Fungal Nail Disease

David de Berker, M.R.C.P.

A 68-year-old man reports changes in his left big toenail. It has been discolored distally for the past 2 years. It has become thickened and difficult to cut and is painful when the man is walking in certain shoes. He is otherwise well. On physical examination, the nail appears thickened, has crumbling yellow material beneath, and is more discolored distally than proximally. The nearby skin is normal, although the interdigital space of the little toe is macerated. How should his case be managed?

The reported prevalence of toenail onychomycosis in Western adult populations is 2 to 14% and increases with age. The higher estimate includes patients who visit medical clinics for other diseases. Fungal nail disease is most common in people with other nail problems (e.g., a history of nail trauma), in immunocompromised persons (e.g., those with diabetes mellitus or human immunodeficiency virus infection or those taking immunosuppressive medications), in persons with peripheral vascular insufficiency, and in children with Down's syndrome.

Onychomycosis is associated with tinea pedis in one third of cases; cracking of the skin of the sole and interdigital clefts increases the risk of soft-tissue infection and, in particular, cellulitis of the leg. Onychomycosis may result in pain and a negative self-image.

The most common pathogens are the dermatophytes *Trichophyton rubrum* and *T. mentagrophytes*. Nondermatophytes account for 10 to 20% of toenail onychomycosis in temperate climates, with the higher prevalence in areas of greater humidity. Of the nondermatophytes, candida species is the most common, and saprophytes (molds, such as acremonium species, scopulariopsis species, scytalidium species, aspergillus species, and fusarium species) account for most of the rest. Many of these are found in soil or plant material (see the Supplementary Appendix, available with the full text of this article at NEJM.org).

Most commonly, fungus invades the nail and nail bed by penetrating the distal or lateral margins (distolateral subungual onychomycosis). In other cases, it invades the nail plate directly from above, resulting in a powdery, white, patchy discoloration of the nail surface (superficial white onychomycosis); this presentation is most common in children. Invasion through the proximal margin, which is embedded within the proximal nail fold, is more prevalent in those with immunodeficiency and results in the appearance of infection emerging from beneath the nail as it grows (proximal subungual onychomycosis) (Fig. 1). Progression of disease can lead to variants and overlap of these presentations.

The standard for the diagnosis of fungal nail disease is a positive result on microscopical examination and culture of nail clippings with subungual debris or from sur-
face debris in superficial white onychomycosis (Fig. 2). However, a European survey of primary care physicians and dermatologists indicated that treatment was commonly prescribed in the absence of confirmatory sampling. Positive microscopic examination after preparation with potassium hydroxide and staining with chlorazol black E to increase sensitivity was reported to have a positive predictive value of 94% for confirmed fungal infection, as compared with 99% for histopathological assessment of the nail plate, which was a more costly procedure. Some clinicians use microscopy alone to make a diagnosis. An advantage of this strategy is that a diagnosis may be made at the initial visit; however, fungal hyphae identified in abnormal nails may be dead or may represent bystanders that are not contributing to the nail pathology.

Documentation of a positive culture shows that the fungus is viable and also identifies it and indicates whether it is likely to be pathogenic. When culture reveals nondermatophyte fungi, it may be unclear whether they represent a contaminant or are the cause of the clinical findings. Repeated heavy growth on culture media, positive direct microscopical examination, and characteristic clinical features indicate likely relevance. Culture has poor sensitivity, with false negative rates of 30 to 50%. This rate is minimized when the specimen includes a large sample of nail (a clipping of 2 to 3 mm in thickness) and subungual debris from the most discolored and friable area of the nail and nail bed.

Certain clinical criteria are sensitive for the diagnosis of fungal nail disease. Evidence of tinea pedis — including redness with peripheral scaling and central clearing (which may be multicentric on the sole), maceration and a margin of advancing scaling between the toes, or both — or a history of tinea pedis in the preceding year and discoloration of the nail are highly predictive of the diagnosis. However, confirmatory testing is recommended, to avoid the unnecessary use of antifungal treatment and to highlight the possibility of an alternative cause of the nail changes.

