Topical Ciclopirox - Recalling a Forgotten Ally in the Fight against Cutaneous Mycoses

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Abstract

The injudicious use of antifungals, indiscriminate use of corticosteroids for instant relief, persistence of predisposing factors like sweat retention, in uncontrolled diabetes, and emerging resistance to antifungals across the globe have rendered the management of an erstwhile simple infection, the superficial cutaneous mycoses highly complicated and tricky. Ciclopirox is an old yet efficacious, versatile, and safe topical antifungal of the hydroxypyridone family. Despite its numerous beneficial properties over majority of other topical antifungals, it is being under-utilized owing to aggressive focus and tactics of the pharmaceutical industry on promoting ‘newer azoles’. The antifungal spectrum of ciclopirox is one of the broadest and includes nearly all clinically relevant fungi (dermatophytes, yeasts and moulds). It is also effective against manyazole-resistant dermatophytes and Candida albicans and Non-albicans Candida spp. like C. glabrata and C. krusei. The mechanism of action of ciclopirox, a fungicidal agent, is different from that of other topical antifungals that usually inhibit ergosterol synthesis. The drug chelates trivalent metal cations especially iron resulting in inhibition of metal-dependent enzymes that protect the fungal cell by scavenging reactive oxygen species, disrupts cellular activities such as mitochondrial electron transport processes, blocks intracellular transport of precursors by cell membrane alteration, and disrupts DNA repair. This set of multilevel fungicidal mechanisms being unique to ciclopirox minimizes the possibility of development of drug resistance, which till date has never been reported clinically. The drug also has potent anti-bacterial activity (against Gram Positive as well as Gram Negative bacteria) and bears anti-inflammatory effects comparable to 2.5% hydrocortisone. Ciclopirox olamine 1% cream, equivalent to 0.77% ciclopirox penetrates into the deep layers of the skin and mucosae. It is indicated for dermatophytosis, pityriasis versicolor, seborrhoeic dermatitis, vulvovaginal and cutaneous candidiasis, usually as twice-a-day application for 2 - 4 weeks. For onychomycosis, 8% nail lacquer formulation is used. The topical drug is devoid of systemic adverse effects. Only mild transient local reactions have been reported in less than 5% of treated patients. It is perhaps one of the best and most versatile topical antifungal with potential of being instrumental in the management of current epidemic of rampant antifungal therapy failure.

Keywords: Ciclopirox Olamine; Mycoses; Tinea; Candida; Pityriasis Versicolor; Seborrhoeic Dermatitis; dermatophyte

Abbreviations

ALL: Acute Lymphocytic Leukemia; CDC 25: Cell Division Cycle 25; CDK: Cyclin-Dependent Kinase; CPO: Ciclopirox Olamine; ER: Endoplasmic Reticulum; FDC: Fixed Drug Combination; GN: Gram Negative; GP: Gram Positive; MIC: Minimum Inhibitory Concentration; NCAC: Non- C. albicans Candida; ONM: Onychomycosis; PV: Pityriasis Versicolor; SD: Seborrhoeic Dermatitis; RCT: Randomized Controlled Trial; ROS: Reactive Oxygen Species; SE: Squalene Epoxidase; US-FDA: United States Food and Drug Administration; VVC: Vulvovaginal Candidiasis; ZPO: Zinc Pyrithione

Background

The injudicious use of topical as well as oral azoles and allylamines, and indiscriminate use of topical steroids alone or FDC of an antifungal and a topical corticosteroid on the prescription of practitioners, and self-use by patients recommended by a friendly neighborhood pharmacist, family members and peers has plunged us into a crisis of rampant antifungal therapy failures [1]. Although, recurrent infection, persistence of predisposing factors such as excessive sweat retention and uncontrolled diabetes, use of inappropriate choice of antifungal agent, inadequate duration of treatment, parasitization of the vellus hair with dermatophytes, and self-medication with steroid-containing preparations contribute to the majority of antifungal therapy failures, true resistance to antifungal agents is also seemingly becoming a nuisance in this regard. Not only the number of patients with uncomplicated dermatophytic infections has increased, patients with atypical lesions, extensive lesions, frequent recurrences, and recalcitrant dermatophytosis are being commonly encountered now (Figures 1-5). Several biochemical mechanisms contribute to the phenotype of drug resistance in fungi (Table 1). The major ones include decrease in drug uptake, structural alterations in the antifungal drug target site, over-expression of target enzymes, increase in drug efflux, and stress adaptation [2]. With few exceptions, the antifungal drugs in common usage (allylamines and azoles) are directed against the ergosterol biosynthetic pathway [2]. Imidazoles, and, in part, the more recent triazoles fluconazole, itraconazole, voriconazole, and luliconazole, share a common mechanism of ergosterol depletion, i.e. inhibition of cytochrome P450 14a-lanosterol demethylase, and accumulation of sterol precursors [2]. Allylamines such as terbinafine potently inhibit SE, an enzyme involved in the early steps of ergosterol biosynthesis and result in the accumulation of squalene, which is toxic to the fungal cells. Increased drug efflux, and modification of the target (i.e. SE) by gene mutation constitute the chief mechanism of resistance of dermatophytes to azoles and allylamines respectively [2]. Another crucial aspect of antifungal drug resistance, especially in yeasts like Candida albicans is the formation of biofilms, differentiated masses of microbes surrounded by a matrix of extracellular polymers that adhere to surfaces and offer resistance to standard antimicrobials [2]. Formation of biofilms by dermatophytes results in ONM refractory to standard antifungal therapies owing to the formation of dermatophytomas that are dense white mass of fungus tenaciously adherent to the surrounding nail plate that often require surgical or laser ablation [2].

