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Review

Trends in the Management of Cutaneous Fungal Infections

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Abstract

The modern antimycotic era began with the introduction of griseofulvin in the 1950's, which had a tremendous impact on the management of dermatophytoses. Subsequent advances in therapy have lowered our threshold to treat recalcitrant cutaneous mycoses, such as onychomycosls. Newer generation antifungals including the triazoles, itraconazole and fluconazole, as well as the allylamine, terbinafine, may significantly reduce the prevalence of onychomycosis, as fungal nails are no longer incurable. The AIDS epidemic has been associated with an increase in the number of cutaneous and systemic mycotic infections. In spite of recent advances, organisms recalcitrant or resistant to therapy are common. Newer antifungal agents, improved diagnostic techniques, and standardization of fungal susceptibility testing are required to adequately treat patients with systemic and cutaneous mycoses.

Historical perspective

The past few decades have realized major advances in antifungal therapy for cutaneous mycoses[1,2]. The first oral agent for dermatophytoses, griseofulvin, which was initially used to treat fungal diseases in plants, was introduced for human use in 1958[1-3]. Prior to this, only relatively non-specific and ineffective topical compounds such as Whitfield's ointment, Castellani's paint and potassium permanganate were available for superficial fungal infections. Most patients were inadequately treated and certain dermatophytoses, such as tinea capitis flourished into epidemic proportion.

Historically, griseofulvin had a dramatic, but limited, impact on the management of cutaneous mycoses. Its narrow spectrum of activity includes the genera *Microsporum*, *Trichophyton*, and *Epidermophyton*. It is not effective against *Candida*, *Malassezia* and non-dermatophyte moulds[3]. Griseofulvin probably made its largest contribution in the management of tinea capitis, which was a major public health dilemma of the time[1,2,4,5]. Indeed in the early 20th century the presence of tinea capitis would prohibit entry or emigration into many countries. Prior to griseofulvin, there was no adequate therapy for patients with tinea capitis, and some infections persisted for years. The subsequent eradication of the *M. audouinii* tinea capitis epidemic best exemplifies griseofulvin's role in history.

Griseofulvin is a fungistatic drug and must be given until the patient is clinically and mycologically cured. It is delivered via the eccrine sweat, and is not bound to the stratum corneum after administration[6]. Although effective in tinea capitis, particularly when caused by *Microsporum* spp, it has been of limited benefit in onychomycosis and other dermatophytoses caused predominantly by *T. rubrum*. Treatment failures with *Trichophyton rubrum* have correlated with *in vitro* resistance[7-10]. Since the introduction of griseofulvin almost four decades ago, there has been a surge in tinea capitis infections by the genera *Trichophyton* such as *T. tonsurans* in the United States, and now recently Europe, as well as *T. violaceum* in Europe. Onychomycosis caused by *T. rubrum* has also shown an increased incidence, and has generally been regarded as incurable[5,11-13].

Although not useful in cutaneous mycoses, amphotericin B became the first available antimycotic for systemic mycoses in the late 1950's [1,2]. Due to poor oral absorption, it must be administered intravenously or intrathecally. More than 90% of the drug is bound to proteins, resulting in poor penetration into body fluids and stratum corneum. Although available in topical formulations, it has no activity against dermatophytic fungi. These factors account for the ineffec-

tiveness of amphotericin B in treating cutaneous dermatomycoses[6]. However, the drug is effective in many systemic mycoses, including disseminated candidiasis, aspergillosis and the dimorphic organisms[1,2,14,15]. It is still the most effective antifungal drug available, yet one of the most toxic antimicrobics in clinical use. In many instances amphotericin B is given in conjunction with 5 fluorocytosine. Fungal susceptibility testing can guide the selection of antimycotics.

The 1960's and 1970's witnessed the discovery of the topical azole family including clotrimazole, miconazole, econazole and ketoconazole. With the exception of tinea capitis and onychomycosis which usually require systemic therapy, topical azoles are effective in eradicating most dermatomycoses of the stratum corneum. More importantly, however, this family of antimycotics heralded a new generation of oral azoles and triazoles. Oral ketoconazole was introduced two decades after griseofulvin, and was the first orally administered member of the azole family. The spectrum of oral ketoconazole includes the dermatophyte fungi, *Candida*, plus a variety of nondermatophyte moulds and yeasts[1,2,16-20]. Ketoconazole is more effective *in vitro* than griseofulvin on fungi in the genera *Trichophyton*[9]. Ketoconazole was the first orally delivered antimycotic with activity against *Candida*, and significant improvement occurred in those patients with chronic mucocutaneous candidiasis, who had previously endured disfiguring cutaneous lesions. Further, many patients with systemic mycoses could also be treated with an oral, rather than intravenous, agent[16,19]. Unfortunately, the potential of hepatotoxicity has limited its use[1,2,21].

