



Review Article

## Therapeutic drug monitoring in dermatophytosis: Time to reconsider itraconazole and terbinafine exposure targets

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### ABSTRACT

Superficial fungal infections affect nearly one-quarter of the global population and are now a major clinical and public health challenge in South Asia. Dermatophytosis, once a nuisance infection, has become chronic, widespread, and increasingly resistant to therapy. The rise of *Trichophyton indotineae* and terbinafine (TBF) resistance exceeding 70% in some centers has left dermatologists struggling with high relapse rates and limited effective options. Much of this crisis reflects the gap between prescribed dose and achieved drug exposure. Itraconazole (ITZ) absorption is highly variable, influenced by gastric acidity, diet, and formulation quality, while TBF's reliability is undermined by genetic resistance. These pharmacological realities explain why standard regimens often fail in practice. Therapeutic drug monitoring (TDM), already standard for triazoles in invasive fungal disease, has untapped value in dermatology. Measuring early ITZ levels can identify underexposed patients, guide use of newer super-bioavailable formulations, and avoid unnecessary treatment failure. TBF monitoring is less often required but can help distinguish poor absorption from true resistance. Newer tools, such as finger-prick microsampling, may make drug level testing practical even in routine dermatology clinics. Reframing dermatophytosis as a disorder of drug exposure as well as resistance highlights the need for precision therapy. Incorporating TDM into dermatology practice could improve cure rates, reduce relapse, and restore confidence in systemic antifungal therapy in the face of rising resistance.

**Keywords:** Antifungal resistance, Dermatophytosis, Itraconazole, Pharmacokinetics, Terbinafine, Therapeutic drug monitoring

### INTRODUCTION

Superficial fungal infections are among the most common human diseases, yet they remain a neglected global health problem. They affect an estimated 20-25% of the population worldwide and rank fourth in incidence among skin disorders, contributing substantially to disability-adjusted life years.<sup>[1]</sup> While often dismissed as minor ailments, these infections carry profound social and economic costs, particularly in low- and middle-income countries where crowded living conditions, high humidity, and limited access to effective treatment sustain their transmission.<sup>[2]</sup>

In South Asia, and India in particular, the clinical profile of dermatophytosis has shifted dramatically. Once regarded as a limited and treatable nuisance, it has evolved into an epidemic characterized by chronic, widespread, and relapsing lesions that frequently defy standard therapy.

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This change is underpinned by the emergence of *Trichophyton indotinea* (formerly *T. mentagrophytes* genotype VIII), a highly transmissible and inflammatory species that has displaced *Trichophyton rubrum* as the dominant pathogen.<sup>[2,3]</sup> Resistance has accelerated the epidemic. A multicenter study spanning India found terbinafine (TBF) resistance in 71% of isolates, most linked to mutations in the *squalene epoxidase* (*SQLE*) gene, and noted rising itraconazole (ITZ) minimum inhibitory concentrations (MICs) that signal an impending multidrug threat.<sup>[3]</sup> Yet, resistance tells only part of the story. The pharmacokinetics (PK) of oral antifungals are notoriously erratic: Both ITZ and TBF show wide inter-patient variability, with absorption shaped by gastric acidity, diet, and formulation, making consistent therapeutic exposure elusive. Absorption is influenced by gastric pH, food intake, and formulation differences, while distribution into keratinized tissues is unpredictable.<sup>[4]</sup> The indiscriminate use of pulse regimens, often adopted without pharmacological justification, further destabilizes drug exposure. At the same time, widespread misuse of fixed-dose steroid-antifungal combinations has worsened clinical outcomes and accelerated the selection of resistant strains.<sup>[1,3]</sup> The convergence of these pharmacological, microbial, and behavioral drivers has created a crisis of recalcitrant infection and therapeutic failure. Therapeutic drug monitoring (TDM) has the potential to provide a rational corrective. In invasive mycoses, TDM is already established as a standard of care for triazoles, where it improves clinical outcomes, reduces toxicity, and mitigates resistance emergence.<sup>[4]</sup> ITZ and TBF precisely possess the pharmacological characteristics, unpredictable absorption, narrow therapeutic margins, and concentration-linked outcomes that make them prime candidates for monitoring. Yet, concentration targets for dermatophytosis remain unvalidated, extrapolated largely from studies in invasive disease.<sup>[4]</sup> Furthermore, access to reliable assays remains uneven, particularly in resource-limited settings, raising questions of feasibility and equity.