Azole resistance in dermatophytes and yeasts is on the rise. Although documented terbinafine resistance remains anecdotal, clinical

<table>
<thead>
<tr>
<th>Drug Category</th>
<th>Mechanism/Site of action</th>
<th>Mechanism of drug resistance</th>
</tr>
</thead>
</table>
| Azoles        | Block lanosterol 14α-demethylase (Erg11p) | - Efflux of drug by multi-drug transporters; ABC gene family  
|               |                          | - Amino acid substitution to Erg1p affecting drug-target binding  
|               |                          | - Over-expression of Erg1p minimizing effect of drug  
|               |                          | - Change in toxic-sterol concentration due to mutation in Erg3 alleles |
| Allylamines   | Inhibit squalene epoxidase (Erg1p) | - Modification of drug target (Squalene epoxidase) |
| Polenes       | Formation of pores in cell membranes | - Reduction of ergosterol concentration ablating drug-target binding  
|               |                          | - Alteration in POL gene family |

*Table 1: Mechanisms of drug resistance in superficial mycoses causing fungi.*
therapeutic failures to the standard doses of oral terbinafine are being increasingly encountered. Moreover, azole antifungals, unlike allylamines, potentiate resistance development in dermatophytes.

**Ciclopirox and Ciclopirox Olamine - Introduction**

Ciclopirox (and piroctone) are hydroxypyridone derivatives that differ in structure and mechanism of action from the other known antifungal agents [3]. Ciclopirox is the ethanolamine salt of 6-cyclohexyl-1-hydroxy-4-methyl-2 (1H)-pyridone [4]. Ciclopirox, an efficacious and safe topical antifungal agent for superficial cutaneous mycoses has been in use for over three decades and received its US-FDA approval for this indication in December 1996. However, ciclopirox-based topical antifungal formulations remain grossly underutilized. The pleiotropic effects and certain unique properties of ciclopirox make a strong case for its resurgence as a topical anti-fungal. Majority of extant literature addresses its usage as a treatment modality for ONM in conventional and evolving topical laquer formulations; but in

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**Figure 1:** Case of steroid-modified tinea cruris. Extensive tinea cruris in a young male showing multiple erythematous polycyclic scales in the groins and upper inner thigh region. The lesions have an atypical appearance with suppressed scaling and visible telangiectasias due to steroid application by the patient.

**Figure 2:** Case of tinea corporis incognito. Single pink to violaceous colored plaque over the lower abdomen without typical polycyclic margins and scaling. The patient had been applying clotrimazole-mometasone combination cream himself for a week.

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Pharmacodynamics

Ciclopirox is a broad-spectrum antifungal medication with additional antibacterial and anti-inflammatory properties (vide infra). Its

Figure 3: Florid case of tinea faciei in an otherwise healthy young male with erythematous semi-annular scaly plaques involving the left jaw angle and extending onto the upper neck. The patient was a gym instructor who admitted having taken regular injections of testosterone and dexamethasone for the past one month. Face is otherwise a relatively uncommon site for dermatophytic infection in a healthy young adult.
main mode of action is thought to be its high affinity for trivalent cations, which inhibit essential co-factors in enzymes [3,4]. Ciclopirox exhibits either fungistatic or fungicidal activity in vitro against a broad spectrum of fungal organisms, such as dermatophytes, yeasts, dimorphic fungi, eumycetes, and actinomycetes.

**Skin Penetration and Topical pharmacokinetics**

In in vivo human studies conducted in healthy volunteers, after two hours contact time of 1% ciclopirox cream applied to the forearm, a high concentration of drug was detected in the most superficial layer with low levels in deeper layers. Humans studies with radiolabeled 1% CPO solution in polyethylene glycol 400 showed an average of 1.3% absorption of the dose when it was applied topically over 750 cm² on the back followed by occlusion of 6 hours [4]. The biological half-life was 1.7 hours, and after metabolism via glucuronidation, excretion occurs renally. Further studies with radiolabeled ciclopirox olamine have revealed that after 1.5 to 6-hour application of 1% CPO cream, the drug levels in the dermis were maintained to the tune of 10 - 15 times the MIC for superficial fungi [4]. Ciclopirox penetrates into the hair, and through the epidermis and hair follicles into the sebaceous glands and dermis with a small portion remaining within the stratum corneum (reservoir effect).

The systemic absorption of ciclopirox following two protocols of intravaginal administration over 3 - 6 days revealed very low systemic levels with an estimated absorption range of 7 - 9% [5]. The penetration of ciclopirox into the nail unit, evaluated by in vivo application of 8% ciclopirox nail lacquer once daily in healthy volunteers revealed attainment of clinically efficacious mean ciclopirox concentration of 3.4 mg/mg and 7 mg/mg in the nails after 30 days and 45 days respectively [5]. New technology and approaches are being constantly explored to enhance the transungual delivery of ciclopirox; but this subject is beyond the scope of this review article.

**Mechanism of Antifungal Action**

The majority of topical antimycotic agents including the two major groups, i.e. azoles and allylamines, act by means of a similar mechanism, i.e. the inhibition of the biosynthesis of or the molecular interaction with ergosterol, the major component of the fungal cell membrane. Hydroxypyridones, ciclopirox being the prototype, are the sole class of topical antifungal agents that have a completely different mechanism of action [5].

Ciclopirox is thought to act through the chelation of polyvalent metal cations, such as ferric (Fe³⁺) and aluminum (Al³⁺) thereby caus-

<table>
<thead>
<tr>
<th>Chelation of polyvalent metal cations, especially iron (Fe³⁺)</th>
</tr>
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<tbody>
<tr>
<td>Inhibition of metal dependent enzymes (cytochromes, catalase, peroxidase)</td>
</tr>
<tr>
<td>Disruption of cellular activities such as mitochondrial electron transport processes, energy production, and nutrient intake across cell membrane</td>
</tr>
<tr>
<td>Alteration of membrane permeability causing blockage of intracellular transport of precursors</td>
</tr>
<tr>
<td>Disruption of DNA repair, cell division signals and disorganization of internal structures (mitotic spindles) of the fungi.</td>
</tr>
<tr>
<td>At higher concentrations, compromising the integrity of the cell membrane of susceptible organisms followed by leakage of potassium ions and other intracellular material.</td>
</tr>
<tr>
<td>Inhibitory effect on secreted aspartyl proteinases, important virulence factors for several types of C. albicans infections that favour the adhesion of the yeast to epithelial cells. This may be significant in the drug effect on mucosal candidiasis</td>
</tr>
</tbody>
</table>

**Table 2: Postulated anti-mycotic mechanisms of action of ciclopirox.**

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ing inhibition of metal dependent enzymes (cytochromes, catalase, peroxidase) leading to disruption of cellular activities such as mitochondrial electron transport processes, energy production, and nutrient intake across cell membrane [3]. It has also been known to alter membrane permeability causing blockage of intracellular transport of precursors. Many other mechanisms have also been postulated [5,7]. Table 2 summarizes these anti-mycotic mechanisms of ciclopirox.

