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An Overview of Topical Antifungal Therapy in Dermatomycoses

A North American Perspective

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Contents

Summary . . . 646
1. Overview of Dermatomycoses . . . 647
   1.1 Transmission and Contagion . . . 647
2. Diagnosis . . . 647
   2.1 Direct Microscopic Examination and Isolation Media . . . 648
   2.2 Other Diagnostic Techniques . . . 649
3. Clinical Manifestations . . . 649
4. Practical Considerations When Using Topical Antifungal Agents . . . 650
5. When Should Systemic Antifungal Agents Be Considered? . . . 650
6. Topical Antifungal Agents . . . 651
   6.1 Nonspecific Topical Antifungal Agents . . . 651
      6.1.1 Whitfield's Ointment . . . 651
      6.1.2 Castellani's Paint . . . 651
      6.1.3 Aluminium Chloride . . . 651
      6.1.4 Gentian Violet . . . 652
      6.1.5 Compound Undecylenic Acid . . . 652
      6.1.6 Potassium Permanganate . . . 652
      6.1.7 Selenium Sulphide . . . 652
      6.1.8 Zinc Pyrithione . . . 652
      6.1.9 Sodium Thiosulfate Plus Salicylic Acid . . . 652
      6.1.10 Propylene Glycol . . . 652
      6.1.11 Urea . . . 652
      6.1.12 Oil of Bitter Orange . . . 653
   6.2 Specific Topical Antifungal Agents . . . 653
      6.2.1 Topical Griseofulvin . . . 653
      6.2.2 Ciloquinol . . . 653
      6.2.3 Thiabendazole . . . 653
      6.2.4 Tolnaftate and Tolciclate . . . 653

6.2.5 Haloprogin 654
6.2.6 Polyenes 654
6.2.7 Ciclopirox 655
6.2.8 Amorolfine 655
6.2.9 Butenafine 656
6.2.10 Azoles 656
6.2.11 Allylamines 660
7. Pharmacoeconomic Evaluation of Topical Antifungal Therapies 662
8. Conclusions 663

Summary

Dermatophytes cause fungal infections of keratinised tissues, e.g. skin, hair and nails. The organisms belong to 3 genera, *Trichophyton*, *Epidermophyton* and *Microsporum*. Dermatophytes may be grouped into 3 categories based on host preference and natural habitat. Anthropophilic species predominantly infect humans, geophilic species are soil based and may infect both humans and animals, zoophilic species generally infect non-human mammals.

It is important to confirm mycologically the clinical diagnosis of onychomycosis and other tinea infections prior to commencing therapy. The identity of the fungal organism may provide guidance about the appropriateness of a given topical antifungal agent. Special techniques may be required to obtain the best yield of fungal organisms from a given site, especially the scalp and nails.

It is also important to realise the limitations of certain diagnostic aids e.g., Wood's light examination is positive in tinea capitis due to *M. canis* and *M. audouinii* (ectothrix organisms); however, Wood's light examination is negative in *T. tonsurans* (endothrix organism). Similarly, it is important to be aware that cycloheximide in culture medium will inhibit growth of non-dermatophytes. Appropriate media are therefore required to evaluate the growth of some significant non-dermatophyte moulds.

For tinea infections other than tinea capitis and tinea unguium, topical antifungals may be considered. For effective therapy of tinea capitis an oral antifungal is generally necessary. Similarly, oral antifungals are the therapy of choice, especially if onychomycosis is moderate to severe. Furthermore, where the tinea infection involves a large area, in an immunocompromised host or if infection is recurrent with poor response to topical agents, then oral antifungal therapy may be necessary.

Topical antifungal agents may be broadly divided into specific and nonspecific agents. The former group includes the polyenes, azoles, allylamines, amorolfine, ciclopirox and butenafine. Generally the topical agent is available as a cream, sometimes for use intravaginally. Less commonly, the formulation may be in the form of a powder, lacquer, spray, gel or solution. Many of these agents have a broad spectrum of activity, being effective against dermatophytes, yeasts and *Malassezia furfur*. For the treatment of tinea corporis, tinea cruris tinea versicolor and cutaneous candidosis, once or twice daily application may be required, the most common duration of therapy being 2 to 4 weeks. For tinea pedis the most common treatment duration is 4 to 6 weeks.

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1. Overview of Dermatomycoses

Dermatophytes cause fungal infections of keratinised tissues such as the skin, hair and nails. The dermatophytes belong to the anamorphic (asexual or imperfect) genera *Epidermophyton*, *Microsporum* and *Trichophyton*, of anamorphic class Hyphomycetes of the Deuteromycota.[1] There are approximately 22 species of *Trichophyton*, 16 species of *Microsporum* and 2 of *Epidermophyton*, of which only *E. floccosum* is pathogenic.[2]

Yeasts and other unrelated filamentous fungi that are normally saprophytes or plant pathogens can cause opportunistic dermatomycoses which resemble the cutaneous fungal infections caused by dermatophytes.[3] The term tinea is used to describe fungal infections caused by dermatophytes. Tissue invasion by the dermatophytes is generally confined to the skin because of the inability of the fungi to penetrate deeper tissues or organs. This could be the result of inhibition of fungal keratinases or the presence of nonspecific inhibitory factors in the serum.[4,5] Occasionally, subcutaneous tissue is invaded, for example, in Majocchi's granuloma or kerion. In an immunocompromised host deep local invasion, multivisceral dissemination or even death due to dermatophyte infection may occur.[6-11]

Some dermatophytes, mostly the zoophilic and geophilic species of *Microsporum* and *Trichophyton*, are also able to reproduce sexually, producing ascomata with asci and ascospores. These species are classified in the teleomorphic genus *Arthroderma*,[12] family Arthrodermataceae of the Onygenales,[13] phylum Ascomycota.

The distribution of dermatophytes may vary geographically; for example, *T. rubrum* has a global distribution. On the other hand, *T. concentricum* is geographically limited to the Pacific Islands and regions in Southeast Asia and Central and South America.

Infections caused by dermatophytes are mostly named according to the anatomical location involved, e.g. tinea barbae (ringworm of the beard and moustache), tinea capitis (scalp, eyebrows, eyelashes), tinea corporis (glabrous skin), tinea cruris (groin), tinea manuum (hand), tinea pedis (feet) and tinea unguium (nails). Two additional categories recognised are tinea favosa (favus) and tinea imbricata (ringworm caused by *T. concentricum*).

Dermatophytoses affect 8.1% of the Canadian population and dermatomycoses were ranked second to acne as the most frequent skin disease in the US.[14-16]

1.1 Transmission and Contagion

Dermatophytes are usually grouped into 3 categories based on the host preference and natural habitat.[17] Anthropophilic species almost exclusively infect humans, with animals being rarely infected. Anthropophilic fungi are usually transmitted by close human contact or indirectly, e.g. by sharing clothes, combs, brushes, towels, bedsheets, etc. Geophilic species are associated with soilborne keratinous debris which serves as a source of infection to both humans and other animals. Zoophilic species generally infect nonhuman mammals, although animal-to-human transmission is not uncommon. Also, indirect transmission may involve fomites. The one exception is *M. gallinae*, which is primarily established in the gallinaceous fowl.

2. Diagnosis

Accurate diagnosis is the key to successful therapy. The aetiology of infection can be multifactorial; eradication of all pathogens is required for control of the infection. Whenever feasible, clinical material should be obtained for direct microscopic examination and for culture.

The equipment that is used to collect the specimen will vary in part upon the location of the dermatophyte infection. Often 70% alcohol (ethanol) is used to disinfect the skin or nail surface, with sterile water for painful surfaces. Sterile scalpels, nail clippers, scissors or forceps may be needed. When tinea capitis is suspected, forceps can be used to epilate hair. Disposable brushes, a

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gauze pad or scalpel may aid in collecting material from the scalp to rule out tinea capitis.[18-21]

Wood's lamp may help in the diagnosis of fluorescent tinea capitis or the exclusion of erythrasma. Bright green fluorescence is typically seen in the small-spore ectothrix infection caused by *M. audouinii*, *M. canis* and *M. ferrugineum*.[22] Dull green fluorescence may be seen following infection with *T. schoenleinii*. The fluorescence may be due to pteridines that are produced when the actively growing hair becomes infected. Inflammatory lesions including kerion may produce minimal to no fluorescence. Wood's lamp examination can also help in distinguishing erythrasma (caused by the bacterium *Corynebacterium minutissimum* with orange to coral red fluorescence) and dermatophyte infection (no fluorescence with Wood's light). Early *Pseudomonas* superinfection of a chronic candidal paronychia may fluoresce green.

