the causative organisms, but *Scopulariopsis brevicaulis*, a ubiquitous soil fungus, is the most common cause of nondermatophyte nail infection. *Neoscytalidium dimidiatum* (formerly called *Scytalidium dimidiatum* or *Hendersonula toruloidea*) has been isolated from diseased nails as well as from skin infections of the hand and foot in patients from the tropics. Other causes of nail infection include *Acremonium* species, *Aspergillus* species, *Fusarium* species and *Onychocola canadensis*.

8.8.1 Epidemiology

Mould infections of nails have been reported in all age groups, but are most prevalent in older individuals. Men are more commonly affected than women, and toenails are more frequently involved than fingernails. The incidence of mould infection of the nails is difficult to assess from published work, because many reports do not distinguish between dermatophytosis and other forms of onychomycosis. However, it has been estimated that nondermatophyte moulds account for about 5% of cases of onychomycosis diagnosed in the U.K., and around 20% of cases diagnosed in North America.[26] Unlike dermatophytosis, these mould infections are not contagious, but many of them will not respond to the standard treatments for dermatophyte or *Candida* onychomycosis.

Similarly to dermatophytic onychomycosis, many risk factors for nondermatophytic disease have been identified.[5] They include increasing age, occlusive footwear, local trauma, peripheral vascular disease, hyperhidrosis and psoriasis. Mould infections of the nails are more prevalent in individuals with other nail problems, in persons with immunosuppressive conditions such as diabetes mellitus or HIV infection, and in those taking immunosuppressive medications.

8.8.2 Clinical manifestations

With the exception of *Neoscytalidium* infection, nondermatophyte moulds occur usually as secondary invaders in nails that

have previously been diseased or traumatized. This may account for the fact that these infections often affect only one nail.[26] The toenails, especially the big toenail, are more frequently affected than the fingernails.

A nondermatophyte mould should be suspected as the aetiological agent of onychomycosis when previous antifungal treatment has failed on several occasions, direct microscopic examination has been positive but no dermatophyte has been isolated, and there is no sign of associated skin infection.[26]

9.0 Diagnosis

9.1 Introduction

The clinical signs of tinea unguium are often difficult to distinguish from those of a number of other infectious causes of nail damage, such as *Candida*, mould or bacterial infection.[5] Unlike dermatophytosis, candidosis of the nails usually begins in the proximal nail plate, and nail fold infection (paronychia) is also present. Bacterial infection, particularly when due to *Pseudomonas aeruginosa*, tends to result in green or black discoloration of the nails. Sometimes bacterial infection can coexist with fungal infection and may require treatment in its own right.

Many noninfectious conditions can produce nail changes that mimic onychomycosis, but the nail surface does not usually become soft and friable as in a fungal infection. Nonfungal causes of nail dystrophies include chronic trauma, psoriasis, onycholysis, onychogryphosis, subungual malignant melanoma and lichen planus.

Other less common dystrophic nail conditions mimicking onychomycosis are Darier disease and lichen planus, and ichthyotic conditions such as keratosis, ichthyosis and deafness syndrome. Approximately 10% of subjects affected with lichen planus have abnormal nails, but in the majority of cases they are associated with clinical signs such as thinning of the nail plate, subungual hyperkeratosis, onycholysis and dorsal pterygium.[5] Often yellow nail syndrome is falsely identified as a fungal infection. Light green-yellowish pigmentation of the nail plate, hardness and elevated longitudinal curvature are the key clinical characteristics of this nail disease.

Repetitive trauma to the nail plate can also result in the abnormal appearance of nails. It can result in distal onycholysis leading to the colonization of the affected space by infectious pathogens and discoloration of the nail plate. A clipping of the infected nail area followed by examination of the nail bed will help to differentiate between nail trauma and onychomycosis. The nail bed will appear normal if the symptoms are caused by trauma rather than onychomycosis, with a characteristic pattern of intact longitudinal epidermal ridges stretching to the lunula.

9.2 Essential investigations and their interpretation

The clinical characteristics of dystrophic nails must alert the clinician to the possibility of onychomycosis. Laboratory confirmation of a clinical diagnosis of tinea unguium should be obtained before starting treatment. This is important for several reasons: to eliminate nonfungal dermatological conditions from the diagnosis; to detect mixed infections; and to diagnose patients with less responsive forms of onychomycosis, such as toenail infections due to *T. rubrum*. Good nail specimens are difficult to obtain but are crucial for maximizing laboratory diagnosis. Material should be taken from any discoloured, dystrophic or brittle parts of the nail. The affected nail should be cut as far back as possible through the entire thickness and should include any crumbly material. Nail drills, scalpels and nail elevators may be helpful but must be sterilized between patients. When there is superficial involvement (as in SWO) nail scrapings may be taken with a curette. If associated skin lesions are present, samples from these are likely to be infected with the same organism, and are more likely to give a positive culture.[27]

Traditionally, laboratory detection and identification of dermatophytes consists of culture and microscopy, which yields results within approximately 2–6 weeks.[5,27] Calcofluor white is exceedingly useful for direct microscopic examination of nail specimens, as the fungal elements are seen much more easily than with potassium hydroxide, thereby increasing sensitivity.[27]

9.3 Molecular diagnostics

Newer diagnostic techniques have been developed in recent years using molecular genetic tools for diagnosing dermatophytes, *Candida* species and nondermatophytic moulds.[28]

Many mycology diagnostic laboratories have implemented a molecular method for the detection of dermatophytes.[29,30] Real-time polymerase chain reaction (PCR) assays have been developed, which simultaneously detect and identify the most prevalent dermatophytes directly in nail, skin and hair samples and have a turnaround time of < 2 days.[31–34] It appears that real-time PCR significantly increased the detection rate of dermatophytes compared with culture. However, PCR may detect nonpathogenic or dead fungus, which could limit its use in identifying the true pathogen. Restriction fragment length polymorphism analysis, which identifies fungal ribosomal DNA, is very helpful for defining whether the disease is caused by repeat infection or another fungal strain when there is a lack of response to treatment.[35] However, this technique has not been implemented into routine clinical practice.

9.4 Histology

Recent studies have shown that histopathological analysis using periodic acid–Schiff staining is more sensitive than direct microscopy or culture.[36] However, this technique is not currently available in the majority of dermatology clinics or mycology laboratories. Other diagnostic techniques under investigation include flow cytometry and confocal and scanning electron microscopy.

9.5 *Candida* nail infection

Candida infection accounts for 5–10% of all cases of onychomycosis.[5] Three forms of infection are recognized: infection of the nail folds (or *Candida* paronychia), distal nail infection and total dystrophic onychomycosis. The last is a manifestation of chronic mucocutaneous candidosis. Nail and nail fold infections with *Candida* are more common in women than in men. Fingernails are more commonly affected than toenails. These infections often occur in individuals whose occupations necessitate repeated immersion of the hands in water, and the nails affected tend to be those of the dominant hand. The fourth and fifth fingers are involved less frequently than the thumbs and middle fingers. Among the various species implicated, *C. albicans* and *C. parapsilosis* are the most common.

Candida paronychia usually starts in the proximal nail fold, but the lateral margins are sometimes the first site to be affected. The periungual skin becomes swollen, erythematous and painful, and a prominent gap often develops between the fold and the nail plate. Nail plate involvement often follows, with infection usually commencing in the proximal section. White, green or black marks appear in the proximal and lateral portions of the nail and then in the distal parts. The nail becomes more opaque, and transverse or longitudinal furrowing or pitting occurs. The nail becomes friable and may become detached from its bed. Unlike dermatophyte infections, pressure on and movement of the nail is painful. Bacterial superinfection is common and it is often difficult, if not impossible, to determine which organism is the cause of the nail damage.

Distal *Candida* nail infection presents as onycholysis and subungual hyperkeratosis. It is often difficult to distinguish from dermatophytosis, but the degree of nail damage tends to be less than that seen in dermatophyte infections. Moreover, the fingernails are nearly always involved, while 80% of dermatophyte infections affect the toenails. Distal nail infection with *Candida* is uncommon and nearly all patients with this condition suffer from Raynaud phenomenon or some other underlying vascular problem.

In patients with chronic mucocutaneous candidosis, the organism invades the nail plate from the outset, causing gross thickening and hyperkeratosis. This condition is often referred to as total dystrophic onychomycosis.

9.6 Mould infection

Mould infections of nails have few specific clinical features. For this reason mycological and histological examinations should be performed on any patient with nail lesions of undetermined origin.

The correct diagnosis of onychomycosis caused by nondermatophyte moulds can be especially challenging. These nondermatophyte filamentous fungi can easily be ascertained as causing onychomycosis if distinctive morphological elements such as conidiophores are seen in addition to filaments in direct microscopy of the nail specimen, or if a fungus from warm latitudes, such as a *Neoscytalidium*, is isolated in an area in which only such fungi occur in infected patients. Most cases are more ambiguous. A fungal species such as *Aspergillus sydowii* may be isolated either as a contaminant or as an aetiological agent, and filaments seen in direct microscopy may be either nonviable dermatophyte elements or genuine nondermatophyte elements. Therefore, even exclusive and heavy isolation of such a nondermatophyte from a specimen positive for fungal filaments does not guarantee that the nail is infected by the same nondermatophyte.

10.0 Treatments

10.1 Topical treatment

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. The concentration of topically applied drug can drop by 1000 times from the outer to inner surface.[37] The hydrophilic nature of the nail plate also precludes absorption of most lipophilic molecules with high molecular weights. The role of monotherapy with topical antifungals is limited to SWO (except in transverse or striate infections), early DLSO (except in the presence of longitudinal streaks) when < 80% of the nail plate is affected with lack of involvement of the lunula, or when systemic antifungals are contraindicated. Studies comparing the efficacy of topical treatments in onychomycosis are rare. Technologies that enhance the penetration of topical antifungals into the nail plate are a matter of current research.

10.1.1 Amorolfine (strength of recommendation D; level of evidence 3; see Appendices 1 and 2)

Amorolfine (Loceryl®; Galderma, Amersham, U.K.) belongs to the morpholine group of synthetic antifungal drugs and exhibits broad-spectrum fungistatic and fungicidal activity. It inhibits the delta 14 reductase and delta 8 and delta 7 isomerase enzymes in the ergosterol biosynthetic pathway and is fungicidal against *C. albicans* and *T. mentagrophytes*. It is available as a 5% lacquer and is applied to the affected nail once or twice weekly for 6–12 months, after removal of as much of the diseased areas of the nail as possible by gentle filing. It persists in the nail for 14 days after treatment is completed. Amorolfine nail lacquer has been shown to be effective in around 50% of cases of distal fingernail and toenail onychomycosis.[38] Similar results have been obtained in other studies that have confirmed the greater efficacy of amorolfine 5% vs. the 2% concentration.[39] Once-weekly application is as effective as twice-weekly application.[40] An important observation is that the clinical improvement obtained with amorolfine and other topical antifungals may not be synonymous with mycological cure, which has invariably lower rates, often by 30%.[41] Amorolfine has also been found to be effective as a prophylactic treatment for recurrence of onychomycosis.[42] Side-effects

following amorolfine lacquer treatment are rare and are limited to local burning, pruritus and erythema.