**Antifungal Spectrum and comparative efficacy**

Ciclopirox expresses one of the broadest spectrum of antimycotic activity and inhibits nearly all clinically relevant dermatophytes, yeasts and moulds, including certain frequently azole-resistant Candida species, such as *Candida glabrata* and *Candida krusei* [5]. Ciclopirox can be both fungistatic and fungicidal depending on the concentration and on the duration of contact with target organisms. A unique property of ciclopirox is that it exerts fungicidal activity against nongrowing cells as well. Ciclopirox MIC values are strongly influenced by the composition and pH of the medium, in particular by the presence of iron salts. For practically all types of superficial mycoses, the MIC values of ciclopirox are lower than the concentrations attained in vivo after topical application. According to the results of Gupta and Kohli [6], for dermatophytes, ciclopirox was considerably more effective against all species tested (110 strains of dermatophytes) than itraconazole and ketoconazole, being only minimally inferior to terbinafine. For yeasts (14 strains of Candida) and non-dermatophyte moulds (9 strains), ciclopirox was the most potent with lowest MIC values for these fungi, compared to ketoconazole, itraconazole and terbinafine. Ciclopirox has also demonstrated low MIC values and high clinical efficacy against *Malassezia globosa* and *Malassezia restricta*, the predominant species involved in Pityriasis versicolor and seborrheic dermatitis [6].

Other than the yeasts (*Candida sp.*, *Malassezia sp.*, *cryptococcus neoformans*), it also displays inhibitory effect over *Saccharomyces cerevisiae*, and some *Aspergillus* and *Penicillium* species, although selected strains of aspergilli have higher MIC values compared to dermatophytes [7]. Some moulds, especially certain strains of zygomycetes (e.g. *Rhizopus* and *Mucor*) are more susceptible to ciclopirox [5].

In vitro fungicidal activity against *T. mentagrophytes* [8]: CPO cream 1% > naftifine cream 1% > oxiconazole cream 1% > bifonazole cream 1%.

In vitro activity against *C albicans* [4]: CPO cream 1% > tioconazole cream 1% > oxiconazole cream 1% > miconazole cream 2% > econazole cream 1% > clotrimazole cream.

Overall, an analysis of existing MIC data revealed that for the common species that cause tinea corporis/cruris/pedis/faciei, like *Trichophyton rubrum*, *Trichophyton mentagrophytes*, *Trichophyton verrucosum*, *Trichophyton tonsurans* and *Trichophyton violaceum*, ciclopirox is inferior to amorolfine, terbinafine and itraconazole, but better or almost comparable to ketoconazole, clotrimazole and fluconazole. On the other hand, for *Malassezia* and candida species like *Candida albicans*, *Candida glabrata*, *Candida tropicalis*, *Candida krusei* and *Candida parapsilosis*, it has superior efficacy to terbinafine, econazole and butenafine.

It is important to note that the fungicidal effect of ciclopirox is different from other topical fungicidal drugs since it is effective even against non-growing cells; making it suitable in the treatment of onychomycosis, since the local condition of the infected nail does not promote optimum fungal growth. However, in this paper, we shall restrict the discussion of ciclopirox for fungal infections other than onychomycosis.

**Activity against non-fungal microorganisms: Bacteria, viruses, parasitic agents**

Ciclopirox has in vitro activity against many GP and GN bacteria [5,8]. The GP bacteria inhibited by ciclopirox include *Staphylococcus* spp., *Streptococci*, *Micrococi*, amongst others. Although some azoles also demonstrate variable activity against some GP bacteria, the additional activity of ciclopirox against GN strains (like *Proteus* spp. and *Pseudomonas aeruginosa*) is an advantage over

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**the azoles.** This combined broad spectrum antifungal and antibacterial activity of ciclopirox is of particular advantage in the treatment of macerated tinea pedis and "dermatophytosis complex", both conditions characterized by symptomatic intertriginous fungal affections secondarily infected by bacteria. Ciclopirox also exerts activity against *Gardnerella vaginalis* (leading cause of bacterial vaginosis) as well as the parasite *Trichomonas vaginalis*, while sparing *Lactobacilli* sp., the physiological vaginal flora; making it a selectively useful topical agent for multiple vaginal infections [5]. Ciclopirox has another important property, clinical relevance of which remains to be explored.

<table>
<thead>
<tr>
<th>Category of microorganism</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gram Positive bacteria</td>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td></td>
<td>β-haemolytic Streptococci (group A)</td>
</tr>
<tr>
<td></td>
<td><em>Micrococcus luteus</em></td>
</tr>
<tr>
<td></td>
<td><em>Micrococcus sedentarius</em></td>
</tr>
<tr>
<td></td>
<td><em>Corynebacterium minutissimum</em></td>
</tr>
<tr>
<td></td>
<td><em>Brevibacterium spp.</em></td>
</tr>
<tr>
<td>Gram Negative bacteria</td>
<td><em>Pseudomonas aeruginosa</em></td>
</tr>
<tr>
<td></td>
<td><em>Proteus mirabilis</em></td>
</tr>
<tr>
<td></td>
<td><em>Escherichia coli</em></td>
</tr>
<tr>
<td></td>
<td><em>Klebsiella pneumoniae</em></td>
</tr>
<tr>
<td>Other bacteria</td>
<td><em>Mycoplasma spp.</em></td>
</tr>
<tr>
<td></td>
<td><em>Gardnerella vaginalis</em></td>
</tr>
<tr>
<td>Parasitic agent(s)</td>
<td><em>Trichomonas vaginalis</em></td>
</tr>
<tr>
<td>Viruses</td>
<td>HIV-1</td>
</tr>
</tbody>
</table>

**Table 3:** Non-fungal microorganisms (bacteria, viruses, parasitic agents etc.) against which ciclopirox displays inhibitory activity.