When the nails are suspected of having onychomycosis, nail material and subungual debris can be obtained using one or more of the following: a nail clipper, a No. 15 scalpel blade and a curette.[23-25] It is important to sample the nail as far proximally as possible, since viable fungi are most likely to be found at the interface between the diseased and normal nail.[26] When superficial white onychomycosis is present the surface of the nail plate can be scraped and examined for fungal filaments.

In the case of tinea corporis/cruris and tinea pedis, the affected area should be surface-disinfected with alcohol or cleansed with water. The recommended site for obtaining the specimen is the active border. When vesicular lesions are present, for example in tinea pedis or manuum, the vesicle can be unroofed and this material used for mycological examination.

2.1 Direct Microscopic Examination and Isolation Media

Skin scrapings or hair may be treated with potassium hydroxide (KOH) or sodium hydroxide (NaOH) followed by gentle heat. Details of the technique are beyond the scope of this article and the reader is referred elsewhere.[1,3] The KOH or NaOH helps dissolve the keratin, leaving fungal elements intact. The use of dimethyl-sulfoxide (DMSO) hastens the clearing of keratinocytes.[27]

The detection of hyphae and spores may be facilitated using counterstains, such as chlorazol black E (which is chitin specific) or Parker's blue-black ink (not chitin specific).[28] Demonstration of fungi may also be accomplished by the use of nonspecific fluorochrome stains such as calcofluor.[29] Direct microscopy is a test for the presence or absence of fungi; it does not enable the identity of the fungus to be determined.

Infected hair may appear as ectothrix, endothrix or favic hair. In ectothrix hair the arthroconidia form a mosaic sheath around the hair or chains on the surface of the hair shaft. Arthroconidia 1 to 3μm diameter, that form a mosaic sheath around the hair, are seen in infections due to *M. audouinii*, *M. canis* or *M. ferrugineum*. The infected hairs are Wood's lamp positive. In infection due to *M. gypseum* and *M. fulvum* the hairs do not fluoresce under Wood's light. The arthroconidia are larger (3 to 4μm in diameter), few in number and scattered on the outside surface of the hair. In *T. mentagrophytes* infection there is no fluorescence under the Wood's lamp. The arthroconidia, 3 to 4μm in diameter, are present in chains on the surface of the hair. *T. verrucosum* also produces ectothrix infection which is nonfluorescent. The arthroconidia are large, 8 to 12μm in diameter, forming large dense chains around the hair shaft.

Endothrix infection occurs with *T. tonsurans*, *T. violaceum* and *T. gourvilii*. *T. rubrum* causes ectothrix and, rarely, endothrix infection. Arthroconidia (3 to 4μm in diameter) are present as chains within the hair shaft.

In favic hair hyphal filaments, air bubbles and tunnels are present within the hair shaft. Hyphae may also be present within the hair shaft. Under Wood's lamp dull green fluorescence is typically observed.

A common medium used for isolating dermatophytes is Sabouraud's peptone-glucose agar. Chloramphenicol may be added to inhibit bacteria, and cycloheximide to inhibit most nondermato-

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phyte moulds. Such a medium is available commercially, for example, in North America as Mycobiotic agar [DIFCO Laboratories, Detroit (MI)] or Mycosel agar [BBL, Becton-Dickinson, Cockeysville (MD)].[1]

For the isolation of nondermatophytes, cycloheximide-free Sabouraud glucose agar with antibiotics such as gentamicin and chloramphenicol may be used. Littman oxgall agar (DIFCO) has been used since it reduces the colony diameter of fast-growing contaminants, facilitating outgrowth of the slower-growing aetiological agents. Dermatophyte test medium turns red when a dermatophyte is present.[30,31] The alkalinity generated as a result of dermatophyte growth causes the phenol red indicator to turn red. False positive and false negative reactions may occur.[1] Reverse pigmentation cannot be visualised.

For the above reasons the utility of the dermatophyte test medium is reduced. Media with and without cycloheximide should be used to determine the identity of organism(s) causing onychomycosis.

Another medium that can be used is the Casamino acids-erythritol-albumin medium (Candida inhibitory agar, Biomedics, Toronto, Ont). This is a highly selective medium for isolating dermatophytes from a sample heavily contaminated by bacteria or by the cycloheximide-tolerant *Candida albicans*. The egg albumin in this medium inhibits yeasts such as *C. albicans* which have an absolute requirement for exogenous biotin.[32]

2.2 Other Diagnostic Techniques

When the clinical diagnosis is consistent with onychomycosis, but the light microscopy and culture are repeatedly negative, the clinician should consider submitting the nail for histopathological evaluation. Fungal stains such as periodic acid-Schiff can then be performed.[33] In some instances a nail biopsy may become necessary, and help in excluding other possible causes of nail dystrophy such as psoriasis or lichen planus.

Two new diagnostic techniques, which are currently not widely available, are the use of immunohistochemistry and flow cytometry.[34] The first employs antibodies to certain fungi to obtain positive identification within the nail. Flow cytometry enables fungi to be differentiated on the basis of molecular differences.

3. Clinical Manifestations

The manifestation of tinea infection in an individual may be dependent upon the causative organism, the virulence of the dermatophyte and the response of the host defence mechanisms. Both humoral and cell-mediated reactions may be involved in clearing the dermatophyte infection and preventing spread into deeper tissues.[35,36]

In keeping with the above, the majority of patients who develop a chronic or recurrent infection with *T. rubrum* may fail to express a delayed-type hypersensitivity response to intradermally injected trichophytin.[37,38] Furthermore, infections due to anthropophilic organisms produce an inflammatory response that is less intense compared with zoophilic and geophilic organisms. Consequently, the delayed-type hypersensitivity response is not as marked with anthropophilic organisms and they are less likely to be cleared immunologically.[39] Certain dermatophytes, such as *T. rubrum*, may produce substances that reduce the immune response mounted by the host.[39]

The identity of the causative dermatophyte is not only of clinical significance but may also have epidemiological relevance. For example, tinea capitis due to *T. tonsurans* is usually acquired from infected humans or their fomites. Some subjects become long term carriers and harbour a subclinical scalp infection, intermittently shedding viable inoculum, possibly for decades.[40,41] In contrast, tinea capitis caused by *M. canis* may be acquired from infected pets such as cats; rarely, human-to-human transfer may occur.[42,43]

In general, the dermatophytoses caused by zoophilic and geophilic organisms are more inflammatory in nature than those caused by anthropophilic species; furthermore, the former two are also more likely to resolve spontaneously as a result of the immune response mounted by the infected host.

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4. Practical Considerations When Using Topical Antifungal Agents

In general, the topical antifungal agents should be applied over an area that is at least 2cm beyond the visible advancing edge of the cutaneous lesion. Some topical antifungal preparations are marketed in combination with a potent topical corticosteroid. The use of such combinations in certain anatomical locations, for example the perineum, may result in adverse effects such as striae.

It is imperative for the patient to apply the topical antimycotic therapy for the duration prescribed; it should not be discontinued at the first sign of improvement.

For most tinea infections measures can be taken to prevent relapse and reinfection. The reinfections in tinea cruris can be reduced by wearing loose-fitting cotton underwear, such as that of the 'boxer' variety. Weight reduction, thorough cleaning and drying of the affected area, and the use of an absorbent powder will help decrease the chance of reinfection.

There are several measures that can help prevent reinfection with tinea pedis and onychomycosis. Feet should be washed regularly and completely dried before wearing socks and shoes. Nails should be cut short and kept clean. The patient should avoid walking barefoot over surfaces that may harbour a high density of fungal filaments and spores, e.g. communal changing rooms and swimming baths, gymnasiums, other athletic and public facilities. Similarly, patients with tinea pedis and/or onychomycosis should avoid sharing shoes and socks, since these may serve as a source of infection. Poorly fitting shoes and those of inappropriate material may induce trauma and set up a milieu that predisposes to fungal infections. Similarly, socks should be made of cotton or other natural absorbent material.

Whenever feasible, family members and other personal contacts should be examined for tinea pedis/onychomycosis and treated appropriately. Following apparently successful treatment for tinea pedis/onychomycosis, the patient should be counselled about the symptoms/signs, and encouraged to seek early medical help so that prompt treatment can be given. Early disease is likely to respond better and more completely than advanced infection.

Superficial candidosis affects the skin and nails and is caused by *C. albicans*; less commonly other *Candida* spp. are involved. Moist and occluded parts of the body may be affected. When appropriate, predisposing factors including those causing maceration of moist tissues should be eliminated. In chronic mucocutaneous candidosis oral antimycotic agents are required.

