

Mycological Considerations in the Topical Treatment of Superficial Fungal Infections

Ted Rosen MD
Baylor College of Medicine, Houston, TX

ABSTRACT

Trichophyton rubrum remains the most common pathogenic dermatophyte in the United States, Europe, and industrialized Asia, although other species are predminant elsewhere. Candida albicans is the most common pathogenic yeast, with other species occasionally encountered. Just a few of the 14 described species of Malassezia cause pityriasis versicolor worldwide. FDA approval does not always accurately reflect the potential utility of any given topical antifungal agent. Azole, hydroxypyridone, and allylamine agents are beneficial in the management of dermatophytosis; however, the allylamines may lead to faster symptom resolution and a higher degree of sustained response. Although in actual clinical use the allylamines have all shown some activity against superficial cutaneous candidiasis and pityriasis versicolor, the azole agents remain drugs of choice. Ciclopirox is an excellent broad-spectrum antifungal agent. Optimal topical therapy for superficial fungal infections cannot yet be reliably based upon in-vitro laboratory determination of sensitivity. Inherent antibacterial and anti-inflammatory properties possessed by some antifungal agents may be exploited for clinical purposes. Candida species may be azole-insensitive due to efflux pumps or an altered target enzyme. So-called "antifungal resistance" of dermatophyets is actually due to poor patient adherence (either in dosing or treatment duration), or to reinfection.

J Drugs Dermatol. 2016;15(Suppl 2):s49-55.

INTRODUCTION

Superficial fungal infections – those affecting the skin, hair and nails – are extraordinarily common worldwide. About 20% to 25% of the world's population will be affected by at least one superficial fungal infection during their lifetime.[1] Superficial mycoses are caused by Candida species, the yeast forms responsible for pityriasis versicolor, select nondermatophyte molds, and dermatophytes, with the latter being the most prevalent globally.[2,3] The justifications for treatment of superficial mycoses include: cosmetic distress, presence of pruritus or pain, potential for spread from one body site to another, possible transmission to unaffected individuals, and prevention of secondary bacterial superinfection or persistent nail dystrophy.[4-7] When measured, successful therapy of superficial mycoses is associated with an improved quality of life.[8-10]

For a variety of reasons detailed elsewhere,[11] it is likely that both the incidence and prevalence of superficial fungal infections will increase. Thus, health care practitioners (HCPs) remain in search of simple, safe, convenient, and effective therapeutic interventions. This manuscript reviews mycologic aspects of this subject, with a goal of offering concrete and clinically relevant suggestions. This review will not address superficial mycoses, which typically require oral therapy (such as tinea capitis).

Epidemiology of Superficial Mycoses

It is difficult to reliably determine both the overall incidence and prevalence of the various superficial mycoses worldwide because epidemiologic studies performed in one city/locale may not be representative of the overall disease pattern of that country; similarly, findings in one country may not be representative of the overall disease pattern of that region/continent. Finally, fungal disease patterns differ greatly from continent to continent.[1,2] Moreover, the predominant pathogenic fungal species is somewhat dependent on which type of superficial mycosis is most common, tinea pedis or tinea capitis. Finally, the local pattern of highly prevalent dermatophyte organisms may be influenced or modified by such factors as: changes in socioeconomic conditions, alterations in typical lifestyle, recent migration, and expansion of tourism.[1] With the foregoing cautionary caveats in mind, some generalizations can be made[1,2,12-14]:

Some species are worldwide T. rubrum, T. mentagrophytes var. interdigitale (now simply called T. interdigitale), M. canis, and E. floccosum.

Other species are characteristically restricted to select geographic regions; examples include: T. schoenleinii (Eurasia, Africa), T. soudanense (Africa), T. violaceum (Africa, Asia, and Europe), and T. concentricum (Pacific Islands, Far East, and India). Patients presenting with dermatophytosis who are visiting or emigrating from these areas may well harbor an organism common in their native land. Cultural identification of the offending pathogen is advisable in order to properly direct treatment.

The vast majority of cases of onychomycosis, tinea cruris, tinea corporis, and tinea pedis are currently caused by T. rubrum, the

most common dermatophyte in both industrialized countries and in urban settings of emerging nations; In North America, as well as in most of Europe and Asia, the second most commonly encountered dermatophyte is T. interdigitale.

By contrast, in Southern Europe, Arabic countries, and rural locations in the Americas, zoophilic dermatophytes, such as M. canis or T. verrucosum, may be common pathogens.

When dealing with dermatophytes, the HCP must always take into account specific, individualized circumstances. For example, a patient who is involved with breeding, caring for, or riding horses might develop a dermatophytosis due to T. equinum, an otherwise unusual isolate.

Improvements in sanitation and socio-economic status may accompany urbanization, and the latter is generally associated with a decline in zoophilic and geophilic dermatophyte and a concurrent increase in anthropophilic dermatophyte infections.

