

## Current treatment of onychomycosis

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Onychomycosis accounts for one-third of integumentary fungal infections and one-half of all nail disease.<sup>[1]</sup> Onychomycosis is most commonly caused by dermatophytes, although *Candida* species and nondermatophyte molds may also cause disease.<sup>[2]</sup>

Therapeutic options for the treatment of onychomycosis range from no therapy, palliative care, mechanical or chemical debridement, topical and systemic antifungal agents to a combination of two or more of these modalities.<sup>[3]</sup> Factors that influence the choice of therapy include the presentation and severity of the disease, current medications the patient is taking, previous therapies for onychomycosis and their response, physician and patient preference and the cost of therapy.<sup>[3]</sup>

The primary aim of treatment is to eradicate the organism as demonstrated by microscopy and culture. However, eradication of the fungus does not always render the nails normal as they may have been dystrophic prior to infection. Such dystrophy may be due to trauma or nonfungal nail disease; this is particularly likely in cases where yeasts or nondermatophyte molds (secondary pathogens and saprophytes respectively) are isolated.<sup>[4]</sup>

### TOPICAL THERAPY

The active antifungal agent in these preparations is an imidazole, an allylamine or a polyene. Two transungual delivery systems are currently available in India: amorolfine 5% nail lacquer and ciclopirox olamine 8% nail lacquer. After evaporation of the solvent, the concentration of the active ingredient, ciclopirox or amorolfine, increases to 34.8 and 25% respectively; this enhances transungual diffusion.<sup>[3]</sup>

Amorolfine nail lacquer is applied once a week, whereas ciclopirox olamine nail lacquer is applied daily.<sup>[4]</sup> Long-term (6-12 months) monotherapy has been used in the treatment of white superficial onychomycosis and distal subungual onychomycosis limited to the distal nail of a few digits. Nail lacquers are also utilized as adjunctive therapy or for secondary prophylaxis in severe onychomycosis. Amorolfine nail lacquer alone was effective in around 50% of cases of distal subungual onychomycosis.<sup>[5]</sup> Although no recent reports are available, tioconazole 28% nail solution was suggested as one of the topical therapies for onychomycosis in past studies.<sup>[6]</sup> Recently, topical acidified nitrite treatment has shown promising results.<sup>[7]</sup>

### SYSTEMIC THERAPY

Orally administered griseofulvin has been available for many years, but its use is limited by its narrow spectrum, the necessity for long courses of treatment, disappointing cure rates (around 30%) and high relapse rates.<sup>[1,8]</sup> It is the only antifungal agent licensed for use in children with onychomycosis in USA and UK. The oral form of ketoconazole is much more effective but carries risk of hepatotoxicity.<sup>[1,8]</sup> Current evidence supports the use of newer antifungal agents as part of individualized treatment plans that consider patient profiles, nail characteristics, infecting organism(s), potential drug toxicities and interactions and adjuvant treatments.<sup>[3]</sup> The newer agents include triazoles and allylamines that have become first-line medications in the treatment of onychomycosis [Table 1].<sup>[1,8,9]</sup> These agents offer shorter treatment courses, higher cure rates and fewer relapses. Of the newer drugs, terbinafine and itraconazole are most widely used.

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**Table 1: Oral antifungal agents for the treatment of onychomycosis**

Antifungal agent	Indication	Dosage	Monitoring
Terbinafine	First-line therapy for dermatophytic infections (most cases of onychomycosis)	Continuous therapy: 250 mg per day for 6 weeks to treat fingernails and for 12 weeks to treat toenails Pulse therapy: 250 mg twice a day for 1 week of each month over 3 months	Complete blood count and ALT and AST levels at baseline, then every 4 to 6 weeks during therapy None recommended
Itraconazole	Alternative first-line therapy for dermatophytic infections  Preferred therapy for nondermatophytic and candidal infections	Continuous therapy: 200 mg per day for 6 weeks to treat fingernails and for 12 weeks to treat toenails  Pulse therapy: 200 mg twice daily for 7 days per month, with the treatment repeated for 2 to 3 months ("pulses") to treat fingernails and for 3 to 4 months to treat toenails	ALT and AST levels at baseline, then every 4 to 6 weeks during therapy  None recommended
Fluconazole	First-line therapy for candidal infections but also active against dermatophytes Consider for use in patients with complicated medication regimens	450 mg once weekly until nail is normal or acceptably improved (treatment often requires 6 to 9 months)	None recommended