10.1.2 Ciclopirox (strength of recommendation D; level of evidence 3)

Ciclopirox is a hydroxypyridone derivative with broad-spectrum antifungal activity against *T. rubrum*, *S. brevicaulis* and *Candida* species. Ciclopirox inhibits metal-dependent enzymatic processes including nutrient uptake, cellular energy production and degradation of toxic intracellular peroxide.[43] It is available as an 8% lacquer applied once daily for up to 48 weeks. Ciclopirox lacquer once daily was shown to be more effective than placebo in the treatment of toenail onychomycosis (34% mycological cure vs. 10% with placebo, and a clinical cure of 8% vs. 1% with placebo).[44] The recommended duration of treatment is up to 24 weeks on the fingernails and up to 48 weeks on the toenails. There are no head-to-head trials comparing amorolfine with ciclopirox in the treatment of onychomycosis; however, cure rates are usually lower with ciclopirox.[45,46] Periungual and nail fold erythema are the most common side-effects.

10.1.3 Tioconazole (strength of recommendation D; level of evidence 3)

Tioconazole is an imidazole antifungal available as a 28% solution (Trosyl®; Pfizer, Sandwich, U.K.). In an open-ended study of 27 patients with onychomycosis treated with tioconazole, mycological and clinical cure was achieved in 22% of patients.[47] Allergic contact dermatitis to tioconazole is not uncommon.[48]

10.1.4 Other topical treatments (strength of recommendation D; level of evidence 3)

Once-daily application of topical 10% efinaconazole, a new triazole antifungal agent, has recently been found to be more effective than vehicle in the treatment of onychomycosis, with mycological cure rates approaching 50% and complete cure (defined as mycological and clinical cure) in 15% of patients after 48 weeks of application.[49]

New topical formulations of terbinafine are being investigated, with early data showing promising clinical and mycological results.[50]

Butenafine, bifonazole, salicylic acid, over-the-counter mentholated ointment,[51] ozonized sunflower oil[52] and undecenoates have been used, but there are limited data to support their use as monotherapy for onychomycosis. A 40% urea ointment is now available as an over-the-counter preparation for the treatment of onychomycosis.

10.2 Systemic therapy

The main systemic drugs approved and widely used for the treatment of onychomycosis are the allylamine terbinafine and the triazole itraconazole. Griseofulvin is also licensed for treating onychomycosis but is much less commonly used now given the higher efficacy and compliance rates and lower relapse rates of the other systemic agents. Fluconazole is not licensed for the treatment of onychomycosis, but may represent a useful third-line therapy. Ketoconazole also demonstrates efficacy but the risk of hepatotoxicity with long-term therapy limits its use. In the U.S.A. and Europe, including the U.K., it has been removed from the market for the treatment of superficial mycoses. The rate of treatment failure with standard antifungal drugs is in the range of 25–40%, and this failure has been attributed to poor patient compliance, low bioavailability, lack of drug penetration into the nail, drug resistance and drug interactions.[53] The new second-generation triazoles represent a further group of therapeutic agents that may have a role in the treatment of refractory cases of onychomycosis.

10.2.1 Griseofulvin (strength of recommendation C; level of evidence 2+)

Griseofulvin (Fulcin®; Grisovin®; GlaxoSmithKline, Uxbridge, U.K.) is weakly fungistatic, and acts by inhibiting nucleic acid synthesis, arresting cell division and inhibiting fungal cell wall synthesis.[54] It is the only antifungal agent licensed for use in children with onychomycosis, with a recommended dose for the age group of 1 month and above of 10 mg kg^{-1} per day. It should be taken with fatty food to increase absorption and aid bioavailability. In adults the recommended dose is 500–1000 mg per day for 6–9 months in fingernail infection and 12–18 months in toenail infection. Mycological cure rates for toenail infection are only 30–40%. Side-effects include nausea and rashes in 8–15% of patients.[55] In adults, it is contraindicated in pregnancy and the manufacturers caution against men fathering a child for 6 months after therapy. Studies comparing griseofulvin therapy with terbinafine[56–58] and itraconazole[59,60] have demonstrated lower cure rates for griseofulvin. Griseofulvin has several limitations including lower efficacy, long treatment duration, risk of greater drug interactions and the availability of newer antifungal agents. For these reasons it is no longer a treatment of choice for onychomycosis unless other drugs are unavailable or contraindicated.

10.2.2 Terbinafine (strength of recommendation A; level of evidence 1+)

Terbinafine (Lamisil®; Novartis, Camberley, U.K.) acts by inhibiting squalene epoxidase, which is essential for the biosynthesis of ergosterol, an integral component of the fungal cell wall. Its action results in both a depletion of ergosterol, which has a fungistatic effect, and an accumulation of squalene, which appears to be directly fungicidal. It is presently the only oral fungicidal antimycotic.[61] More than 70% of terbinafine is absorbed when taken orally, and absorption is not affected by food intake; 99% of oral terbinafine binds to plasma proteins, and it is cleared mostly by the kidney and

excreted in urine. Terbinafine clearance is decreased when patients have severe liver or kidney disease. Terbinafine is strongly lipophilic and therefore distributes well in skin and nails. It is detected in the nail within 1 week of starting therapy and persists for 6 months after the completion of treatment, as it has a long half-life.[62] Terbinafine has broad and potent fungicidal effects against dermatophytes, particularly *T. rubrum* and *T. mentagrophytes*, but has lower fungistatic activity against *Candida* species than the azoles.[63] Oral terbinafine is generally well tolerated but there have been rare reports of serious adverse reactions, including Stevens–Johnson syndrome and toxic epidermal necrolysis.[64] A postmarketing surveillance study revealed that the most common side-effects were gastrointestinal (4·9%), such as nausea, diarrhoea or taste disturbance, and dermatological events (2·3%) such as rash, pruritus, urticaria or eczema. The incidence of serious adverse events was 0·04%.[65] Although studies have demonstrated that terbinafine is associated with only minimal hepatic toxicity,[66] there have been rare reports of serious hepatic toxicity, which occurred usually in patients with pre-existing liver disease.[67] Therefore, systemic terbinafine is not recommended in patients with active or chronic liver disease. Baseline liver function tests and a complete full blood count are recommended in patients with a history of heavy alcohol consumption, hepatitis or haematological abnormalities.[68] Baseline monitoring should also be considered for children, as terbinafine is not licensed for use in treating paediatric onychomycosis. Oral terbinafine has minimal drug–drug interactions. The only potentially significant drug interaction with terbinafine is with drugs metabolized by the cytochrome P450 2D6 isoenzyme. Taste disturbance is a very rarely reported adverse effect, but it can be permanent and patients should be warned of this.

10.2.3 Itraconazole (strength of recommendation A; level of evidence 1+)

Itraconazole (Sporonox®; Janssen-Cilag, High Wycombe, U.K.) is active against a range of fungi including yeasts, dermatophytes and some nondermatophyte moulds. It is not as active *in vitro* against dermatophytes as terbinafine, its minimum inhibitory concentration (MIC) being 10 times greater.[63] Although it is generally felt to be a fungistatic agent, it can achieve fungicidal concentrations, although its minimum fungicidal concentration is about 10 times higher than its MIC.[69] The mechanism of action of itraconazole is the same as that of the other azole antifungals: it inhibits the fungal cytochrome P450 oxidase-mediated synthesis of ergosterol, which is required for fungal cell walls.[70] Itraconazole is optimally absorbed with food and an acidic pH. It is highly lipophilic and is metabolized in the liver by the cytochrome P450 3A4 system, which increases the risk of it interacting with other drugs metabolized by this route. Like terbinafine, it also penetrates the nail quickly and is detectable in the nail as early as 7 days after starting therapy, and persists in the nails for up to 6–9 months after therapy discontinuation.[62] The rapid detection, concentration and persistence of itraconazole in the nail plate make the intermittent dosing regimen as efficacious as daily dosing.

The most common adverse reactions to itraconazole include headache and gastrointestinal upset. Adverse effects are lower if itraconazole is given as pulse therapy. Asymptomatic liver function abnormalities occur in 1·9% of patients treated with pulse itraconazole and in 3% of those treated with continuous itraconazole.[71] Hepatitis tends to occur with continuous therapy usually after 4 weeks. Monitoring hepatic function tests is recommended in patients with pre-existing deranged results, those receiving continuous therapy for more than a month, and with concomitant use of hepatotoxic drugs. Itraconazole is contraindicated in patients with congestive cardiac failure due to the increased risk of negative inotropic effects. Itraconazole may also prolong the QT interval, and therefore coadministration with other drugs that also increase the QT interval is contraindicated.

10.2.4 Terbinafine vs. itraconazole in dermatophyte onychomycosis

Both of these drugs have been shown to be more effective than griseofulvin in dermatophyte onychomycosis, and therefore the optimum choice of treatment lies between terbinafine and itraconazole. As both terbinafine and itraconazole persist in the nail for a considerable period after elimination from the plasma,[72] intermittent or 'pulse' treatment regimens have been developed. Unless there are contraindications, terbinafine should be considered as the first choice based on its higher efficacy and tolerability.

Terbinafine is licensed at a dose of 250 mg per day for 6 weeks in fingernail and 12–16 weeks in toenail infection. Patients should be re-evaluated 3–6 months after treatment initiation and further treatment should be given if the disease persists.[68] Itraconazole is licensed at a dose of 200 mg per day for 12 weeks continuously, or alternatively as pulse therapy at a dose of 400 mg per day for 1 week per month. Two pulses are recommended for fingernail onychomycosis and three pulses for toenail onychomycosis.

Several large studies demonstrate higher efficacy rates for terbinafine in comparison with itraconazole. A multicentre, randomized trial involving 508 subjects demonstrated complete cure (defined as negative mycological analysis and a normal nail) in 55% or 26% of patients receiving 16 weeks of continuous terbinafine or pulsed itraconazole, respectively, at follow-up at 72 weeks (*strength of recommendation A; level of evidence* 1).[73] The 151 patients in the Icelandic arm of this study were further studied for the long-term effectiveness of treatment during a 5-year blinded prospective follow-up study.[74] At the end of the study mycological cure without a second therapeutic intervention was found in 46% and 13% of the terbinafine- and itraconazole-treated patients, respectively. Mycological and clinical relapse was significantly higher in the itraconazole group (53% and 48%, respectively) than in the terbinafine group (23% and 21%) (*strength of recommendation A; level of evidence*

1). Other subsequent studies have reported similar cure rates for terbinafine and itraconazole.[75–78] Terbinafine and itraconazole have also been used to treat onychomycosis effectively and safely in special patient populations, such as children, the elderly, immunocompromised patients, diabetics and those with Down syndrome.[68,77,79] However, efficacy appears to be lower in patients over the age of 65 years, with one study demonstrating complete cure with terbinafine in only 15% of patients.[80] In patients with psoriasis, too, it has been demonstrated that response to treatment of onychomycosis with itraconazole is lower.[81]

Since the publication of the last guidelines there have been trials investigating the efficacy and tolerability of pulse terbinafine treatment for onychomycosis (500 mg per day for 1 week per month for 3 months). Results have been conflicting, with smaller studies suggesting comparable efficacy between pulse and continuous terbinafine (250 mg per day for 3 months).[82,83] However, a larger randomized trial demonstrated a mycological cure rate of 70·9% vs. 58·7% at follow-up at 18 months for continuous vs. pulse terbinafine, respectively.[76] Other regimens using 'intermittent' as opposed to pulse terbinafine therapy have also been trialled, again with variable success.[84,85] A recent meta-analysis of the efficacy of continuous and intermittent terbinafine regimens for toenail onychomycosis concluded that although continuous terbinafine is generally more effective than a pulse regimen for mycological cure, both are equally effective for complete clinical cure.[86]

In theory, it should be possible to offer an effective pulse terbinafine treatment regimen, given that terbinafine persists in nails for at least as long as itraconazole following treatment discontinuation, and it represents an attractive option as it can reduce the costs of treatment as well as drug-associated adverse effects.