Dermatophytes traditionally and primarily associated with tinea capitis can cause tinea corporis and even tines pedis (eg, M. canis, T. tonsurans).

Clinical infections, which unequivocally suggest dermatophytosis, may, in fact, be due to non-dermatophyte molds. Examples include: Neoscytalidium dimidiatum and N. hyalinum-induced tines pedis and as well as onychomycosis due to Acremonium, Aspergillus species, Fusarium species, Scopulariopsis brevicaulis, and other opportunistic molds. Such infections are highly treatment resistant, and failure of routine therapy should prompt mycological investigation for such rare organisms.

Although Malassezia species were discovered over a century and a half ago, their fastidious nature coupled with difficult culture and speciation techniques, have restricted research. New molecular techniques have facilitated understanding these lipophilic, non-keratolytic fungi. There are now 14 species within the genus Malassezia; M. globosa, M. furfur, M. restrica, and M. sympodialis are the common etiologic organisms associated with pityriasis versicolor.[15] The prevalence of pityriasis versicolor varies from negligible to up to 50% of populations in tropical and subtropical environments.[16] It is also more common among physically active, young individuals.[17] Under the correct conditions, the fungi responsible for pityriasis versicolor can cause: catheter-associated fungal sepsis, peritoneal dialysis-associated peritonitis, mastitis, sinusitis, malignant otitis, and septic arthritis.[15]

There are somewhere between 150 and 200 species of Candida, speciation being performed by conventional mycologic methods, manual and automated commercial systems, and newer molecular analyses.[18] Common pathogens include: C. albicans (~75% of all pathogenic isolates), C. glabrata, C. tropicalis, C. guilliermondii , C. parapsilosis, and C. krusei. Cutaneous infection with Candida species causes many morphologically distinct entities, including: congenital candidiasis, dermal lesions associated with candida sepsis, chronic mucocutaneous candidiasis, candida onychomycosis, paronychia, perleche, vulvovaginal candidiasis, candida balanitis, erosio interdigitale blastomycetica, diaper dermatitis, and intertriginous candidiasis. The last five of those enumerated previously are particularly amenable to topical therapy. C. albicans is the major pathogen in all types of cutaneous candidiasis throughout the world.[19] Many individuals with cutaneous candidiasis have some form of underlying predisposition that must be addressed and, if possible, corrected in order to achieve maximum clinical outcome and to prevent prompt relapse. Some underlying conditions include: innate or acquired immunocompromise (including HIV/AIDS); administration of steroids, chemotherapeutic agents, or other immunosuppressive drugs; broad spectrum antibiotic treatment; endocrine disorders (eg, diabetes mellitus and Cushing's syndrome); debilitation, immobility and malnutrition; obesity and hyperhidrosis; and prolonged occupational exposure to water (eg, bartender, maid).[20]

Epidemiologic Correlation with FDA-Approved Treatments

Table 1 lists the most readily available topical antifungal agents in the United States, including both prescription only and over-the-counter (OTC) formulations, along with corresponding FDA approved indications. The Table does not include the myriad of primarily OTC "peeling" agents based upon salicylic acid and other "non-specific" agents (such as selenium sulfide).

The three products solely formulated for nail application along with every topical antifungal agent in all chemical groups (excepting nystatin), are approved to deal with the most common dermatophye, T. rubrum. Most are also approved for use with the second most common causative dermatophyte, T. interdigitale. However, it behooves us to remember that FDA-approved indications listed in package insets are based entirely upon the results of pivotal trials. Just because an agent lacks an "indication" does not mean that the drug will fail. Most often, lacking an "indication" reflects the fact that too few patients in the pivotal studies yielded positive culture for the fungus that is not indicated. Another possibility is that the disease state was simply not studied, as FDA labeling was not sought. These factors create serious anomalies. For example, note the difference between FDA-approved indications for 1% naftifine cream/gel and the comparable 2% formulations. Does anyone seriously believe that increasing the concentration of active antifungal drug will lead to a reduced spectrum of activity? Clearly, 2% naftifine cream has not been "proven" effective, to the FDA's satisfaction, in management of any dermatophytosis other than those caused by T. rubrum, even though the 1% naftifine

TABLE 1.