ALT = Alanine transaminase; AST = Aspartate transaminase

Terbinafine is superior to itraconazole both *in vitro* and *in vivo* for dermatophyte onychomycosis and should be considered first-line treatment, with itraconazole as the next best alternative.<sup>[3]</sup> Cure rates of 80-90% for fingernail infection and 70–80% for toenail infection can be expected. These medications share characteristics that enhance their effectiveness: prompt penetration of the nail and nail bed, persistence in the nail for months after discontinuation of therapy and generally good safety profiles.

### Terbinafine

Terbinafine is the drug of choice in tinea unguium. This agent is notably less effective against nondermatophytes, including *Candida* species and molds. In addition to transient tolerance problems, terbinafine has several important drug interactions because of its hepatic metabolism.<sup>[1,10,11]</sup> Terbinafine is not recommended for patients with chronic or active liver disease.<sup>[12,13]</sup>

Terbinafine 250 mg per day is given continuously for 12 weeks to treat toenail infections and for 6 weeks to treat fingernail infections.<sup>[1,14]</sup> Studies have shown that the regimen for toenails results in a mycologic cure rate of 71–82% and a clinical cure rate of 60–70%.<sup>[15,16]</sup> Studies comparing terbinafine pulse therapy of 250 mg twice a day for 1 week of each month for 3 months with continuous therapy over 3 months showed no difference in efficacy.<sup>[9]</sup>

### Itraconazole

Itraconazole has a broad antifungal spectrum that includes dermatophytes, many nondermatophytic molds and *Candida*

species.<sup>[1]</sup> Headache, rash and gastrointestinal upset occur in about 7% of treated patients, but hepatic toxicity is rare.<sup>[13,14]</sup> Because itraconazole is metabolized by the hepatic cytochrome P450 system, significant drug interactions can occur notably with statins, quinidine, pimozide, and benzodiazepines, amongst others.<sup>[1,11,13]</sup> Increased gastric pH decreases the absorption of itraconazole.<sup>[1,11,13]</sup> Therefore, the effectiveness of this antifungal agent can be decreased by histamine H<sub>2</sub> blockers and proton pump inhibitors.

The dosage of itraconazole is 200 mg once daily taken continuously for 12 weeks to treat toenail infections and for 6 weeks to treat fingernail infections. Pulse treatment consists of 200 mg taken twice daily for 1 week per month, with the treatment repeated for 2–3 months (i.e., two to three 'pulses') for fingernail infections.<sup>[14,17,18]</sup> This dosage, given in three to four pulses, has also been shown to be effective in the treatment of toenail infections.<sup>[19–21]</sup> Published studies have demonstrated similar success rates for continuous and pulse therapies, with mycologic cure rates ranging from 45 to 70% and clinical cure rates ranging from 35 to 80%.<sup>[14,19,20]</sup>

### Fluconazole

Like itraconazole, fluconazole is active against common dermatophytes, *Candida* species and some nondermatophytic molds.<sup>[1]</sup> Fluconazole is not currently approved for the treatment of onychomycosis, but attention has been focused on once-weekly dosing (450 mg), taking advantage of the drug's pharmacokinetics to reduce treatment costs, and potentially improve compliance.<sup>[22–24]</sup> In fingernail onychomycosis,<sup>[25]</sup> fluconazole in a dosage of 450 mg taken

once weekly for 3 months was associated with a 90% clinical cure rate and nearly total mycologic eradication. Lower dosages were slightly less effective.