This review synthesizes PK, pharmacodynamics (PD), and tissue-distribution evidence for ITZ and TBF in dermatophytosis, critically appraises the potential role of TDM, and explores whether exposure targets can be meaningfully recalibrated. By linking drug concentrations to pathogen susceptibility and clinical outcomes, we aim to outline a translational agenda that informs antifungal stewardship, addresses the epidemic of recalcitrant dermatophytosis in South Asia, and generates lessons applicable worldwide.

## PK OF ITZ AND TBF

### Why PK matters for TDM in dermatophytosis

Dermatophytes reside predominantly in keratinized compartments (stratum corneum, hair, nail). Systemic therapy must therefore (1) achieve sufficient plasma exposure to

drive delivery into keratin and (2) persist within those compartments long enough to outlast the turnover of infected keratin. When absorption is variable or interactions are likely, verifying exposure becomes central to care and motivates TDM.<sup>[5]</sup>

### ITZ

ITZ absorption is formulation- and condition-sensitive: Food enhances uptake, whereas acid suppression reduces bioavailability, rendering H<sub>2</sub> blockers and antacids clinically relevant modifiers of exposure.<sup>[5]</sup> With 200 mg/day, steady-state plasma concentrations (~0.7 µg/mL) emerge after ~2-3 weeks, reflecting non-linear kinetics and progressive distribution into tissues.<sup>[5]</sup> Highly lipophilic and keratinophilic, ITZ concentrates in the stratum corneum and nail. Drug becomes detectable in nail within ~1 week and persists for months after treatment, up to ~6 months after a 3-month course; residual nail levels are also observed after pulsed regimens, indicating delivery through both nail matrix and nail-bed vasculature.<sup>[6,7]</sup> These properties support post-treatment kill, whereby the antifungal effect continues as diseased keratin grows out. Extensive hepatic CYP3A4 metabolism creates a broad interaction burden (e.g., calcineurin inhibitors, antiarrhythmics, benzodiazepines, rifampin, statins, warfarin, oral contraceptives; acid-suppressants through pH-dependent absorption), risking subtherapeutic exposure or toxicity.<sup>[5,8,9]</sup> Given absorption variability and drug-drug interactions, ITZ is the archetypal candidate for TDM to verify systemic exposure sufficient to load keratin, particularly in patients on acid suppressants, with gastrointestinal variability, or on interacting polypharmacy.<sup>[5]</sup>

### TBF

TBF is well absorbed and food-independent; an empty stomach does not reduce absorption (unlike ITZ). C<sub>max</sub> ~0.8-1.5 µg/mL occurs ~2 h post-dose.<sup>[5]</sup> TBF rapidly accumulates in lipid-rich and keratinized tissues, with quantitative rises during 250 mg/day dosing: stratum corneum 0.9 → 2.8 → 9.1 mg/kg (days 2, 6, 12), epidermis/dermis 0.1 → 0.2 → 0.4 mg/kg, and sebum ~38-43 mg/kg by day 6.<sup>[10]</sup> Nail concentrations are detectable by ~3 weeks and persist for months after only a 1-month course.<sup>[5]</sup> Although the plasma half-life is ~16 h, a terminal half-life of ~80-100 h reflects slow egress from deep lipid/keratin reservoirs.<sup>[5]</sup> Despite hepatic metabolism, TBF does not meaningfully inhibit CYP-450 and has few clinically significant interactions, reducing the routine need for exposure verification.<sup>[5]</sup> With predictable absorption, rapid keratin loading, and low interaction risk, routine TDM is generally unnecessary. In refractory disease, suspected malabsorption, or advanced hepatic dysfunction, a 1-time level may help distinguish PK failure from microbiological or host factors.<sup>[5]</sup> Unlike ITZ,

there are currently no international or national guidelines that recommend routine TDM for TBF. Any consideration of TBF level measurement is therefore selective, hypothesis-generating, and not guideline-driven.