The triazoles, fluconazole and itraconazole, became available in the 1990's and immediately a vitally important resource for the management of HIV infected patients, and other patients with other primary or secondary immunodeficiencies[1,2,22,24,25]. The triazole ring may be responsible for increased potency, decreased toxicity, and a wider spectrum of action than the azoles[1,2,22]. Fluconazole is effective against the dermatophyte fungi, *Candida*, *Malassezia*, *Cryptococcus* and other organisms[22]. Itraconazole has a similar spectrum of activity, but is more effective against *Aspergillus* spp. and dematiaceous fungi[22,26]. Fluconazole is available in an oral and parenteral form; itraconazole is available only in an oral form. Itraconazole has been particularly helpful in cutaneous mycoses such as chronic tinea manuum, tinea pedis and onychomycosis due to the "reservoir" effect of persisting in the stratum corneum for weeks to months after administration[6,23,27]. Being lipophilic, it binds to the keratinocytes and is incorporated into the epidermal basal layer where it may persist for weeks after therapy is discontinued[6]. Both itraconazole and fluconazole are fungistatic. Fluconazole is delivered to the outer integument via eccrine sweat; itraconazole is transported in the sebum[6].

The inadvertent discovery of the allylamine family in the mid 1970's led to the recent introduction of oral terbinafine, which has proven to be a valuable resource in the management of traditionally recalcitrant cutaneous infections such as onychomycosis and tinea capitis[1,2]. Terbinafine is fungicidal *in vitro*, and like itraconazole, is lipophilic with a "reservoir" effect of persisting in keratinized tissue after discontinuation of therapy[28]. It apparently binds to the lipophilic keratinocytes and is delivered to the outer integument via the sebum. The combination of its fungicidal activity, and persistence in the stratum corneum permit short courses of therapy in even traditionally recalcitrant tinea capitis and onychomycosis. Although its *in vitro* activity is broad spectrum including most yeasts, nondermatophyte moulds and the dermatophyte fungi, in therapeutic concentrations, it is primarily used for the dermatophytoses. Higher doses may be needed for other mycoses[6].

Onychomycosis

Onychomycosis, rare until the later part of the 20th century, is now in epidemic proportion. Although predominantly caused by dermatophyte fungi, other yeasts and nondermatophyte moulds can occasionally cause fungal nail infection (Table 1).

Due to the fungistatic mode of action, lack of nail plate adhesion, the inherent slow growth of the nail, the need to administer until the nail has grown out, and potential adverse events, griseofulvin has proven to be an inadequate agent for fungal nail infection[28-32]. Further, the dominant

Table 1. Common etiologic agents of onychomycosis

Dermatophyte fungi
Trichophyton rubrum
Trichophyton mentagrophytes
Epidermophyton floccosum
Yeasts
Candida albicans
Non-dermatophyte moulds
Scopulariopsis brevicaulis
Scytalidium dimidiatum
Scytalidium hyalinum
Fusarium spp.
Aspergillus spp.

organism in many countries is *T. rubrum*, and there are reports of *in vitro* resistance to griseofulvin[7]. Moreover, some patients with onychomycosis may have mixed infection with a dermatophyte and non-dermatophyte pathogen, and griseofulvin would therefore be ineffective. Systemic ketoconazole, although broad spectrum and more effective than griseofulvin against *T. rubrum*, is limited by hepatotoxicity. However, the newer oral antimycotics (fluconazole, itraconazole and terbinafine) and topical (amorolfine, ticonazole, ciclopirox olamine) antifungals formulated for onychomycosis, have excellent safety profiles and have greatly improved the prognosis of onychomycosis. Due to these agents, onychomycosis is no longer considered incurable[1,2,28].

