Treatment of Onychomycosis (Nail Fungus)
Focus on Terbinafine Resistance and the Role of Genetic Testing

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Executive Summary

Onychomycosis is a prevalent nail infection with meaningful impacts on pain, function, and quality of life. Oral terbinafine remains the first-line therapy for dermatophyte disease due to superior mycologic cure rates and favorable safety in appropriately selected patients. However, terbinafine-resistant dermatophytes—predominantly via squalene epoxidase (SQLE) gene mutations—are increasingly reported. When adequate courses fail despite adherence, clinicians should re-confirm the diagnosis, evaluate for resistance, and pivot to alternative or combination regimens. Molecular resistance testing (e.g., detection of SQLE mutations) can inform management in refractory cases, but it is not comprehensive and must be interpreted in clinical context.

Background & Diagnosis

Dermatophytes such as Trichophyton rubrum and T. mentagrophytes account for most cases; non-dermatophyte molds and Candida spp. are less common but important in refractory disease. Because many nail dystrophies mimic fungus (psoriasis, trauma, lichen planus), laboratory confirmation is recommended before prolonged systemic therapy. Useful modalities include direct microscopy (KOH), histology of nail clippings (e.g., PAS), fungal culture for species identification, and PCR-based assays. Combining methods improves diagnostic yield.

Primary Treatment

First-line systemic therapy for confirmed dermatophyte onychomycosis is oral terbinafine (commonly 250 mg daily; 12 weeks for toenails, ~6 weeks for fingernails). Randomized trials and meta-analyses show higher mycologic cure versus azoles in many settings, though complete cure rates are more modest. Monitoring for drug–drug interactions and hepatic adverse effects is prudent. Itraconazole is a principal alternative (continuous or pulse regimens), particularly when terbinafine is contraindicated or non-dermatophytes are suspected. Fluconazole (often off-label) and newer azoles such as voriconazole or posaconazole may be considered in selected refractory cases.

Topical and Adjunctive Measures

Topical therapies (efinaconazole, tavaborole, ciclopirox) have lower complete-cure rates as monotherapy in moderate-to-severe disease but are useful for mild/distal involvement or as adjuncts. Mechanical or chemical debridement and partial avulsion can reduce fungal burden and enhance drug penetration. Combination systemic-topical strategies may improve outcomes in recalcitrant cases.

Terbinafine Resistance

Terbinafine resistance is most often mediated by point mutations in SQLE that diminish drug binding while preserving ergosterol synthesis. Prevalence varies by region but resistant isolates are now reported globally, including in the United States. Some resistant strains retain susceptibility to itraconazole and other

azoles, enabling class switching. A minority of isolates show elevated MICs without known SQLE mutations, suggesting additional mechanisms (e.g., efflux, biofilms).

Genetic Resistance Testing (SQLE)

Genetic resistance testing (e.g., PCR detection of SQLE mutations) can be valuable after clinical nonresponse to an adequate terbinafine course or in areas with documented resistance. Benefits include earlier avoidance of ineffective therapy and antifungal stewardship. Limitations include incomplete mutation coverage, mixed populations (wild-type + mutant), variable availability, cost, and the reality that a negative test does not guarantee clinical success, nor does a positive test absolutely predict failure. Testing should complement—not replace—culture, microscopy, and clinical judgment.

Pragmatic Decision Algorithm

1) Confirm diagnosis (KOH ± PAS, culture, PCR) and assess severity, comorbidities, and interactions.
2) Start first-line therapy when appropriate (terbinafine) with debridement and consider adjunct topical therapy.
3) Reassess at ~3 months: if response is inadequate, verify adherence/interactions and consider re-sampling.
4) For nonresponse, obtain culture ± susceptibility and molecular resistance testing if available; switch to itraconazole or other azoles, and intensify with adjunct topicals and debridement.
5) After cure, use prophylactic topical strategies, foot hygiene, and footwear sanitation; monitor for relapse.

Conclusion

Terbinafine remains the cornerstone of evidence-based therapy for dermatophyte onychomycosis, but clinicians should recognize and rapidly address potential resistance. A pragmatic, stepwise approach—anchored in diagnostic confirmation, early recognition of nonresponse, judicious use of molecular testing, and timely class-switching or combination therapy—optimizes outcomes while stewarding antifungal efficacy.

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