5. When Should Systemic Antifungal Agents Be Considered?

Topical therapy is usually preferred because there is less potential for serious adverse effects. Other factors that determine the choice of therapy are immunocompetence of the host, identity of the causative organism, the site and extent of infection, patient preference for the oral *vs* the topical route, and the cost effectiveness of the 2 forms of therapy.

It is generally recognised that systemic therapy may be needed when a patient has tinea capitis, infection involving the hair follicles such as in Majocchi's granuloma, chronic tinea pedis and onychomycosis. Topical agents may be used as an adjunct to systemic therapy for the aforementioned tineas. When the tinea infection involves a large surface area of skin, in instances where the host immunity is reduced or abnormal, and when there is chronic or recurrent infection with a poor response to topical agents, then systemic therapy should be considered.

Infections of zoophilic origin may manifest with intense inflammation, making rapid eradication urgent. Spread of infection is not uncommon in such cases because of multiple inoculations from the infection source; therefore, oral antifungal therapy may be required.

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Table I. Topical antifungal agents. Note: The information given here is only a guideline. The need to obtain a drug by prescription may change over time. The reader must therefore consult an up-to-date standard textbook or other appropriate source for current data before applying the information to the clinical situation

Nonspecific	Specific
Whitfield's ointment[a]	Griseofulvin
Castellani'spaint (carbol-fuschin paint)[a]	8-Hydroxyquinoline ciloquinol (iodochlorhydroxyquin)[b]
Aluminium chloride 30%[a]	Thiobendazole
Gentian violet[a]	Thiocarbamates
Compound undecylenic acid[a]	tolnaftate[a]
Potassium permanganate[a]	tolciclate
Selenium sulphide 2.5% lotion[b]	Haloprogin[b]
Zinc pyrithione[a]	Polyenes
Sodium thiosulfate 25% aqueous	nystatin[b]
solution plus salicylic acid 1%[a]	natamycin[b]
Propylene glycol (50% in water)[a]	amphotericin B[b]
Urea preparations[a]	Hydroxypyridone
Oil of bitter orange	ciclopirox olamine[b]
	Morpholine
	amorolfine
	Benzylamine
	butenafine[b]
	Allylamines
	naftifine[b]
	terbinafine[b]
	Azoles
	imidazoles:
	bifonazole
	butaconazole nitrate[b]
	clotrimazole[a]
	croconazole
	eberconazole
	econazole[b]
	fenticonazole
	flutimazole
	isoconazole
	ketoconazole[b]
	lanoconazole
	miconazole[a,b]
	neticonazole
	omoconazole
	oxiconazole nitrate[b]
	sertaconazole
	sulconazole nitrate[b]
	tioconazole[b]
	triazole:
	terconazole[b]

a Over-the-counter (OTC) in the US.
b Available by prescription in the US.

6. Topical Antifungal Agents

6.1 Nonspecific Topical Antifungal Agents

At the beginning of the twentieth century the topical compounds used for the treatment of superficial fungal infection had a nonspecific action spectrum (table I) and were often minimally effective. In 1950, Sulzberger observed that the treatment of superficial fungal infections was dependent mainly on the physical and/or chemical removal of the infected dead tissue and prevention of invasion of newly formed or forming horny and macerated nonviable materials.[44,45]

6.1.1 Whitfield's Ointment

In 1907, Arthur Whitfield compounded a preparation containing 12% benzoic acid and 6% salicylic acid.[46] This fungistatic compound with a nonspecific activity acts as a keratolytic and produces desquamation of the keratinised epidermis that contains fungal organisms.[47]

When this ointment is applied to glabrous skin or the perineum, or used in children, the concentration should be reduced by one-half.[48] Furthermore, the preparation can be irritating, especially if applied over a large surface area. Also, systemic absorption can occur, leading to salicylic acid toxicity, especially in individuals with impaired renal function.[46] Other keratolytic agents include salicylic acid and retinoic acid.

6.1.2 Castellani's Paint

Castellani's paint (carbol-fuchsin paint) has antifungal and antibacterial activity.[47,49,50] Applications include the treatment of seborrhoeic eczema, interdigital athlete's foot, and more recently tinea imbricata in the tropics.[51] Adverse effects are irritant and toxic reactions to the phenol.[49] Elimination of the phenol has not resulted in reduced efficacy.[49,51,52]

6.1.3 Aluminium Chloride

Aluminium chloride 30% may have a similar efficacy to Castellani's paint in tinea pedis; however, the former may be more acceptable.[53,54]

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6.1.4 Gentian Violet

Gentian violet is a triphenylmethane (rosaniline) dye. Marketed products may contain up to 4% of the tetramethyl and pentamethyl congeners, the pure compound being crystal violet. Gentian violet solution is usually used in 0.5 to 2% concentrations for mucosal yeast infections.[55] It has antifungal and antibacterial properties. Gentian violet may stain clothing and cause skin irritation.

6.1.5 Compound Undecylenic Acid

Compound undecylenic acid contains the undecylenic acid and its zinc, calcium or sodium salt.[55,56] Undecylenic preparations are used in the treatment of various dermatomycoses including tinea pedis, napkin (diaper) rash and tinea cruris. A common combination is 5% undecylenic acid and 20% zinc undecylenate.[54,57] It is fungistatic and available as an aerosol, powder, cream or solution.[47] Calcium undecylenate is available as a powder.[57]

6.1.6 Potassium Permanganate

Potassium permanganate has nonspecific antifungal activity.[47] When diluted to 1 : 5000 it has been used to treat inflammatory candidosis in intertriginous areas.[58]

6.1.7 Selenium Sulphide

Selenium sulphide 2.5% lotion is effective in the treatment of pityriasis versicolor and seborrhoeic dermatitis.[59-63] When the lotion is used for 10 minutes once daily for 7 consecutive days, no significant percutaneous absorption of selenium occurs.[64] Selenium sulphide 2.5% shampoo can irritate the scalp or discolour the hair.[65] Selenium sulphide lotion used as a shampoo may be an adjunctive therapy to griseofulvin in tinea capitis.[66]

6.1.8 Zinc Pyrithione

Zinc pyrithione is an antifungal and antibacterial agent that has been used to treat dandruff.[67,68] Zinc pyrithione 1% shampoo is effective in the treatment of pityriasis versicolor when applied daily for 2 weeks.[69,70]

6.1.9 Sodium Thiosulfate Plus Salicylic Acid

A 25% aqueous solution of sodium thiosulfate combined with 1% salicylic acid is available as a commercial preparation in some countries and may be effective in pityriasis versicolor.[71] Other topical agents that have been used in pityriasis versicolor include povidone-iodine paint,[72] 2% micropulverised sulphur and 2% salicylic acid in a shampoo base,[73,74] topical griseofulvin,[75] benzoyl peroxide[76] and tretinoin cream 0.1%.[77]

6.1.10 Propylene Glycol

Propylene glycol (50% in water) has been used to treat pityriasis versicolor.[78] It is an effective keratolytic agent, with *in vitro* fungistatic activity against members of the *Malassezia furfur* complex (formerly *Pityrosporum* spp.) when used in concentrations of 4 to 6%.[79] Propylene glycol-urea-lactic acid solution has also been used in onychomycosis.[80]

6.1.11 Urea

Urea preparations have been employed by dermatologists for several years, with several properties being ascribed to them, including antifungal,[81] keratolytic[82] and hydrating.[82-85] Urea ointments have been used as a nonsurgical and atraumatic method of avulsing dystrophic nails.[86-88] Subsequently, a combination of urea and imidazole (1% bifonazole and 40% urea) was reported in the treatment of onychomycosis.[89-94] The combination of 20% urea with 2% tolnaftate ointment has also been used.[95]

Before the introduction of the recent generation of oral antifungal agents for *Candida* onychomycosis, e.g. itraconazole, fluconazole and terbinafine, White and Clayton[96] reported the use of chemical avulsion to treat dystrophic nails infected by fungus or yeast that was resistant to griseofulvin or ketoconazole. Chemical partial nail avulsion followed by topical miconazole may be of some benefit in the treatment of onychomycosis limited to a few nails.[97] The same procedure followed by the application of topical ciclopirox to fingernail onychomycosis has been reported to clear *Scytalidium dimidiatum* (formerly *Hendersonula toruloidea*) infection, a nondermatophyte mould for which there is currently no consistently effective therapy.