There is currently no multicenter clinical trial comparing the efficacy of the various topical and oral agent in onychomycosis. Further, there is no single best agent because patients have different tolerances to medication, not all antimycotics are available in every country, nor is the dominant pathogen the same in each country. For these reasons, the selection of an appropriate antimycotic for onychomycosis can be derived from a combination of factors, including determination of MIC's of organisms cultured from nail infections, as well as considering potential adverse events, drug interactions, therapy schedules, amount of nail involvement, and cost. Cost would include that of treating recurrent infections.

Unlike griseofulvin, the newer antimycotics, terbinafine and itraconazole, are generally not dosed daily until the nail is clinically and mycologically normal. Due to its fungicidal activity and persistence in the nail plate, terbinafine is effective at 250 mg administered daily for only 6 weeks in fingernail and 12 weeks for toenail infections[1,2,33]. Cure rates are over 80%, and best results occur if a dermatophyte is the primary pathogen. In *Candida albicans* nail infections, fluconazole or itraconazole is probably a better choice. Based on its pharmacokinetics, itraconazole can be given in two dosage schedules referred to as either the "fixed course" or the "pulse dosage"[27,34,35]. Particularly pivotal on determination of these dosage schedules were studies showing that if itraconazole is doubled from 100 mg to 200 mg daily, the level in the nail rises ten fold. Furthermore, as with terbinafine, a "reservoir" effect occurs with itraconazole persisting in the nail after therapy is discontinued. Itraconazole persists 6-9 months, and terbinafine about 4 months in the nail following termination of therapy. In the fixed dosage schedule, 200 mg of itraconazole is administered daily for 6 weeks in fingernail disease and 12 weeks in toenail disease. The nail is not normal at the time of discontinuation, but grows out normal. The pulse dosage or interrupted therapy is 400 mg daily for 1 week, administered one week per month for 1-2 months in fingernail and 3-4 months in toenail disease. The cure rates of both these regimens are about 80%. Although the pharmacokinetics of fluconazole have not been well studied, preliminary data suggest it to be a safe and effective agent in onychomycosis. A dose of 150 mg administered once weekly until the nail is clinically and mycologically normal has been an effective regimen in clinical studies[36].

The AIDS epidemic

Patients with Acquired Immunodeficiency Syndrome (AIDS) frequently develop a variety of superficial cutaneous and systemic mycoses[37-39]. The superficial cutaneous fungal infections include oral and genital *Candida*, and extensive and rapidly spreading dermatophytoses. Additionally, conditions associated with the yeast *Malassezia* occur, including severe seborrheic dermatitis and pityriasis (tinea) versicolor[40,41]. The systemic mycoses common in AIDS include disseminated cryptococcosis, and the dimorphic infections: histoplasmosis, coccidioidomycosis, sporotrichosis, and the emerging pathogen, *Penicillium marneffei* (Table 2). Cutaneous involvement occurs in many systemic fungal infections. The newer triazoles have been invaluable in the management of many mycoses in the HIV infected person[42-44]. However, drug resistance can develop and new organisms which are nonresponsive to the current assortment of antimycotics are emerging. New and more potent antifungals are needed to cope with the AIDS epidemic.

Table 2. Mycotic infections in AIDS patients

Superficial cutaneous mycoses	Systemic mycoses
Chronic oral/genital candidiasis	Cryptococcosis
Extensive dermatophytoses	Dimorphic infections
Malassezia furfur	Histoplasmosis
Extensive seborrheic dermatitis	Coccidioidomycosis
Extensive pityriasis (tinea) versicolor	Sporotrichosis
Malassezia folliculitis	*Penicillium marneffei*

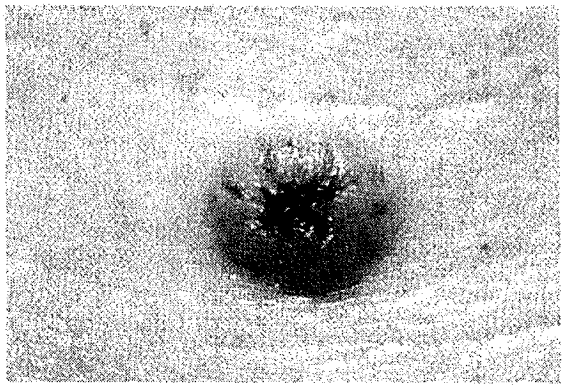

Fig. 1. Umbilicated nodules resembling the viral infection molluscum contagiosum is a typical cutaneous presentation in an AIDS patient with either disseminated *Cryptococcus neoformans* or *Penicillium marneffei*. This patient had disseminated cryptococcosis.