## TREATMENT OF YEAST INFECTIONS

Itraconazole is the most effective agent for the treatment of candidal onychomycosis where the nail plate is invaded by the organism. It is used in the same dosage regimen as for dermatophytes; treatment duration is 2 months for fingernails and 3-4 months for toenails. Fluconazole is thought to be equally effective in candidal onychomycosis and can be used at the dosage of 50 mg daily or as pulse therapy at the dosage of 300 mg per week. Duration of treatment is 6 weeks for fingernails and 3 months for toenails. Patients with chronic mucocutaneous candidiasis may fail to respond to normal dosages and require higher or even double dosages of antifungals, that too for longer durations.<sup>[26]</sup>

## TREATMENT OF NONDERMATOPHYTE MOLDS

Many varieties of saprophytic molds can invade diseased nail.<sup>[3]</sup> Although itraconazole has a broader spectrum, there is little categorical evidence to support the choice of one drug.<sup>[3]</sup> In USA and Europe, ciclopirox nail lacquer has its advocates. Nail avulsion followed by an oral agent during the period of regrowth is probably the best method.<sup>[4]</sup>

## TREATMENT OF ONYCHOMYCOSIS IN CHILDREN

Onychomycosis in children is rare, with an estimated prevalence of 0.2%.<sup>[21]</sup> Although griseofulvin is still considered the treatment of choice in dermatophyte infections of children, this possibly may not apply to onychomycosis.<sup>[27]</sup> Topical antifungals can possibly better penetrate the thin nail plate of children and are used as first choice treatment by several authors.<sup>[27]</sup> Terbinafine, itraconazole and fluconazole have all been used in children safely.

## IMPROVISED REGIMENS

Sequential treatment with itraconazole and terbinafine increases cure rates; the regimen is two pulses of itraconazole 400 mg/day for 1 week a month followed by one or two pulses of terbinafine 500 mg/day for 1 week a month.<sup>[28]</sup>

Supplemental systemic therapy for onychomycosis of the toes should be considered when the nail has slow outgrowth; in case of a thick nail, lateral onychomycosis,

**Table 2: Strategies to improve efficacy<sup>[29,30]</sup>**

- Correctly diagnose or confirm diagnosis
- Choosing the oral antifungal agent based on the causative organism of onychomycosis
- Poor bioavailability of oral antifungal agent may contribute to low efficacy
- Drug interaction resulting in a reduced concentration of oral antifungal agent and unfavorable results
- Poor compliance resulting in inadequate drug levels and failure to eradicate fungus
- Treatment resistance
- Boosted antifungal therapy for onychomycosis
- Booster or supplemental dosage of oral antifungal agent
- Special nail presentations that may require additional or combination therapy
- Sequential therapy with itraconazole and terbinafine
- Combination therapy for onychomycosis with oral and topical antifungal agents
- Combination therapy for onychomycosis with two oral antifungal agents
- Immunological considerations predisposing to chronic *T. rubrum* infection

severe onychomycosis or a patient with immunosuppression or peripheral vascular disease or diabetes.<sup>[29,30]</sup> A terbinafine booster is administered for an extra period of 4 weeks between months 6 and 9 from the start of therapy; similarly, an extra pulse of itraconazole may be given.<sup>[31,32]</sup>

## ADJUVANT TREATMENTS

Surgical or chemical nail avulsion may be useful in patients with severe onycholysis, extensive nail thickening or longitudinal streaks or 'spikes' in the nail. These nail changes can be caused by a granulated nidus of infection (dermatophytoma), which responds poorly to standard courses of medical therapy.<sup>[33,34]</sup>

To improve treatment outcomes and prevent recurrence, nails should be cut short and kept clean. The feet need to be dried completely following a bath or shower.<sup>[29,30]</sup> Recognizing and improving chronic health conditions (e.g., controlling diabetes, quitting smoking, etc.) may also affect the outcome of therapy. It would be appropriate to discard, or perhaps 'rest,' old pairs of shoes, once cure of onychomycosis has been achieved.

Measures that may be helpful in managing unsuccessful treatment or relapse are listed in Table 2. There has been some concern about evolving drug resistance among fungal pathogens. However, the impact of antifungal resistance on the treatment of onychomycosis is not yet clear. Failure to respond to therapy for onychomycosis could be related to the presence of dormant chlamydo spores and arthroconidia within the diseased nail plate.<sup>[35,36]</sup>

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