Topical Antifungal Drugs and Approved Uses

Drug	Class	Tinea corporis/ cruris	Tinea pedis	Tinea versicolor	Onychomycosis	Cutaneous candidiasis
Butenafine 1% Cream	Allylamine*	1,2,3,4	1,2,3,4	Yes	No	No
Naftifine 1% Cream/ Gel	Allylamine	1,2,3,4	1,2,3,4	No	No	No
Naftifine 2% Cream	Allylamine	1	1	No	No	No
Naftifine 2% Gel	Allylamine	No	1,2,4	No	No	No
Terbinafine 1% Cream/Spray	Allylamine	1,2,4	1,2,4	Spray only	No	No
Clotrimazole 1% Cream	Azole	1,2,4,5	1,2,4,5	Yes	No	Yes
Econazole 1% Cream	Azole	1,2,3,4,5,6	1,2,3,4,5,6	Yes	No	Yes
Econazole 1% Foam	Azole	No	1,2,4	No	No	No
Efinaconazole 10% Sol	Azole	No	No	No	1,2	No
Ketoconazole 2% Cream	Azole	1,2,4	1,2,4	Yes	No	Yes
Luliconazole 1% Cream	Azole	1,4	1,4	No	No	No
Miconazole 2% Cream	Azole	1,2,4	1,2,4	Yes	No	Yes
Oxiconazole 1% Cream	Azole	1,2,4	1,2,4	Yes	No	No
Oxiconazole 1% Lotion	Azole	1,2,4	1,2,4	No	No	No
Sertaconazole 2% Cream	Azole	No	1,2,4	No	No	No
Sulconazole 1% Cream	Azole	1,2,4,5	1,2,4,5	Yes	No	No
Ciclopriox 0.77% Cream/Gel	Hydroxpyridone	1,2,4,5	1,2,4,5	Yes	No	Yes
Ciclopirox 8% lacquer	Hydroxpyridone	No	No	No	1	No
Tavaborole 5% Solution	Oxaborole	No	No	No	1,2	No
Nystatin Cream/ Ointment	Polyene	No	No	No	No	Yes
Tolnaftate	Thiocarbamate	1,2,3,4,5,6	1,2,3,4,5,6	No	No	No

Key:
1. Trichophyton rubrum
2. Trichophyton mentagrophytes
3. Trichophyton tonsurans
4. Epidermophyton floccosum
5. Microsporum canis
6. Other Microsporum species

Notes: *Butenafine is technically a benzylamine, a close structural relative to allylamines

cream has a wide range of indication. Nonetheless, this simply defies logic and common sense. In a similar manner, 2% naftifine gel is approved only for the treatment of interdigital tinea pedis. Considering that 1% naftifine gel is indicated for management of tinea corporis and cruris, is there any reason why the 2% formulation lacks the same indication, other than the fact that this study was not done? As another example of a glaring anomaly, consider the only current FDA-approved indication for sertaconazole cream: interdigital tinea pedis. Yet, in the European Union, sertaconazole is indicated for the treatment of tinea corporis, tinea cruris, tinea manum, tinea barbae, and tinea pedis, as well as both cutaneous candidiasis and pityriasis versicolor.[21] Should we believe that this agent somehow works less well in North America than in Europe, especially for the same causative fungi?

"About 20% to 25% of the world's population will be affected by at least one superficial fungal infection during their lifetime."

FDA-approved indication also does not address relative (comparative) efficacy, safety, and tolerability. While tonaftate is "approved" for the treatment of tinea corporis, cruris, and pedis due to an extended range of dermatophyte species, clinical experience dictates that both azole and allylamine agents are more efficacious. When comparing the relative efficacy of azoles and allylamines, the situation becomes considerably less clear despite comprehensive and thoughtful attempts to do so. In such systematic and meta-analyses, the authors concluded two important things: 1. Allylamine, benzylamine, azole, hydroxypyridone, and thiocarbamate agents are all routinely superior to placebo and 2. Since no trials sort subjects who failed treatment by etiologic species, no conclusions can be drawn about clinical susceptibility of various fungi to individual drugs in a manner that meaningfully impacts decision making.[22-25] A few additional pearls can be gleaned from these heroic attempts to compare different topical agents. In a systematic review of 67 randomized-controlled trials (RCTs) of topical tinea pedis treatment, authors concluded that: allylamines produce slightly higher complete cure rates than do azoles, and that, for the same agent, longer durations of therapy tend to work somewhat better than shorter durations of therapy.[22] In a systematic review of 129 RCTs of topical treatments for tinea corporis and cruris, the authors concluded that naftifine and terbinafine were very effective, but that other classes (such as azoles and hydroxypyridones) are also quite beneficial.[25] Finally, in a pair of reports representing the most ambitious attempts to compare efficacy between various topical antifungal drugs, as well as between classes of topical antifungals, Rotta and co-wokers[23,24] concluded that: 1. There is no significant and consistent difference between classes of antifungal drugs in terms of short-term efficacy 2. Safety and tolerability is excellent across all classes of topical antifungals, with adverse events (burning, stinging, pruritus, true allergic contact dermatitis) being reported in about 1-3% of treated patients and 3. Allylamine agents (and the related benzylamine, butenafine) show a higher degree of sustained cure compared to classic imidazoles. It is noted that these exhaustive reviews included many RTC which were sub-optimally designed, inadequately reported, subject to considerable heterogeneity, and at risk for bias; none included newer formulations or concentrations of older agents or recently released agents (eg, luliconazole).

