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Short Communication

# Griseofulvin and Whitfield's ointment- time for their resurrection as part of multidrug therapy in management of recalcitrant dermatophyte infections?

**Sujata R. Mehta Ambalal**[1,*]

[1] *Skin clinic @ Sumeru, SHREI, Ahmedabad, Gujarat, India*

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ABSTRACT

We are facing a resurgence of dermatophytic infections in epidemic proportions in India, and the newer anti fungals don't seem to give the desired results in all patients. Is it time to go back to the older antifungals like Griseofulvin and Whitfield's ointment? This article looks at the why's and how's of this dilemma. Author's experience corroborating the use of Griseofulvin and Whitfield's ointment as part of a multidrug regimen for glabrous tinea infections is also included.



## 1. Introduction

We're currently facing a major dermatophytoses epidemic in India. Till a few years ago, cutaneous dermatophytes were an easily treatable minor inconvenience, but now they are a cause of significant morbidity. While we grapple with the ineffectiveness of currently popular antifungals, one is tempted to look back in time for traditional and 'older' treatments.

### *1.1. Whitfield's ointment.*

Salicylic acid has been used for 2000 years to treat skin disorders. By reducing cohesion between keratinocytes, it causes exfoliation of the stratum corneum, resulting in the removal of dead, infected skin.[1] Whitfield's ointment is a time-honoured, century old remedy for tinea. It contains the keratolytic salicylic acid [6%] and fungistatic benzoic acid [12%] in wool fat and petrolatum. It is a cost effective and surprisingly well tolerated addition to our antifungal armamentarium. For those patients who may get irritation, a reduced strength or reduced frequency of application may be tried.

### *1.2. Griseofulvin*

Griseofulvin was first isolated in 1939 from the culture of Penicillium griseofulvum dierckx after the serendipitous observation of a toxin in soil that prevented the growth of fungi.[2] In 1946, it was identified as the 'curling factor', an antibiotic that produced changes in the morphology of several fungi. It inhibited growth and caused abnormal hyphal formations, including stunting, spiraling, thickening of the cell wall, and disorientation of growth.[3] Its antifungal properties were first found in crops which it protected from invading fungi. It was in 1955 that workers at Glaxo Laboratories found griseofulvin to be very active in vitro against pathogenic skin fungi.[4] Griseofulvin acts by inhibition of fungal cell mitosis and nuclear acid synthesis, probably interfering with the function of microtubules. In 1962, it was found that reducing the particle size improved the absorption and enabled the same blood levels at half the doses hitherto used. As it is poorly water soluble, absorption is enhanced by administration with fatty meal.[5]

Dermatophytes live in the keratin of skin and hair. By an enzyme process, they can digest, live on and distort

* *Corresponding author.*
*E-mail address*: sujata.ambalal@gmail.com (S. R. M. Ambalal).

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the keratin. Their existence depends upon their growing fast enough to avoid being cast off by the superficial desquamation and slow enough to escape the living lethal cells below. Griseofulvin makes newly formed keratin immune to fungal infection.[6]

Griseofulvin resistant strains have a multiple-layered thick cell wall may act as a barrier responsible for the impermeability of the cell of fungi to griseofulvin.[7]

### *1.3. Antifungal timeline*

After the widespread use of Griseofulvin, its resistance also became more prevalent. The next effective antifungal for dermatophytes came in the 1980s in the form of ketoconazole, followed by fluconazole and itraconazole almost a decade later.[8] Terbinafine was introduced in the 90s. These potent drugs led to rapid control of infections. Griseofulvin was almost forgotten or ignored. For two to three decades we became quite complacent with antifungals. There was a dearth of new research as focus shifted to chronic non-infectious and lifestyle diseases. Thus, we were caught unawares when our treatments started failing.

A similar scenario has occurred with bacterial infections. There is selective overgrowth of organisms resistant to currently used antibiotics, so we are now shifting back to the 'older' antibiotics which have maintained a good in vitro activity.[9]

Recent infective organisms may not have been exposed to the older antibiotics and are likely to be sensitive to them. We can apply the same concept to the management of recalcitrant tinea infections. What's old for us maybe new for the fungi.

### *1.4. Multidrug therapy- experience and rationale*

Doctors in India have been struggling to treat glabrous tinea with oral and topical azoles and Terbinafine. For lack of other options, and in an attempt to up the attack on dermatophytes without untoward systemic side effects, we tried the following multidrug therapy regimen in our clinic- Griseofulvin (Fine Particle) 250 mg twice daily orally after meals along with three topical antifungals –Eberconazole in the morning, Amorolfine in the afternoon and Whitfield's ointment at bedtime. (Illustration 1) Griseofulvin was given for one and half to two months or at least for a month after all lesions healed, whichever was longer. Topicals were continued for a month after discontinuation of Griseofulvin, giving time for a full turnover of stratum corneum, the target site of dermatophytes.

After using this combination with good results, we collected retrospective data of 96 patients (43 males and 53 females) either during follow up or telephonically. These patients had received the multidrug treatment for cutaneous dermatophytic infections in the form of tinea corporis, tinea cruris or tinea faceii at our clinic between the years 2016-19. 90 of them had completed the treatment. Two patients had discontinued treatment because of side effects and four were lost to follow up.

