The Spread of Resistant Tinea and the Ingredients of a Perfect Storm

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Ever since the introduction of griseofulvin as a specific treatment for dermatophytosis (ringworm), dermatologists have noticed that a small proportion of patients do not respond to antifungal drugs. Although this may be explained, in some cases, by underlying disease that affects immunity, or, in the case of onychomycosis, a location where drug penetration is often compromised, some patients, usually with tinea cruris or corporis, do not respond to therapy or relapse rapidly afterwards [1]. A few investigators confirmed the presence of increased minimum inhibitory concentrations to griseofulvin, indicating drug resistance, in dermatophytes isolated from these cases [2]. The introduction of the oral azole antifungals, such as ketoconazole, promised a solution to this problem [3]. Yet, before long, therapeutic failure as well as in vitro resistance occurred with azoles used to treat these infections [4]. Azoles have a different drug target to griseofulvin, inhibiting the α -demethylase enzyme in the fungal cell membrane, thereby blocking the biosynthesis of ergosterol biosynthesis.

Until recently the development of resistance to terbinafine, the target of which is squalene epoxidase, was thought to be less likely, although as Shen et al. [5] show, there has been a trickle of reports describing this. The new

development highlighted in their paper [5] is an amplification of the problem through a recent and progressive increase in cases of widespread and treatment-unresponsive tinea corporis/cruris. Originally reported in India, the patients have predominantly been infected by a new strain of *Trichophyton mentagrophytes*, although some cases are caused by *T. rubrum*. There have been anecdotal reports of very similar recalcitrant infections in Bangladesh and possibly elsewhere in the Middle East and sub-Saharan Africa. Cases have also occurred in Europe and a noteworthy feature is treatment failure with terbinafine.

What started as a sporadic nuisance, with the odd case of tinea corporis/cruris that did not respond to antifungals, is evolving into a global public health crisis. The situation raises many questions. What is the relationship, if any, between the old cases and the new emerging strains in India with evidence of resistance to terbinafine and, in some instances, azoles? Where did the new epidemic arise and how far, globally, has it spread? What can be done about it? In some cases of azole resistance amongst dermatophytes there is evidence of overexpression of a trans-membrane drug transporter, TruMDR3, and in vitro studies suggest that its effects can be countered by the milbemycins, a drug

family used in veterinary medicine as antiparasitics [6]. However, research on some of the new resistant strains has identified a mutation in the squalene epoxidase gene itself [5] – rather than a defect in trans-membrane drug transport. The transcontinental spread of resistant infections, the different resistance mechanisms, and the emergence of a new dermatophyte strain all underline the urgent need for answers.

Key Message

Antifungal resistance, once rare in dermatophyte infections, is increasing and spreading.

Conflict of Interest Statement

There are no conflicts of interest to declare.

References

- 1 Hay RJ. Chronic dermatophyte infections. I. Clinical and mycological features. [Br J Dermatol](#). 1982 Jan;106(1):1–7.
- 2 Artis WM, Odle BM, Jones HE. Griseofulvin-resistant dermatophytosis correlates with in vitro resistance. [Arch Dermatol](#). 1981 Jan; 117(1):16–9.
- 3 Robertson MH, Hanifin JM, Parker F. Oral therapy with ketoconazole for dermatophyte infections unresponsive to griseofulvin. [Rev Infect Dis](#). 1980 Jul-Aug;2(4):578–81.
- 4 Balci DD, Cetin M. Widespread, chronic, and fluconazole-resistant *Trichophyton rubrum* infection in an immunocompetent patient. [Mycoses](#). 2008 Nov;51(6):546–8.
- 5 Shen JJ, Arendrup MC, Verma S, Saunte DML. The emerging terbinafine-resistant trichophyton epidemic: what is the role of antifungal susceptibility testing? [Dermatology](#). 2021. doi: 10.1159/000515290.
- 6 Monod M, Feuerman M, Salamin K, et al. *Trichophyton rubrum* azole resistance mediated by a new ABC transporter, TruMDR3. [Antimicrob Agents Chemother](#). 2019; 63(11):e00863-19.