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6.1.12 Oil of Bitter Orange

The oil of bitter orange (OBO) has been shown to be active topically against several dermatophyte infections.[98] It is a volatile oil obtained from the peel of bitter orange (*Citrus aurantium*).[99] In one study a 25% emulsion of OBO was comparable with an imidazole derivative for the treatment of dermatophyte infections.[98] OBO appears to be especially effective against *T. rubrum*.

6.2 Specific Topical Antifungal Agents

These are listed in table I.

6.2.1 Topical Griseofulvin

Griseofulvin was discovered by Oxford and his group in 1939.[100] Its use as an oral agent was reported by Gentles[101] and Blank and Roth,[102] and several other investigators.[103,104] As early as 1959 topical griseofulvin was found to have some effectiveness in the treatment of dermatomycoses;[105,106] subsequently, varying degrees of success were reported by investigators who used a variety of vehicles in which to dissolve the agent.[107-116]

Epstein et al.[117] applied saturated solutions of griseofulvin in several solvent systems including DMSO, trichloroethanol, alcohol and an ether-acetone solution to the palm and forearm of subjects. Skin scrapings were obtained from 3 levels of the stratum corneum and assayed for drug. From the preliminary studies the authors selected an alcohol solution containing 0.45% griseofulvin for further studies. The drug appeared in high concentrations in all levels of the stratum corneum, and it generally persisted there in measurable amounts for 4 or more days following a single application.[117] Epstein et al.[117] observed that topically applied griseofulvin in alcohol solution was highly effective in preventing experimentally induced *T. mentagrophytes* infection; however, it had no therapeutic effect once the infection was initiated.

Subsequently, Wallace et al.[118] showed that topically applied griseofulvin was a significantly better prophylactic agent than either miconazole or clotrimazole. In a placebo-controlled study, Aly et al.[119] demonstrated that a 1% griseofulvin spray formulation was effective against experimentally induced *T. mentagrophytes* lesions on the forearms of healthy volunteers. In tinea pedis patients the medication was applied once daily for 4 weeks with a mycological cure of 79.2% on the fourth week and 80.9% 2 weeks after treatment.[119] In contrast, the mycological cure rate in the placebo group at week 6 was 34%. Montes et al.[120] found that topical griseofulvin had some effectiveness against tinea versicolor, although it is not active against *C. albicans*.

6.2.2 Ciloquinol

Ciloquinol (iodochlorhydroxyquin) is an 8-hydroxy-quinoline.[121] Both oral and topical formulations are available.[122,123] The topical formulation has been used in the treatment of napkin dermatitis. However, it should be used cautiously if applied for prolonged periods, and over a large surface area.[124,125] Also, skin irritation, contact dermatitis and yellow staining of clothes may occur.[126]

6.2.3 Thiabendazole

Thiabendazole was first introduced in the US in 1961 as a broad spectrum anthelmintic.[127-131] In a 10% concentration its effectiveness in tinea corporis, tinea cruris and tinea capitis was comparable with that of systemically administered griseofulvin. In 70% alcohol, thiabendazole was effective in concentrations as low as 0.25%. However, in a propylene glycol vehicle it appeared to be comparatively ineffective. Oral thiabendazole is used as an anthelminthic. In the US the topical form is not available.

6.2.4 Tolnaftate and Tolciclate

Tolnaftate[132] and tolciclate belong to the thiocarbamate group of antifungal agents. The primary mode of action of the thiocarbamates is the blockage of sterol biosynthesis in fungal cells by inhibiting squalene epoxidase.[133,134] The biochemical action is thus similar to that of the allylamine antimycotics naftifine and terbinafine. Tolnaftate is effective in the treatment of the majority of cutaneous mycoses caused by *T. rubrum*, *T. mentagrophytes*, *T. tonsurans*, *E. floccosum*, *M.*

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canis, *M. audouinii*, *M. gypseum* and *M. furfur*; however, it is ineffective against bacteria and *Candida* spp.[58,135,136] This is in keeping with it being active against squalene epoxidation in broken *C. albicans* cells, but much less potent against whole cells, suggesting that there may be a barrier to penetration in yeast cells.[134]

Tolnaftate 1% is available as a cream, gel, powder, aerosol powder, aerosol or topical solution and topical aerosol liquid. It is ineffective by the oral or parenteral route in guinea-pigs.[45] The recommended frequency of use is twice daily. It is effective in tinea pedis, tinea manuum, tinea corporis/cruris and tinea versicolor.[137,138] Like nystatin, tolnaftate is almost completely devoid of irritating or sensitising properties.[45]

After the introduction of nystatin and tolnaftate, which had a narrow spectrum of activity, came the broad spectrum topical antifungal agents with activity against dermatophytes and *C. albicans*. These compounds include haloprogin, miconazole and clotrimazole. Tolciclate is a thiocarbamate topical antifungal agent.[139-141] It is not available in the US.

6.2.5 Haloprogin

Haloprogin is a halogenated phenolic ether that is fungicidal *in vitro* to various species of *Epidermophyton*, *Malassezia*, *Microsporum*, *Trichophyton* and *Candida*. It is available as a 1% cream or solution which should be applied twice daily for 2 to 4 weeks. Haloprogin is more effective than placebo and as effective as tolnaftate in treating dermatophytoses.[142-144]

Clotrimazole may be more effective than haloprogin in the treatment of tinea cruris.[145] Clayton et al.[146] reported that haloprogin had the same broad range of activity as miconazole, being effective against dermatophytes, *Malassezia*, *Candida* and erythrasma infections. However, the patient acceptability of haloprogin was not as good as that of miconazole. Haloprogin cream has the same efficacy as nystatin ointment in cutaneous candidosis.[147] Possible adverse effects include irritation, pruritus, and (rarely) vesicle formation or an allergic contact dermatitis.[148-150]

6.2.6 Polyenes

Polyenes are characterised by a macrolide ring of carbon atoms closed by an internal ester or lactose.[47,151] The 3 clinically significant polyenes are nystatin, natamycin and amphotericin B.

Nystatin, the first specific antifungal antibiotic for human use, was discovered in 1949 by Hazen and Brown in the New York State Health Laboratory and named accordingly.[58,152,153] It is a tetraene macrolide antibiotic produced by *Streptomyces noursei* and *S. albidus*.[151] The actinomycete was isolated from a pasture of the Nourse dairy farm in the state of Virginia.[45] Nystatin is structurally similar to amphotericin B and has the same mechanism of action; however, it is more toxic and is not used systemically. Nystatin is not absorbed from the gastrointestinal tract, skin or vagina.[58] It was first approved by the FDA in 1955 as a vaginal treatment for candidosis.

Nystatin is useful only for candidosis and is not effective against dermatophytes. It is available as an oral suspension or lozenges (pastilles), vaginal tablets and topical preparations including ointment, cream and powder. There is no parenteral preparation. The topical preparations contain 100 000 IU/g. They are indicated in the treatment of cutaneous or mucocutaneous mycotic infections caused by *C. albicans* or other *Candida* spp.[154] Nystatin is well tolerated, with rare reports of allergic contact dermatitis.[155-157]

Natamycin is a tetraene polyene antibiotic derived from *S. natalensis*. In a 5% ophthalmic suspension it is indicated for the treatment of fungal blepharitis, conjunctivitis, and keratitis caused by susceptible organisms.[158] Natamycin may be the initial drug of choice in *Fusariam solani* keratitis. Whenever possible, its *in vitro* activity against the responsible fungus should be determined. Topical natamycin may produce effective concentrations within the corneal stroma, but not in the intraocular fluid. Thus, it may not reach deep corneal mycoses.[58]

Topical amphotericin B is available as a lotion or ointment at a concentration of 3%. It is indicated for the treatment of cutaneous and mucocutaneous

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mycotic infections caused by *Candida* spp. This topical preparation may have been superseded by newer antifungal agents. The systemic use of nystatin and amphotericin B is not discussed and the reader is referred to other sources.

6.2.7 Ciclopirox

Ciclopirox is a hydroxy-pyridone whose structure is not related to the azoles or other antifungal agents.[159-172] In contrast to many antifungal agents, ciclopirox does not affect sterol biosynthesis.[159] The primary mode of action is interference with the uptake and accumulation of products required for cell membrane synthesis.[159,160]

Ciclopirox is a broad spectrum antifungal agent that inhibits the growth of pathogenic dermatophytes, yeasts and *M. furfur*. It exhibits fungicidal activity *in vitro* against isolates of *T. rubrum*, *T. mentagrophytes*, *E. floccosum*, *M. canis* and *C. albicans*. Ciclopirox has demonstrated *in vitro* activity against many Gram-positive and Gram-negative bacteria.