The most common alternative diagnoses are chronic trauma and psoriasis (Table 1). Both conditions respond well to podiatric management if they are limited to the toes; more widespread psoriatic nail disease warrants assessment by a dermatologist. About a quarter of dystrophic psoriatic big toenails may harbor fungal infection. Inflammatory and neoplastic diseases of the periunguim can result in misdiagnosis. Although they may be distinguishable from onychomycosis by the finding of soft-tissue changes with secondary alteration of nail shape or inadequate nail production, biopsy may be needed for diagnosis (Fig. 3).
Treatment

There are several considerations in the decision whether to treat onychomycosis. These include complications of the condition, the certainty of diagnosis, and the efficacy, costs, and potential side effects of treatment.

It is reasonable not to treat persons who have minimal toenail involvement and no associated symptoms. Onychomycosis often affects more
than one family member.17 However, it is unclear whether familial cases reflect transmission within a shared living space or similar susceptibility due to shared genetic, environmental, or behavioral characteristics. Thus, although simple measures that might minimize the risk of transmission — such as not sharing nail clippers or footwear — are reasonable, pharmacologic treatment cannot be justified for the purpose of reducing transmission. Data are lacking on the risk of progression of untreated disease.

Even in persons whose onychomycosis is not treated, associated tinea pedis should be treated5 (to reduce the risk of associated cellulitis) and relapse should be prevented by maintaining appropriate foot care. This includes the use of footwear that minimizes humidity, careful drying of the feet and interdigital spaces after washing, and the use of emollient on cracked skin that might otherwise allow entry of fungus.

Aggressive débridement may serve to curb minimal nail disease, although its efficacy has not been well studied. Débridement may be accomplished with nail clippers on nails softened by bathing or with a file. A podiatrist may use a nail burr.

**TOPICAL THERAPY**

Amorolfine 5% (Loceryl, not available in the United States), tioconazole 28% (Trosyl, not available in the United States), and ciclopirox olamine 8% (Penlac), formulated as lacquers, are the topical agents that have been most studied for onychomycosis (Table 2). All are best suited to use for distal dermatophyte infection. Open-label studies and limited randomized trials of these drugs have suggested a benefit, with reported mycologic cure rates for distal fungal nail disease (caused by infection with dermatophytes) of 38 to 54% with amorolfine 5% lacquer used twice a week for 6 months,18,19 20 to 70% with tioconazole 28% solution used twice a day for 6 to 12 months,20 and 28 to 36% for ciclopirox olamine 8% lacquer used daily for 48 weeks.21 However, the lack of control groups is a serious limitation of many of these studies, and several are published in non–peer-reviewed supplements. Furthermore, mycologic cure does not equal clinical cure; in the study of ciclopirox olamine 8% lacquer, a normal nail was achieved in only 7% of cases.22 Clinical experience suggests that when topical therapy is used, combining it with vigorous débridement (filing the upper surface of the nail, which diminishes the amount of infected nail to treat) may increase the likelihood that therapy is successful.

Topical therapy should be considered for those in whom systemic treatment is contraindicated or declined. Filing the upper surface of the nail may almost normalize appearance and improves access for topical medication (Fig. 2).

| Table 1. Differential Diagnosis of Fungal Nail Disease. |
|---|---|---|
| **Diagnosis** | **Features Suggesting the Diagnosis** | **Management** |
| Psoriasis | Nail pitting, rash on elbows and knees, and family history of psoriasis | Keep nails short, protect periungual skin with emollient and wear gloves during wet work, apply medium-potency topical corticosteroid to affected periungual skin at night, and manage more severe disease with systemic psoriatic treatments |
| Trauma | Single nail affected, homogeneous alteration of nail color, and altered shape of nail | Wear appropriate footwear, which may involve orthotic devices, and seek podiatric consultation |
| Lichen planus | May have nail atrophy and appearance of scarring at the proximal aspect of the nail; on the fingernails, it can reduce dexterity and hinder social interaction (see Fig. 1 in the Supplementary Appendix) | Biopsy may be needed for diagnosis; may require systemic immunosuppressive therapy |
| Periungual squamous-cell carcinoma | Single nail affected, pain, warty nail-fold change, or ooze from edge of nail; often mistaken for paronychia, fungal nail, or wart | Diagnosis may require nail biopsy followed by surgical treatment |
| Yellow-nail syndrome | Multiple nails become yellow, grow slowly, have increased longitudinal and transverse curvature, and are intermittently painful and shed; associated with chronic sinusitis, bronchiectasis, and lymphedema; candida can be grown in some instances but has little or no pathologic relevance | Provide intensive therapy for systemic elements, combined with local management of periungual inflammation; oral itraconazole and vitamin E might be helpful |

