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Narrative Article

Ring of Fire: The Global Rise of DrugResistant Ringworm and the Race to Outpace It: A Narrative Review of Dermatophytosis and Emerging Antifungal Resistance

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ABSTRACT

Background: Dermatophytosis is one of the most common superficial fungal infections worldwide, but increasing antifungal resistance has transformed recurrent and treatmentresistant tinea into an emerging publichealth concern. Trichophyton indotineae has gained particular attention because of frequent terbinafine resistance.

Objective: This narrative review examines the epidemiology, clinical manifestations, diagnostic challenges, molecular mechanisms of antifungal resistance, and evolving therapeutic approaches in dermatophytosis.

Discussion: Terbinafine resistance is strongly associated with mutations in the squalene epoxidase (SQLE) gene, while additional mechanisms may contribute to reduced antifungal susceptibility. Accurate species identification and antifungal susceptibility testing are increasingly important in refractory infections. Itraconazole remains an important therapeutic option, while newer antifungal agents are being investigated.

Conclusion: Drugresistant dermatophytosis highlights the need for improved surveillance, diagnostic capacity, rational antifungal use, and continued development of effective treatment strategies.

Keywords: dermatophytosis; ringworm; *Trichophyton indotineae*; terbinafine resistance; antifungal stewardship; squalene epoxidase.

INTRODUCTION

Dermatophytosis commonly called ringworm, tinea, or by the body site it colonizes (Tinea corporis, cruris, pedis, capitis, unguium) is one of the oldest diagnoses in medicine and, until recently, one of the most boring to treat. A short course of terbinafine or itraconazole, sometimes a topical azole, and the problem usually went away. That predictability is gone. Dermatophyte infections affect an estimated onefifth to onequarter of the world's population at any given time[1], and in the last several years clinicians across India, the Middle East, Europe, North America, and Southeast Asia have described the same unsettling pattern: widespread, intensely itchy, treatmentrefractory plaques that persist through and sometimes worsen despite full courses of firstline antifungals.

The culprit in most of these cases is not a new disease but a new strain: Trichophyton indotineae, first characterized in India around 2018 and formally named in 2020 after years of being mistaken for an unusually stubborn variant of T. mentagrophytes or T. interdigitale [2,5]. What makes it newsworthy is not its appearance under the microscope indistinguishable from its cousins without genetic sequencing but its behavior in the clinic: extensive, inflamed, often persontoperson transmitted lesions that shrug off terbinafine, and sometimes azoles as well.

FROM LOCAL OUTBREAK TO GLOBAL TRAVELER

What began as a regional phenomenon on the Indian subcontinent has not stayed regional. Confirmed cases of T. indotineae have now been reported in Belgium, France, Germany, the Netherlands, Canada, Singapore, Malaysia, and Australia, among others[2,4,5,6]. Some of the earliest imported cases in Europe and Canada were traceable to travel or family contact with South Asia, but that pattern is fraying: clusters in Malaysia and France, for instance, have included patients with no travel history at all, implying local, sustained transmission[5]. A cluster reported from France even documented transmission through sexual contact, a route not traditionally associated with dermatophytes and one that broadens the epidemiological map considerably [3].

The numbers behind the resistance are sobering. In the French cohort, resistance to terbinafine was documented in up to threequarters of isolates[3], and surveillance in Belgium found resistant T. indotineae strains circulating alongside largely susceptible T. interdigitale and only mildly affected T. mentagrophytes a reminder that specieslevel identification, not just a KOH mount, is now clinically necessary[4].

THE MOLECULAR STORY: WHY TERBINAFINE STOPS WORKING

Terbinafine works by blocking squalene epoxidase (SQLE), an enzyme dermatophytes need to build ergosterol, the fungal equivalent of cholesterol in their cell membranes. Block the enzyme, and squalene piles up to toxic levels while the membrane starves for ergosterol a twopronged mechanism that made terbinafine so reliable for so long[14,18]. Resistance, it turns out, is a game of molecular real estate: single aminoacid substitutions in SQLE most famously Leu393Phe and Phe397Leu, later joined by others such as Ala448Thr subtly reshape the drugbinding pocket enough that terbinafine can no longer dock effectively, while the enzyme itself keeps functioning normally[15,16,18].

Structural modeling work has since catalogued more than a dozen such mutations and ranked them by how destabilizing they are to the protein, with a handful (including Leu393Phe/Ser and Phe397Leu) standing out as the most disruptive to drug binding[16,17]. SQLE mutations are not the whole story. Several isolates of T. indotineae show heatdependent upregulation of an alternate epoxidase gene (Erg11B) alongside overexpression of major facilitator superfamily (MFS1) efflux transporters a backup system that can pump the drug back out of the cell even when the primary target is untouched[14]. This layered resistance (target modification plus active efflux) helps explain why some strains are resistant not just to terbinafine but show reduced susceptibility to azoles as well, a pattern rarely seen in classical dermatophyte infections. None of this happened in a vacuum. Widespread selfmedication, easy overthecounter access to antifungalcorticosteroid combination creams, inconsistent dosing, and premature discontinuation of therapy have all been implicated as selective pressures that favored resistant clones a familiar story from bacterial antimicrobial resistance, replayed here in a fungal key.