It has been shown to block HIV-1 infection of human peripheral blood mononuclear cells at clinically relevant concentrations. Eukaryotic translation initiation factor eIF5A (a protein that contains the unique amino acid hypusine formed by activity of deoxyhypusine synthase and deoxyhypusine hydroxylase enzymes) has been implicated in HIV-1 replication. Ciclopirox seems to exert its HIV-1 replication inhibition by inhibition of deoxyhypusine synthase and deoxyhypusine hydroxylase enzymes, possibly through its iron-chelation activity [9].

**Anti-inflammatory activity**

Ciclopirox also possesses good anti-inflammatory activity that involves inhibition of prostaglandin (especially PGE2) and leukotriene synthesis in human polymorphonuclear cells. This action of ciclopirox is most likely due to inhibition of 5-lipoxygenase and cyclooxygenase enzymes. Reported to be as potent an anti-inflammatory agent as indomethacin and desoximetasone, **many in vivo studies have reported its anti-inflammatory activity to be superior to most of the other topical antifungals** (naftifine, terbinafine, econazole, ketoconazole, miconazole, fluconazole, oxiconazole) [4,8].

In a double-blind protocol, ciclopirox also demonstrated the highest anti-inflammatory property (more than allylamines like terbinafine, azoles and even 2.5% hydrocortisone) in suppressing the delayed erythema response following *in vivo* human exposure to ultraviolet B irradiation [10]. Reactive oxygen species released from inflammatory cells are well-known to be contributory to the inflammatory symptoms of various dermatoses like SD and atopic dermatitis. Ciclopirox has been demonstrated to not only decrease ROS production by chelating transition metals such as iron and copper, but also through a direct and potent scavenging effect over the hydroxyl radical [5].
One study reported the anti-inflammatory activity of ciclopirox 1% cream to be similar to that of a combination of ciclopirox 1% and hydrocortisone 1% cream [11]. The implication of the robust anti-inflammatory effect of ciclopirox is its great potential to be used as a single-agent non-steroidal preparation even for inflamed tinea. The use of ciclopirox alone instead of antifungal-steroid combination for inflamed tinea may substantially contribute to the reduction of the widespread therapeutic failure of antifungal treatments.

**Currently available formulations of ciclopirox (in India)**

- **Shampoo** (for seborrheic dermatitis) - Available in concentrations of 1% [8x shampoo; manufactured by Cipla Inc.] and 1.5% [STEIPROX shampoo; manufactured by GSK (Steifel)]
- **CPO** (for dermatophytic and yeast infections) - 1% cream [SYNPIROX 1% CREAM and SYNPIROX 1% Vaginal cream with applicator; manufactured by Synmedic Laboratories]
- **Nail lacquer** (for ONM) - 8% [NAILON nail lacquer solution; manufactured by Apple Therapeutics Pvt. Ltd.] - to be used daily over the affected nail(s)

Ciclopirox 0.77% gel, although not available in India, is one of the more common preparations of this molecule available in US and many other western nations.

**Table 4:** Standard recommended dosing and duration of application of ciclopirox olamine 1% cream in different indications.

<table>
<thead>
<tr>
<th>Indication</th>
<th>Application protocol</th>
<th>Duration of therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tinea corporis/cruris</td>
<td>Twice-a-day</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Tinea pedis</td>
<td>Twice-a-day</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Pityriasis versicolor</td>
<td>Twice-a-day</td>
<td>2 weeks</td>
</tr>
<tr>
<td>Seborrheic Dermatitis</td>
<td>Twice-a-day</td>
<td>4 weeks</td>
</tr>
<tr>
<td></td>
<td>Maintenance with Once-a-day (optional/situational)</td>
<td>4 weeks</td>
</tr>
<tr>
<td>Vulvovaginal Candidiasis</td>
<td>Twice-a-day</td>
<td>4 weeks</td>
</tr>
</tbody>
</table>

**Indications and Efficacy of CPO 1% in the treatment of different superficial mycoses**

After being introduced in 1975, ciclopirox became widely popular in Europe and also received US-FDA approval for the treatment of superficial fungal infections, including tinea pedis, tinea corporis, tinea cruris, pityriasis versicolor, seborrheic dermatitis and cutaneous and vulvovaginal candidiasis [12]. The details of recommended dosing, frequency per day and duration of therapy are summarized in Table 4.

**Dermatophytic (Tinea) Infections**

The results of two multicentric studies that compared CPO cream 1% (ciclopirox 0.77%) with the cream vehicle and clotrimazole cream 1% respectively, in patients with tinea corporis/cruris showed that the mycological as well as overall response rate at the 6th week (2 weeks after 4 weeks treatment with twice-daily application of the cream/vehicle) were better in the ciclopirox treated group compared to the vehicle alone while they were almost equal to the clotrimazole-treated group [13].

Ciclopirox demonstrated results superior to clotrimazole in tinea pedis. Four weeks treatment regime of twice daily application of both the creams in different groups showed significantly better clinical cure rates with ciclopirox, both during the therapy (2nd and 3rd week) and post-treatment (5th and 6th week). At week 6, the combined clinical and mycologic cure in the ciclopirox group was 33/43 vs. clotrimazole 37/42 (P<0.05) [14]. The efficacy of ciclopirox in the treatment of tinea pedis interdigitalis-associated dermatophytosis complex stemming from its pleiotropic effect has been reported in a prospective, randomized, double-blind, placebo-controlled 8-week
临床研究的100名患者中，盐酸特比萘芬凝胶每天一次或两次显著减少了第8周的体征和症状，与对照组相比，盐酸特比萘芬的真菌学治愈率、完全治愈率和细菌计数减少率都明显高于对照组。第15篇。在盐酸特比萘芬组和安慰剂组之间没有显著的不良事件差异。

**Figure 4:** Case of extensive tinea cruris-corporis in an infant partially modified by off-and-on application of a fluocinolone-miconazole-neomycin triple combination cream. Apart from the peripheral raised inflammatory edge, there are multiple small ring-ling lesions within the lesion accompanied with multiple foci of hypo-to depigmentation.

