

Review

## Mycoses in Thailand: Current Concerns

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### Abstract

*Scytalidium dimidiatum* is the leading cause of fungal foot diseases in Thailand, in contrast to similar studies in which dermatophytes have been identified as the predominant pathogens. By contrast, the prevalence of *Candida albicans* in our study was only 2.6~3.0%. *Scytalidium* fungal foot infection is clinically indistinguishable from that caused by dermatophytes and should be included as a possible cause of treatment failure in tinea pedis and onychomycosis. Without proper culture identification, clinically diagnosed patients would be treated with a standard antifungal regimen leading to minimal response and be interpreted as drug resistant cases resulting in switching of drugs and more aggressive management procedures.

Tinea capitis is another health problem in young children. However, for *Microsporum canis* and some ectothrix organisms, the effectiveness of treatment may be less than endothrix infection. Griseofulvin is still the mainstay antifungal although itraconazole and terbinafine are as effective. Pulse regimen may be another option with advantages of increased compliance and convenience. Two pulses of terbinafine may be sufficient for treating most cases of *Microsporum* infection, although additional treatment may be needed if clinical improvement is not evident at week 8 after initiating therapy.

Chromoblastomycosis is another subcutaneous infection that requires long treatment duration with costly antifungal drugs. The most common pathogen in Thailand is *Fonsecaea pedrosoi*. Preliminary study of pulse itraconazole 400 mg/d 1 week monthly for 9-12 consecutive months showed promising results.

The prevalence of *Penicillium marneffei* infection is alarming in HIV infected patients living in endemic areas. Diagnosis relies on direct examination of the specimens and confirmation by culture. Treatment regimens include systemic amphotericin B or itraconazole followed by long-term prophylaxis. Treatment outcome depends on the immune status of the patient.

**Key words:** mycoses, non dermatophyte, tinea capitis, chromoblastomycosis, *Penicillium marneffei*

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### Introduction

Fungal infections are major health problems in tropical countries. Although most superficial fungal infections, such as cutaneous candidiasis and pityriasis versicolor can be managed satisfactorily with presently available antifungals, there are still great concerns with regards to particular infections such as tinea capitis and onychomycosis. *Microsporum* tinea capitis poses difficulties in treatment due to its intrinsic resistance to therapy. The issue of whether dosage or duration of antifungal treatment may improve efficacy is still a controversy. Chromoblastomycosis, an uncommon subcutaneous mycosis,

is a challenge in terms of high relapse rates and long duration of treatment. Disseminated *Penicillium marneffei* infection, an endemic opportunistic disease especially in AIDS patients, is a threat due to the pandemic of HIV infection. The objective of this article is to discuss the above mentioned issues in fungal infections that are of health concern in Thailand.

### Tinea pedis and onychomycosis by non dermatophytes

In the past, epidemiological studies concerning fungal infections like tinea pedis and onychomycosis were performed in small and specific population groups such as schoolchildren, subjects visiting swimming baths<sup>1-3</sup>; individuals with specific occupations like coal-miners and soldiers<sup>4, 5</sup>; or with underlying diseases like

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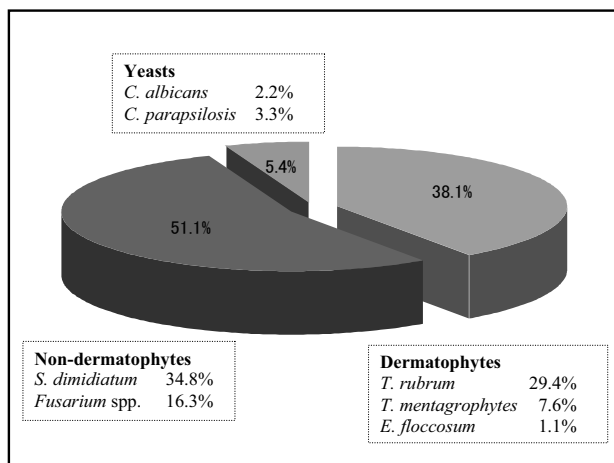


Fig. 1. Prevalence of onychomycosis in Thailand from epidemiological survey of 10,000 patients with foot fungal infections (Achilles Study 2001).

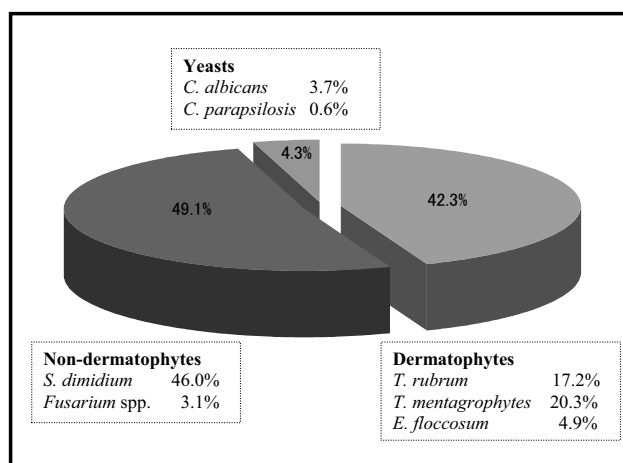


Fig. 2. Prevalence of tinea pedis in Thailand from epidemiological survey of 10,000 patients with foot fungal infections (Achilles Study 2001).