Hyphanox™ (Stiefel; a GSK Company, Research Triangle Park, NC, U.S.A.) is a patented formulation of itraconazole with higher bioavailability. Stiefel completed a phase III randomized controlled trial for onychomycosis comparing a dose of 200 mg per day of Hyphanox with itraconazole 100 mg twice daily for 3 months. Although Hyphanox demonstrated no significant advantage over itraconazole (44% vs. 37% mycological cure rate, respectively) this was the largest ever clinical trial for onychomycosis, enrolling 1381 patients and demonstrating good tolerability with both formulations of itraconazole.[87]

In a meta-analysis of systemic antifungals for the treatment of onychomycosis, adverse effects led to treatment discontinuation in 3·4% of patients receiving continuous terbinafine, 2·1% of patients receiving pulse terbinafine, 4·2% of patients receiving continuous itraconazole and 2·6% of patients receiving pulsed itraconazole.[88] A recent meta-analysis comparing long-term mycological recurrences of toenail onychomycosis after successful treatment with terbinafine vs. itraconazole demonstrated a significantly lower mycological recurrence rate with terbinafine compared with itraconazole. The authors suggest that the reason for this is the fungicidal action of terbinafine compared with the fungistatic action of itraconazole.[89] Terbinafine, in comparison with itraconazole, is also associated with a lower risk of drug interactions.[90] In conclusion, terbinafine is superior to itraconazole both *in vitro* and *in vivo* for dermatophyte onychomycosis and should be considered the first-line treatment, with itraconazole as the next best alternative.

10.2.5 Fluconazole (strength of recommendation B; level of evidence 2++)

Fluconazole has a long half-life, allowing once-daily dosing. It is excreted predominantly in the urine and therefore the dose needs to be adjusted depending on the creatinine clearance. It remains detectable in toenails for up to 6 months after therapy discontinuation.[91] It has some activity against dermatophytes and some *Candida* species. Although it is currently not licensed for use in onychomycosis, attention has been focused on using it in a once-weekly dosing (450 mg) regimen. This is possible because of its pharmacokinetic properties, and it offers the advantage of improving compliance and reducing treatment costs.

Seven studies have evaluated fluconazole for the treatment of onychomycosis.[92] However, only three of these were randomized, double-blind placebo-controlled trials, which evaluated different weekly dosages of fluconazole (150–450 mg) and different treatment durations (4, 6, 9 or 12 months).[93–95] Mycological cure rates ranged from 47% to 62% in toenail infections and from 89% to 100% in fingernail infections. Clinical cure rates were lower (28–36% for toenail infections and 76–90% for fingernail infections). Higher doses (450 mg per week) and longer treatment duration (9 and 12 months) were associated with higher cure rates. There are few comparative trials, but fluconazole appears to be less effective than itraconazole or terbinafine.[96] However, fluconazole 450 mg per week for 3 months in fingernail infections, and for at least 6 months in toenail infections, may be a useful alternative in patients unable to tolerate terbinafine or itraconazole, and its once-weekly dosing regimen may improve compliance in some patients compared with daily terbinafine or itraconazole.

The common adverse effects of fluconazole include headache, skin rash, gastrointestinal complaints and insomnia. Adverse effects leading to treatment discontinuation occur in 2·0% of patients receiving fluconazole 150 mg per week, which increases to 5·8% for higher weekly doses (300–450 mg).[88] Fluconazole is a weaker inhibitor of the cytochrome P450 enzymes than itraconazole, and therefore may have fewer drug interactions.[97]

10.2.6 Second-generation triazoles (new triazoles)

The second-generation triazoles have broad-spectrum antifungal activity, particularly to yeasts and nondermatophyte moulds. They have an improved safety profile and fewer drug interactions than the first-generation triazoles. Clinical trials assessing their efficacy for onychomycosis are presently limited or ongoing. Their utility is restricted by their high cost, and to date they have been reserved primarily for the treatment of

invasive opportunistic fungal infections, particularly in the immunocompromised.

10.2.6.a. Voriconazole has demonstrated high *in vitro* activity against onychomycosis-causing dermatophytes, as well as *Candida* species, *Scopulariopsis*, *Neoscytalidium* and *Fusarium* species.[63,98] It may therefore represent a useful alternative therapeutic option for recalcitrant nail infections.[98]

10.2.6.b. Posaconazole (*strength of recommendation C; level of evidence* 2++) has broad-spectrum activity and high efficacy against yeasts and moulds. It exhibits MICs comparable with terbinafine against dermatophytes.[99] A recently completed phase II multicentre randomized double-blinded, placebo-controlled, dose-ranging study compared the efficacy of posaconazole (100, 200 or 400 mg per day for 24 weeks, or 400 mg per day for 12 weeks) with terbinafine (250 mg per day for 12 weeks) for DLSO in 218 patients. Complete cure at 48 weeks was significantly higher for posaconazole 200 mg per day for 24 weeks (54·1%) and 400 mg per day for 24 weeks (45·5%), but lower for 200 mg per day for 12 weeks (20%) compared with terbinafine (37%). Treatment was generally well tolerated. The most commonly reported adverse effects were headaches (6%), diarrhoea (5%), nausea (4%) and fatigue (4%). Seven patients receiving posaconazole had to withdraw from the study because of asymptomatic liver enzyme increases, as dictated by protocol.[100] The authors suggest that the failure to demonstrate a higher cure rate with the higher dose of posaconazole may be due to small sample sizes, or because the absorption of posaconazole into the toenail does not increase in a dose-proportional manner.

10.2.6.c. Ravuconazole (*strength of recommendation D; level of evidence* 2+) has been investigated for the treatment of distal subungual toenail onychomycosis. A phase I/II randomized, double-blind, placebo-controlled, dose-ranging study demonstrated high tolerability and mycological cure in 59% of subjects treated with oral ravuconazole 200 mg per day for 12 weeks.[101] The drug has not yet undergone phase III trials.

10.2.6.d. Albaconazole has broad-spectrum antifungal activity and good pharmacokinetic and bioavailability properties. It has already demonstrated potent activity against *Candida* and *Aspergillus* species. Its long half-life allows for weekly dosing schedules. A recent phase II double-blind, placebo-controlled study enrolled 584 patients with distal subungual toenail onychomycosis, who were randomized to receive albaconazole 100, 200 or 400 mg or placebo weekly for 24 or 36 weeks. Cure rates of 21–54% were demonstrated in the treatment groups at week 52. Efficacy was dose dependent and was highest in the group treated with 400 mg weekly for 36 weeks. Cure rates increased until week 52, and so it is possible that they might have been higher with longer follow-up periods. Treatment-related adverse effects occurred in < 3% of patients and were mild to moderate. The most common adverse effects were headache, nausea, diarrhoea and a transient and mild increase in liver enzymes.[102] The weekly dosing schedule of albaconazole has the potential to improve compliance, particularly as longer courses of antifungal therapy may be required for some patients.

10.2.6.e. Pramiconazole was developed with the objective of treating superficial infections of the skin, mucosae and nails. It has broad-spectrum action, with preclinical studies demonstrating similar or superior antifungal activity to itraconazole and ketoconazole. It has excellent bioavailability and a long half-life, permitting once-daily dosing.[103] Encouraging results from phase II clinical trials against cutaneous dermatophyte and yeast infections warrant further development and trials of this drug for onychomycosis.[104]

In conclusion, the new triazoles may play a useful role in onychomycosis that is resistant to standard antifungal agents, for the treatment of nondermatophyte moulds that have traditionally responded poorly to established antifungal therapies, and for treating special patient populations such as the immunocompromised.

10.3 Echinocandins

The echinocandins are a new class of antifungal drugs that inhibit the synthesis of glucan, an essential component of fungal cell walls. They have broad range and potent fungicidal effects against yeasts, and are used as salvage therapy for invasive candidosis and aspergillosis. They are available only as intravenous formulations and therefore are unlikely to be used for the treatment of onychomycosis.[105]

10.4 *Candida*

Clinical studies have demonstrated that itraconazole has significantly greater efficacy than terbinafine for the treatment of onychomycosis. However, studies to date are limited by relatively small patient numbers, and they do not always define the clinical subtype (DLSO, TDO or onychomycosis associated with paronychia). A study conducted in India demonstrated cure rates of 92% (12/13) vs. 40% (four of 10) for 4-month courses of pulse itraconazole (400 mg per day for 1 week each month) and pulse terbinafine (250 mg per day for 1 week each month), respectively, in the treatment of *Candida* onychomycosis.[82] A higher cure rate of 60% was achieved when *Candida* onychomycosis was treated with terbinafine 250 mg per day for 4 months.[106] Cure rates are reported to be even higher with long treatment schedules of terbinafine: mycological cure rates of 70% and 85% were demonstrated for *C. albicans* and *C. parapsilosis*, respectively, after 48 weeks of terbinafine 250 mg per day.[107] These studies suggest that terbinafine is effective, but only when given for long treatment periods. Itraconazole and fluconazole are believed to be equally effective in the treatment of *Candida* onychomycosis and should be given for a minimum of 4 weeks for fingernail and 12 weeks for toenail onychomycosis. Itraconazole can be given at a dose of 200 mg per day or as pulse therapy (400 mg per day for 1 week each month), and fluconazole can be given either as 50 mg per day or 300 mg per week.[108]

In summary, unless there are contraindications against its use, itraconazole should be considered the first-line treatment for *Candida* onychomycosis, given its shorter treatment

duration. This also means that itraconazole is more cost–effective and more likely to be associated with greater compliance. Fluconazole can be used as an alternative if there are contraindications to using itraconazole.

Chronic mucocutaneous candidosis is characterized by frequent relapses, and patients with chronic mucocutaneous candidosis often fail to respond to normal drug dosages. Therefore, it is recommended that high-dose therapy is given for long periods.[108] However, this can lead to the development of drug-resistant strains. Therefore, for this reason, other antifungals such as flucytosine, amphotericin, the new azoles such as voriconazole and posaconazole, and echinocandins have sometimes been used.[109] Some patients with chronic mucocutaneous candidiasis also develop dermatophyte onychomycosis, which can also respond poorly to treatment.