Ciclopirox 1% cream is significantly more effective than its vehicle and clotrimazole 1% cream in the treatment of tinea pedis.[161,162] It is also effective in treating cutaneous candidosis,[167] tinea corporis and tinea cruris.[163] In cutaneous mycotic lesions ciclopirox 1% spray may be equally as effective as fenticonazole spray.[168] In inflamed superficial mycoses, ciclopirox cream 1% is as effective as the combination of ciclopirox 1% and hydrocortisone acetate 1%.[164] The 1% cream[165] and 0.1% solution[169] are effective in pityriasis versicolor.

Ciclopirox nail lacquer 8% may be able to penetrate nails.[170] Applied daily for 4 and 6 months in fingernail and toenail onychomycosis, respectively, it resulted in complete clinical and mycological cure in 40% patients in one study.[171] It may also be effective in onychomycosis due to yeasts and nondermatophyte moulds such as *Scopulariopsis brevicaulis*, *Aspergillus niger*, *A. fumigatus* and *S. dimidiatum*.[172]

6.2.8 Amorolfine

Amorolfine is a morpholine derivative and a phenylpropylpiperadine. It is not related to the polyenes, the imidazoles or the allylamines.[173-183] Amorolfine demonstrates *in vitro* activity against dermatophytes, filamentous fungi (moulds) and pathogenic yeasts, including *Malassezia* spp. It is also active against some dimorphic and dematiaceous fungi.

The primary mode of action of amorolfine is to inhibit the formation of ergosterol, an essential component of the fungal cell membrane.[176] In the presence of amorolfine, ignosterol, a sterol containing a Δ_{14}-double bond, is formed instead of ergosterol. Ignosterol formation is a major feature in *C. albicans*. However, in *T. mentagrophytes* and other dermatophytes, a large accumulation of squalene is also seen at the higher concentrations of amorolfine. At low concentration the same accumulation of ignosterol and other Δ_{14}-sterols occurs as in the yeast *C. albicans*.[176] Thus, in yeasts amorolfine appears to interfere with the enzymes in the ergosterol biosynthesis pathway, the Δ_{14}-reductase and the $\Delta_{7\text{-}8}$-isomerase.[176] It is possible that in some species squalene epoxidase is also inhibited.

In the treatment of dermatomycoses, application of amorolfine cream 0.25% once daily for 3 to 4 weeks is recommended.[175] The mean percutaneous absorption following topical application of the 0.25% cream formulation should not exceed 8 to 10% of the applied dose.[177]

Amorolfine 0.25% cream applied once daily is effective in the treatment of tinea pedis plantaris/interdigitalis and tinea corporis/cruris, including infections due to *Candida* spp.[175] In some reports the cure rates for the treatment of dermatomycoses are similar to those achieved with terbinafine cream 1%, ciclopirox and clotrimazole cream 1%.[175] In patients with foot mycoses, amorolfine spray 0.5 and 2% used once daily for 4 weeks on average was found to be effective against dermatophytes, yeasts and some moulds, with cure rates similar to those observed with amorolfine cream 0.5%.[178]

Amorolfine is also used to treat onychomycosis. The drug is absorbed through the human nail plate when it is formulated as the alcohol or methylene

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chloride lacquer.[179-181] Pretreatment of the nail with DMSO results in a large increase in amorolfine penetration.[179] Amorolfine nail lacquer 5% is more effective than the 2% concentration, and the higher concentration should be applied once or twice weekly until clinical cure, usually 6 months for fingernails and 12 months for toenails.[175] The affected nail should be filed down before the application of the lacquer.

The drug is effective in both dermatophytes and yeasts. In toenail onychomycosis, without matrix involvement, treated once weekly with amorolfine 5% nail lacquer, the response (cure plus improvement) and mycological cure rates were 77.6 and 52.1%, respectively, at follow-up 3 months after a 6-month course of therapy.[182] With fingernails, at follow-up 3 months after 6 months of once-weekly therapy, the respective response and mycological cure rates were 83.7 and 64.3%.[182]

The treatment is generally well tolerated, with chromonychia developing rarely.[183] The nailplate discoloration may be due to the oxidation of methylmethacrylate polymer, a plasticiser and vehicle in the nail lacquer.

6.2.9 Butenafine

Butenafine is a benzylamine derivative with a structure and mode of action similar to the those of the allylamines.[184-186] It has a structure that resembles the allylamines; however, a butylbenzyl group replaces the allylamine group.

Butenafine inhibits fungal squalene epoxidase, causing accumulation of squalene, depletion of ergosterol and disruption of fungal cell membranes. In contrast to the azoles, benzylamines have no effect on the cytochrome P450–dependent synthesis of steroidal hormones. Benzylamine drugs, like the allylamines, are fungicidal *in vitro* against dermatophytes and fungistatic against *C. albicans* at therapeutically achievable drug concentrations.[187]

Butenafine was approved for topical use in Japan in 1992. It is effective against tinea pedis and other dermatophytoses.[188-191] It is used once daily for 4 weeks for interdigital tinea pedis, with effectiveness lasting at least 4 weeks after stopping therapy.[188] It was approved for use in the US in February 1997.

6.2.10 Azoles

The first imidazole developed as a topical antifungal agent was chlormidazole in 1959.[192] The azoles inhibit the biosynthesis of ergosterol, an essential component of the fungal cell membrane, by inhibiting the enzyme lanosterol 14-α-demethylase, a cytochrome P450–dependent enzyme.

Bifonazole

Bifonazole is a halogen-free imidazole derivative that is not currently approved for use in the US. It has a broad range of activity against dermatophytes, some *Candida* spp. and *Malassezia* spp. reported as *Pityrosporum ovale* (particularly *P. ovale* and *P. orbiculare*).[193,194] Bifonazole also has significant *in vitro* activity against *Corynebacterium* spp. and Gram-positive cocci (staphylococci and streptococci but not enterococci).

Following a single application of bifonazole 1% cream or solution to healthy skin, less than 1% of the dose is absorbed during a 6-hour contact period.[195,196] Bifonazole 1% is available in many countries other than the US in cream, solution, gel and powder forms. It was registered in Germany in December 1982.[196] Used once daily, the 1% formulation is effective in dermatophytosis and superficial candidosis,[196-200] and in the treatment of seborrhoeic dermatitis and tinea versicolor.[200-211] In tinea versicolor, bifonazole 1% solution applied for 3 days (days 1, 3 and 6) was an effective treatment strategy.[203] Bifonazole spray 1% applied on the first day of the first month followed by the first day on each of the following 3 months was found to be as effective for treating pityriasis versicolor as applying the spray on the first 3 days of the first month followed by a monthly application on the first day of each of the next 3 months.[210] The use of bifonazole 1% in combination with urea preparations for the management of onychomycosis is discussed above (section 6.2.9).[89-94]

Butoconazole

Butoconazole is an imidazole derivative.[212-216] It was introduced in the US in 1985 for the short

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term management of vaginal infections caused by *Candida* spp.[214] Butaconazole has fungicidal activity *in vitro* against *Candida*, *Trichophyton*, *Microsporum* and *Epidermophyton*. It also has some activity against Gram-positive bacteria.

Following a single intravaginal dose of butoconazole, approximately 5.5% of the drug is absorbed.[214] The plasma half-life is approximately 21 to 24 hours. Butoconazole 2% vaginal cream applied daily for 3 days has been found to be as effective as longer treatment periods with clotrimazole cream 1%[215] and miconazole.[216]

Clotrimazole

Clotrimazole is a chlorinated tritylimidazole first synthesised in Germany in 1967.[217] *In vitro*, clotrimazole inhibits most strains of *Trichophyton*, *Microsporum* and *Epidermophyton*.[218] It is about as active as nystatin against *Candida* spp. and also inhibits some strains of Gram-positive bacteria. It is a broad spectrum imidazole applied twice daily to treat superficial dermatomycoses, cutaneous *Candida* infections, oropharyngeal and vaginal candidosis and tinea versicolor.[219-230] Although this agent is active orally, the associated toxicity and other adverse effects have generally limited its use to topical applications.[231] The oral formulation is not discussed further.

Croconazole

Croconazole is an imidazole first reported in 1983;[232] it is currently not available in the US. It is a broad spectrum agent effective against dermatophytes, yeasts, dimorphic fungi, moulds and a broad spectrum of bacteria.[233,234] In addition, it has anti-inflammatory properties.