DIAGNOSIS: CATCHING A MOVING TARGET

Standard potassium hydroxide (KOH) microscopy and culture confirm dermatophytosis but cannot distinguish T. indotineae from its close relatives that requires molecular methods, typically ITS region sequencing of the ribosomal DNA, which remains the reference standard for species identification[5]. Antifungal susceptibility testing, where available, is usually performed by CLSI or EUCAST broth microdilution, but the field still lacks internationally agreed clinical breakpoints for dermatophytes; most laboratories fall back on epidemiological cutoff values or provisional thresholds (for example, a terbinafine MIC above 0.2 mg/L has been proposed as a marker of likely resistance) rather than a validated resistant/susceptible cut off [2]. Faster, PCRbased approaches targeting known resistance mutations have been explored as a way to shortcut the multiweek cultureandsequence pipeline and flag resistance at the point of care[21], but these remain confined to research and reference laboratories rather than routine clinical use.

TREATING THE UNTREATABLE: CURRENT AND EMERGING OPTIONS

With terbinafine compromised, clinicians have leaned on a mix of older drugs used differently and newer agents borrowed from the invasivefungalinfection toolbox. Itraconazole remains the most consistent fallback. Even though some isolates show moderately elevated minimum inhibitory concentrations, itraconazole still performs better than terbinafine against T. indotineae in most invitro panels and case series, and it is frequently listed as the preferred first alternative [7, 8]. Topical luliconazole and amorolfine show low minimum inhibitory concentrations against resistant strains and are increasingly used as adjuncts to systemic therapy [7, 10]. Newer triazoles fosravuconazole (a prodrug of ravuconazole with better absorption and fewer drug interactions than itraconazole), posaconazole, voriconazole, and oteseconazole have all produced successful outcomes in small case series and onychomycosis trials, though none currently carries formal regulatory approval specifically for dermatophytosis[8,9,11]. Older tools are also being revisited: a large randomized trial from India found ultramicronized griseofulvin to be a safe, effective, and notably cheaper alternative to itraconazole for Tinea corporis and T. cruris, which matters enormously in the highburden, costsensitive settings where this epidemic is centered[12].

Echinocandins and investigational agents. Echinocandins such as anidulafungin show favorable invitro activity and have rescued at least one recalcitrant case in combination with itraconazole, though their pharmacokinetics make them an awkward fit for a superficial skin infection rather than a bloodstream one [1, 7]. Further down the pipeline, agents with genuinely new mechanisms olorofim (which targets fungal pyrimidine biosynthesis) and ME1111 along with nanotechnologybased topical formulations and even antifungal vaccine concepts, are being explored specifically because they sidestep the ergosterol pathway altogether and would not be expected to share crossresistance with terbinafine or the azoles [13].

Agent / Class	**Typical Use**	**Key Notes**
Itraconazole	Systemic, first alternative	Bestsupported fallback; some MIC creep reported
Fosravuconazole	Systemic (oral)	Prodrug of ravuconazole; better absorption than itraconazole
Posaconazole / Voriconazole	Systemic, refractory cases	Reserved for recalcitrant or nail disease
Oteseconazole (VT1161)	Systemic, investigational use	Novel tetrazole; limited dermatophytespecific data
Luliconazole / Amorolfine	Topical, adjunct	Low MICs against resistant strains
Griseofulvin (ultramicronized)	Systemic, costsensitive settings	RCTsupported, cheaper alternative to itraconazole
Echinocandins (e.g., anidulafungin)	Systemic, salvage combination	Good invitro activity; pharmacokinetic mismatch for skin
Olorofim / ME1111 (investigational)	Not yet clinical standard	Novel mechanisms; no ergosterolpathway crossresistance

Table 1. Selected Antifungal Options in TerbinafineResistant Dermatophytosis

BEYOND THE PRESCRIPTION PAD: A STEWARDSHIP PROBLEM

The parallels with bacterial antimicrobial resistance are hard to ignore, and so are the lessons. Unregulated sale of combination antifungalsteroid creams, inadequate treatment duration, and a lack of routine susceptibility testing have created ideal conditions for resistant clones to emerge and spread persontoperson. Addressing the problem will require the same multipronged approach that has (imperfectly) worked for bacteria: restricting inappropriate overthecounter formulations, building laboratory capacity for species identification and susceptibility testing in highburden regions, establishing internationally harmonized breakpoints, and treating dermatophytosis surveillance as a genuine component of antimicrobial resistance monitoring rather than an afterthought.

CONCLUSION

Ringworm has outgrown its reputation as a trivial, selflimited nuisance. The emergence and rapid international spread of terbinafineresistant Trichophyton indotineae is a case study in how quickly a superficial fungal infection can evolve into a genuine antimicrobial resistance concern when selective pressure, global travel, and diagnostic blind spots align. The clinical response smarter use of existing triazoles, revived interest in griseofulvin, and a slowly maturing pipeline of new mechanisms is encouraging but incomplete. What is missing is the infrastructure: agreed susceptibility breakpoints, accessible molecular diagnostics, and stewardship of the antifungalsteroid combination creams that likely helped create this problem in the first place. Until those pieces are in place, ringworm will keep testing the limits of what "a simple skin infection" is allowed to mean.

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