What is the clinical relevance of the foregoing? Basically, assuming diligent patient adherence to the prescribed treatment regimen, any approved agent will work for common dermatophyte infections due to the most common pathogens.[11] However, some interventions may be more "appealing" to both HCP and patient because they require fewer applications per day, fewer total applications, and/or shorter duration of therapy. For example, whereas four weeks of topical antifungal therapy were once considered required to achieve clinical benefit in tinea pedis, newer agents (1% luliconazole cream and 2% naftifine cream/gel) prove satisfactory after only two weeks of therapy.[26-28] Luliconazole cream has even been successfully administered once daily for only one week for tinea cruris.[29]

Although not apparent in large scale retrospective analysis, there is some evidence that dermatomycoses due to Microsporum species (in particular M. canis) may be somewhat less responsive to topical azole agents compared to topical allylamines, especially if one utilizes the older azoles such as clotrimazole.[30,31]

With respect to cutaneous candidiasis, the various approved azoles and ciclopirox are considered superior to allylamines and are deemed the appropriate drugs of choice.[32] That said, in contrast to accepted dogma and FDA approved indication, both butenafine and terbinafine have proven modestly successful (efficacy rates ranging from 73-85%) in the treatment of interdigital and intertriginous candidiasis.[33,34] Butenafine is particularly interesting in that it may not only block squalene epoxidase, but also possess a direct membrane damaging effect on Candida albicans.[35] Due to its potent anti-inflammatory effects and relative low cost (now being available OTC), butenafine may be a viable (off-label) alternative for rapid relief of symptomatic cutaneous candidiasis. Nystatin is the only specific topical anti-Candidal agent, and is available as a powder, cream and ointment (100,000 units per gram). The powder may be untenable in the face of excessive exudation, but may be an optimal method of topical prophylaxis in cases of recurrent intertriginous candidiasis. Nystatin regularly demonstrates a

higher in-vitro MIC when compared to azole antifungals worldwide (studies cited from Brazil, Cuba and Singapore).[36-38]

Virtually no cases of pityriasis versicolor are investigated to determine the precise causative Malssezia species. The absence of standardized collection and reporting practices during clinical studies or during routine use, precludes any conclusions to be drawn regarding the relative efficacy of the many approved topical agents with regards to specific Malassezia species.[39] In general, topical azoles are felt to be superior to topical allylamines in the management of pityriasis versicolor. However, topical prescription treatments for pityriasis versicolor may be logistically and economically impractical in extensive disease. Several OTC preparations are suitable for treatment of pityriasis versicolor, including zinc pyrithione and selenium sulfide.[32] Short courses of generic oral antifungal agents (such as fluconazole, off-label) may actually be more cost effective, not to mention more convenient, than two-eight weeks of topical application of either prescription or OTC agents.[39] As another deviation from FDA approvals, both terbinafine and naftifine have been utilized successfully in pityriasis versicolor, although neither is considered a drug of choice for this superficial mycosis.

In-vitro Data

Perhaps therapeutic decisions could (or should) be based upon in-vitro anti-fungal drug sensitivities of clinical isolates, akin to the manner in which bacterial diseases are treated? Alas, such is not the case. Stringent but cumbersome broth microdilution standards do exist: Clinical Laboratory Standards Institute (CLSI: M38-A1 and M38-A2) in the United States and the European Committee on Antimicrobial Susceptibility Testing (EUCAST: E.DEF 7.2 and 9.1) in Europe. However, even these reference techniques differ in inoculum size, incubation time and medium composition.[40] They are also designed and validated only for yeasts and molds and, as a consequence, do not directly address the antifungal susceptibility of dermatophyte species. While reference tests can be adapted for dermatophytes,[41-43] results may vary depending upon exact parameters employed during testing. There are also alternative methods in use, including: macro-dilution, agar-based disk diffusion, colorimetric modifications, bioluminescence assays, flow cytometry, ergosterol quantitation and a number of automated and semi-automated commercial kits.[44,45] The various techniques available for antifungal susceptibility testing do not always correlate with reference techniques or with eachother.[42,45] Finally, as pointed out repeatedly, correlation between in-vitro dermatophyte MICs and in-vivo clinical outcomes remains unclear and yet to be determined.[32,41,42,45] Even when dealing with Candida species, isolates from patients whose condition does not respond to azole therapy may be apparently sensitive based upon standardized in-vitro testing, whereas patients whose condition responds to treatment may have strains that show MIC values consistent with in-vitro resistance.[46] In short, when it comes to topical therapy for superficial fungal infections, in-vitro laboratory determination of sensitivity is not a "surefire" manner to predict clinical success.