Croconazole 1% cream, applied once daily, is effective in the treatment of tinea infections, cutaneous candidosis and pityriasis versicolor.[235,236] Croconazole is available as 1% gel and 1% cream. It has been reported to cause an allergic contact dermatitis.[237]

Eberconazole

Eberconazole is a broad spectrum topical imidazole that was synthesised in Spain.[238,239] It has demonstrated *in vitro* activity against dermatophytes, *Candida* spp., *Malassezia* spp., and Gram-positive bacteria.[238-240] In experimental animal studies it has been found to be active in dermatophytosis and experimental candidosis.[238-240] Eberconazole possesses anti-inflammatory activity.[238]

In a phase II pilot dose-finding study, eberconazole 1% twice daily applied for 2 weeks after clinical cure or for a maximum of 6 weeks in tinea corporis/cruris demonstrated a 100% cure rate when assessment was carried out 6 weeks after therapy. There were no adverse effects.

Econazole

Econazole is a deschloro derivative of miconazole synthesised in 1969.[241-253] In *in vitro* studies econazole exhibits a broad spectrum of antifungal activity against dermatophytes, *C. albicans*, *M. furfur* and some Gram-positive bacteria.[242] When the compound is applied topically, the concentrations in the stratum corneum far exceed the minimum inhibitory concentration (MIC) for dermatophytes.[242,243] Inhibitory concentrations are achieved in the epidermis and as deep as the middle region of the dermis. Less than 1% of the applied dose is recovered in the urine and faeces.

Econazole 1% cream is as effective as clotrimazole 1% cream in the treatment of tinea infections and cutaneous candidosis, although the onset of action of the former is more rapid.[244] The antibacterial activity of econazole, particularly against Gram-positive bacteria, may make it an effective agent for the treatment of interdigital bacterial infections uncomplicated by dermatophyte colonisation.[242,245]

Econazole 1% is effective in the treatment of tinea pedis, intertriginous candidosis, paronychia due to *Candida* spp. and tinea versicolor.[246-253] The cream is also effective in napkin dermatitis in children due to *C. albicans* and/or bacterial growth.[254]

Fenticonazole

Fenticonazole is an imidazole derivative first synthesised in Italy, with the first reports appearing in 1981.[255,256] It is a broad spectrum antifungal

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agent with fungistatic or fungicidal activity against dermatophytes and *Candida* spp.[257-260]

In controlled trials fenticonazole 2% cream has been shown to be equal in efficacy, or superior, to miconazole 2% cream, each applied twice daily, in the treatment of dermatophytosis, cutaneous candidosis and pityriasis versicolor.[261] This drug has a retention time, and hence a preventative activity on fungal infections, of 48 to 72h, suggesting that once-daily application would be sufficient.[262]

Fenticonazole 2% cream or bifonazole 1% cream, each applied once daily, are equally effective in the treatment of dermatomycoses, with a more rapid therapeutic activity of fenticonazole.[263] Fenticonazole is also effective in cutaneous candidosis and pityriasis versicolor.[261,263-268]

Flutrimazole

Flutrimazole is a topical imidazole that is not currently approved in the US. It is active *in vitro* and *in vivo* against a number of micro-organisms including dermatophytes, filamentous fungi, yeasts and other pathogenic fungi.[269,270] No systemic adverse effects have been reported after topical administration, with <0.5% of the administered dose being recovered in the urine.[271,272]

In a comparative trial flutrimazole cream 1% was more effective than bifonazole cream 1%, each used once daily, in the treatment of dermatophytosis, cutaneous candidosis and pityriasis versicolor.[273] Flutrimazole 1% solution is as effective as bifonazole 1% solution when used once daily in dermatomycosis.[274] Flutrimazole 1% cream is as effective as clotrimazole 1% cream, each used twice daily in the treatment of dermatomycoses.[275]

Isoconazole

Isoconazole is a broad spectrum imidazole that is currently not approved in the US. It has *in vitro* activity against dermatophytes, pathogenic yeasts and some Gram-positive bacteria.[276] When it is applied topically a reservoir of drug builds up in the horny layer, suggesting that once-daily application may suffice.[277] Isoconazole 1% is available as a cream, solution or spray. It may be effective in the treatment of dermatophyte infections, cutaneous candidosis and pityriasis versicolor.[278] Isoconazole may be beneficial as a once-daily treatment for vaginal candidosis caused by *Candida* spp.[279,280]

Ketoconazole

Ketoconazole was first synthesised in 1977 and is a broad spectrum synthetic antimycotic that inhibits the *in vitro* growth of dermatophytes and yeasts by impairing the synthesis of ergosterol and altering the permeability of cell membranes.[281,282] The dermatophytes include *Trichophyton*, *Microsporum* and *Epidermophyton* spp. The yeasts include *C. albicans*, *C. tropicalis* and *M. furfur*; the last-named is thought to be responsible for tinea versicolor.[283,284] Following a single application to the chest, back and arms of healthy volunteers, no systemic absorption was detected at a sensitivity level of 5 μg/L in the blood over the following 72 hours.[285]

Ketoconazole 2% cream applied once daily is effective in tinea pedis, tinea cruris and tinea corporis.[286]. At the end of 4 weeks of treatment, 82% of patients has a marked or excellent response to therapy. The incidence of adverse advents was 1.2% (3 of 256 patients), with only 2 requiring discontinuation of therapy. Topical ketoconazole 2% cream applied once daily is also effective in cutaneous candidosis.[287] This article does not focus on the oral formulation.

M. furfur (reported as *P. ovale*) may have a central role in seborrhoeic dermatitis. Ketoconazole cream 2% and shampoo are effective in this complaint.[288-301] Topical ketoconazole has been used effectively when applied once daily for 10 days in infantile seborrhoeic dermatitis.[302] The mean age of the 19 infants was 2.8 months (range 1 to 11 months). A good to excellent response was seen in 15 (78.9%) of 19 patients at day 10. Percutaneous absorption was minimal. No plasma ketoconazole accumulation was observed over the 10-day treatment period. Ketoconazole 2% cream and shampoo are effective in tinea versicolor.[63,303-305]

To reduce the possibility of recurrence of infection, tinea corporis, tinea cruris, pityriasis versicolor and *Candida* infections should be treated for

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at least 2 weeks, seborrhoeic dermatitis for at least 4 weeks or until clearing, and tinea pedis for approximately 6 weeks.[306]

Lanoconazole

Lanoconazole is a synthetic imidazole first synthesised in Japan and available as a 1% cream.[307-311] It has not been approved for use in the US. It may be effective in various dermatomycoses including tinea pedis, tinea corporis and cutaneous candidosis.

Miconazole

Miconazole is a synthetic phenethyl imidazole derivative and is a close chemical congener of econazole. It was synthesised in 1969 and, although relatively toxic in comparison with other systemic antifungals, was the first azole derivative of sufficiently low toxicity to permit intravenous administration for the treatment of systemic mycoses.[195,312]

Miconazole inhibits the growth of the common dermatophytes (*T. rubrum*, *T. mentagrophytes*, *E. floccosum*), *C. albicans* and *M. furfur*. It also has activity against some Gram-positive bacteria.[313-316] Topically applied miconazole easily penetrates the stratum corneum, where it may be detected for more than 4 days following application.[58] Less than 1% is absorbed into the systemic circulation.

Miconazole is effective for the treatment of tinea corporis/cruris, tinea pedis, cutaneous candidosis, pityriasis versicolor, erythrasma, impetigo or echthyma caused by Group A β-haemolytic streptococci or pathogenic staphylococci.[317-322] This agent may have the same broad range of activity as haloprogin against superficial mycoses and erythrasma.[146] A combination of miconazole 2% and benzoyl peroxide 5% has been used in the treatment of acne vulgaris.[323] The intravenous formulation is not discussed here.

Neticonazole

Neticonazole is a topical imidazole characterised in relationship to the other imidazoles by the absence of a halogen group and the presence of an S-methyl group.[324-326] It has been used as a topical antifungal agent in Japan since 1993; however, it is not approved for use in the US as yet.[325]

In a double-blind, multicentre trial, neticonazole 1% cream applied once daily was as effective as bifonazole 1% in the treatment of dermatophytoses, cutaneous candidosis and tinea versicolor.[325] Neticonazole was well tolerated, with adverse effects in 1.9% of patients.