**Figure 5:** Case of onychomycosis (ONM) involving all the fingers of this displayed hand, characterized by thickened nail plates with yellow-brown discoloration, distal onycholysis and subungual hyperkeratosis. Also note the mild inflammation (paronychia) of the proximal nail folds.
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Figure 6: Treatment efficacy of Ciclopirox in an itraconazole resistant case of tinea corporis - (a) A large lesion of recalcitrant tinea corporis over the abdomen of a 38-year old diabetic male that did not improve despite multiple 2-3 week courses of oral itraconazole and alternating application of luliconazole, amrolfine and mometasone creams used for 3-4 months; (b) The patient was clinically cured with just a patch of residual post-inflammatory hyperpigmentation (white arrow) on stopping oral itraconazole and all topicals and treated with only ciclopirox olamine 1% cream twice-a-day for 8 weeks. The patient by choice had started maintaining a completely shaved torso.

Figure 7: Copious curdy white discharge visible on per speculum examination of a 27-year old non-pregnant lady with first episode of vulvovaginal candidiasis. Candida albicans was grown on fungal culture. (Image Courtesy DR NINA MADNANI, Department Coordinator, Department of Dermatology, PD Hinduja National Hospital, Mumbai, India)
**Pityriasis Versicolor**

Ciclopirox olamine cream 1% applied twice daily for 14 days is a well-known, efficacious and safe therapy for PV. When compared with the vehicle in a double-blind RCT, ciclopirox olamine cream 1% applied twice daily for 2 weeks provided superior cure rates for PV; with 49% of the 73 patients using ciclopirox attaining clinical and mycological cure compared to 24% of 72 patients applying the vehicle (P < 0.0001) [17]. In another RCT comparing 2-week application of ciclopirox with clotrimazole 1% for treatment of PV, clinicomycologic cures were observed in 77% and 45% patients respectively [4]. Although, follow-up evaluation 2 weeks after treatment course completion revealed comparable responses in both the groups. Maintaining the application protocol of 1% CPO for 4 additional weeks has been shown to increase the response rate from 74% to 86% [18].

**Seborrheic Dermatitis**

Ketoconazole-based creams, shampoos and other formulations with or without ZPO have been the standard of care for SD for decades. In a recent systematic review on topical treatments for facial SD published by Gupta and Versteeg, topical ciclopirox olamine was accorded a strong recommendation (Grade A practice recommendation) based upon its consistent efficacy established in multiple high quality RCTs [19]. Topical ketoconazole, tacrolimus and lithium gluconate/succinate were considered at par with topical CPO in this review. In a meta-analysis of topical antifungals for SD published by the Cochrane Skin Group in 2015, topical ciclopirox as well as ketoconazole were reported to be more effective than placebo in yielding total clearance and improving symptoms of erythema, pruritus and scaling. Occurrence of side effects was similar to that with placebo [20]. The metaanalysis however, found limited evidence in suggesting superiority of either antifungal over the other. The major limitation of the trials included in the Cochrane meta-analysis was the lack of follow-up beyond 4 weeks.

**Figure 8:** Unlike Figure 7, this image, taken from a 44-year old lady with 7th episode of vulvovaginal candidiasis (in 2 years) shows mild floccular white discharge with prominent hyperemia of the vaginal walls. Candida glabrata was grown on fungal culture. (Image Courtesy DR NINA MADNANI, Department Coordinator, Department of Dermatology, PD Hinduja National Hospital, Mumbai, India)

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Despite meta-analyses concluding similar efficacy for these topical antifungals, individual RCTs comparing ciclopirox with ketoconazole revealed that the efficacy of the former was either comparable to, or better than the latter. In a randomized, open-labeled, non-inferiority study, Chosidow, et al. compared long-term effectiveness of this treatment (consisting of 28 days of active treatment followed by 28 days of maintenance once-a-week application) and reported that not only the treatment response to ciclopirox was greater than ketoconazole in both intention-to-treat and per-protocol populations (p = 0.03), but maintenance of effect was better with ciclopirox, with fewer participants exhibiting persistence of SD compared with 2% ketoconazole (p = 0.001) [21].

Various other comparative trials have established relatively superior efficacy, longer duration of persistence of improvement, and/or lesser adverse effects with the use of ciclopirox based cream/shampoo compared to formulations containing ketoconazole [19,22-24]. A multicentre, single-blind, clinical study that evaluated the efficacy of a shampoo containing 1.5% CPO/1% ZPO combination compared to the vehicle shampoo and 2% ketoconazole foaming gel for SD (twice-a-week application for 28 days) established statistical superiority of the CPO/ZPO shampoo in reducing pruritus at day 7 over ketoconazole gel and the vehicle [23].

Ciclopirox has been administered in varying doses and protocols for SD [20,24-26]. In the study by Altmeyer, et al. ciclopirox 1% resulted in better treatment effect than 0.3% and 0.1%, but the difference was not statistically significant [26].