### Comparative absorption, distribution, and PD relevance

ITZ absorption depends on food intake and gastric acidity, whereas TBF absorption is stable and unaffected by feeding status or gastric pH.<sup>[5]</sup> TBF achieves therapeutic concentrations in the stratum corneum and sebum within days, while ITZ accumulates more slowly but persists for months in keratinized tissues, maintaining antifungal activity after dosing ends.<sup>[8-10]</sup> ITZ's primarily fungistatic action requires sustained tissue exposure, whereas TBF is fungicidal, achieving minimum inhibitory and fungicidal concentrations at similar levels.<sup>[11,12]</sup> Consequently, ITZ efficacy is more vulnerable to absorption variability and drug-drug interactions, while TBF's rapid, stable tissue penetration and prolonged keratin reservoir allow a durable effect even with modest fluctuations in plasma concentrations.

## EVIDENCE LINKING DRUG LEVELS WITH CLINICAL OUTCOMES

### ITZ: Plasma troughs versus keratin/nail compartments

ITZ achieves disproportionately high concentrations in sebum and stratum corneum relative to plasma after the first treatment week; sebum levels can exceed peak plasma by an order of magnitude, and stratum corneum drug persists for weeks after plasma becomes undetectable, explaining clinical carry-over despite variable serum troughs. These classic human PK data underscore that target-site exposure (keratinized compartments) can decouple from contemporaneous plasma levels once a tissue reservoir is established.<sup>[13]</sup> ITZ deposition in nails parallels its cutaneous kinetics, becoming detectable within weeks and sustained for months; increasing doses produce higher nail concentrations and a dose-response improvement in cure rates. However, when nail/plasma levels are broadly adequate across arms, correlations with response may disappear, implying a "threshold" rather than linear exposure-response at the site.<sup>[14,15]</sup>

### Implication for TDM

For glabrous tinea (corporis/cruris), early systemic exposure still matters in a prospective Indian trial; all patients with serum ITZ >0.2 µg/mL achieved cure, while sub-0.2 µg/mL levels concentrated failures, supporting a pragmatic lower bound for therapeutic monitoring during the uptake phase. In contrast, a separate randomized Indian study measuring week-2/4 levels found no correlation with week-4 outcomes,

likely because short follow-up and maturing tissue depots weaken contemporaneous plasma-response links. Taken together, these data suggest: (i) verify early systemic exposure (e.g., by week 2) to cross a minimum effective threshold; (ii) later, in therapy, tissue stores dominate and simple trough-outcome correlations attenuate.<sup>[16]</sup>

### TBF: Nail plate levels and mycological cure

TBF reaches high, durable levels in nails and keratinized tissues after oral dosing (weeks-months), a PK signature that aligns with high mycological cure and low long-term relapse in onychomycosis cohorts versus azoles. Quantitative sampling studies document substantial TBF in stratum corneum and adnexal secretions, while long-term follow-up trials show markedly lower 5-year recurrence after TBF than after ITZ, consistent with a more persistent keratin reservoir. Although most datasets are from onychomycosis, they provide biological plausibility that sustained keratin exposure drives durable cure across dermatophyte niches.<sup>[17,18]</sup>

### Do low plasma levels predict relapse?

Direct, prospective links between plasma troughs and relapse are limited. In tinea corporis/cruris, the best evidence indicates that low early serum ITZ (<0.2 µg/mL) predicts failure (not relapse) in the index course, whereas later relapse reflects organismal factors, host reservoirs, and reinfection; in a double-blind randomized controlled trial, relapse remained substantial across 100-400 mg/day regimens despite high cure, implying that beyond a certain exposure threshold, non-PK drivers dominate recurrence. Bottom line: Use early TDM to avoid underexposure-driven failure; preventing relapse likely requires antifungal stewardship, source control, and species-aware strategies in addition to exposure optimization.<sup>[16,19]</sup>

### Evidence from Indian studies on therapeutic failures

Randomized and pragmatic Indian trials during the *T. indotineae* era report limited effectiveness of legacy regimens (fluconazole, griseofulvin, ITZ, TBF) and high relapse, despite adequate susceptibility to ITZ in many cohorts, pointing to heterogeneous exposure, brand/formulation variability, host/behavioral factors, and evolving pathogen biology. *SQL*E mutations, identified through clinicogenomic analyses, underpin TBF resistance and directly account for clinical non-response despite adequate or prolonged dosing. These findings justify selective TDM (to rule out subexposure, especially early), species/antimicrobial susceptibility testing, informed therapy, and formulation-quality vigilance in India's dermatophytosis epidemic.<sup>[19,20]</sup>