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There is no good rationale for treating onychomycosis with antifungal creams applied to the intact nail, except possibly in cases of superficial white onychomycosis, in which fungus occupies the upper surface of the nail. I am aware of no studies that have specifically examined this issue.

**SYSTEMIC THERAPY**

Oral agents that randomized trials have shown are effective for onychomycosis and that are approved by the Food and Drug Administration (FDA) for the treatment of onychomycosis include terbinafine (Lamisil) and itraconazole (Sporanox) (Table 2). In head-to-head trials comparing these agents, terbinafine appears superior, although the efficacies and the differences between the drugs vary substantially in different reports. A multicenter, randomized trial, involving 508 subjects, that compared terbinafine and itraconazole showed “clinical cure” (i.e., negative mycologic analysis and clearance of more than 87.5% of the nail) at 72 weeks in 54% of the patients taking terbinafine for 12 weeks and 60% of the patients taking terbinafine for 16 weeks, as compared with 32% of the patients receiving 7-day pulses of itraconazole each month for 3 or 4 months. “Complete cure” rates (i.e., negative mycologic analysis and a normal nail) were 46% and 23% for terbinafine and

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**Figure 3. Conditions Misdiagnosed as Fungal Nail Infection.**

Conditions that may be misdiagnosed as fungal nail infection include psoriasis (Panel A), although fungus and nail psoriasis may coexist; chronic trauma, particularly in the elderly (Panel B); squamous-cell carcinoma of the nail bed (Panel C) and proximal nail fold (Panel D) (absence of a clear diagnosis mandates biopsy); and the yellow-nail syndrome (Panel E), which is often seen in association with chronic sinusitis or bronchiectasis and lymphedema.
itraconazole, respectively, after 12 weeks of treatment and 55% and 26%, respectively, after 16 weeks.23 Consistent with these data, clinical cure rates for terbinafine have been approximately 50% in several other studies.24-26 Reported success rates appear lower in patients over 65 years of age, with one report noting rates of clinical cure and complete cure of 26% and 15%, respectively.27

Most studies focus on disease of the big toenail because it is commonly involved and provides a sufficiently large surface to quantitatively assess results. Follow-up between 48 and 72 weeks is required for meaningful interpretation of outcome, since a big toenail can take 18 months to grow and, except for superficial white onychomycosis, the effect of treatment is to allow new uninfected nail growth, rather than to change the appearance of the existing nail. The slow growth of the large toenail can mean that even these ranges of time are inadequate to assess the final outcome. The longer the follow-up period, however, the more likely it is that there will be a relapse or re-infection of a nail that is incompletely cured or inherently abnormal and prone to further infection. Among 151 subjects followed for 42 months after completion of the trial comparing terbinafine and itraconazole,23 clinical cure rates had fallen to 42% and 18%, respectively, and complete cure rates to 35% and 14%, respectively. These outcomes are consistent with a 25 to 30% relapse rate,28 with marginally lower relapse rates when patients were treated with terbinafine for 16 weeks rather than 12 weeks.29