Candidal Infection - Vulvovaginal Candidiasis

It has been estimated that 75% of women will have at least one episode of VVC, and 40%–45% will have two or more episodes. VVC is usually caused by *C. albicans* but can be caused by other *Candida* sp. or yeasts. Vulvar pruritus, vaginal soreness, dyspareunia, external dysuria, and abnormal vaginal discharge are the typical symptoms of this infection. VVC due to *C. albicans* generally has an acute course and presents with copious curdy-white discharge on per speculum examination (Figure 7) and severe vaginitis. In contrast, VVC due to NCAC like *C. glabrata* tends to have a more indolent course and presents with spotty or floccular discharge and diffuse hyperemia of the vagina (Figure 8). Uncomplicated VVC (usually caused by *C. albicans*) is typically sporadic, occurs in immunocompetent women, and presents with mild to moderate symptoms. Complicated VVC affects 10-20% women and is considered when VVC is severe presentation, or recurrent (RVVC - 4 or more episodes in 1 year), affects women with diabetes, immunocompromising conditions (e.g., HIV infection), debilitation, or immunosuppressive therapy (e.g., corticosteroids), and when it is caused by NCAC. The incidence of recurrent VVC and complicated VVC is on the rise. Although *Candida albicans* used to be the major cause of VVC, there is an ongoing epidemiological shift both in terms of the species of candida and their anti-fungal resistance. *C. albicans* remains the most common causative yeast of VVC, followed by *C. glabrata* and *C. tropicalis*. The overall incidence of NCAC causing VVC is on the rise; additionally, resistance of *C. albicans* as well as NCAC to azoles, polynes and now even echinocandins (used for invasive candidiasis) is becoming colossal [27]. Formation of biofilms is a huge contributory factor towards drug resistance. In an Indian study of 300 women of reproductive age group with VVC, *C. tropicalis* was the second most prevalent *Candida* species, corresponding to 26.4% of the isolates, of which 42.9% were resistant to fluconazole and 14.3% to voriconazole [28]. In an Iranian study, out of the 67 *Candida* isolates obtained from vaginal secretion samples from patients with VVC, *C. tropicalis* was present in 5.9% of cases, with 100% resistance to fluconazole, 50% resistance to clotrimazole, 25% to ketoconazole, and 75% against terbinafine [29].

Ciclopirox has traditionally been one of the most popular antinmyotic for the treatment of vulvovaginal candidiasis [5]. However, inundation of the antinmyotic armamentarium with newer azoles and allylamines in the past two decades resulted in inadvertent neglect of this versatile anti-candidal agent. Before reviewing the evidence favouring CPO 1% cream for VVC, few points merit attention:

1. Comparison of different antifungals against candidal species in multiple *in vitro* susceptibility testing studies proves ciclopirox to be active in the same range of concentrations against *C. albicans*, *C. glabrata*, *C. krusei*, *C. parapsilosis* and *C. tropicalis* [5]. Fluconazole is poorly active against *C. glabrata*, practically inactive against *C. krusei* and is facing increasing resistance from *C. albicans*. Itraconazole and voriconazole resistance is also on the rise (*vide supra*). Terbinafine is generally devoid of activity against Candida, except for *C. parapsilosis* [5].
2. In addition to offering anti-fungal activity against all the major candidal species that cause VVC, ciclopirox is claimed to be effective against azole-resistant Candida species like *C. glabrata, C. krusei,* and *C. guilliermondii* due to its unique mode of action. *In vitro* studies by Niewerth, *et al.,* have shown a concentration of 0.6g/ml to be sub-inhibitory and a slightly higher 0.7g/ml to be almost completely inhibitory for candidal growth, thus reflecting the steep dose response curve of ciclopirox [30].

3. The fact that resistance to yeasts of the genus Candida is unlikely to develop against ciclopirox makes this drug a useful option, alone or in combination with other interventions, for the treatment of recurrent vaginal candidiasis [31].

4. In addition to anti-candidal efficacy, the additional inhibitory effect of CPO on *Gardnerella vaginalis* and *Trichomonas vaginalis* (*vide supra*) makes it an obvious choice over azoles in mixed infections of the female lower genitalia.

In Europe, for the treatment of VVC, various ciclopirox formulations are available including CPO 1% vaginal cream, 100 mg pessaries and 0.2% vaginal douche. Recommendations include 1% vaginal cream (5 g/day, containing CPO 50 mg) for 6 days, usage of the cream till 12 days, or 100 mg pessaries for 6 days. The 0.2% vaginal douche is mostly recommended as an adjunct therapy to the former two formulations, by instructing the patient to use the cream or pessaries in the evening and the douches in the following morning. Douching will help to remove the residual dose of the previous night, as well as the spores or vegetative forms from the vaginal fornix.

The formulations employed in the studies evaluating the efficacy of ciclopirox for VVC were 1% CPO cream (50 mg once-daily × 6 - 14 days) or pessaries (100 mg once-daily × 3-6 days) [31 - 42]. If these studies are summarily analysed, CPO provided microbiological cure rates of 51% to 100% and clinical cure in 61% to 91% patients. The effects of CPO cream and pessaries were similar to miconazole and terconazole creams, and clotrimazole vaginal tablets respectively.

Beikert FC., *et al.,* evaluated the efficacy of combination of oral fluconazole (100 mg daily × 20 days) and topical CPO for culture proven *C. albicans* associated recurrent VVC. Overall, 81 of 122 women (66%, CI 0.57-0.76) experienced no mycologic recurrence throughout the 12-month observation phase. Authors favoured the addition of a topical fungicidal agent like ciclopirox in such cases to attempt eliminating candida from the vulval stratum corneum thereby preventing re-infection [43].

Newer liposomal formulation in a mucoadhesive gel base has been successfully tried recently by Karimunnisa S., *et al.,* for sustained vaginal release [44]. The gel prolongs the contact with vaginal wall; avoiding frequent and large dosing and is more convenient for patients.

**Candidal Infection - Extravaginal**

The RCT by Bagatell FK., *et al.,* that compared the improvement in cutaneous candidiasis (over 4 weeks) by 1% CPO cream with placebo and 1% clotrimazole cream demonstrated clear superiority of CPO over placebo and faster onset of improvement and better combined cure rates than clotrimazole [45].

CPO is also effective in diaper dermatitis. Ciclopirox topical suspension 0.77% applied twice daily for 7 days to the affected diaper area in babies (6 to 29 months old) provided statistically significant improvement in severity scores as well as mycological cure [46].