## PULSE VERSUS CONTINUOUS REGIMENS: PK/PD CONSIDERATIONS

### Rationale behind pulse dosing (the “keratin reservoir”)

ITZ concentrates in skin appendages and persists in keratin after plasma falls, providing a pharmacologic basis for intermittent (pulse) schedules. Human studies show skin/appendage levels exceed plasma, with high sebum partitioning and persistence in stratum corneum for weeks after dosing; nails retain drug for months post-therapy, consistent with matrix incorporation and outgrowth elimination. These PK features underpinned early pulse regimens.<sup>[13,21]</sup>

### What trials actually found: Pulse versus continuous (historical evidence)

In classic onychomycosis trials, pulse ITZ (400 mg/day for 1 week each month, 3-4 cycles) achieved nail concentrations well above MICs and clinical/mycologic responses comparable to longer continuous dosing. A head-to-head randomized trial found no superiority of continuous over pulse; equivalence testing slightly favored pulse, though both were effective and well tolerated. A modern network meta-analysis likewise found no significant difference between pulse and continuous regimens for ITZ or TBF in dermatophyte toe-nail disease.<sup>[21,22]</sup>

### The resistant-strain era (glabrous tinea)

Since 2017, *SQLE* mutation-mediated TBF resistance has been widely reported, particularly across South Asia. Clinical response to TBF correlates with MIC and *SQLE* changes, and many contemporary *Trichophyton* isolates (e.g., *T. indotineae*) show high TBF MICs but low ITZ MICs. These shifts explain poor “pulse-style” short courses in some settings, independent of the interval schedule per se.<sup>[23]</sup>

### Does TDM favor continuous dosing?

TDM is inherently easier to interpret under continuous dosing, because troughs are steady and align with guideline practice for azoles. In cutaneous dermatophytosis, a prospective trial found that serum ITZ concentrations >0.2 µg/mL were consistently associated with cure, whereas levels <0.2 µg/mL predicted failure, evidence that achieving/maintaining exposure matters in current resistant-strain epidemiology. Continuous daily regimens, therefore, facilitate attaining target concentrations and adjusting dose when interacting drugs, variable absorption, or formulation issues (e.g., conventional versus “super-bioavailable” ITZ) complicate exposure.<sup>[16]</sup>

## ASSAY AVAILABILITY AND ANALYTIC PERFORMANCE

Quantification of ITZ and hydroxy-ITZ (OH-ITZ) by liquid chromatography-tandem mass spectrometry (LC-MS/MS) is widely implemented; validated methods demonstrate low-ng/mL limits of quantification, robust selectivity, and incurred-sample reproducibility across clinical ranges.<sup>[24]</sup> Plasma TBF is reliably quantified by high-performance liquid chromatography or LC-MS/MS, with assays demonstrating linearity across clinically relevant concentrations.<sup>[25]</sup> Authoritative azole TDM guidance endorses predose (trough) sampling once steady state is achieved, with LC-MS/MS preferred.<sup>[26,27]</sup>

### Pre-analytical requirements

Reference laboratories specify trough collection at steady state, prompt separation from cells (within 2 h), frozen storage/transport, and avoidance of gel-separator tubes owing to adsorptive loss.<sup>[28,29]</sup> These steps are readily implementable in routine phlebotomy and should be embedded in dermatology clinic workflows.

### Measuring drugs in keratinized matrices and practical sampling

ITZ and TBF accumulate extensively in keratin-rich tissues, including the stratum corneum, hair, sebum, and nail, where concentrations may persist for months after treatment.<sup>[5,30]</sup> Owing to heterogeneous growth rates, slow equilibration with plasma, and risk of external contamination, drug measurement in these matrices is unsuitable for routine therapeutic adjustment and is best reserved for research or forensic applications.<sup>[31]</sup> For clinical monitoring, plasma quantification using validated LC-MS/MS remains the analytical standard, offering sensitivity and reproducibility across clinically relevant ranges.<sup>[24,26,27]</sup> Simplified microsampling approaches, such as dried-blood spots and volumetric absorptive microsampling (VAMS), enable low-volume capillary collection and may facilitate decentralized testing in resource-limited settings.<sup>[32,33]</sup> These techniques lessen dependence on cold-chain transport and shorten turnaround times, but dermatology-specific validation, including whole-blood-to-plasma translation, stability in hot or humid climates, and cross-comparison with venous assays, remains essential before wider implementation.<sup>[28,34]</sup>

