Onychomycosis: Practical Approaches to Minimize Relapse and Recurrence

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Key Words

Onychomycosis · Topical prophylaxis · Antifungal agents · Recurrence · Relapse

Abstract

Introduction: Toenail onychomycosis is a common disease in which treatment options are limited and treatment failures and disease recurrence are frequently encountered. It usually requires many months of treatment, and recurrence may occur in more than half of the patients within 1 year or more after the infection has been eradicated. Data on long-term treatment, follow-up and recurrence are limited. **Objective:** Our objective is to interpret these data and recommend practical approaches that should minimize recurrence based on our clinical experience. **Results:** Several factors have been suggested to play a role in the high incidence of recurrence, but only the extent of nail involvement and co-existing diabetes mellitus have been shown to have a significant impact. **Conclusion:** The use of topical antifungals to prevent recurrences after complete cure was achieved has been suggested by various workers and used successfully in our practice. However, it has never been validated through clinical studies. Topical prophylaxis once weekly or twice monthly would seem appropriate in those patients most at risk. Prompt treatment of tinea pedis is essential, as is ensur-

ing family members are free from disease. Patient education and pharmacologic intervention are equally important, and there are a number of simple strategies patients can employ. Managing onychomycosis is a significant long-term commitment for any patient, and minimizing recurrence is critical to meet their expectations.

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Introduction

Onychomycosis is a common and growing problem in dermatology practice and is most frequently seen in toenails. Successful treatment of the disease remains difficult [1, 2]. Onychomycosis is not self-healing and may become the source of more widespread disease [3]. It can have a significant impact on the individual and spread to other family members [4–6]. Many patients suffer from long-standing disease affecting several toenails, especially if they are not treated early and effectively [7].

Effective management of onychomycosis usually requires many months of treatment. Recurrence can arise 1 year or more after the infection was eradicated and is commonplace, possibly affecting more than half of the patients who have been treated successfully. A relapse/reinfection rate of 20–25% has been quoted in the litera-

ture following initial successful therapy [8–10], with recurrence rates varying from 6.5 to 53% [9, 11]. It has been suggested that the actual recurrence rate may be more than 10% higher than these figures because clinical trial populations are usually not representative of those encountered in clinical practice [12]. Also we may not see many of our patients whose disease recurs given the thought of another lengthy, and perhaps costly, treatment program. In some patients, the nail(s) may never return back to normal, despite our best efforts [13].

Multiple factors may contribute to the high rate of onychomycosis recurrence. Patients who have a genetic predisposition or belong to a susceptible population (i.e., elderly, diabetic) are more likely to experience recurrence [14, 15]. In the elderly, physical trauma may precipitate recurrence. Others who are more susceptible to onychomycosis may also be more susceptible to recurrence and are often not permanently cured with therapy [9]. Recurrence of dermatophyte onychomycosis seems to be more common in children, perhaps due to their strong predisposing factors [16]. Recurrence secondary to nondermatophyte molds is also common because of the lack of definitive treatment for these fungi [17]. Failure to cure the infected nails is not related to the development of resistance but likely due to host-related factors [18].

Knowledge relating to onychomycosis recurrence and its effective management is lacking. Few clinical studies have followed patients beyond 12 months [19, 20]. Our objective is to review the data that exist and recommend practical approaches that should minimize recurrence.

The Effect of Longer Treatment Courses

It has been suggested that extending the length of treatment (or study duration of clinical trials) beyond 48 weeks and increasing the washout period to at least 3–6 months would allow a more accurate interpretation of mycological outcome, afford more time for nails to grow out, eliminate nonviable fungal elements, and provide more time for the nail's appearance to improve [21]. However, there are few well-designed studies with treatment durations longer than 12 months, and longer washout periods would increase the risk of recurrence or reinfection.

An open randomized study in patients with severe dermatophyte toenail onychomycosis with matrix involvement compared 15 months of once-weekly amorolfine lacquer in combination with either initial 6 or 12 weeks daily terbinafine and 12 weeks of terbinafine monotherapy (active control). Global response (mycological and

clinical cure) at 18 months was greatest in those patients treated with combination therapy (44 and 72.3%, respectively, with 6 and 12 weeks terbinafine) compared to controls (37.5%) [22]. This study was not set up to assess recurrence; however, it is interesting to note that the longer course of terbinafine resulted in the greatest efficacy at the end of the 3-month follow-up period. As a follow-up to this pilot study, a larger trial in 249 onychomycosis patients with matrix involvement compared 12 months of amorolfine lacquer once weekly in combination with initial 12 weeks daily terbinafine to 12 weeks of terbinafine monotherapy and reported similar success rates in both groups at 9 months. However, by month 18 (6 months after treatment), combination treatment with amorolfine and terbinafine resulted in a significantly higher success rate (59.2%) compared to treatment with terbinafine alone (45.0%, $p = 0.03$). The success rate with terbinafine monotherapy had plateaued by month 12, with no further improvement during the 6-month washout period [23].