### Table 2. Therapeutic Interventions for Fungal Nail Disease.*

<table>
<thead>
<tr>
<th>Variable</th>
<th>Considerations</th>
<th>Treatment</th>
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<tr>
<td><strong>Topical therapy</strong></td>
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<td><strong>Nail</strong></td>
<td>For superficial white onychomycosis or fungal infection limited to the distal third; should be continued until there is no evidence of residual viable fungus</td>
<td>Amorolfine 5% lacquer (Loceryl and Curanail, not available in the United States) once or twice a week for 6 to 12 months Ciclopirox olamine 8% lacquer (Penlac) daily for 48 weeks Tioconazole 28% paint (not available in the United States) twice daily for 6 to 12 months</td>
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<td><strong>Skin</strong></td>
<td>For associated tinea pedis; should be repeated if relapse occurs</td>
<td>Terbinafine cream (Lamisil) Ketoconazole (Nizoral) or other azole cream Foot care, including washing, careful drying, and wearing footwear that minimizes trauma, warmth, and humidity</td>
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<td><strong>Oral therapy</strong></td>
<td>Has a success rate of approximately 50% in extensive or proximal subungual onychomycosis; less successful in the elderly</td>
<td>Terbinafine (Lamisil); 250 mg daily for 6 weeks (fingernails) or 12 weeks (toenails) Itraconazole (Sporanox): 200 mg daily for 12 weeks for a toenail (U.S. guidelines) or 200 mg twice daily for 1 week a month for 2 months (fingernails) or 3 months (toenails) (European guidelines)</td>
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<td><strong>Topical and systemic therapy combined</strong></td>
<td>Inconsistent evidence that combined therapy leads to a better cure rate than does oral therapy alone</td>
<td>Débridement can require the care of a podiatrist, especially as the nail becomes thicker, harder, and more difficult to cut; in patients with diabetes mellitus or peripheral vascular disease, particular care is needed during débridement to avoid damage to adjacent soft tissues</td>
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<tr>
<td><strong>Débridement or avulsion combined with topical or systemic therapy</strong></td>
<td>Has a general role in reducing the main part of the infected nail; may reduce discomfort; may have a particular role in treating more resistant nondermatophytes and for managing deformed nails</td>
<td>Débridement can require the care of a podiatrist, especially as the nail becomes thicker, harder, and more difficult to cut; in patients with diabetes mellitus or peripheral vascular disease, particular care is needed during débridement to avoid damage to adjacent soft tissues</td>
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*In cases of minimal distal involvement, with no discomfort or progression, some people may choose treatment with podiatric débridement alone. This can also be a preferred option when the pathogen is a nondermatophyte that has only a small chance of responding to standard therapies."
Terbinafine is given for 12 to 16 weeks for a big toenail and 6 weeks for a fingernail. In the United States, it is recommended that oral itraconazole be given for the treatment of fingernail onychomycosis, in doses of 200 mg twice daily on weeks 1 and 5 (pulsed itraconazole), whereas toenails should be treated with 200 mg once daily for 12 weeks (continuous itraconazole).

The efficacy of systemic treatment must be balanced against the risk of side effects. In a meta-analysis of treatment trials, side effects led to discontinuation of therapy in 3.4% of patients who received terbinafine, 2.6% of those who received pulsed itraconazole, and 4.2% of those who received continuous itraconazole.30 Common side effects of terbinafine include gastrointestinal upset, headache, and minor rashes. Serious side effects are reported in less than 1% of patients31 but include serious or even fatal liver toxicity. Thus, systemic therapy is not recommended in patients with chronic or active liver disease, and liver-function testing is recommended by the FDA before treatment. Monitoring liver function at 4 to 6 weeks is recommended by several experts.32 The side effects of itraconazole are similar to those of terbinafine but also include congestive heart failure, which represents a contraindication. Side effects of itraconazole can be diminished when the drug is taken as pulsed doses rather than continuously. Drug interactions are more common with itraconazole than terbinafine. Fluconazole (Diflucan) is rarely used, given the superiority of alternatives.33

**COMBINED TOPICAL AND SYSTEMIC THERAPY**

It remains unclear whether combined topical and systemic therapy is more effective than systemic therapy alone.34 In one randomized trial, the combination of topical amorolfine weekly for 12 months and 250 mg of oral terbinafine daily for 3 months resulted in a 59% success rate (i.e., negative mycologic analysis with clearance of at least 90% of the nail) at 18 months, as compared with a 45% rate with terbinafine alone (P=0.03).26 A similar but smaller trial comparing terbinafine alone with the combination of ciclopirox and terbinafine failed to show significant benefit from the addition of ciclopirox olamine.35

