

Current Advances and Challenges in Mycological Dermatology: Treatment-resistant *Trichophyton indotineae*, Onychomycosis, and Tinea Pedis with a Focus on Nitric Oxide Releasing Gels

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Objectives

To review advances in epidemiology, diagnosis, treatment resistance and novel nitric oxide–releasing gel therapies across three key mycological dermatology entities: tinea pedis, *Trichophyton indotineae* and onychomycosis.

Methods

The methodological approach was designed to ensure scientific rigor, comprehensiveness, and translational relevance in synthesizing evidence on dermatophytosis and emerging antifungal therapies. A structured integrative literature review was conducted, encompassing epidemiological, clinical, microbiological, and pharmacological aspects of tinea pedis, *Trichophyton indotineae*, and onychomycosis. Peer-reviewed studies, clinical trial data, and authoritative dermatology texts published between 1990 and mid-2025 were systematically identified through PubMed, Scopus, and Web of Science using MeSH terms and free-text keywords including “tinea pedis,” “onychomycosis,” “*Trichophyton indotineae*,” “antifungal resistance,” “biofilm,” and “nitric oxide.” Eligible studies included original research, meta-analyses, and clinical trials addressing diagnostics, antifungal susceptibility, resistance mechanisms, or nitric oxide therapeutics; case reports lacking microbiological confirmation and methodologically limited studies were excluded. Reference lists of key reviews and guidelines were hand-searched to capture seminal and emerging evidence. Data were synthesized across domains of epidemiology, resistance mechanisms, diagnostic innovations, therapeutic strategies, and nitric-oxide–based interventions. Evidence appraisal prioritized methodological quality, reproducibility, and clinical applicability. Comparative insights were drawn where possible, supporting a clinically relevant synthesis that informs future mechanistic research and therapeutic development.

Results

Domain	Tinea Pedis	Onychomycosis	Trichophyton indotineae
Global Burden	15–25% prevalence; high recurrence in humid climates	5–10% prevalence; up to 60% in elderly	Rapid global spread from South Asia; major emerging pathogen
Key Etiologic Agents	<i>T. rubrum</i> , <i>T. interdigitale</i>	<i>T. rubrum</i> , <i>T. interdigitale</i> , NDMs, yeasts	<i>T. indotineae</i> with high terbinafine resistance
Major Risk Factors	Hyperhidrosis, occlusive footwear, communal bathing, diabetes	Nail trauma, tinea pedis reservoir, diabetes, immunosuppression	Steroid misuse, hot/humid environments, crowding
Clinical Challenges	Recurrent disease; bacterial superinfection	Thick nail plate barrier; poor penetration of topicals	Extensive inflammatory plaques; misdiagnosis; rapid spread
Resistance Landscape	Rising allylamine resistance in <i>T. rubrum</i>	Biofilm-mediated persistence; rising <i>T. rubrum</i> resistance	SQLE mutations (Phe397Leu, Leu393Phe, Phe415Val) → terbinafine failure
Diagnostic Considerations	KOH/culture; PCR increasingly useful	KOH, culture, PAS, PCR for species ID	Requires molecular diagnostics (ITS sequencing/PCR)
Therapeutic Limitations	Adherence, reinfection; limited effect of topicals in chronic cases	Oral antifungals limited by safety and interactions	Itraconazole effective but emerging resistance seen
Translational Potential of Nitric Oxide Releasing Gels	Adjunct to topical/systemic regimens	Novel alternative for recalcitrant disease	Candidate therapy for resistant and steroid-modified disease

Role of Nitric Oxide–Releasing Gels			
Targets infections refractory to standard therapy; broad applicability	Broad-spectrum activity vs. dermatophytes, yeasts, and molds	Suitable for patients with antifungal contraindications or resistance	Overcomes penetration barriers; disrupts fungal biofilms
Multi-target mechanism → low risk of resistance development	Mechanistic complement, potential synergy with existing agents	Fungicidal, biofilm-disruptive, immunomodulatory	Positioned as next-generation antifungal therapy

Results

Synopsis

- Addresses urgent and evolving clinical challenges:** Infections such as athlete’s foot and nail fungus are becoming harder to treat and the global spread of drug-resistant strains like *Trichophyton indotineae* underscore the need for updated diagnostic and treatment strategies.
- Bridges mycology and clinical dermatology:** By integrating epidemiological, diagnostic, and therapeutic perspectives, this review provides clinicians with a comprehensive framework for managing dermatophyte infections in the context of rising antifungal resistance.
- Highlights diagnostic and stewardship priorities:** The review underscores the importance of molecular diagnostic adoption, antifungal susceptibility testing, and rational therapeutic stewardship to mitigate resistance development and recurrence.
- Introduces nitric oxide–releasing gels as an innovative therapeutic platform:** Nitric oxide formulations demonstrate unique fungicidal and biofilm-disruptive mechanisms, representing a novel, non-systemic treatment option for drug-resistant or recalcitrant superficial mycoses.
- Supports translational advancement and public health relevance:** By connecting mechanistic insights with clinical applications, this review outlines future research directions and reinforces the need for updated global guidelines to address the growing burden of mycological dermatology.

Financial Disclosure

Teskey, Jagdev, Cannon, and Miller are employees of SaNOtize Research & Development Corporation.