There is a distinction between the treatment of someone with a local reason for having *Candida* in the nail (e.g. Raynaud phenomenon or occupational disease) and someone with immune suppression or mucocutaneous disease. The former will also benefit from local measures, such as warm hands and work practices, both in eradication and prevention of relapse.

10.5 Nondermatophyte moulds

Onychomycosis caused by nondermatophyte moulds is often difficult to eradicate. Although clinical studies have shown that terbinafine is more efficacious than itraconazole for onychomycosis caused by dermatophytes, itraconazole has broader antimicrobial coverage for *Candida* and nondermatophyte moulds.[63] *In vitro* susceptibility testing of the common antifungals against nondermatophyte moulds has demonstrated that *Aspergillus* has excellent susceptibility to itraconazole, followed by miconazole, ketoconazole and terbinafine. *Scopulariopsis* had wide MIC ranges for nearly all antifungal drugs including terbinafine. *Fusarium* and *Acremonium* were the agents with reduced susceptibility to nearly all of the antifungal drugs tested. Of the antifungal drugs, terbinafine demonstrated the lowest activity against the majority of the nondermatophyte moulds.[110] Despite these results, it is often apparent that the clinical efficacy of drug therapy does not always correlate with the *in vitro* activity.

There are far fewer trial data of the treatment of nondermatophyte onychomycosis, perhaps because it is less common, particularly in temperate climates. The following studies, unless otherwise indicated, have used standard 3-month courses of pulse itraconazole 200–400 mg per day for 1 week each month, or terbinafine 250 mg per day. In a study of 59 cases of *Scopulariopsis* onychomycosis treated with different antifungals, there was no efficacy with griseofulvin (600 mg twice daily for 12 months), low efficacy with fluconazole (150 mg per day for 12 weeks) and ketoconazole (200 mg per day for 4 months), but high and comparable efficacy with itraconazole and terbinafine.[111] Treatment of 36 cases in Belgium, the majority of which had infection with *Scopulariopsis* (64%) followed by *Aspergillus* (22%), also demonstrated a high cure rate of 88% with itraconazole.[112] A study from India demonstrated clinical and mycological cure rates of 62% (five of eight) and 44% (four of nine) with itraconazole and terbinafine, respectively, in the treatment of nondermatophyte onychomycosis.[82] Another small study comparing itraconazole with terbinafine demonstrated higher cure rates with pulse itraconazole in the treatment of *Scopulariopsis* or *Fusarium* species responsible for onychomycosis.[113] However, terbinafine does demonstrate high efficacy against *Aspergillus* onychomycosis: pulse therapy with 500 mg per day of terbinafine for 1 week each month for 3 months led to an 88% (30/34) clinical and mycological cure rate after 1 year.[114]

In conclusion, the clinical data show that cases of onychomycosis caused by *Aspergillus* in particular, as well as *Scopulariopsis*, are generally easier to eradicate by drug therapy than other agents causing nondermatophyte mould onychomycosis. Tosti *et al.* recommend either terbinafine (250 mg per day) or pulse itraconazole (400 mg per day for 1 week per month) for 2–3 months for the treatment of *Aspergillus* species distal lateral subungual onychomycosis. For the more difficult-to-treat nondermatophyte moulds, recommended treatment should involve a combination of approaches such as systemic antifungal therapy combined with topical nail lacquers,[108] or surgical or chemical avulsion combined with topical therapy. In a trial of 59 cases of nondermatophyte onychomycosis, a significantly higher cure rate (approximately 60%) was seen with a combination of topical treatment with surgical avulsion compared with monotherapy with either terbinafine or itraconazole, which demonstrated cure rates of approximately only 20–40%, depending on species.[115] In a recent review it was concluded that systemic and/or topical therapy combined with periodic chemical or surgical nail debridement/avulsion may be the best option in the management of nondermatophyte mould onychomycosis.[24]

The new azoles may have a role in the future management of nondermatophyte mould onychomycosis, but at present there are limited clinical data. A single case report of *Neoscytalidium* onychomycosis showed good response to pulse posaconazole therapy (400 mg twice daily for 5 days each month for 3 months), but there was subsequent relapse.[116] Voriconazole was more successful in the treatment of *Neoscytalidium* onychomycosis.[117]

10.6 Treatment of paediatric onychomycosis

Onychomycosis is less common in children, with an approximate worldwide prevalence of $< 0{\cdot}5\%$.[118] However, as in adults, the toenails are more commonly affected, and DLSO is the most common presentation.[9] The dominant aetiological agents in childhood cases of onychomycosis are *T. rubrum*, *T. mentagrophytes* and *Candida* species. Children with onychomycosis should be examined carefully for concomitant tinea capitis and tinea pedis. Their parents and siblings should also be checked for onychomycosis and tinea pedis.

As the nail plate in children is thin and grows faster than in adults, topical treatment is often advocated. However, there are no clinical trials demonstrating the efficacy of topical therapies

for onychomycosis in paediatric populations. In addition, some experts believe that, as in adult onychomycosis, topical therapies alone are generally ineffective, particularly when there is significant nail plate disease or nail matrix involvement.[119]

There are clinical trial data demonstrating the efficacy and safety of systemic treatment for paediatric onychomycosis. A systematic review of all data was recently published by Gupta and Paquet, and describes five clinical trials, three retrospective analyses and a number of case reports.[120] The following two studies demonstrated efficacy for both itraconazole and terbinafine. A study of only 17 cases (age 3–14 years, mean 8·5) treated with pulse itraconazole (5 mg kg^{-1} per day for 1 week each month) for 3–5 months demonstrated a high clinical cure rate of 94% with no relapse for 1–4·25 years after therapy initiation.[121] A more recent study of 36 cases (age 4–17 years) of onychomycosis treated with either a 12-week course of itraconazole 200 mg per day, or daily terbinafine at a dose determined by body weight, demonstrated clinical cure in 100% of cases treated with itraconazole and in 88% of cases treated with terbinafine.[79] Treatment with both drugs is well tolerated in paediatric populations.[79,121,122] These studies demonstrate higher cure rates for paediatric onychomycosis than adult onychomycosis and also a faster response to treatment in paediatric populations.

In summary, the three drugs that are proposed for use in the systemic management of paediatric onychomycosis are terbinafine, itraconazole and fluconazole. The azoles are advocated when onychomycosis is caused by *Candida* species.[123] Griseofulvin is no longer recommended as the first line of treatment for paediatric onychomycosis, because of long treatment duration and low efficacy. Pulse itraconazole therapy (5 mg kg^{-1} per day for 1 week every month) is recommended for 2 months for fingernail infection and 3 months for toenail infection. Fluconazole is recommended at 3–6 mg kg^{-1} once weekly for 12–16 weeks for fingernail infection and 18–26 weeks for toenail infection. Daily terbinafine is recommended for 6 weeks for fingernail and 12 weeks for toenail infection at 62·5 mg per day if weight is < 20 kg, 125 mg per day for 20–40 kg weight, and 250 mg per day if weight exceeds 40 kg.[119,122–124]

Griseofulvin is the only systemic antifungal drug licensed for use in children. Although terbinafine is presently not licensed for use in children under the age of 12 years, it is now accepted as being recommended by consensus for the treatment of paediatric onychomycosis. It is helpful that the safety of systemic terbinafine for the treatment of tinea capitis in children has been established, although the duration of drug therapy required for tinea capitis is usually not as long as for onychomycosis.

10.7 Combination treatment (strength of recommendation D; level of evidence 3)

Slow nail growth and suboptimal concentration in the affected nail may explain failure of topical antifungal monotherapy in many cases of onychomycosis. It has been suggested that a combination of topical and systemic antifungal treatments for onychomycosis provides antimicrobial synergy, wider antifungal spectrum with improved fungicidal activity, increased cure rates, suppression of resistant mutants and enhancement of tolerability and safety.[125] Topical imidazoles, ciclopirox and amorolfine have all been used in combination with systemic antifungal agents.

Tioconazole 28% solution combined with 1 g oral griseofulvin for 1 year resulted in 69% clinical and mycological cure, compared with 41% in a griseofulvin-only group.[126]

Amorolfine 5% nail lacquer in association with two pulses of itraconazole therapy was at least as effective as three pulses of itraconazole alone in moderate-to-severe fingernail onychomycosis caused by *Candida*.[127] The combination was also shown to be more effective in severe toenail onychomycosis.[128] A multicentre randomized controlled study showed that in the treatment of dermatophytic toenail onychomycosis with matrix involvement, amorolfine 5% nail lacquer once weekly for 12 months in combination with oral terbinafine 250 mg per day for 3 months was more effective than oral terbinafine alone for 3 months.[78] Similarly, combination therapy with topical ciclopirox and oral terbinafine has been suggested to improve cure rates when compared with systemic treatment alone.[129]

However, another study found that combination of amorolfine or ciclopirox nail lacquers with oral terbinafine pulse therapy did not offer any advantage over oral terbinafine pulse monotherapy in the treatment of onychomycosis caused by dermatophytes, yeasts and nondermatophyte moulds.[130]

There is sufficient evidence to recommend combination therapy if response to topical monotherapy is likely to be poor, such as may be the case in proximal nail disease.

10.8 Onychomycosis in special groups

10.8.1 Diabetics

Up to one-third of diabetics may have onychomyosis.[14] This high prevalence of onychomycosis in diabetics is attributed to a combination of host factors including impaired glycaemic index, ischaemia, neuropathy and local immunosuppression. Onychomycosis is a significant predictor for the development of foot ulcers in diabetes.[131] Low risk of drug interactions and hypoglycaemia makes terbinafine the oral antifungal agent of choice in the treatment of onychomycosis in diabetics.[132] Itraconazole is contraindicated in congestive heart failure due to increased risk of negative ionotropic effect. As there is increased prevalence of cardiac disease in diabetics, terbinafine is preferred over itraconazole in the treatment of onychomycosis in this population. Topical treatments may be appropriate for mild-to-moderate infections and where risk of drug interaction is considered high.

10.8.2 Immunosuppression

The prevalence of onychomycosis in HIV-positive patients is approximately 30%, and correlates with CD4 counts of

450 mm.[133] While PSO was over-represented in patients with AIDS in the 1990s, introduction of highly active antiretroviral treatments and fluconazole treatment of oropharyngeal candidosis may explain the reduction in incidence of PSO in this patient population.[134,135] Iatrogenic immunosuppression also increases the risk of onychomycosis.[136] Most cases of onychomycosis in immunosuppressed patients are due to *T. rubrum*. Nondermatophytes account for only a small proportion of the cases of onychomycosis in immunosuppressed patients.[137] Griseofulvin is the least effective oral antifungal in the treatment of onychomycosis in patients with HIV.[138] As there is an increased risk of interaction of itraconazole and ketoconazole with antiretrovirals, terbinafine and fluconazole are preferred for the treatment of onychomycosis in this patient population.[139]

10.9 Surgery, lights and lasers (level of evidence 1−)

Surgical avulsion followed by topical antifungal therapy would seem a logical approach for single-nail onychomycosis, but results from a randomized controlled trial were disappointing.[140] Further studies are needed in this area, and at present this treatment is not recommended based on the evidence available.

Debridement alone cannot be recommended as a treatment for onychomycosis.[141] Mechanical intervention may be necessary to remove the dermatophytomas within the nail plate or nail bed.