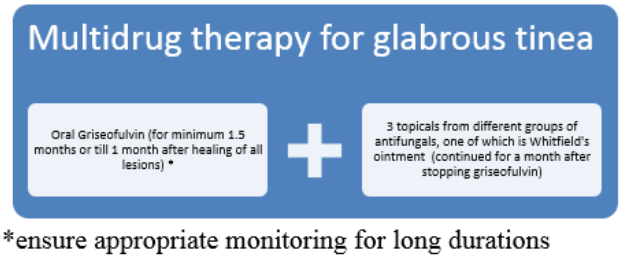


**Fig. 1:** Illustration 1.

Of the 90 patients who completed the entire course of treatment under our supervision, 82 (91%) achieved complete clinical cure within three months, six (6.6%) patients had improvement but not cure. Of these, three had diabetes mellitus, one had obesity and two had no known co morbid factors. Two patients had small new or residual areas of involvement which could be treated only by the topicals' combination. A few patients reported occurrence of lesions at new sites while on this protocol. This signifies that griseofulvin should never be used as monotherapy. We could see/ contact 72 patients after six months of completion of treatment. 4 (5%) of those contacted reported a recurrence. Side effects reported were nausea (10), headache (8), uneasiness (8), irritant contact dermatitis (2) and rash (1).

The rationale of this regimen is that a combination of drugs with different mechanisms of action (Table 1) may take care of poor sensitivity and prevent resistance.[10] Eberconazole and Amorolfine are ergosterol inhibitors having different target enzymes that inhibit cell wall synthesis. As thick cell walls are present in Griseofulvin resistant strains, cell wall synthesis inhibitors would help prevent development of such resistance. Eberconazole was selected among the azoles because it's not available OTC, has an added anti-inflammatory effect and is available in large pack sizes. Amorolfine was selected over Terbinafine as it is still relatively unknown among general practitioners and the chances of a patient having been exposed to it previously are minimal. Larger prospective randomized control studies may be helpful to establish the efficacy of this regimen.

Combination therapy is already the treatment of choice for many infectious diseases including HIV, tuberculosis and malaria. Consequently, the use of drug combinations to treat fungal pathogens has garnered considerable interest over the past several years.[12]

Combining oral antifungals has the potential for numerous drug interactions, may cause hepatotoxicity and requires monitoring. Moreover, oral azoles but not Griseofulvin are also useful for life threatening invasive fungal infections and their oral use for superficial fungal

**Table 1:** Mechanism of action of drugs used in the multidrug regimen

| Antifungal | Target | Mode of action |
|---|---|---|
| Griseofulvin | Microtubules | Mitotic inhibitor of fungal cell |
| Eberconazole (imidazole) | Lanosterol alpha demethylase enzyme | Ergosterol biosynthesis (cell membrane), inhibitor of fungal cell wall |
| Amorolfine (morpholine) | Delta-14-reductase and delta-7,8-isomerase | Ergosterol biosynthesis (cell membrane), inhibitor of fungal cell wall |
| Whitfield's Ointment | Reduced pH, keratinocyte swelling and dissolution of intercellular cement substance by salicylic acid, reduced intracellular pH and ATP formation by benzoic acid [11] | Exfoliation of stratum corneum, inhibition of cell growth of fungus (fungistatic) |

infections is better avoided to maintain the sensitivity of systemic pathogens. Dermatophytic infections are easily accessible for topical treatment. Topical azoles are minimally or not absorbed systemically. Hence, they are unlikely to cause resistance in invasive fungal infections.[13] With candida, sometimes development of resistance to an azole drug leads to cross-resistance to other azoles, and sometimes the resistance is azole specific; this will depend on the specificity of the resistance mechanism[14] Practically, we have experienced that tinea not responding to one azole may respond to a different azole.

In vitro studies show that there is varying degree of resistance to almost all types of antifungals.[15] Hence in practice, the combination of Griseofulvin (mitotic inhibitor) and topicals having different mechanisms of action and having fungistatic, fungicidal and keratolytic effects may be responsible for the positive clinical cure rates. Of course, one must treat their patients keeping in mind the extent and duration of infection, interactions and side effects of the drugs and co morbid conditions. If Griseofulvin is used for longer than 8 weeks in a patient with other risk factors for side effects, laboratory monitoring of WBC counts, hepatic and renal function is needed.[16]

## 2. Conclusion

The expression of resistance to antimicrobial agents is the logical and inevitable consequence of using these agents to treat human infections.[10] Antifungal drug resistance is part of their evolution which requires that our treatment approach also evolve from time to time. Across specialties, the number of cases of fungal infection and antifungal resistance are alarmingly high, and control of fungal diseases is far from being achieved.[17] As new classes of antifungals are sadly lacking in the market, it may be wise to resurrect what was once used more than half a century ago.

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## 4. Conflict of Interest

The authors declare they have no conflict of interest.

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## Author biography

**Sujata R. Mehta Ambalal,** Director