## SPECIAL POPULATIONS

### Pediatrics and adolescents

Among pediatric and adolescent patients, higher total body water, fluctuating gastric pH, maturing CYP3A4/2C19, and

frequent acid suppression collectively introduce marked variability in azole exposure. ITZ capsules are pH- and food-dependent; the oral solution and super-bioavailable formulations (SUBA) ITZ attenuate these constraints, but interindividual variability persists.<sup>[4,35]</sup> Accordingly, TDM should be used at a low threshold in refractory tinea or where adherence, formulation, or gastric-pH concerns exist. Target trough concentrations ( $C_{\min}$ ) of  $\geq 0.5$ -1.0 mg/L and avoidance of sustained levels  $>3.0$ -3.5 mg/L are pragmatic, acknowledging that supportive evidence in dermatophytosis is indirect and extrapolated from invasive-mycoses guidance.<sup>[35,36]</sup> Weight-normalized dosing does not guarantee target attainment; capsule absorption is often suboptimal with PPIs/H<sub>2</sub> blockers. When  $C_{\min}$  is low, switching from capsules to solution or SUBA ITZ, splitting the daily dose (reflecting non-linear kinetics), and aligning administration with food (capsules) or an empty stomach (solution) are rational first steps before up-titration.<sup>[37,38]</sup> For TBF, routine TDM is not established; its advantage in children is rapid partitioning into sebum/stratum corneum with prolonged tissue persistence, permitting intermittent or abbreviated courses when clinically appropriate. An early level at day 7-14 is useful when using ITZ in the setting of unavoidable acid suppression or recalcitrant tinea corporis/cruris or extensive tinea capitis.<sup>[39]</sup>

#### Metabolic syndrome/obesity (common in India)

Obesity can alter antifungal disposition through increased volume of distribution for lipophilic agents, changes in splanchnic blood flow, and potential increases in clearance; across antimicrobials, up to one-third of dosing strategies under-expose patients with obesity.<sup>[40]</sup> Contemporary reviews emphasize individualized dosing and exposure verification rather than automatic mg/kg escalation for ITZ.<sup>[41]</sup> In practice, ITZ's lipophilicity and extensive tissue binding mean obese patients may show lower early  $C_{\min}$  with conventional capsules. Prefer SUBA ITZ, less sensitive to food/pH, with higher and less variable bioavailability, and verify  $C_{\min}$  at day 7-14; escalate total daily dose or split dosing only if levels remain  $<0.5$  mg/L.<sup>[37,38,42]</sup> Owing to accumulation in sebum, stratum corneum, and adipose, TBF is usually suitable for fixed dosing across weights; however, its prolonged washout and tissue persistence necessitate vigilance for cumulative toxicity at very high body mass index (BMI).<sup>[39]</sup>

#### Polypharmacy with tuberculosis/human immunodeficiency virus (TB/HIV)/diabetes drugs, why TDM matters?

Rifamycins (rifampicin, rifabutin) are strong CYP3A inducers that markedly lower ITZ exposure; coadministration, especially with pH-dependent capsules, is generally inadvisable and may be contraindicated. When azole

therapy is essential, use a non-rifamycin TB regimen; for dermatophytosis, TBF is usually preferred.<sup>[43]</sup> Likewise, non-nucleoside reverse-transcriptase inhibitors (efavirenz, nevirapine) reduce ITZ and OH-ITZ concentrations with reported clinical failures; if an azole is required, modify the antiretroviral backbone or optimize ITZ formulation and intensify TDM.<sup>[44]</sup> Protease inhibitors or booster regimens (ritonavir, cobicistat) can increase ITZ exposure through CYP3A4 inhibition, mandating lower ITZ doses and closer TDM to avoid toxicity.<sup>[43]</sup> For diabetes therapies, strong CYP3A4 inhibition by ITZ increases meglitinide exposure (repaglinide, nateglinide) with hypoglycemia risk; TBF is often safer, or glucose-lowering therapy must be adjusted and monitored.<sup>[45]</sup> TBF is a CYP2D6 inhibitor; interactions with tricyclics, SSRIs, certain antiarrhythmics, and  $\beta$ -blockers should be anticipated with appropriate medication review and monitoring.<sup>[46]</sup>