**Onychomycosis**

CPO 1% cream is not indicated for ONM; for which the 8% CPO nail lacquer is commercially available. The discussion of CPO for ONM is beyond the scope of this review. Readers are advised to go through an exhaustive article on management of onychomycosis by Gupta, *et al,[47]*

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**Citation:** Sidharth Sonthalia and Mahima Agrawal. “Topical Ciclopirox - Recalling a Forgotten Ally in the Fight against Cutaneous Mycoses.” *EC Microbiology* 14.9 (2018): 515-534.
Adverse effects and Use in Special Situations

The topical drug is devoid of systemic adverse reactions. Pooled analysis from most of the CPO-based studies suggests that even local adverse events are infrequent (reported by < 5% of treated patients), the most common including a burning sensation, irritation, redness, pain or pruritus, and have rarely led to discontinuation of therapy [48]. Allergic contact dermatitis to CPO is rare excepting an anecdotal report [49]. The burning sensation experienced by some patients of SD and tinea applying ciclopirox gel is most likely due to the isopropyl alcohol content of the formulation.

The safety of intra-vaginal ciclopirox cream or pessaries reviewed in more than 4000 patients included in 30 clinical trials has been well established with only 4.4% of the patients reporting mild and self-limiting adverse effects, most common being vulvovaginal discomfort, experienced mostly in the initial few days of therapy [48].

The tolerance with ciclopirox nail lacquers has also been very good; a mild reaction (e.g. periungual redness, application site tingling) was reported by 5% of the treated population. Events like ingrown toenail and nail discoloration were infrequent, observed even in placebo-arm of the studies, and resolved spontaneously despite continued application of the ciclopirox nail lacquer [50]. CPO cream 1% is not associated with delayed hypersensitivity-type contact sensitization, irritation, phototoxicity, or photocontact sensitization.

The use of topical ciclopirox in special situations has been summarized in **Table 5**. It is a pregnancy category B drug and safe to use in patients older than 10 years of age [51,52].

<table>
<thead>
<tr>
<th>Pregnancy [51]</th>
<th>Category B</th>
</tr>
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<tbody>
<tr>
<td>Reproduction studies performed in animal models via various routes of administration, at doses &gt;10 times the topical human dose revealed no significant evidence of impaired fertility or harm to the fetus. However, adequate or well-controlled studies in pregnant women are lacking. The drug should be used during pregnancy only if clearly needed.</td>
<td></td>
</tr>
<tr>
<td>Nursing mothers</td>
<td>It is not known whether this drug is excreted in human milk; caution should be exercised if topical ciclopirox is administered to a nursing woman.</td>
</tr>
<tr>
<td>Pediatric Use [52]</td>
<td>Safety and effectiveness in pediatric patients less than 10 years of age have not been established.</td>
</tr>
<tr>
<td>Carcinogenesis, Mutagenesis and Fertility Impairment</td>
<td>Various in vivo and in vitro genotoxicity tests including the Ames assay have failed to show any carcinogenesis, mutagenesis or impairment of fertility with ciclopirox olamine.</td>
</tr>
</tbody>
</table>

**Table 5**: Use of topical Ciclopirox in Special Situations.

Resistance to Ciclopirox

Ciclopirox olamine could be the answer to the emerging antifungal resistance. Even after more than 2 decades of frequent use of CPO for tinea, PV and VVC not even a single case of clinical or in vivo resistance has been reported. Till date, in a single in vitro study, a single strain of *C. glabrata* has been reported to be CPO-resistant out of 208 strains of yeasts obtained from 225 clinical isolates that were tested for in vitro susceptibility to CPO and compared with clotrimazole, econazole, ketoconazole, miconazole, toconazole, fluconazole, itraconazole and nystatin using a standardized agar diffusion method [53]. The in vitro antifungal susceptibility profile of CPO was better than all compared antymycotics against a wide variety of clinically important yeasts. In the experiment by Niewerth., *et al.* [30] to investigate the potential of ciclopirox of producing resistance in yeasts, long-term resistance induction by culturing *C. albicans* to a ciclopirox sub-inhibitory concentration (0.6 mg/mL) for over 6 months was attempted. Although upregulation of the drug resistance genes CDR1 and CDR2 (which are implicated in the development of fluconazole resistance) was attained, *C. albicans* did not develop increased tolerance or
Topical Ciclopirox - Recalling a Forgotten Ally in the Fight against Cutaneous Mycoses

529 resistance to ciclopirox [30]. In another study, the effect of pH on in vitro susceptibility of C. albicans and C. glabrata (since in vitro studies are usually conducted at pH of 7, whereas the physiological pH of the vaginal mucosa is 4.5) to fluconazole, fluconazole, voriconazole, posaconazole, itraconazole, ketoconazole, clotrimazole, miconazole, CPO, amphotericin B, and caspofungin was evaluated by CLSI broth microdilution method [54]. While at a pH of 7 the susceptibility of native strains to most of the drugs was appreciable, at reduced pH of 4 the yeast isolates retained susceptibility to CPO, caspofungin and fluconazole but demonstrated up to 16-fold elevation in the MIC90 for amphotericin B and every azole.

The widespread resistance of dermatophytes to various azoles (including the new generation voriconazole) has been discussed (vide supra). Although in vitro and clinical resistance of dermatophytes to terbinafine has not yet attained epidemic proportions, it seems to be on the rise. In an in vitro study that evaluated the potential of ergosterol synthesis inhibitors to cause resistance or cross-resistance in T. rubrum, the dermatophyte was propagated for 10 transfers in media containing sub-inhibitory drug concentrations [55]. The resistance to itraconazole, terbinafine, and amorpholine emerged at a higher frequency than was seen with resistant strains that developed due to spontaneous mutation. Development of cross resistance was frequent with itraconazole-resistant mutants showing decreased susceptibility to amorpholine as well as to terbinafine, and amorpholine-resistant mutants being less susceptible to terbinafine. But even after prolonged exposure to sub-inhibitory drug concentrations for several growth generations, no CPO-resistant mutant evolved, suggesting that the potential of dermatophytes of developing resistance to CPO by biochemical or molecular means is extremely low. The most plausible reasons behind the inability of superficial fungi (both dermatophytes and yeasts) of mounting or evolving mechanisms to resist CPO are its fungicidal mode of action, unique anti-fungal property of inhibition of the trivalent metal ion dependent enzymes that scavenge the intracellular peroxides, irreversible binding to intracellular structures preventing the drug from being used as a substrate for drug efflux pumps, and a steep dose-response curve.