Similarly, whether an agent is considered "fungicidal" or "fungistatic" has minimal real world importance. A high enough concentration of virtually any of the agents listed (except for nystatin and tonaftate) will result in in-vitro fungicidal activity for at least some dermatophytes and yeast. Moreover, as noted by a leading Japanese mycologist, we are far from understanding how to devise accurate, reproducible and standardized methods of determining minimal fungicidal drug concentrations for dermatophytes.[47] It is, however, generally accepted that, with the exception of luliconazole, sertaconazole, and possibly oxiconazole, the azoles are predominantly fungistatic; by contrast, butenafine, naftifine, terbinafine, and ciclopirox are considered fungicidal.[32] The possible benefit to a fungicidal agent is the potential for more rapid onset of action, and therefore somewhat more prompt relief of symptoms.

> "Many individuals with cutaneous candidiasis have some form of underlying predisposition that must be addressed and, if possible, corrected in order to achieve maximum clinical outcome and to prevent prompt relapse."

Ancillary Antifungal Properties

These properties may influence, to some extent, the choice of specific agents in certain clinical settings. For example, when concurrent bacterial infection is probable, or already present (such as severe interdigital tinea pedis), an antifungal agent which helps eradicate bacterial superinfection might be preferable. In those situations where the inflammatory response to superficial mycoses is extreme and symptoms are overwhelming, an antifungal agent which is inherently anti-inflammatory may be preferable.

Some of the azole antifungal drugs are antibacterial: clotrimazole, econazole, miconazole, oxiconazole, sertaconazole, and sulconazole demonstrate inhibitory activity in vitro and in vivo against some Gram-positive and a few Gram-negative bacteria.[32] In particular, sertaconazole has a lower geometric mean MIC for Streptococcal and Staphylococcal species than other azoles.[48] Both naftifine and terbinafine have some demonstrable in-vitro and in-vivo anti-bacterial properties according to a German group of investigators.[49,50] Of all the anti-mycotic agents, ciclopirox olamine has the broadest spectrum of antibacterial

activity, including low MICs for Pseudomonas aeruginosa, Proteus mirabilis, Escherichia coli, and Klebsiella pneumoniae, as well common Streptococcal and Staphylococcal species.[51,52] By contrast, butenafine has no activity against Gram-negative bacteria and Gram-positive activity limited only to Group A beta-hemolytic Streptococcus.[52] Despite evidence of antibacterial activity, none of these antifungal agents should be considered drugs of choice when treating either uncomplicated or complicated primary bacterial pyodermas.

Anti-inflammatory properties have been investigated in a variety of ways, including: inhibition of neutrophil chemotaxis, reduction in inflammation-associated skin temperature, reduction of croton oil or arachidonic acid-induced ear edema in a murine model, reduced erythema-wheal formation following intracutaneous histamine injection, direct inhibition of 5-lipoxygenase and/or cyclo-oxygenase activity and inhibition of UV-induced erythema. Although many antifungals possess some degree of inherent anti-inflammatory activity, when tested in a head-to-head manner, ciclopirox olamine, naftifine and terbinafine proved more effective than the any of the azole drugs.[53,54] This suggests, but does not prove, that these three antifungal agents might be more effective at reducing erythema and pruritus. An example would be tinea corporis or faciei due to M. canis acquired from a new pet kitten or puppy.

Antifungal Resistance

Candida albicans resistance to antifungal drugs seems to be increasing, and such resistance appears to be related to prolonged exposure to these agents.[55,56] Candidal resistance appears primarily related to upregulation of CDR1, CDR2 genes, which enhance efflux (removal) of anti-infective drugs, as well as mutations in ergosterol biosynthesis gene (ERG11) leading to an altered (resistant) form of the azole target enzyme, 14C-lanosterol demethylase.

Dermatophyte resistance has been most widely studied in T. rubrum. Antifungal resistance to allylamines depends mostly upon an altered target enzyme, wherein amino acid substitutions in squalene epoxidase occur in the allylamine binding site.[57,58] In addition, there appears to be the potential for inducible upregulation of TruMDR1 and TruMDR2 genes which encode for drug efflux structures.[59,60] Finally, T. rubrum may over-express salicylate mono-oxygenase which is capable of degrading allylamines.[60] Dermatophyte resistance to azole agents depends on the same efflux mechanisms detailed above, and also to compensatory over-production of the target enzyme, 14C-lanosterol demethylase.[61] Despite the foregoing, naturally occurring resistant dermatophytes are exceedingly rare. One study estimated that innately azole resistant T. rubrum occurred in about 1 in 10^7 organisms and innately terbinafine resistant T. rubrum in about 1 in 10^9 organisms.[62] The same investigators noted that repeated exposures (10 passages) of T. rubrum to subinhibitory concentrations of azole and allylamine antifungal agents led to appearance of resistant strains. Thus, failure of one antifungal agent might be due to acquired resistance, even though innate resistance is rare. Interestingly, despite multiple exposures of T. rubrum to subinhibitory concentrations of ciclopirox olamine, no mutant resistant strains were isolated.[62]