In a single-centre open trial, photodynamic therapy (PDT) has recently been reported to achieve cure rates of 44·3% at 12 months, reducing to 36·6% at 18 months.[142]

Based on the paucity of available evidence, PDT cannot currently be recommended for the treatment of onychomycosis (*strength of recommendation D; level of evidence* 3).

Newer devices such as near infrared diode at 870 and 930 nm, and millisecond 1064-nm neodymium-doped yttrium aluminium garnet lasers are showing promising results in the treatment of onychomycosis, but recommendations cannot be made at this stage.[143–145]

11.0 Treatment failure or relapse?

Onychomycosis has often been associated with high recurrence rates (40–70%), and many patients have a long history of disease recurrence.[146] The term 'recurrence' suggests both relapse and reinfection. In treatment relapse, infection is not completely cured and returns. This implies treatment failure. In reinfection the ailment is completely cured and is followed by a new infection by the same or a different organism. Fungal-free nails are the goal of antifungal therapy in onychomycosis. Because of the slow growth pattern of the toenails, up to 18 months is required for the nail plate to grow out fully. Therapeutic success of antifungal therapy of onychomycosis depends on the newly grown-out nail plate being fungus free.

Onychomycosis is a deep-seated, recalcitrant fungal infection. The *in vitro* activity of antifungal drugs does not always correlate with their clinical efficacy. This may be attributed to the carriage of arthroconidia and chlamydoconidia (resting fungal elements) in the nail plate. In occasional cases, pockets of tightly packed hyphae develop in the subungual space, leading to a dense white lesion (termed a dermatophytoma) visible beneath the nail. This type of infection can be resistant to antifungal treatment without prior removal of the lesion. This appearance is most often seen in the great toenail. Other nail characteristics such as nail thickness (> 2 mm), slow outgrowth, severe onycholysis and dermatophytoma also contribute to the failure of antifungal therapy. The resting fungal elements are highly resistant to antifungal therapy and appear to survive in the nail plate environment and in footwear for long periods of time, even contributing to the recurrence of infection after therapy is stopped.

The major risk factors for recurrence include family history, coexisting ancillary clinical conditions (diabetes, arterial and vascular diseases, Down syndrome, Raynaud syndrome), immune suppression and acquired or inherent immunodeficiency. Other previously implicated prognostic factors are coexisting bacterial/viral nail infections, erroneous diagnosis, poor compliance, antifungal resistance and poor choice of antifungal therapy. Furthermore, the role of disease-causing fungi is also critical. Generally, onychomycosis caused by nondermatophytic moulds does not respond to oral antifungal therapy, and current effective management options are limited.

12.0 Prevention

Recurrence of onychomycosis may occur in some patients after discontinuation of therapy. *T. rubrum* is commonly found in hotel bedrooms, carpeting, gyms and the changing rooms of most public bathing facilities. For this reason, it is essential that the importance of always wearing protective footwear to avoid re-exposure is emphasized to patients at risk. Other strategies include application of an absorbent powder, and antifungal powders containing miconazole, clotrimazole or tolnaftate in shoes and on the feet, and wearing cotton, absorbent socks. It is also important for patients to keep their nails as short as possible and to avoid sharing toenail clippers with family members and friends.

Shoes can contain a large number of infective fungal elements. In many instances, it is best to discard all 'old and mouldy' footwear. If this is impossible, fungal elements can be eliminated by putting naphthalene mothballs in the shoes and then leaving them enclosed within a tightly tied plastic bag for a minimum of 3 days. Afterwards, the patient can air the shoes to remove the odour of the naphthalene. The fungal arthroconidia should be dead. However, it is still helpful to continue to apply antifungal powders inside shoes to ensure that all infective fungal elements are eliminated. An alternative is to spray a terbinafine solution into shoes on a periodic basis. Because both onychomycosis and tinea pedis are contagious, all infected family members must also be treated at the

Table 1 Summary of drug therapies in adults

Strength of recommendation	Treatment in adults	Contraindications and cautions	Suggested method of use and monitoring	Common adverse reactions
	Systemics			
A	Itraconazole: first line of treatment for dermatophyte onychomycosis	Heart failure, hepatotoxicity	200 mg per day for 12 weeks continuously, or alternatively as 'pulse therapy' at a dose of 400 mg per day for 1 week per month. Two pulses are recommended for fingernails and three pulses for toenails. It is optimally absorbed with food and an acidic pH Monitoring hepatic function tests is recommended in patients with pre-existing deranged results, in those receiving continuous therapy for more than a month, and with concomitant use of hepatotoxic drugs	Headache and gastrointestinal upset
	Terbinafine: first line of treatment for dermatophyte onychomycosis, and generally preferred over itraconazole	Hepatic impairment, renal impairment	250 mg per day for 6 weeks in fingernail and 12–16 weeks in toenail infection Baseline liver function tests and a complete full blood count are recommended in adult patients with a history of hepatotoxicity or haematological abnormalities	Headache, taste disturbance and gastrointestinal upset. Can aggravate psoriasis and cause a subacute lupus-like syndrome
B	Fluconazole: may be a useful alternative in patients unable to tolerate terbinafine or itraconazole	Hepatic impairment, renal impairment	150–450 mg per week for 3 months in fingernail infections and for at least 6 months in toenail infections Perform baseline liver function tests and full blood count. Monitor liver function tests in high-dose or prolonged therapy and in those at risk because of concomitant hepatotoxic drug use	Headache and gastrointestinal upset
C	Griseofulvin: lower efficacy and higher relapse rates compared with terbinafine and itraconazole	Liver impairment	500–1000 mg per day given for 6–9 months in fingernail infection and 12–18 months in toenail infection. It should be taken with fatty food to increase absorption	Headache and gastrointestinal upset
D	Combination treatment: recommended if response to topical monotherapy is likely to be poor			
	Topicals			
D	Amorolfine: useful for superficial and distal onychomycosis		5% lacquer applied once or twice a week for 6–12 months	Adverse effects are rare: local burning, pruritus and erythema
	Ciclopirox: useful for superficial and distal onychomycosis and for patients in whom systemic therapy is contraindicated		8% lacquer applied once daily for up to 48 weeks	Adverse effects are rare: periungual and nail fold erythema
	Tioconazole: useful for superficial and distal onychomycosis		28% solution applied twice daily for 6–12 months	Allergic contact dermatitis

Table 2 Summary of drug therapies in children (age 1–12 years)

Strength of recommendation	Treatment in children	Contraindications and cautions	Suggested method of use and monitoring	Common adverse reactions
A	Itraconazole: first line of treatment for dermatophyte onychomycosis	Heart failure, hepatotoxicity	'Pulse therapy' 5 mg kg^{-1} per day for 1 week per month. Two pulses are recommended for fingernails and three pulses for toenails. It is optimally absorbed with food and an acidic pH Monitoring hepatic function tests is recommended in patients with pre-existing deranged results, in those receiving continuous therapy for more than a month, and with concomitant use of hepatotoxic drugs	Headache and gastrointestinal upset
	Terbinafine: first line of treatment for dermatophyte onychomycosis and generally preferred over itraconazole	Hepatic impairment, renal impairment	62·5 mg per day if weight is < 20 kg, 125 mg per day for 20–40 kg weight, and 250 mg per day for > 40 kg, for 6 weeks in fingernail and 12 weeks in toenail infection Baseline liver function tests and a complete full blood count are recommended in paediatric patients as it is unlicensed for use in children	Headache, taste disturbance and gastrointestinal upset. Can aggravate psoriasis and cause a subacute lupus-like syndrome
B	Fluconazole: consider as second line if itraconazole and terbinafine contraindicated or not tolerated	Hepatic impairment, renal impairment	3–6 mg kg^{-1} once a week for 12–16 weeks for fingernail and 18–26 weeks for toenail infection Perform baseline liver function tests and full blood count. Monitor liver function tests in high-dose or prolonged therapy and in those at risk because of concomitant hepatotoxic drug use	Headache and gastrointestinal upset
C	Griseofulvin: consider as second line if itraconazole and terbinafine contraindicated or not tolerated	Liver impairment	10 mg kg^{-1} per day for age groups of 1 month and above (maximum 500 mg) It should be taken with fatty food to increase absorption	Headache and gastrointestinal upset

same time to avoid reinfection. It is helpful to recommend comfortable, well-fitting shoes and to avoid trauma to the nail.

It is important to discuss the role of nail salons to patients who develop nail infections. Frequent manicures and pedicures predispose many patients to a variety of nail problems, including paronychial infections and primary onycholysis due to *Candida*, as well as dermatophytic nail infections. Patients who have developed these infections should be advised to frequent salons that employ a sterile technique.

13.0 Mycological resistance

Oral antifungal therapy with agents such as terbinafine and itraconazole is the treatment of choice for onychomycosis and dermatophytosis that does not respond to topical therapies. The activity spectrum of these drugs is variable, leading to treatment failure in 25–40% of treated patients, possibly due to poor patient compliance, lack of drug penetration into the nail, medication bioavailability, or drug interactions and resistance.

The European Committee on Antimicrobial Susceptibility Testing has described a reference broth microdilution method for testing *Candida* susceptibility,[147] and the Clinical and Laboratory Standards Institute has developed the M38-A technique for testing filamentous moulds; however, dermatophytes have not been included in this method.[148] Little research has focused on the drug resistance of dermatophytes and nondermatophytic species. Importantly, the *in vitro* activity of antifungal medications has not been shown to be a predictor of clinical outcomes. In an illustrative study, terbinafine and voriconazole were the most potent agents against dermatophytes. Itraconazole and voriconazole were the most active agents against yeast species.[63]

Importantly, these studies cannot be used for clinical guidelines, and the MIC values obtained must be tested in a well-designed clinical study. Such future work is necessary to assist clinicians in choosing the best therapeutic option.

14.0 Pharmacoeconomic considerations

Systemic drug therapy for onychomycosis is costly, as generally long treatment courses are required, especially for toenail onychomycosis. Moreover, treatment duration is often increased in the context of immunosuppression. Consideration of the cost of drug therapy may be taken into account when assessing the risk-to-benefit ratio of onychomycosis treatment. Clinical trials of three of the major drug therapies for onychomycosis (itraconazole, terbinafine and fluconazole) have all investigated the efficacy of weekly or 'pulse' therapy, which would considerably decrease the cost of treatment. There are some encouraging data suggesting comparable efficacy with daily dosing and supporting these intermittent dosing regimens when cost issues are important. In resource-limited regions of the world fluconazole is often more readily available and cheaper than other antifungal agents, making it a more attractive therapeutic option for onychomycosis.

15.0 Future directions

Areas of unmet need and uncertainty in the treatment of onychomycosis that require further studies include (i) physical therapies, including surgery, lasers and PDT; (ii) a greater understanding of the pharmacodynamics and pharmacokinetics of antifungal drugs and the potential role for therapeutic drug monitoring; (iii) a greater role for combination therapy, either systemic and topical or systemic in combination, which should improve efficacy and drug-related adverse effects; (iv) greater understanding of drug resistance and (v) poor compliance.