How Common Is Relapse or Recurrence of Disease?

If cure has been achieved, for how long is it maintained? When the literature is examined, there is surprisingly little information about this point. From clinical experience, it is obvious that some patients are very easily reinfected if they come into contact with a fungus.

A meta-analysis of five nonrandomized trials involving 251 eligible patients [8, 14, 15, 24, 25] found that relapses (defined as occurring more than 2 years after the end of therapy) were more common after treatment with itraconazole (intermittent or continuous) compared to continuous terbinafine [risk ratio 0.44, (95% CI 0.29–0.66)] [26]. Successful treatment was defined as mycological cure with at least clinical improvement. It was suggested that the apparent superiority of terbinafine was related to its fungicidal action [26]. Others have suggested that the difference might be partially explained by the fact that terbinafine is better at suppressing conidia production in *Trichophyton rubrum* [27].

We were only able to find one study with any data on recurrence following topical therapy. In a retrospective study of 637 medical records of Korean onychomycosis patients, 6 were cured following amorolfine treatment, and the reported recurrence rate of 33.3% after 1 year was similar to that observed following itraconazole and terbinafine therapy [28]. A case report reviewed 1 patient who had had multiple relapses over a 27-year period despite oral terbinafine (up to 18 months) or itraconazole treat-

ment. Miconazole cream applied to the toenail once weekly and webspaces over the last 4 years has prevented any further relapse [29].

Onychomycosis is a progressive disease, and recurrence also appears to be progressive. In a follow-up study of 47 patients with mycological cure following either intermittent itraconazole, intermittent or continuous terbinafine therapy, the relapse rate increased from 8.3% at month 12 to 19.4% at month 24 and 22.2% at month 36 [14].

A prospective long-term study (1.25 to 7 years after enrolment) in 166 patients with mycological cure and in 43 completely cured onychomycosis patients compared recurrence rates following treatment with pulsed itraconazole, intermittent terbinafine, continuous terbinafine, and an overlapping continuous terbinafine and itraconazole combination. Although pulsed itraconazole (59%) and combination therapy (57%) were associated with higher mycological recurrence rates, no statistically significant differences were detected [30].

What Factors Influence Recurrence?

Several factors have been suggested to play a role in the high incidence of recurrence, including family history, occupation, lifestyle or underlying physiology, therapy, properties of the infecting fungus, and environmental conditions (table 1). In our experience, patients with a genetic predisposition are most prone to experience repetition of the disease, although genetic factors have not been evaluated in clinical studies. It is important to look for signs of the disease in other family members and ensure infected footwear is not passed on to siblings. In the Korean study mentioned above, six clinical factors were assessed to evaluate their impact on recurrence: age, gender, clinical type, treatment pattern, presence of diabetes mellitus, and the extent of nail involvement [28]. Recurrence rates were only influenced significantly by the extent of nail involvement ($p = 0.010$ comparing $>50\%$ nail involvement with 50% nail involvement at baseline) and diabetes mellitus ($p = 0.03$) [28].

Can Recurrence Be Prevented with Topical Prophylaxis?

The use of topical antifungal lacquers or solutions to prevent recurrence of onychomycosis following complete cure has been suggested by various authors and has been

Table 1. Factors that influence recurrence

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- Family history and occurrence of onychomycosis or tinea pedis in family members
 - Lifestyle including wearing occlusive footwear and moist environments such as health clubs and swimming pools
 - Underlying physiology including patients suffering from diabetes mellitus or severe onychomycosis
 - Therapy choice, duration, treatment success, and adherence
 - Properties of the infecting fungus
 - Environmental conditions and nail injuries
-

supported by our experience. However, it has never been sufficiently validated by clinical studies.