In reality, most antifungal "resistance" is actually due to: poor patient adherence (either in dosing or treatment duration), or to reinfection following re-exposure.[63]

CONCLUSION

The ideal topical antifungal agent for superficial mycoses should have broad-spectrum activity, high mycologic and clinical cure rates, efficacy at low concentrations, fungicidal activity with a convenient dosing schedule, keratinophilic and lipophilic properties, a reservoir effect in the stratum corneum, lack of potential for development of antifungal drug resistance, low relapse rate, few to no adverse effects, and a low cost. While this "ideal" agent does not yet exist, many of the FDA-approved topical agents have some of these characteristics.

DISCLOSURES

The author has received honoraria from the following pharmaceutical companies in conjunction with participation in advisory boards: Anacor, Merz, and Valeant.

This article includes discussion of published and/or investigational use of agents that are not indicated by the United States FDA.

REFERENCES

1. Ameen M. Epidemiology of superficial fungal infections. *Clin Dermatol.* 2010;28(2):197-201.
2. Havlickova B, Czaika VA, Friedrich M. Epidemiological trends in skin mycoses worldwide. *Mycoses.* 2008;51(suppl 4):s2-s15.
3. Pires CA, Cruz NF, Lobato AM, et al. Clinical, epidemiological, and therapeutic profile of dermatophytosis. *An Bras Dermatol.* 2014;89(2):259-264.
4. Zeichner JA. New topical therapeutic options in the management of superficial fungal infections. *J Drugs Dermatol.* 2015;14(suppl 10):s35-41.
5. Rich P. Efinaconazole topical solution, 10%: the benefits of treating onychomycosis early. *J Drugs Dermatol.* 2015;14(1):58-62.
6. Ghannoum MA, Mukherjee PK, Warshaw EM, et al. Molecular analysis of dermatophytes suggest spread of infection among household members. *Cutis.* 2013;91(5):237-246.
7. Zaias N, Rebell G. Chronic dermatophytosis syndrome due to Trichophyton rubrum. *Int J Dermatol.* 1996;35(9):614-617.
8. Kircik LH. Observational evaluation of sertaconazole nitrate cream 2% in the treatment of pruritus related to tinea pedis. *Cutis.* 2009;84(5):279-83.
9. Milobratović D, Janković S, Vukičević J, et al. Quality of life in patients with toenail onychomycosis. *Mycoses.* 2013;56(5):543-51.
10. Warshaw EM, Foster JK, Cham PM, et al. NailQoL: a quality-of-life instrument for onychomycosis. *Int J Dermatol.* 2007;46(12):1279-86.
11. Rosen T. Assessment of dermatophytosis treatment studies: Interpreting the data. *J Drugs Dermatol.* 2015;14(suppl 10):s48-54.
12. Seebacher C1, Bouchara JP, Mignon B. Updates on the epidemiology of dermatophyte infections. *Mycopathologia.* 2008;166(5-6):335-52.
13. Canavan TN, Elewski BE. Identifying signs of tines pedis: A key to understanding clinical variables. *J Drugs Dermatol* 2015;14(suppl 10):s42-47.
14. Martínez-Herrera EO, Arroyo-Camarena S, Tejada-García DL, et al. Onychomycosis due to opportunistic molds. An Bras Dermatol. 2015;90(3):334-7.