16.0 Recommended audit points

- In the last 30 consecutive patients with onychomycosis treated with a systemic agent, has a positive culture been obtained before commencing therapy?
- In the last 30 consecutive patients with onychomycosis, has an appropriate treatment agent been chosen based on the type of organism cultured?
- In the last 30 consecutive patients with onychomycosis, were arrangements made for adequate duration of treatment to be supplied from the hospital or general practitioner?
- In the last 30 consecutive patients with atypical onychomycosis and in nonresponders, has immunosuppression been considered?
- In the last 30 consecutive patients, has culture at the end of treatment to confirm mycological clearance been considered, at least in high-risk groups?

The audit recommendation of 30 cases per department is to reduce variation in the results due to a single patient, and to allow benchmarking between different units. However, departments unable to achieve this recommendation may choose to audit all cases seen in the preceding 12 months.

17.0 Summary

Onychomycosis is among the most common nail disorders in adults.[7] The management of onychomycosis requires the correct mycological identification where possible, assessing disease susceptibility and risk factors and deciding what therapy options are most suitable for the clinical form of onychomycosis and aetiological agent. Some patients will require monitoring, particularly high-risk patients, and at the end of the recommended course of treatment they should be reassessed for mycological cure. Tables 1 and 2 summarize the drug therapies recommended in this guideline. Full details of the evidence have been provided in the main text.

Acknowledgments

We are very grateful to Lesley Exton (BAD Information Scientist) and Sara Haveron (BAD Scientific Administrator), as well as everyone who commented on the draft during the consultation period.

References

1 Bell HK, Ormerod AD. Writing a British Association of Dermatologists clinical guideline: an update on the process and guidance for authors. *Br J Dermatol* 2009; **160**:725–8.
2 Brouwers M, Kho ME, Browman GP *et al.* AGREE II: Advancing guideline development, reporting and evaluation in healthcare. *CMAJ* 2010; **182**:E839–42.
3 de Berker D. Clinical practice. Fungal nail disease. *N Engl J Med* 2009; **360**:2108–16.
4 Thomas J, Jacobson GA, Narkowicz CK *et al.* Toenail onychomycosis: an important global disease burden. *J Clin Pharm Ther* 2010; **35**:497–519.
5 Richardson MD, Warnock DW. *Fungal Infection: Diagnosis and Management*, 4th edn. Chichester: Wiley-Blackwell, 2012.
6 Roberts DT, Taylor WD, Boyle J. Guidelines for treatment of onychomycosis. *Br J Dermatol* 2003; **148**:402–10.
7 Burns T, Breathnach S, Cox N, Griffiths C, eds. *Rook's Textbook of Dermatology*, 8th edn. Chichester: Wiley-Blackwell, 2010.
8 Roberts DT. Prevalence of dermatophyte onychomycosis in the United Kingdom: results of an omnibus survey. *Br J Dermatol* 1992; **126**(Suppl. 39):23–7.
9 Rodríguez Pazos L, Pereiro Ferreirós M, Pereiro M, Toribio J. Onychomycosis observed in children over a 20-year period. *Mycoses* 2011; **54**:450–3.
10 Field LA, Adams BB. Tinea pedis in athletes. *Int J Dermatol* 2008; **47**:485–92.
11 Gudnadottir G, Hilmarsdottir I, Sigurgeirsson B. Onychomycosis in Icelandic swimmers. *Acta Derm Venereol* 1999; **79**:376–7.
12 Caputo R, De Boulle K, Del Rosso J, Nowicki R. Prevalence of superficial fungal infections among sports-active individuals: results from the Achilles survey, a review of the literature. *J Eur Acad Dermatol Venereol* 2001; **15**:312–16.
13 Al-Mutairi N, Eassa BI, Al-Rqobah DA. Clinical and mycologic characteristics of onychomycosis in diabetic patients. *Acta Dermatovenerol Croat* 2010; **18**:84–91.
14 Gupta AK, Konnikov N, MacDonald P *et al.* Prevalence and epidemiology of toenail onychomycosis in diabetic subjects: a multicentre survey. *Br J Dermatol* 1998; **139**:665–71.
15 Romano C, Massai L, Asta F, Signorini AM. Prevalence of dermatophytic skin and nail infections in diabetic patients. *Mycoses* 2001; **44**:83–6.
16 Baran R. The nail in the elderly. *Clin Dermatol* 2011; **29**:54–60.
17 Faergemann J, Correia O, Nowicki R, Ro BI. Genetic predisposition – understanding underlying mechanisms of onychomycosis. *J Eur Acad Dermatol Venereol* 2005; **19**:17–19.
18 Richardson MD, Edward M. Model systems for the study of dermatophyte and non-dermatophyte invasion of human keratin. In: *Biology of Dermatophytes and Other Keratinophilic Fungi* (Kushwaha RKS, Guarro J, eds). Bilbao: Revista Iberoamericana de Micologia, 2000; 115–21.
19 Yazdanparast SA, Barton RC. Arthroconidia production in *Trichophyton rubrum* and a new *ex vivo* model of onychomycosis. *J Med Microbiol* 2006; **55**:1577–81.
20 Elewski BE. Onychomycosis. Treatment, quality of life, and economic issues. *Am J Clin Dermatol* 2000; **1**:19–26.
21 Tan JS, Joseph WS. Common fungal infections of the feet in patients with diabetes mellitus. *Drugs Aging* 2004; **21**:101–12.
22 Reich A, Szepietowski JC. Health-related quality of life in patients with nail disorders. *Am J Clin Dermatol* 2011; **12**:313–20.
23 Hay RJ, Baran R. Onychomycosis: a proposed revision of the clinical classification. *J Am Acad Dermatol* 2011; **65**:1219–27.
24 Gupta AK, Drummond-Main C, Cooper EA *et al.* Systematic review of nondermatophyte mold onychomycosis: diagnosis, clinical types, epidemiology, and treatment. *J Am Acad Dermatol* 2012; **66**:494–502.
25 Hwang SM, Suh MK, Ha GY. Onychomycosis due to nondermatophytic molds. *Ann Dermatol* 2012; **24**:175–80.
26 Gupta A, Drummond-Main C. Systematic review of nondermatophyte mold onychomycosis: diagnosis, clinical types, epidemiology, and treatment. *J Am Acad Dermatol* 2012; **66**:AB122.
27 Public Health England. UK standards for microbiology inverstigations. investigation of dermatological specimens for superficial mycoses. Available at: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317132858351 (last accessed 30 July 2014).
28 Hay RJ, Jones RM. New molecular tools in the diagnosis of superficial fungal infections. *Clin Dermatol* 2010; **28**:190–6.
29 Monod M, Bontems O, Zaugg C *et al.* Fast and reliable PCR/sequencing/RFLP assay for identification of fungi in onychomycoses. *J Med Microbiol* 2006; **55**:1211–16.
30 Alexander CL, Shankland GS, Carman W, Williams C. Introduction of a dermatophyte polymerase chain reaction assay to the diagnostic mycology service in Scotland. *Br J Dermatol* 2011; **164**:966–72.
31 Bergmans AM, van der Ent M, Klaassen A *et al.* Evaluation of a single-tube real-time PCR for detection and identification of 11 dermatophyte species in clinical material. *Clin Microbiol Infect* 2010; **16**:704–10.
32 Kondori N, Abrahamsson AL, Ataollahy N, Wennerås C. Comparison of a new commercial test, Dermatophyte-PCR kit, with conventional methods for rapid detection and identification of *Trichophyton rubrum* in nail specimens. *Med Mycol* 2010; **48**:1005–8.
33 Litz CE, Cavagnolo RZ. Polymerase chain reaction in the diagnosis of onychomycosis: a large, single-institute study. *Br J Dermatol* 2010; **163**:511–14.
34 Wisselink GJ, van Zanten E, Kooistra-Smid AM. Trapped in keratin; a comparison of dermatophyte detection in nail, skin and hair samples directly from clinical samples using culture and real-time PCR. *J Microbiol Methods* 2011; **85**:62–6.
35 Li XF, Tian W, Wang H *et al.* Direct detection and differentiation of causative fungi of onychomycosis by multiplex polymerase chain reaction-based assay. *Eur J Dermatol* 2011; **21**:37–42.
36 Barak O, Asarch A, Horn T. PAS is optimal for diagnosing onychomycosis. *J Cutan Pathol* 2010; **37**:1038–40.
37 Stuttgen G, Bauer E. Bioavailability, skin- and nail-penetration of topically applied antimycotics. *Mykosen* 1982; **25**:74–80.
38 Zaug M, Bergstraesser M. Amorolfine in the treatment of onychomycoses and dermatomycoses (an overview). *Clin Exp Dermatol* 1992; **17**(Suppl. 1):S61–70.
39 Lauharanta J. Comparative efficacy and safety of amorolfine nail lacquer 2% versus 5% once weekly. *Clin Exp Dermatol* 1992; **17** (Suppl. 1):S41–3.
40 Reinel D, Clarke C. Comparative efficacy and safety of amorolfine nail lacquer 5% in onychomycosis, once-weekly versus twice-weekly. *Clin Exp Dermatol* 1992; **17** (Suppl. 1):S44–9.
41 Einarson TR. Pharmacoeconomic applications of meta-analysis for single groups using antifungal onychomycosis lacquers as an example. *Clin Ther* 1997; **19**:559–69.

42 Sigurgeirsson B, Olafsson JH, Steinsson JT *et al.* Efficacy of amorolfine nail lacquer for the prophylaxis of onychomycosis over 3 years. *J Eur Acad Dermatol Venereol* 2010; **24**:910–15.

43 Bohn M, Kraemer KT. Dermatopharmacology of ciclopirox nail lacquer topical solution 8% in the treatment of onychomycosis. *J Am Acad Dermatol* 2000; **43** (Suppl.):S57–69.

44 Gupta AK, Fleckman P, Baran R. Ciclopirox nail lacquer topical solution 8% in the treatment of toenail onychomycosis. *J Am Acad Dermatol* 2000; **43** (Suppl.):S70–80.

45 Shemer A, Nathansohn N, Trau H *et al.* Ciclopirox nail lacquer for the treatment of onychomycosis: an open non-comparative study. *J Dermatol* 2010; **37**:137–9.

46 Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. *Cochrane Database Syst Rev* 2007; **3**: CD001434.

47 Hay RJ, Mackie RM, Clayton YM. Tioconazole nail solution – an open study of its efficacy in onychomycosis. *Clin Exp Dermatol* 1985; **10**:111–15.

48 Stubb S, Heikkilä H, Reitamo S, Förström L. Contact allergy to tioconazole. *Contact Dermatitis* 1992; **26**:155–8.

49 Elewski BE, Rich P, Pollak R *et al.* Efinaconazole 10% solution in the treatment of toenail onychomycosis: two phase III multicentre, randomized, double-blind studies. *J Am Acad Dermatol* 2013; **68**:600–8.

50 Hartmane I, Dervenice A, Mailland F *et al.* Evaluation of safety profile, pharmacokinetics, and clinical benefit of an innovative terbinafine transungual solution (P-3058): a phase I study in patients with mild-to-moderate distal subungual onychomycosis. *J Am Acad Dermatol* 2013; **68** (Suppl. 1):AB105.