A 7-year prospective study of 73 onychomycosis patients who were successfully treated (mycological and clinical cure) with continuous terbinafine or intermittent itraconazole showed that recurrence occurred at a mean time of 36 months after successful treatment [8]. All patients who relapsed developed distal subungual onychomycosis in one or both of the great toenails, and the responsible fungus was the same as in the first episode of onychomycosis. Risk factors were present in 3/12 of the patients who relapsed (occlusive shoes, diabetes, and family history). Half of the patients (6/12) who developed recurrence had been regularly applying topical antifungal post-initial cure (amorolfine nail lacquer once weekly). A similar percentage of patients who remained cured during follow-up were using amorolfine (57.4%), suggesting that application of amorolfine did not prevent relapse [8].

These findings were in contrast to a small open-label study ($n = 52$) of amorolfine prophylaxis in patients previously cured following treatment with terbinafine, or terbinafine and amorolfine, showing statistical significance in favor of those patients treated with amorolfine compared with untreated controls. Relapse rates at month 12 were 8.3 and 31.8%, respectively ($p = 0.047$). By month 36, the differences between the two groups were not significant (recurrence rate 29.2 vs. 50.0%, $p = 0.153$). It was estimated that recurrence was delayed by nearly 200 days with amorolfine prophylaxis twice weekly [31].

Practical Approaches to Minimize Relapse and Recurrence

Controlling onychomycosis recurrence involves both pharmacologic intervention and patient education (table 2). Although published data are limited, in our experi-

Table 2. Steps that can minimize or prevent disease recurrence

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- Patient education to improve adherence and recognize early signs of disease recurrence
 - Discarding or disinfecting old footwear and socks
 - Keeping feet cool and dry
 - Avoiding going barefoot in public places
 - Topical antifungal prophylaxis
 - Prompt treatment of any tinea pedis, including that of family members
-

ence patients may benefit from application of topical antifungal agents on the soles and possibly on and around the toenails after the initial episode has been successfully cleared. It is not known what the optimal duration of topical prophylaxis should be, although data from the long-term recurrence studies would suggest at least 2–3 years, and in some cases prophylaxis may have to be considered indefinitely [12]. Prophylaxis would seem most appropriate in patients with co-existing diabetes, or those that had suffered more severe disease [28].

Prompt treatment of tinea pedis is very important for preventing recurrence of onychomycosis, because the fungal pathogens infecting the skin may act as a reservoir for reinfection of the nail [32].

Patient education is just as critical as pharmacologic therapy for controlling the recurrence of onychomycosis. Physicians need to explain to their patients about the chronic, infectious, and potentially serious nature of the disease. Patients must also understand that they will need to take an active role in preventing recurrence or relapse. There are a number of simple and effective patient strategies. Discarding old footwear eliminates the fungal reservoir that can cause reinfection. If this is impractical, patients should consider replacing insoles or disinfecting footwear and socks. Dermatophytes have been shown to survive in socks, even after they have been washed, especially when using cold water [33]. In one study, at least 10.46% of the patients with onychomycosis and tinea pedis were shown to be at risk of reinfection by contact with their socks [34]. A number of techniques have been shown to be effective in disinfecting footwear, including terbinafine, ultraviolet light, and ozone [35–38].

Physicians should educate patients as to the early signs of onychomycosis, and patients should be encouraged to contact their physician at the first sign of any recurrence. In addition, prompt recognition of tinea pedis and treatment is important to prevent fungal entry into the nails [32]. The likelihood of resolution improves when the

condition is detected and treated early. The severity of a recurring infection may also be reduced if a patient receives a full regimen of pharmacologic treatment during the early stages of infection. Adherence is an important modifiable factor in the recurrence of onychomycosis. The patient may perceive that the medication is not working fast enough (new nail growth is not recognized) or well enough (new nail growth does not appear normal). It is important to discuss expectations prior to initiation of therapy and at follow-up. The more thoroughly patients understand the nature of onychomycosis, the more likely they will be to implement these recurrence-reducing measures and to seek treatment when they experience recurrences.

Concluding Remarks

Onychomycosis is a progressive disease associated with a number of clinical sequelae. Successful treatment depends on an accurate diagnosis and patient adherence to long-term therapy, as well as the recognition that recurrence is commonplace and will likely require follow-up treatment. It is possible that a maintenance regimen of topical therapy may either prevent or reduce recurrence, and there are a number of simple things patients can do to help. Clinical studies would be helpful in our understanding of optimized patient care.

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