Omnoconazole

Omnoconazole is an imidazole derivative that has broad spectrum *in vitro* antifungal activity against dermatophytes, yeasts and dimorphic fungi.[327-330] A single application of omnoconazole 1% cream demonstrates a lingering effect for at least 48 hours.[329]

Oxiconazole

Oxiconazole contains the basic structural unit (substituted heterocyclic ring with a nitrogen in the 3-position) common to the imidazoles.[331] However, oxiconazole is an acetophenone-oxime derivative and is structurally distinct from miconazole and econazole (phenethyl derivatives), clotrimazole (tritylimidazole derivative) and ketoconazole (phenylpiperazine derivative).[332]

Oxiconazole is active *in vitro* against the common dermatophytes *C. albicans* and *M. furfur*.[333,334] It also has antibacterial activity against some Gram-positive bacteria, including *C. minutissimum*.[335] Polak[336] reported that in animal models oxiconazole cream remained in the horny layer of the epidermis for as long as 96 hours following a single application. This would suggest that a once-daily application would be sufficient in treating dermatomycoses.

Oxiconazole 1% cream applied once daily is effective in the treatment of tinea pedis, tinea cruris, tinea corporis, erythrasma and pityriasis versicolor.[332,335-342]

Sertaconazole

Sertaconazole is a synthetic imidazole[343] that is not currently approved in the US. It has a broad *in vitro* spectrum against dermatophytes, *Candida* spp. (*C. albicans*, *C. tropicalis*), *M. furfur* and *Aspergillus* spp. Following the application of 2%

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cream, no skin irritation or systemic adverse effects were reported.[344]

Sertaconazole 2% cream applied twice daily is effective in cutaneous candidosis and pityriasis versicolor.[345,346] Once-daily application of the same formulation for 2 weeks was effective and well tolerated in a paediatric population (age 2 to 16 years) with dermatophytosis.[347]

Sulconazole

Sulconazole is a synthetic imidazole that has activity against dermatophytes, *C. albicans*, *M. furfur* and certain Gram-positive bacteria, such as *S. aureus*, *S. epidermidis* and *S. fecalis*.[348,349] It is effective in tinea pedis, tinea corporis/cruris, pityriasis versicolor, cutaneous candidosis, impetigo and ecthyma.[350-358]

Terconazole

Terconazole is a synthetic triazole ketal derivative that exhibits a broad-spectrum antifungal activity *in vitro* against *Candida* spp. and dermatophytes.[359-363] Terconazole vaginal cream or suppositories have been used for the local treatment of vulvovaginal candidosis.[364-368]

Tioconazole

Tioconazole is a 1-substituted imidazole that has activity against dermatophytes, yeasts including *M. furfur* and some bacteria (e.g. *C. minutissimum*, *C. vaginalis* and some chlamydias).[369-373] Although tioconazole is approved in the US and Canada for vaginal use only, the drug has been found to be effective in superficial mycoses including cutaneous candidosis, erythrasma and pityriasis versicolor.[372-378] Tioconazole 28% nail solution has been used in the treatment of onychomycosis,[379] sometimes as adjunctive therapy with griseofulvin.[380]

6.2.11 Allylamines

Naftifine and Terbinafine

Naftifine is an allylamine that is the first in its class to become available for clinical use.[381-383] It inhibits squalene epoxidase, an enzyme in steroid synthesis that converts squalene to ergosterol and is independent of cytochrome P450. The result is a deficiency in ergosterol with an intracellular accumulation of squalene. The latter in particular may account for the fungicidal activity *in vitro* of naftifine. This drug has a high affinity to the cornified epithelium, with amounts several times the MIC for dermatophytes being detected as long as 5 days after a single application.[384]

There may be no difference in the mycological and clinical efficacy following once- or twice-daily application of naftifine.[385,386] It has distinct anti-inflammatory activity which may account, in part, for its effectiveness in inflammatory mycotic infections.[387-389]

Naftifine has been shown to be effective in the treatment of tinea pedis and tinea corporis/cruris.[390-405] In some studies, naftifine has demonstrated an earlier onset of action and a more rapid rate of mycological cure than the imidazole antifungal agent econazole.[399-402] The anti-inflammatory properties of naftifine may be at equivalent to clotrimazole 1% plus hydrocortisone 1%[406,407] or miconazole plus hydrocortisone cream.[408] Naftifine 1% gel may be of some benefit in selected patients with distal subungual onychomycosis of the fingernails.[409]

Terbinafine is the second allylamine to become available, and the only member of its class that is effective both topically and orally. The oral formulation is not discussed here and the reader is referred to other sources.[410-412]

The mechanism of action of terbinafine is the same as that for naftifine.[383] Terbinafine demonstrates *in vitro* fungicidal activity against dermatophytes, some *Candida* spp. and *M. furfur*.[413] The clinical significance of these *in vitro* data is not certain.

Both terbinafine and naftifine penetrate into the upper layers of the stratum corneum and bind efficiently to it because of their lipophilic nature.[388] The drugs also penetrate into the deepest portions of the hair follicles, thus reducing the probability of reinfection.[388] When terbinafine 1% cream was applied once daily to the back of an individual for 7 days, the drug was still detectable in the stratum corneum 7 days after stopping therapy, at a concentration significantly higher than the known

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fungicidal concentration for the common causative organisms of superficial dermatomycoses.[414]

About 3 to 5% of a dose administered to the skin can be recovered the urine and faeces.[388,415] Terbinafine is well tolerated. No significant adverse effects of topical terbinafine or its vehicle have been identified in standard skin studies of irritancy, sensitisation potential, phototoxicity and photosensitivity.

Naftifine has intrinsic anti-inflammatory properties; in contrast, while terbinafine does not, it is as effective as naftifine in rapidly curing dermatomycoses.[388] The data suggest that this property may not be necessary for most patients.

Terbinafine 1% cream applied twice daily for 4 weeks was effective in the treatment of tinea pedis in placebo-controlled studies.[416,417] Subsequently, in placebo-controlled trials, this formulation applied twice daily for 2 weeks produced high cure rates.[418] Applied twice daily for 1 week it is effective in interdigital tinea pedis,[419] more so than clotrimazole cream 1% applied twice daily for 4 weeks.[420-422] After mycological cure, patients who received terbinafine cream demonstrated lower relapse rates than those who used clotrimazole cream.[423]

In a comparative study, terbinafine cream 1%, naftifine gel 1% and oxiconazole lotion 1% were each applied once daily for 2 weeks in the treatment of tinea pedis.[424] At follow-up, 10 weeks after starting therapy, there was no significant difference in efficacy between the 2 allylamines, both of which were more effective than oxiconazole.

Terbinafine exhibits *in vitro* antibacterial activity against potentially pathogenic Gram-positive and Gram-negative bacteria such as *S. aureus*, *S. faecalis*, *Propionibacterium acnes* and *P. aeruginosa*.[425] The ancillary antibacterial activity of terbinafine may be of particular advantage in interdigital tinea pedis (athlete's foot type) where a complex mixed fungal-bacterial infection can be present.

In a randomised, double-blind trial, terbinafine 1% cream applied twice daily for 2 weeks was more effective than placebo in the treatment of tinea cruris.[426,427] Subsequently, terbinafine cream 1% applied once daily for 1 week was found to be effective in the treatment of tinea corporis and tinea cruris.[428-430]

Topical terbinafine is effective in the treatment of tinea corporis/cruris (following therapy lasting 1 to 2 weeks), interdigital tinea pedis (1 to 2 weeks), tinea versicolor (2 weeks), cutaneous candidosis (2 weeks) and chronic tinea pedis (2 to 6 weeks).

To investigate even shorter treatment periods, the efficacy of a single application of terbinafine 1% cream was compared with 3, 5 and 7 days' once-daily therapy in the treatment of tinea pedis and tinea corporis/cruris.[431] When evaluated 28 days after commencing therapy 78, 83, 82 and 83% of patients with tinea pedis in the 1-, 3-, 5-, and 7-day treatment groups, respectively, were 'effectively treated'. There was no statistically significant difference between the treatment groups. Similarly high cure rates were observed in patients with tinea corporis and tinea cruris. At follow-up, 3 months after starting therapy, there was little evidence of relapse.

The high cure rates with short durations of therapy may be explained by the primarily fungicidal mode of action *in vitro* of terbinafine and the pharmacokinetics of drug delivery to the skin. The drug reaches high concentrations following application for short periods.[414] Furthermore, the activity of terbinafine may be prolonged by the use of a cream base for up to 6 days.[431] This could result in a chemical occlusive dressing which helps maintain terbinafine concentrations in the stratum corneum. While it is possible that very short durations of therapy may be associated with a higher relapse rate, the study by Evans et al.[431] suggests the potential for short term effective therapy with terbinafine.