51 Derby R, Rohal P, Jackson C *et al.* Novel treatment of onychomycosis using over-the-counter mentholated ointment: a clinical case series. *J Am Board Fam Med* 2011; **24**:69–74.

52 Menéndez S, Falcón L, Maqueira Y. Therapeutic efficacy of topical OLEOZON® in patients suffering from onychomycosis. *Mycoses* 2011; **54**:e272–7.

53 Hay RJ. The future of onychomycosis therapy may involve a combination of approaches. *Br J Dermatol* 2001; **145** (Suppl. 60):S3–8.

54 Roobol A, Gull K, Pogson CI. Griseofulvin-induced aggregation of microtubule protein. *Biochem J* 1977; **167**:39–43.

55 Davies RR, Everall JD, Hamilton E. Mycological and clinical evaluation of griseofulvin for chronic onychomycosis. *BMJ* 1967; **3**:464–8.

56 Faergemann J, Anderson C, Hersle K *et al.* Double-blind, parallel-group comparison of terbinafine and griseofulvin in the treatment of toenail onychomycosis. *J Am Acad Dermatol* 1995; **32**:750–3.

57 Haneke E, Tausch I, Bräutigam M *et al.* Short-duration treatment of fingernail dermatophytosis: a randomized, double-blind study with terbinafine and griseofulvin. LAGOS III Study Group. *J Am Acad Dermatol* 1995; **32**:72–7.

58 Hofmann H, Bräutigam M, Weidinger G, Zaun H. Treatment of toenail onychomycosis. A randomized, double-blind study with terbinafine and griseofulvin. LAGOS II Study Group. *Arch Dermatol* 1995; **131**:919–22.

59 Walsoe I, Stangerup M, Svejgaard E. Itraconazole in onychomycosis. Open and double-blind studies. *Acta Derm Venereol* 1990; **70**:137–40.

60 Korting HC, Schafer-Korting M, Zienicke H *et al.* Treatment of tinea unguium with medium and high doses of ultramicrosize griseofulvin compared with that with itraconazole. *Antimicrob Agents Chemother* 1993; **37**:2064–8.

61 Ryder NS, Favre B. Antifungal activity and mechanism of action of terbinafine. *Rev Contemp Pharmacother* 1997; **8**:275–87.

62 Debruyne D, Coquerel A. Pharmacokinetics of antifungal agents in onychomycoses. *Clin Pharmacokinet* 2001; **40**:441–72.

63 Bueno JG, Martinez C, Zapata B *et al.* *In vitro* activity of fluconazole, itraconazole, voriconazole and terbinafine against fungi causing onychomycosis. *Clin Exp Dermatol* 2010; **35**:658–63.

64 Bangsgaard N, Saunte DM, Folkenberg M, Zachariae C. Serious adverse events reporting on systemic terbinafine: a Danish register-based study. *Acta Derm Venereol* 2011; **91**:358–9.

65 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**:1213–19.

66 Elewski B, Tavakkol A. Safety and tolerability of oral antifungal agents in the treatment of fungal nail disease: a proven reality. *Ther Clin Risk Manag* 2005; **1**:299–306.

67 O'Sullivan DP, Needham CA, Bangs A *et al.* Postmarketing surveillance of oral terbinafine in the U.K.: report of a large cohort study. *Br J Clin Pharmacol* 1996; **42**:559–65.

68 Gupta AK, Ryder JE, Lynch LE, Tavakkol A. The use of terbinafine in the treatment of onychomycosis in adults and special populations: a review of the evidence. *J Drugs Dermatol* 2005; **4**:302–8.

69 Clayton YM. Relevance of broad-spectrum and fungicidal activity of antifungals in the treatment of dermatomycoses. *Br J Dermatol* 1994; **130**(Suppl. 43):S7–8.

70 Vanden Bossche H, Marichal P, Gorrens J *et al.* Biochemical approaches to selective antifungal activity. Focus on azole antifungals. *Mycoses* 1989; **32** (Suppl. 1):S35–52.

71 Gupta A, Lambert J, Revuz J, Shear N. Update on the safety of itraconazole pulse therapy in onychomycosis and dermatomycoses. *Eur J Dermatol* 2001; **11**:6–10.

72 Faergemann J. Pharmacokinetics of terbinafine. *Rev Contemp Pharmacother* 1997; **8**:289–97.

73 Evans EG, Sigurgeirsson B. Double blind, randomised study of continuous terbinafine compared with intermittent itraconazole in treatment of toenail onychomycosis. The LION Study Group. *BMJ* 1999; **318**:1031–5.

74 Sigurgeirsson B, Olafsson JH, Steinsson JB *et al.* Long-term effectiveness of treatment with terbinafine vs. itraconazole in onychomycosis: a 5-year blinded prospective follow-up study. *Arch Dermatol* 2002; **138**:353–7.

75 Gupta AK, Ryder JE, Johnson AM. Cumulative meta-analysis of systemic antifungal agents for the treatment of onychomycosis. *Br J Dermatol* 2004; **150**:537–44.

76 Warshaw EM, Fett DD, Bloomfield HE *et al.* Pulse versus continuous terbinafine for onychomycosis: a randomized, double-blind, controlled trial. *J Am Acad Dermatol* 2005; **53**:578–84.

77 Gupta AK, Gover MD, Lynde CW. Pulse itraconazole vs. continuous terbinafine for the treatment of dermatophyte toenail onychomycosis in patients with diabetes mellitus. *J Eur Acad Dermatol Venereol* 2006; **20**:1188–93.

78 Baran R, Sigurgeirsson B, de Berker D *et al.* A multicentre, randomized, controlled study of the efficacy, safety and cost-effectiveness of a combination therapy with amorolfine nail lacquer and oral terbinafine compared with oral terbinafine alone for the treatment of onychomycosis with matrix involvement. *Br J Dermatol* 2007; **157**:149–57.

79 Ginter-Hanselmayer G, Weger W, Smolle J. Onychomycosis: a new emerging infectious disease in childhood population and adolescents. Report on treatment experience with terbinafine and itraconazole in 36 patients. *J Eur Acad Dermatol Venereol* 2008; **22**:470–5.

80 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.
81 Shemer A, Trau H, Davidovici B *et al.* Onychomycosis in psoriatic patients – rationalization of systemic treatment. *Mycoses* 2009; **53**:340–3.
82 Mishra M, Panda P, Tripathy S *et al.* An open randomized comparative study of oral itraconazole pulse and terbinafine pulse in the treatment of onychomycosis. *Indian J Dermatol Venereol Leprol* 2005; **71**:262–6.
83 Takahata Y, Hiruma M, Shiraki Y *et al.* Treatment of dermatophyte onychomycosis with three pulses of terbinafine (500 mg day^{-1} for a week). *Mycoses* 2009; **52**:72–6.
84 Sigurgeirsson B, Elewski BE, Rich PA *et al.* Intermittent versus continuous terbinafine in the treatment of toenail onychomycosis: a randomized, double-blind comparison. *J Dermatolog Treat* 2006; **17**:38–44.
85 Gupta AK, Lynch LE, Kogan N, Cooper EA. The use of an intermittent terbinafine regimen for the treatment of dermatophyte toenail onychomycosis. *J Eur Acad Dermatol Venereol* 2009; **23**:256–62.
86 Gupta AK, Paquet M, Simpson F, Tavakkol A. Terbinafine in the treatment of dermatophyte toenail onychomycosis: a meta-analysis of efficacy for continuous and intermittent regimens. *J Eur Acad Dermatol Venereol* 2013; **27**:267–72.
87 Bloomberg. Stiefel Laboratories reaps first fruits of Barrier acquisition. Available at: http://www.bloomberg.com/apps/news?pid=newsarchive&sid=aRIU23CEnqP8 (last accessed 6 August 2014).
88 Chang C-H, Young-Xu Y, Kurth T *et al.* The safety of oral antifungal treatments for superficial dermatophytosis and onychomycosis: a meta-analysis. *Am J Med* 2007; **120**:791–8.
89 Yin Z, Xu J, Luo D. A meta-analysis comparing long-term recurrences of toenail onychomycosis after successful treatment with terbinafine versus itraconazole. *J Dermatolog Treat* 2012; **23**:449–52.
90 Darkes MJM, Scott LJ, Goa KL. Terbinafine: a review of its use in onychomycosis in adults. *Am J Clin Dermatol* 2003; **4**:39–65.
91 Rich P, Scher RK, Breneman D *et al.* Pharmacokinetics of three doses of once-weekly fluconazole (150, 300, and 450 mg) in distal subungual onychomycosis of the toenail. *J Am Acad Dermatol* 1998; **38**:S103–9.
92 Brown SJ. Efficacy of fluconazole for the treatment of onychomycosis. *Ann Pharmacother* 2009; **43**:1684–91.
93 Scher RK, Breneman D, Rich P *et al.* Once-weekly fluconazole (150, 300, or 450 mg) in the treatment of distal subungual onychomycosis of the toenail. *J Am Acad Dermatol* 1998; **38**:S77–86.
94 Drake L, Babel D, Stewart DM *et al.* Once-weekly fluconazole (150, 300, or 450 mg) in the treatment of distal subungual onychomycosis of the fingernail. *J Am Acad Dermatol* 1998; **38**:S87–94.
95 Ling MR, Swinyer LJ, Jarratt MT *et al.* Once-weekly fluconazole (450 mg) for 4, 6, or 9 months of treatment for distal subungual onychomycosis of the toenail. *J Am Acad Dermatol* 1998; **38**:S95–102.
96 Havu V, Heikkilä H, Kuokkanen K *et al.* A double-blind, randomized study to compare the efficacy and safety of terbinafine (Lamisil) with fluconazole (Diflucan) in the treatment of onychomycosis. *Br J Dermatol* 2000; **142**:97–102.
97 Niwa T, Shiraga T, Takagi A. Effect of antifungal drugs on cytochrome P450 (CYP) 2C9, CYP2C19, and CYP3A4 activities in human liver microsomes. *Biol Pharm Bull* 2005; **28**:1805–8.
98 Carrillo-Muñoz AJ, Giusiano G, Guarro J *et al.* *In vitro* activity of voriconazole against dermatophytes, *Scopulariopsis brevicaulis* and other opportunistic fungi as agents of onychomycosis. *Int J Antimicrob Agents* 2007; **30**:157–61.
99 Gupta AK, Kohli Y, Batra R. *In vitro* activities of posaconazole, ravuconazole, terbinafine, itraconazole and fluconazole against dermatophyte, yeast and non-dermatophyte species. *Med Mycol* 2005; **43**:179–85.
100 Elewski B, Pollak R, Ashton S *et al.* A randomized, placebo- and active-controlled, parallel-group, multicentre, investigator-blinded study of four treatment regimens of posaconazole in adults with toenail onychomycosis. *Br J Dermatol* 2012; **166**:389–98.
101 Gupta AK, Leonardi C, Stoltz RR *et al.* A phase I/II randomized, double-blind, placebo-controlled, dose-ranging study evaluating the efficacy, safety and pharmacokinetics of ravuconazole in the treatment of onychomycosis. *J Eur Acad Dermatol Venereol* 2005; **19**:437–43.
102 Sigurgeirsson B, Van Rossem K, Malahias S, Raterink K. A phase II, randomized, double-blind, placebo-controlled, parallel group, dose-ranging study to investigate the efficacy and safety of 4 dose regimens of oral albaconazole in patients with distal subungual onychomycosis. *J Am Acad Dermatol* 2013; **69**:416–25.
103 Geria AN, Scheinfeld NS. Pramiconazole, a triazole compound for the treatment of fungal infections. *IDrugs* 2008; **11**:661–70.
104 Faergemann J, Todd G, Pather S *et al.* A double-blind, randomized, placebo-controlled, dose-finding study of oral pramiconazole in the treatment of pityriasis versicolor. *J Am Acad Dermatol* 2009; **61**:971–6.
105 Kim R, Khachikian D, Reboli AC. A comparative evaluation of properties and clinical efficacy of the echinocandins. *Expert Opin Pharmacother* 2007; **8**:1479–92.
106 Segal R, Kritzman A, Cividalli L *et al.* Treatment of *Candida* nail infection with terbinafine. *J Am Acad Dermatol* 1996; **35**:958–61.
107 Nolting S, Brautigam M, Weidinger G. Terbinafine in onychomycosis with involvement by non-dermatophytic fungi. *Br J Dermatol* 1994; **130**(Suppl. 43):S16–21.
108 Tosti A, Piraccini BM, Lorenzi S, Iorizzo M. Treatment of nondermatophyte mold and *Candida* onychomycosis. *Dermatol Clin* 2003; **21**:491–7.
109 Firinu D, Massidda O, Lorrai MM *et al.* Successful treatment of chronic mucocutaneous candidiasis caused by azole-resistant *Candida albicans* with posaconazole. *Clin Dev Immunol* 2011; **2011**:283239.
110 Trovato L, Rapisarda MF, Greco AM *et al.* *In vitro* susceptibility of nondermatophyte molds isolated from onycomycosis to antifungal drugs. *J Chemother* 2009; **21**:403–7.
111 Gupta AK, Gregurek-Novak T. Efficacy of itraconazole, terbinafine, fluconazole, griseofulvin and ketoconazole in the treatment of *Scopulariopsis brevicaulis* causing onychomycosis of the toes. *Dermatology* 2001; **202**:235–8.
112 De Doncker PR, Scher RK, Baran RL *et al.* Itraconazole therapy is effective for pedal onychomycosis caused by some nondermatophyte molds and in mixed infection with dermatophytes and molds: a multicenter study with 36 patients. *J Am Acad Dermatol* 1997; **36**:173–7.
113 Gupta AK, Gregurek-Novak T, Konnikov N *et al.* Itraconazole and terbinafine treatment of some nondermatophyte molds causing onychomycosis of the toes and a review of the literature. *J Cutan Med Surg* 2001; **5**:206–10.
114 Gianni C, Romano C. Clinical and histological aspects of toenail onychomycosis caused by *Aspergillus* spp.: 34 cases treated with weekly intermittent terbinafine. *Dermatology* 2004; **209**:104–10.
115 Tosti A, Piraccini BM, Lorenzi S. Onychomycosis caused by nondermatophytic molds: clinical features and response to treatment of 59 cases. *J Am Acad Dermatol* 2000; **42**:217–24.