What’s New with Ciclopirox - Drug Repurposing

Antibiotic-resistant infections caused by gram-negative bacteria have emerged as a major healthcare concern. Repurposing drugs circumvents the time and money limitations associated with developing new antimicrobial agents needed to combat these antibiotic-resistant infections. Ciclopirox has potent bacteriostatic activity against laboratory and clinical isolates of E. coli, including ciprofloxacin resistant isolates; it exerts bactericidal effect at higher concentrations. Other GN bacteria (wild as well as multi-drug resistant) against which ciclopirox has shown potent growth inhibition in vitro include A. baumannii, Klebsiella pneumoniae, P. aeruginosa, and Proteus mirabilis [56]. The anti-bacterial activity of ciclopirox against E. coli and other GN bacteria mainly involves interference with galactose metabolism and disruption of LPS biosynthesis [57]. The concept in vogue is that the current topical formulations of CPO being used as antymycotic penetrates deep enough into the skin and mucosal membranes without causing adverse systemic reaction. Ciclopirox also promotes faster wound healing when applied topically by inducing angiogenesis. The excellent tolerability of ciclopirox and its unique mode(s) of action make it an attractive antibiotic to treat gram-negative pathogens, including those resistant to current antibiotic therapies. The lack of any reported fungal resistance to ciclopirox in over 20-30 years of use, its excellent safety profiles, novel target(s), and efficacy, have yielded into repurposing ciclopirox as a promising potential antimicrobial agent to use against multidrug-resistant problematic gram-negative pathogens [56,57].

Oral ciclopirox is being actively pursued as an anti-cancer agent [58]. Few of its pleiotropic anti-proliferative effects include induction of cellular apoptosis via generation of ROS, iron chelation and downregulation of intracellular ferritin, inhibition of specific heat shock proteins (e.g. HSP90), activation of mitogen-activated protein kinases, downregulation of CDKs, inhibition of mTOR, and inhibition of Wnt/β-catenin pathway [58-60]. It also promotes degradation of CDC25A, a protein phosphatase critical for full activation of CDKs and promotes the growth of tumor cells by assisting the progression of both G1/S and G2/M phases of their cell cycles [61]. It is likely to occupy a leading position as a novel and safe anti-tumour drug for hematological malignancies (ALL, lymphomas, multiple myeloma) as well as solid organ cancers (breast, pancreas, neuroblastoma, colon, prostate, rhabdomyosarcoma) [58-62].
A recent study has also demonstrated the therapeutic potential of ciclopirox in diabetes and medical conditions arising out of ER-stress. Pancreatic dysfunction during diabetes has been linked to the induction of ER stress on pancreatic beta (β) cells, a process that is modified by p21 thereby offering protection from diabetes. Ciclopirox is an activator of p21 expression and has been shown to enhance beta cell survival and function both in vitro (cultured islets) and in vivo (diabetic mice) [63].

Update on New Topical Formulations of Ciclopirox - Attempts to further enhance antifungal efficacy

CPO is currently available in cream and gel formulations for the treatment of dermatophytosis and as cream, pessary and vaginal douche for VVC. The gel formulation of CPO or any other topical antymycotic offers the advantage of faster drug release compared to cream or ointment. In a study that compared the in vitro antifungal activity of CPO gels prepared using three different gelificants (hydroxypropyl cellulose, chitosan and poloxamer 407), showed that the highest amounts of CPO were released from the poloxamer 407-based gels although all the CPO gels showed high and comparable inhibition of M. canis [64]. Bigel, a relatively new formulation is a biphasic gel that consists of two phases: hydrogel (polar) and oleogel (non-polar) and offers the advantage of a stable, surfactant-free, non-oily preparation that provides suitable contact of the drug and the skin, improves drug release and ensures uniform distribution of the drug substance on the skin. In a recent study, CPO and terbinafine were incorporated in a bigel prepared using poloxamer 407 gel as the hydrophase and oleogel of liquid paraffin and polyethylene as the non-polar phase. These prepared bigels were found to be physically stable for 6 months at room temperature and at least 4 months at 40°C. Results of the study suggested the tested bigels as promising formulation for antifungal substances [65]; although further comparative studies are needed.

Although this review focuses on topical CPO for superficial cutaneous mycosis excluding onychomycosis, it is worth mentioning that a substantial quantity of research has been conducted to create formulations of CPO and other topical antifungals to enhance their penetration through the hard keratin of the nail plate. Just to summarize, some of the major developments in this field include the use of penetration enhancers such as 5% papain that contains endopeptidase enzyme [66], urea [67,68], N-acetylcysteine [68], lipid diffusion enhancer combinations containing benzyl alcohol, peppermint oil, turpentine and mineral oil [69], and patented multi-ingredient formulations such as Recura [70]. Novel technologies such as hydroxypropyl chitosan (HPCH) technology (P-3051) not only enhance the permeation of water-soluble ciclopirox lacquer but also form an invisible film over the nail surface to prevent fungal invasion and obviate the need for nail filing [71]. The addition to the vehicle of isopropyl alcohol as solvent and potassium hydroxide as an alkalizing agent [67] and use of thermogelling hydrogels of cyclodextrin/poloxamer polypseudorotaxanes [68] have also been reported to substantially enhance transungual penetration of CPO.

Conclusion

In conclusion, the unique mechanism of action, in-vitro and in-vivo efficacy, broad spectrum antymycotic coverage, additional anti-bacterial and anti-inflammatory activity, well established safety and excellent tolerance, lack of drug-resistance at present coupled with an extremely low likelihood of the development of resistance in future, and easy affordability make ciclopirox or CPO an almost ideal topical antifungal for superficial cutaneous mycoses. Its versatility remains unexploited; especially in wake of the pharmaceutical-driven focus on development and sale of ‘newer azoles’. Most importantly, CPO can be instrumental in reducing the menace of steroid-abuse, and management of treatment-refractory dermatophytic infections, tinea incognito, mixed infections and recurrent VVC.

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