In general, dermatophyte infections have a higher mycological and clinical cure rate at follow-up compared with the end of active therapy. This may be explained by the fungicidal *in vitro* nature of the drug and its persistence in the stratum

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corneum for some time after the end of the course of topical therapy. With infections due to *M. canis* and *M. furfur*, longer treatment periods may be required.[388]

7. Pharmacoeconomic Evaluation of Topical Antifungal Therapies

Topical antifungal agents are used to treat tinea corporis/cruris, tinea pedis and tinea versicolor. Oral antifungal agents are usually required for tinea capitis, Majocchi's granuloma and fungal infections resident in the deeper cutaneous structures. For onychomycosis, oral antifungal agents are usually used. For minimal to moderate onychomycosis, topical therapies may include agents such as amorolfine and ciclopirox lacquers. Also, as discussed elsewhere in this article, oral antifungal agents may be required in situations such as when the dermatomycosis is widespread, present in an immunocompromised host or resistant to topical antimycotic therapy.

When deciding whether to use oral or topical antifungal agents for tinea infections, some considerations are the relative differences in efficacy, adverse effects profile, length of therapy compliance and relapse rates. Meinhof et al.[432] report that noncompliance can be reduced by using therapies that require the fewest daily applications and the shortest treatment time. In the following discussion we do not review the literature concerning the use of oral antifungal agents in the treatment of tinea infections,[433,434] or antifungal agents (oral or topical) used in the management of onychomycosis.[435-443]

Chren[444] reviewed the costs incurred when treating a patient with tinea corporis using topical antifungal therapy (15 or 30 g/week for an agent that was applied once or twice daily, respectively). In this US-based study (using August 1993 costs) the least expensive drug regimen was a 4-week course of miconazole ($US11.14), an over-the-counter (OTC) medication. In contrast, the costs of a 4-week course of tolnaftate OTC, a 2-week course of clotrimazole OTC, a 2-week course of econazole, ketoconazole or terbinafine, and a 1-week course of terbinafine were $US12.00, $US16.95, $US18.00, $US20.65, $US78.36 and $US39.18, respectively. Chren[444] also discussed the relative costs of oral antifungal agents to treat tinea infections of the skin and nails; however, these are not in the scope of the present discussion on topical antifungal agents.

In the discussion by Chren,[444] individual efficacy rates for each of the antifungal agents were not calculated using a meta-analysis of efficacy data from published trials. However, that author noted that for most agents the clinical and/or mycological cure rates are at least 80%. It was also acknowledged that with some of the newer agents such as topical terbinafine, the mycological cure rates may be somewhat higher, with a longer remission period in certain instances. Also, compliance may be higher with agents that are applied once rather than twice daily.

In another US study, Chren and Landefeld[445] addressed the question whether patients with tinea pedis should initially receive a lower priced drug and those with unresponsive disease a higher priced drug at a follow-up office visit, or if all patients should receive a higher priced drug from the outset. The reference drug was miconazole, an OTC imidazole in the US, with reported overall efficacy rates of 70 to 100%.[445] Assuming the Medicare-approved charge for a follow-up visit ($US21.98, based on 1993 costings), the authors concluded that it was less expensive to begin therapy with a prescription drug only if the efficacy rate of miconazole is 70%. The extra cost per patient for all patients to receive the least expensive prescription antifungal agent instead of the OTC miconazole first was $US15.23 and $US8.64 if total visit costs were $US0.00 and $US21.98, respectively. Miconazole remained the less expensive alternative as long as the total cost of the follow-up visit was less than $US50.76.

Chren and Landefeld[445] concluded that, for reported efficacy rates and standard costs of a follow-up office visit, using miconazole first and then treating only those patients with unresponsive tinea pedis with a higher priced prescription drug was

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less expensive than treating all patients with the higher priced drug. They also indicate that some patients may prefer to reduce the possibility of a second follow-up visit by choosing to pay more for a higher priced antifungal agent from the outset. Furthermore, some tinea pedis plantaris infections that are of a more chronic nature may respond better to antimycotics such as topical terbinafine that might result in a reduction of the relapse rate. Alternatively, in this subset of patients, oral therapy may become necessary. In their analysis Chren and Landefeld[445] considered only 4-week regimens. With some of the agents, e.g. terbinafine, shorter regimens may also be effective.

Shear et al.[446] performed a pharmacoeconomic analysis comparing the topical antifungal agents terbinafine, ciclopirox, clotrimazole, ketoconazole and miconazole in the management of dermatophytosis major (tinea pedis and tinea manuum) and dermatophytosis minor (tinea corporis and tinea cruris). In this Canadian study the perspective was that of the government payer. A meta-analysis of randomised clinical trials revealed the following cure rates for tinea pedis after 4 weeks of treatment: ciclopirox 42.4%, clotrimazole 69.5%, ketoconazole 86.7%, miconazole 69% and terbinafine 83.3%. The Canadian drug acquisition costs (cost per gram in 1993 Canadian dollars) were: ciclopirox ($Can0.47), clotrimazole ($Can0.48), ketoconazole ($Can0.48), miconazole ($Can0.56) and terbinafine ($Can0.45). Thus, miconazole was the most expensive of the comparator drugs, in contrast to the US study by Chren and Landefeld[445] where it was the cheapest. In the study by Shear et al.[446] the drug therapy costs incurred in treating tinea pedis were (1993 Canadian dollars, 4 weeks' therapy with the imidazoles and ciclopirox; 2 weeks' therapy with terbinafine): ciclopirox $Can66.80, clotrimazole $Can24.95, ketoconazole $Can67.07, miconazole $Can77.60 and terbinafine $Can37.00.

The expected cost analysis represents the total net cost of each treatment regimen plus cost of additional therapy when the initial therapy either fails or leads to relapse. It incorporates all aspects of patient care, hence the title 'total expected costs'. The expected cost analysis for tinea pedis was (1993 Canadian dollars); ciclopirox $Can195, clotrimazole $Can184, ketoconazole $Can182, miconazole $Can206 and terbinafine $Can158.

The authors used a time horizon of 6 months for calculation of disease-free days (DFDs) to allow adequate time for treatment of relapses and failures. For each treatment regimen, the number of days when the patient would be free from tinea pedis was calculated. For each of the comparators used to treat tinea pedis, the DFDs, cost/DFD (Canadian dollars) and relative cost-effectiveness compared with terbinafine was calculated. The results were ciclopirox (132, 1.5, 1.39), clotrimazole (131, 1.4, 1.32), ketoconazole (137, 1.3, 1.26), miconazole (133, 1.5, 1.46) and terbinafine (149, 1.1, 1.00). Thus, for tinea pedis, terbinafine had the highest number of DFDs (149) and the lowest cost per DFD ($Can1.1). The data from this study suggest that the most cost-effective therapy for tinea pedis is terbinafine cream 1% applied twice daily for 2 weeks.

With the increasing limitations on funds available for managing healthcare and the need to limit expenditure on drugs, there is an increase in the pharmacoeconomic analyses.[447] While each study may not come to the same conclusion, it is important to critically evaluate the various analyses and use the data most applicable to the reader's situation.

8. Conclusions

Cutaneous fungal infections are not uncommon, and the majority are treated with topical antifungal agents. When tinea capitis is present, and in the majority of patients with onychomycosis, topical agents are not sufficient and oral therapy is necessary.

In general, topical antifungals may be subdivided into specific and nonspecific agents. Specific agents include polyenes, azoles, allylamines, amorolfine, butenafine and ciclopirox. The polyenes have generally been used for the treatment of *Candida* spp. The topical azoles are usually effec-

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tive against dermatophytes, yeasts and *M. furfur*. Similarly, terbinafine and amorolfine have a broad spectrum of activity. Butenafine is effective against dermatophytes.

In the management of tinea cruris/tinea corporis and tinea versicolor the agents are generally applied once or twice a day, usually for 1 to 2 weeks for tinea corporis/cruris and tinea versicolor, and 2 to 4 weeks for tinea pedis.

When topical antifungal agents are used to treat cutaneous dermatoses, desirable properties include:

- high efficacy
- favourable adverse effects profile
- fewest possible daily applications
- shortest duration of therapy
- low relapse rate
- cost effectiveness.

Being fungicidal *in vitro* is attractive but may not translate into higher *in vivo* efficacy. Comparative trials between the topical antifungals may aid our selection of agents to treat cutaneous dermatoses.

There have been only a handful of pharmacoeconomic studies carried out to evaluate the cost effectiveness of topical antifungal agents in the management of tinea pedis/manuum and tinea corporis/cruris. More work needs to be performed in this area to evaluate better the most cost-effective topical agent available to treat tinea pedis/plantaris/manuum, tinea pedis interdigitalis and tinea corporis/cruris.

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