15. Thayikkannu AB, Kindo AJ, Veeraraghavan M. Malassezia-Can it be Ignored? *Indian J Dermatol.* 2015;60(4):332-9.
16. Renati S, Cukras A, Bigby M. Pityriasis versicolor. *BMJ.* 2015 Apr 7;350:h1394.
17. Kyriakis KP, Terzoudi S, Palamaras I, et al. Pityriasis versicolor prevalence by age and gender. *Mycoses.* 2006;49(6):517-8.
18. Neppelenbroek KH, Seó RS, Urban VM, et al. Identification of Candida species in the clinical laboratory: a review of conventional, commercial, and molecular techniques. *Oral Dis.* 2014;20(4):329-44.
19. Fallahi AA, Korbacheh P, Zaini F, et al. Candida species in cutaneous candidiasis patients in the Guilan province in Iran; identified by PCR-RFLP method *Acta Med Iran.* 2013;51(11):799-804.
20. Hay RJ. The management of superficial candidiasis. *J Am Acad Dermatol.* 1999;40(6 Pt 2):S35-42.
21. Croxtall JD, Plosker GL. Sertaconazole: a review of its use in the management of superficial mycoses in dermatology and gynaecology. *Drugs.* 2009;69(3):339-59.
22. Crawford F, Hollis S. Topical treatments for fungal infections of the skin and nails of the foot. *Cochrane Database Syst Rev.* 2007 Jul 18;(3):CD001434.
23. Rotta I, Sanchez A, Gonçalves PR, et al. Efficacy and safety of topical antifungals in the treatment of dermatomycosis: a systematic review. *Br J Dermatol.* 2012;166(5):927-33.
24. Rotta I, Ziegelmann PK, Otuki MF, et al. Efficacy of topical antifungals in the treatment of dermatophytosis: a mixed-treatment comparison meta-analysis involving 14 treatments. *JAMA Dermatol.* 2013;149(3):341-49.
25. El-Gohary M, van Zuuren EJ, Fedorowicz, Z, et al. Topical antifungal treatments for tinea cruris and tinea corporis. *Cochrane Database Syst Rev.* 2014 Aug 4;8:CD009992.
26. Jarratt M, Jones T, Adelglass J. Efficacy and safety of once-daily luliconazole 1% cream in patients ≥12 years of age with interdigital tinea pedis: a phase 3, randomized, double-blind,vehicle-controlled study. *J Drugs Dermatol.* 2014;13(7):838-46.
27. Stein Gold LF, Parish LC, Vlahovic T, et al. Efficacy and safety of naftifine HCl Gel 2% in the treatment of interdigital and moccasin type tinea pedis: pooled results from two multicenter, randomized, double-blind, vehicle-controlled trials. *J Drugs Dermatol.* 2013;12(8):911-18.
28. Parish LC, Parish JL, Routh HB, et al. A randomized, double-blind, vehicle-controlled efficacy and safety study of naftifine 2% cream in the treatment of tinea pedis. *J Drugs Dermatol.* 2011;10(11):1282-28.
29. Jones TM, Jarratt MT, Mendez-Moguel I, et al. A randomized, multicenter, double-blind, vehicle-controlled study evaluating the efficacy and safety of luliconazole cream 1% once daily for 7 days in patients aged ≥ 12 years with tinea cruris. *J Drugs Dermatol.* 2014;13(1):32-38
30. Pierard GE, Pierard-Franchimont C, Estrada JA. Comparative study of the activity and lingering effect of topical antifungals. *Skin Pharmacol.* 1993;6(3):208- 14.
31. Rosen T, Elewski BE. Failure of clotrimazole-betamethasone dipropionate cream in treatment of Microsporum canis infections. *J Am Acad Dermatol.* 1995;32(6):1050-1
32. Phillips RM, Rosen T. Topical antifungal agents. In: Wolverton S. (ed). Comprehensive Dermatologic Therapy. 3rd edition. Dermatology in General Medicine. 4th ed. New York, NY: Elsevier Saunders. 2013: 460-472.
33. Villars V, Jones TC. Clinical efficacy and tolerability of terbinafine (Lamisil) – a new topical and systemic fungicidal drug for treatment of dermatomycoses. *Clin Exp Dermatol.* 1989;14(2):124-27
34. Fukushiro R, Urabe H, Kagawa S. Butenafine hydrochloride, a new antifungal agent: clinical and experimental study. In: Yamaguchi H, Kobayashi GS, Takahashi H (eds). Recent progress in antifungal therapy. New York, NY: Marcel Dekker. 1992: 147-157
35. Iwatani W1, Arika T, Yamaguchi H. Two mechanisms of butenafine action in Candida albicans. *Antimicrob Agents Chemother.* 1993;37(4):785-8.
36. Brito GN1, Inocêncio AC, Querido SM, et al. In vitro antifungal susceptibility of Candida spp. oral isolates from HIV-positive patients and control individuals *Braz Oral Res.* 2011;25(1):28-33
37. Suárez VL1, Fernández Andreu CM [In vitro susceptibility of vaginal isolates of Candida vs clotrimazole and nystatin]. *Rev Cubana Med Trop.* 2003;55(3):138-45. [Article in Spanish]
38. Kwok YK, Tay YK, Goh CL, Epidemiology and in vitro activity of antimycotics against candidal vaginal/skin/nail infections in Singapore. *Int J Dermatol.* 1998;37(2):145-9.