116 Dunand J, Viguie C, Paugam A. Intermittent posaconazole regimen to treat superficial *Scytalidium dimidiatum* infection. *Eur J Dermatol* 2010; **20**:649–50.
117 Spriet I, Lambrecht C, Lagrou K, Verhamme B. Successful eradication of *Scytalidium dimidiatum*-induced ungual and cutaneous infection with voriconazole. *Eur J Dermatol* 2012; **22**:197–9.
118 Piraccini BM, Starace M, Bruni F. Onychomycosis in children. *Expert Rev Dermatol* 2012; **7**:569–78.
119 Gupta AK, Chang P, Del Rosso JQ *et al.* Onychomycosis in children: prevalence and management. *Pediatr Dermatol* 1998; **15**:464–71.
120 Gupta AK, Paquet M. Systemic antifungals to treat onychomycosis in children: a systematic review. *Pediatr Dermatol* 2013; **30**:294–302.
121 Huang PH, Paller AS. Itraconazole pulse therapy for dermatophyte onychomycosis in children. *Arch Pediatr Adolesc Med* 2000; **154**:614–18.
122 Jones TC. Overview of the use of terbinafine (Lamisil) in children. *Br J Dermatol* 1995; **132**:683–9.
123 Welsh O, Vera-Cabrera L, Welsh E. Onychomycosis. *Clin Dermatol* 2010; **28**:151–9.
124 Suarez S, Friedlander SF. Antifungal therapy in children: an update. *Pediatr Ann* 1998; **27**:177–84.
125 Polak A. The past, present and future of antimycotic combination therapy. *Mycoses* 1999; **42**:355–70.
126 Hay RJ, Clayton YM, Moore MK. A comparison of tioconazole 28% nail solution versus base as an adjunct to oral griseofulvin in patients with onychomycosis. *Clin Exp Dermatol* 1987; **12**:175–7.
127 Rigopoulos D, Katoulis AC, Ioannides D *et al.* A randomized trial of amorolfine 5% solution nail lacquer in association with itraconazole pulse therapy compared with itraconazole alone in the treatment of *Candida* fingernail onychomycosis. *Br J Dermatol* 2003; **149**:151–6.
128 Lecha M. Amorolfine and itraconazole combination for severe toenail onychomycosis; results of an open randomized trial in Spain. *Br J Dermatol* 2001; **145** (Suppl. 60):21–6.
129 Avner S, Nir N, Henri T. Combination of oral terbinafine and topical ciclopirox compared to oral terbinafine for the treatment of onychomycosis. *J Dermatolog Treat* 2005; **16**:327–30.
130 Jaiswal A, Sharma RP, Garg AP. An open randomized comparative study to test the efficacy and safety of oral terbinafine pulse as a monotherapy and in combination with topical ciclopirox olamine 8% or topical amorolfine hydrochloride 5% in the treatment of onychomycosis. *Indian J Dermatol Venereol Leprol* 2007; **73**:393–6.
131 Boyko EJ, Ahroni JH, Cohen V *et al.* Prediction of diabetic foot ulcer occurrence using commonly available clinical information: the Seattle Diabetic Foot Study. *Diabetes Care* 2006; **29**:1202–7.
132 Farkas B, Paul C, Dobozy A *et al.* Terbinafine (Lamisil) treatment of toenail onychomycosis in patients with insulin-dependent and non-insulin-dependent diabetes mellitus: a multicentre trial. *Br J Dermatol* 2002; **146**:254–60.
133 Piraccini BM, Tosti A. White superficial onychomycosis: epidemiological, clinical, and pathological study of 79 patients. *Arch Dermatol* 2004; **140**:696–701.
134 Dompmartin D, Dompmartin A, Deluol AM *et al.* Onychomycosis and AIDS. Clinical and laboratory findings in 62 patients. *Int J Dermatol* 1990; **29**:337–9.
135 Gupta AK, Taborda P, Taborda V *et al.* Epidemiology and prevalence of onychomycosis in HIV-positive individuals. *Int J Dermatol* 2000; **39**:746–53.
136 Güleç AT, Demirbilek M, Seçkin D *et al.* Superficial fungal infections in 102 renal transplant recipients: a case–control study. *J Am Acad Dermatol* 2003; **49**:187–92.
137 Baran R, Hay RJ, Garduno JI. Review of antifungal therapy, part II: treatment rationale, including specific patient populations. *J Dermatolog Treat* 2008; **19**:168–75.
138 Gregory N. Special patient populations: onychomycosis in the HIV-positive patient. *J Am Acad Dermatol* 1996; **35**:S13–16.
139 Ramos-e-Silva M, Lima CMO, Schechtman RC *et al.* Superficial mycoses in immunodepressed patients (AIDS). *Clin Dermatol* 2010; **28**:217–25.
140 Grover C, Bansal S, Nanda S *et al.* Combination of surgical avulsion and topical therapy for single nail onychomycosis: a randomized controlled trial. *Br J Dermatol* 2007; **157**:364–8.
141 Malay DS, Yi S, Borowsky P *et al.* 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.
142 Sotiriou E, Koussidou-Eremonti T, Chaidemenos G *et al.* Photodynamic therapy for distal and lateral subungual toenail onychomycosis caused by *Trichophyton rubrum*: preliminary results of a single-centre open trial. *Acta Derm Venereol* 2010; **90**:216–17.
143 Hochman LG. Laser treatment of onychomycosis using a novel 0.65-millisecond pulsed Nd:YAG 1064-nm laser. *J Cosmet Laser Ther* 2011; **13**:2–5.
144 Landsman AS, Robbins AH, Angelini PF *et al.* Treatment of mild, moderate, and severe onychomycosis using 870- and 930-nm light exposure. *J Am Podiatr Med Assoc* 2010; **100**:166–77.
145 Landsman AS, Robbins AH. Treatment of mild, moderate, and severe onychomycosis using 870- and 930-nm light exposure: some follow-up observations at 270 days. *J Am Podiatr Med Assoc* 2012; **102**:169–71.
146 Singal A, Khanna D. Onychomycosis: diagnosis and management. *Indian J Dermatol Venereol Leprol* 2011; **77**:659–72.
147 Cuenca-Estrella M, Moore CB, Barchiesi F *et al.* Multicenter evaluation of the reproducibility of the proposed antifungal susceptibility testing method for fermentative yeasts of the Antifungal Susceptibility Testing Subcommittee of the European Committee on Antimicrobial Susceptibility Testing (AFST-EUCAST). *Clin Microbiol Infect* 2003; **9**:467–74.
148 National Committee for Clinical Laboratory Standards. *Reference Method for Broth Dilution Antifungal Susceptibility Testing of Filamentous Fungi: Approved Standard* M38-*A*. Wayne, PA: Clinical and Laboratory Standards Institute, 2002.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's website:

Data S1. Literature search strategy.

Appendix 1

Levels of evidence

Level of evidence[a]	Type of evidence
1++	High-quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1−	Meta-analyses, systematic reviews of RCTs, or RCTs with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies High-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2−	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Nonanalytical studies (for example case reports, case series)
4	Expert opinion, formal consensus

RCT, randomized controlled trial. [a]Studies with a level of evidence '−' should not be used as a basis for making a recommendation.

Appendix 2

Strength of recommendation

Class	Evidence
A	At least one meta-analysis, systematic review or RCT rated as 1++, and directly applicable to the target population, or A systematic review of RCTs or a body of evidence consisting principally of studies rated as 1+, directly applicable to the target population and demonstrating overall consistency of results Evidence drawn from a NICE technology appraisal
B	A body of evidence including studies rated as 2++, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+, directly applicable to the target population and demonstrating overall consistency of results, or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4, or Extrapolated evidence from studies rated as 2+, or Formal consensus
D (GPP)	A good practice point (GPP) is a recommendation for best practice based on the experience of the guideline development group

RCT, randomized controlled trial; NICE, National Institute for Health and Care Excellence.