#### RESEARCH GAPS AND FUTURE DIRECTIONS

Most dosing and monitoring advice for ITZ and TBF in dermatophytosis remains extrapolated from invasive mycoses or small PK series, and prospective studies that pair serum troughs with keratin-site levels (stratum corneum, hair, nail) against standardized cure and relapse endpoints are scarce, deriving outcome-anchored thresholds for tinea corporis/cruris and onychomycosis is therefore a first-order need.<sup>[4,35]</sup> Validated dermatophytosis-specific PK-PD indices, AUC/MIC at the skin or nail site, keratin:MIC ratios, and concentration-time targets for reservoir compartments, are not yet established for routine care; breakpoints and targets should be tied to cure, stratified by species/genotype, and stress-tested across formulations and dosing schedules.<sup>[47,48]</sup> Rising TBF resistance in *T. indotineae* and difficult phenotypes (e.g., TMVII) mean TDM must be interpreted alongside contemporaneous susceptibility and genotype data (e.g., *SQLE* mutations), with pragmatic pathways that specify when to escalate dose, switch class (including to SUBA-ITZ), or combine therapies using MIC/genotype-aware rules rather than fixed algorithms.<sup>[49]</sup> Making TDM feasible where dermatophytosis is actually managed will require clinic- or home-based microsampling (e.g., dried blood spots, VAMS) with dermatology-specific validation, capillary-to-venous conversion, stability in hot/humid climates, user training, and LMIC cost-effectiveness, treating turnaround time and adherence as co-primary implementation outcomes.<sup>[50,51]</sup> Measuring the site of action, not just serum, demands harmonized methods for quantifying drug in sebum, tape-stripped stratum corneum, hair shafts, and nail plates, coupled with imaging mass spectrometry, skin microdialysis, nail methodologies, and skin/nail physiologically based pharmacokinetic models linked to outcomes across ages, BMIs, and formulations.<sup>[10,52]</sup>

Formulation and brand variability also warrant rigorous auditing: inconsistent exposure with conventional ITZ capsules (food/pH effects, pellet quality, brand-to-brand variability) should be addressed in head-to-head trials against SUBA-ITZ with embedded TDM targets and outcome readouts, while regulatory/procurement audits include blinded bioavailability and dissolution testing tied to clinical results.<sup>[37,38,53]</sup> Dosing in special populations (pediatrics, obesity/metabolic syndrome, pregnancy/lactation, hepatic disease) and under polypharmacy remains under-studied; model-informed precision dosing should integrate host genetics and common TB/HIV/diabetes co-medications to deliver patient-specific exposure forecasts with guardrails against toxicity.<sup>[54]</sup> Evidence for combination or sequence strategies (ITZ↔TBF, systemic-topical) in deep follicular or recalcitrant disease is thin, and trials should stratify by MIC/genotype while targeting measured exposure rather than nominal dose alone.<sup>[55]</sup> Finally, scale-up will depend on quality systems for antifungal TDM, external-quality assessment, commutable reference materials, reporting conventions (C<sub>min</sub> timing, metabolite handling), and simple laboratory dashboards, particularly across LMIC networks, and on tighter linkage of dermatology with public-health and STI surveillance for faster species/genotype reporting and stewardship triggers for escalation beyond TBF.<sup>[56]</sup>

## CONCLUSION

Recalcitrant dermatophytosis represents the convergence of antifungal resistance, variable PK, and empirical prescribing practices divorced from pharmacological principles. ITZ exhibits features that justify routine TDM, whereas TBF may warrant selective, problem-oriented exposure assessment in difficult cases. Routine early ITZ monitoring, particularly in patients receiving acid suppression, with obesity, malabsorption, or polypharmacy, can identify subexposure and guide formulation or dose adjustment. For TBF, selective TDM may help differentiate PK failure from resistance in difficult disease. Implementation priorities include decentralized microsampling, validated assays, rapid result reporting, and linkage to antifungal stewardship and resistance surveillance. In endemic regions such as South Asia, TDM must be integrated with susceptibility testing and *SQLE* genotyping to enable exposure-guided precision therapy. Future research should define exposure-response thresholds for dermatophytosis, characterize drug distribution within keratinized compartments, and compare formulations using outcome-anchored TDM endpoints. Moving from dose-based empiricism to exposure-guided care offers a feasible path toward predictable cure, reduced relapse, and containment of antifungal resistance, an advance with implications extending beyond dermatology.

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