Amongst the serious mycoses, the dimorphic fungus, *Penicillium marneffei*, is being reported with increasing frequency, and is especially common in certain parts of Asia[45]. A systemic reticuloendotheliosis mimicking histoplasmosis is the usual presentation often with cutaneous lesions resembling molluscum contagiosum. Treatment consists of amphotericin B or itraconazole, and a relapse or resistance is common.

Cryptococcus neoformans is the most common life threatening fungal infection in AIDS patients, occurring in 5–10% of patients. Dissemination occurs in half of HIV infected persons, and skin lesions occur in up to 10% of those with disseminated disease[46-49]. Both of the triazoles, fluconazole and itraconazole, are useful for the management of cryptococcosis, and can be used as prophylactic agents against dissemination[50]. Amphotericin B can also be useful.

Histoplasmosis is also common in many AIDS patients, and is due to reactivation of old disease or to primary infection. Treatment is with amphotericin B, fluconazole or itraconazole[51-53]. Disseminated sporotrichosis in the HIV patient can also be due to reactivation of old disease or via primary inhalation. Cutaneous presentation is atypical, and generalized nodules are common, rather than lymphocutaneous spread. Itraconazole and amphotericin B are useful therapies.

Coccidioidomycosis occurs in 3% of HIV positive patients in endemic areas and occurs as a result of reactivation or primary infection[54,55]. Cutaneous lesions are uncommon. Amphotericin B and itraconazole are options in therapy, but even with treatment, prognosis is poor.

Candidiasis is the most common mycotic infection in AIDS[37,41]. Generally, mucous membrane infection occurs, and dissemination is rare. Oral candidiasis occurs in up to 45% of patients with HIV; women frequently manifest recalcitrant candidal vulvovaginitis. The newer triazoles have proven to be invaluable in the management of mucocutaneous candidiasis.

Extensive and unusual presentations of dermatophytoses are common in HIV infected persons[41]. Although not considered serious or life threatening, extensive dermatophytosis may be cosmetically disfiguring and cause severe pruritus. Nail deformities from onychomycosis is also common. Proximal white subungual onychomycosis is considered pathonumonic for AIDS[56]. Also, pityriasis versicolor and seborrheic dermatitis are typically more extensive in patients with AIDS, and may also cause in severe pruritus[40,41]. Systemic antifungal therapy is often required in the management of superficial and cutaneous mycotic infection in the AIDS patient.

Pseudallescheria boydii has recently been reported to disseminate in patients with AIDS, and is an example of an emerging mycotic pathogen recalcitrant to therapy[57]. Amphotericin B is generally not effective, neither are the azoles and triazoles. Fungal susceptibility testing is generally required.

Future trends

Prior to the introduction of griseofulvin, determination of the causative cutaneous fungal pathogen was often an academic exercise as there was no available effective antimycotic. Given the recent advances in cutaneous antifungal therapy, the correct determination of fungal pathogen is now critical. Onychomycosis best illustrates the problem. Fungal nail disease can be caused by dermatophyte fungi, *Candida*, and several nondermatophyte moulds including *Scytalidium dimidiatum*, *S. hyalinum*, and *Scopulariopsis brevicaulis*. No systemic or topical agent is effective against all these organisms and therefore fungal culture will determine the causative pathogen, and provide data for rational selection of appropriate therapy.

The introduction of new antimycotics and the study of their pharmacokinetic profile in the integument, are recent advances in cutaneous mycology. In many instances, it is no longer necessary to treat until the patient is clinically and mycologically cured. This is again best depicted in the therapy of onychomycosis. Short term treatment schedules with itraconazole and terbinafine were based upon pharmacokinetic data and *in vitro* activity.

Greater choices of antimycotics means more difficult decisions in the selection of an appropriate agent[26]. However, determination of MIC's for

fungal pathogens may provide clinicians a scientific rationale for selection of antimycotics. Worldwide standardization of fungal susceptibility tests for moulds and yeasts is desperately needed. Also required are new antifungal drugs to cope with the recent surge of mycotic infections occurring due to the AIDS epidemic, new transplant techniques and to the rise in immunocompromised patients. Recalcitrant organisms including *Pseudallescheria boydii*, *Penicillium marneffei* and *Fusarium* spp. are becoming more common, and are difficult to manage, underscoring the need for new developments in mycology, and more effective antimycotic therapy.

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