39. Gupta AK, Kogan N, Batra R. Pityriasis versicolor: a review of pharmacological treatment options. . *Expert Opin Pharmacother.* 2005;6(2):165-78
40. Alastruey-Izquierdo A, Melhem MS, Bonfietti LX, et al. Susceptibility test for fungi: Clinical and labratorial correlations in medical mycology. *Rev Inst Med Trop Sao Paulo.* 2015;57 Suppl 19:57-64.
41. Ghannoum MA, Arthington-Skaggs B, Chaturvedi V, et al. Interlaboratory study of quality control isolates for a broth microdilution method (modified CLSI M38-A) for testing susceptibilities of dermatophytes to antifungals. *J Clin Microbiol.* 2006;44(12):4353-6
42. Singh J, Zaman M, Gupta AK. Evaluation of microdilution and disk diffusion methods for antifungal susceptibility testing of dermatophytes. *Med Mycol.* 2007;45(7):595-602.
43. Risslegger B, Lass-Flörl C, Blum G, et al. Evaluation of a modified EUCAST fragmented-mycelium inoculum method for in vitro susceptibility testing of dermatophytes and the activity of novel antifungal agents. *Antimicrob Agents Chemother.* 2015;59(6):3675-82.
44. Rizi K, Murdan S, Danquah C, et al. Development of a rapid, reliable and quantitative method – "SPOTi" for testing antifungal efficacy. *J Microbiol Methods.* 2015;117:36-40
45. Arikan S. Current status of antifungal susceptibility testing methods. *Med Mycol.* 2007;45(7):569-87.
46. Sanguinetti M, Posteraro B, Lass-Flörl C. Antifungal drug resistance among Candida species: mechanisms and clinical impact. *Mycoses.* 2015;58 Suppl 2:2-13.
47. Koga H. Antifungal susceptibility testing method for dermatophytes -determination of MIC and MFC values. *Med Mycol J.* 2014;55(2):J57-63
48. Palacin C, Sacristan A, Ortiz JA. In vitro activity of sertaconazole. *Arzneimittelforschung.* 1992;42 (5A):699-705.
49. Nolting S. Investigation of the antibacterial effect of the antifungal agent naftifine: left versus right clinical comparative study between naftifine and gentamicin in pyoderma. *Mykosen.* 1987;30(suppl 1):70-77.
50. Nolting S, Brautigam M. Clinical relevance of the antibacterial activity of terbinafine: a contralateral comparison between 1% terbinafine cream and 0.1% gentamicin sulphate cream in pyoderma. *Br J Dermatol.* 1992;126(Suppl 39):56–60.
51. Riviera L, Bellotti M. Laboratory evaluation of ciclopirox olamine: In vitro and in vivo studies on its antimicrobial activity. *Chemotherapia.* 1983;2(2):97–102.
52. Kokjohn K, Bradley M, Griffiths B, et al. Evaluation of in vitro activity of ciclopirox olamine, butenafine HCL and econazole nitrate against dermatophytes, yeasts and bacteria. *Int J Dermatol.* 2003;42(Suppl 1):11–7.
53. Hanel H, Smith-Kurtz E, Pastowsky S. Therapy of seborrheic eczema with an antifungal agent with an antiphlogistic effect. *Mycoses.* 1991;34(Suppl 1):91–3.
54. Rosen T, Schell BJ, Orengo I. Anti-inflammatory activity of antifungal preparations. *Int J Dermatol.* 1997;36(10):788–92.
55. Araj GF, Asmar RG, Avedissian AZ. Candida profiles and antifungal resistance evolution over a decade in Lebanon. *J Infect Dev Ctries.* 2015;27;9(9):997-1003.
56. Bailly S, Maubon D, Fournier P, et al. Impact of Antifungal Prescription on relative distribution and susceptibility of Candida spp - Trends over 10 Years. *J Infect.* 2015;Oct 27. pii: S0163-4453(15)00342-4. (e-pub)
57. Favre B, Ghannoum MA, Ryder NS. Biochemical characterization of terbinafine-resistant Trichophyton rubrum isolates. *Med Mycol.* 2004;42(6):525-9.
58. Osborne CS, Leitner I, Favre B, et al. Amino acid substitution in Trichophyton rubrum squalene epoxidase associated with resistance to terbinafine. *Antimicrob Agents Chemother.* 2005 Jul;49(7):2840-4
59. Cervelatti EP, Fachin AL, Ferreira-Nozawa MS, et al. Molecular cloning and characterization of a novel ABC transporter gene in the human pathogen Trichophyton rubrum. *Med Mycol.* 2006;44(2):141-7.
60. Martinez-Rossi NM, Peres NT, Rossi A. Antifungal resistance mechanisms in dermatophytes. *Mycopathologia.* 2008;166(5-6):369-83.
61. Yu L, Zhang W, Wang L, et al. Transcriptional profiles of the response to ketoconazole and amphotericin B in Trichophyton rubrum. *Antimicrob Agents Chemother.* 2007;51(1):144-53
62. Ghelardi E, Celandroni F, Gueye SA, et al. Potential of Ergosterol synthesis inhibitors to cause resistance or cross-resistance in Trichophyton rubrum. *Antimicrob Agents Chemother.* 2014;58(5):2825-9.
63. Gupta AK, Cooper EA. Update in antifungal therapy of dermatophytosis. *Mycopathologia.* 2008;166(5-6):353-67.

AUTHOR CORRESPONDENCE

Ted Rosen MD

E-mail:..... vampireted@aol.com