**DÉBRIDEMENT**

Regardless of the type of treatment used, it is advisable to keep the nail short, and there may be benefit to removing all infected nail. The latter may require the involvement of a podiatrist using a nail burr, or surgical or chemical avulsion using concentrated preparations of urea or salicylic acid. In a randomized trial in which vigorous débridement was compared with routine clipping among two groups of patients treated with terbinafine, there was a nonsignificant benefit to débridement.37 In a report of eight patients with dermatophyte onychomycosis,38 surgical avulsion of the affected toenail (three patients) or fingernail (five) followed by ketoconazole 2% or ciclopirox 8% cream under occlusion with a polyethylene wrap at night until there was nail regrowth was reported to result in clearance in all cases at the 18-month follow-up. Chemical or surgical avulsion in combination with pharmacologic therapy may have a role in cases of infection with fungi that are less responsive to monotherapy with terbinafine or itraconazole (e.g., fusarium species or scupulaliopsis species), although this has not been well studied. Decision making must take into account the risks of avulsion, including pain and the potential for wound infection and scarring.

**AREAS OF UNCERTAINTY**

There is controversy regarding the cost–benefit ratio of treatment of onychomycosis. In one cost-effectiveness analysis, the estimated cost per cure with the use of terbinafine (based on cure rates from clinical trials) ranged from $2,439 to $7,944, depending on disease severity.37 These costs are at the upper end of published calculations but appear more realistic than the lower costs derived from analyses that are based on topical therapies, for which the cure rate is poorly documented. However, people who receive treatment without meeting the diagnostic criteria specified in therapeutic trials, which is common in practice, are not accounted for in this analysis or in other cost–benefit analyses36; inappropriate treatment greatly increases the costs per case cured. Also relevant to decisions regarding therapy are the potential risks of treatment and the effects of treatment on quality of life, which can be improved by cure.38 In one study translating these considerations into a sum of money a patient would deem reasonable to spend on treatment, the amount that the majority of patients reported being prepared to spend30 was considerably less than the current charges for a course of systemic therapy.37
GUIDELINES

Guidelines for the management of fungal nail infections are available from the American Academy of Dermatology39 (these were published in 1996 and thus antedate much current data); national guidelines have been published more recently in the United Kingdom40 and Germany.41 All emphasize the importance of obtaining a sample of a nail plate and subungal debris for mycologic diagnosis, although the U.S. guidelines recommend obtaining the samples for diagnostic accuracy, rather than as a prerequisite to treatment. The guidelines published in the United Kingdom advocate topical therapy only in the case of superficial white onychomycosis or “very early” distolateral onychomycosis, whereas the German recommendations extend the use of topical therapy to cases in which up to 50% of distal nail is infected. Only the guidelines in the United Kingdom recommend terbinafine over itraconazole for infection with dermatophytes. Useful online resources include government agencies (e.g., www.nlm.nih.gov/medlineplus/medlineplus.html and www.library.nhs.uk/Default.aspx) and professional bodies (http://dermnetnz.org/fungal/onychomycosis.html).

CONCLUSIONS AND RECOMMENDATIONS

Patients with an isolated nail dystrophy, such as the patient in the vignette, should have an evaluation to confirm the diagnosis of onychomycosis and to avoid incorrect therapy resulting from misdiagnosis. After confirmation of the diagnosis by means of culture of a sample of discolored nail and subungal debris and microscopic examination after preparation with potassium hydroxide, possible treatments should be discussed with attention to their costs, success rates, and risks. Positive microscopy with negative culture warrants resampling. Regardless of other treatment, the nail should be kept short. Débridement (by a podiatrist) should be considered if the nail is too thick for the patient to cut. I would offer topical therapy with amorolfine (outside the United States), used until clearance or for 12 months, or ciclopirox lacquer, used until clearance or for 48 weeks, although I would point out that the likelihood of complete cure appears low. I would also discuss the possibility of systemic therapy, noting the superiority of terbinafine over itraconazole in a randomized trial. However, I would warn that liver failure, though rare, has been reported and that congestive heart failure may be exacerbated by itraconazole. Liver-function testing is recommended in some countries, including the United States. The patient should understand that it takes approximately 6 to 12 months for the full clinical effects to be apparent. There is a 25 to 30% relapse rate in the long term for those who have an initial cure. Associated tinea pedis should be treated with topical therapy and good foot hygiene.

No potential conflict of interest relevant to this article was reported.

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