diabetes<sup>6)</sup>, renal failure or immunocompromised patients. The prevalence of onychomycosis seems to differ in different studies across the world due to common factors. Patients do not seek treatment because the disease is often minimal or patients are embarrassed to seek medical advice unless the condition becomes serious affecting the quality of life. It was generally accepted that the overall prevalence of onychomycosis was estimated to be between 3 and 5%, but somewhat higher in certain occupational communities and in patients over 40 years of age<sup>4, 7, 8)</sup>.

An epidemiological survey was made of 10,000 outpatients who attended dermatology clinics in Thailand regardless of their type of skin diseases. Diseases were examined and confirmed by mycological diagnosis of fungal infections. The percentage of isolated non-dermatophyte pathogens was much higher than previously reported in European surveys.<sup>9)</sup> Results in this study showed that more than half of the patients who were clinically compatible with tinea pedis or onychomycosis had non-dermatophyte infections (Fig. 1, 2). *Scytalidium dimidiatum* and *Fusarium* spp. were the only non-dermatophytes isolated in the study, in contrast to European surveys in which *Aspergillus* spp. and *Scopulariopsis brevicaulis* were isolated. Only 2.6% had yeast infection by which *Candida albicans* was the predominant pathogen.

Our data showed a 37.1% prevalence of foot abnormalities among patients who visited the hospital regardless of their skin problems. Among non fungal foot infections, eczema was the leading cause in 40.8% of the patients, followed by 28.3% psoriasis and 10.3% metatarsal

corns. The prevalence of fungal foot infections was 6% in which the prevalence of tinea pedis was 2.2 fold than that of onychomycosis.

Non-dermatophyte infection by *S. dimidiatum* was the leading cause of fungal foot diseases in this epidemiology survey in contrast to similar studies in which dermatophytes were the predominant pathogens<sup>10, 11, 12, 13)</sup>. The pan-European surveys showed higher prevalence of dermatophytes, *Trichophyton rubrum* (53.3%) and *T. mentagrophytes* (12.9%), as major pathogens for onychomycosis in those with fungal foot infection. The prevalence of mold and yeast infections was comparable (approximately 10%) with *Aspergillus* spp., *S. brevicaulis* and *C. albicans* being the major pathogens<sup>9)</sup>.

*S. dimidiatum* (*Hendersonula toruloidea*, *Natrasia mangiferae*) is a recognised pathogen of fruit trees in the tropics. It can cause a chronic disease of the soles, toe spaces, palms and nails which is indistinguishable from that of infection by dermatophytes. At least 4 cases of vesicular type tinea pedis, previously believed to be absent in *Scytalidium* infection<sup>14)</sup>, have been established in our series of patients (unpublished report). Higher prevalence in Asia may be due to geographical distribution and climate. Discoloration, onycholysis with thickening of the infected nail plates may be present. However, recent study from the Institute of Dermatology, Thailand, showed a predominance of toenail infection with only distal and lateral nail involvement. No other types of onychomycosis, i.e. proximal or superficial white, were seen in the study. Direct examination showed hyphae that varied in width and double-contoured appearance (Fig. 3). Culture must be prepared on a medium

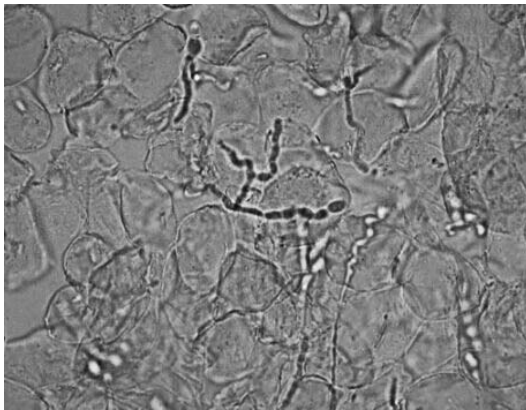


Fig. 3. Direct examination of *S. dimidiatum* showed brownish hyphae with irregular wall and septation (40×).

without cycloheximide in order to isolate the fungus, although duplicate plates with and without the antibiotics are preferable, as combined infection with dermatophytes can occur.

This epidemiological survey indicates that *S. dimidiatum* is the leading pathogen for tinea pedis and onychomycosis. The study demonstrated a higher prevalence of *S. dimidiatum* than previously reported dermatophyte infection. Direct examination alone can be misleading since treatment with presently available antifungal preparations is still less than satisfactory. *S. dimidiatum* may be one of the causes of treatment failure in fungal foot and nail infections unless diagnosis is confirmed by mycological examination. No single drug has been reported to treat all cases of *Scytalidium* infection with reproducible results. A combination of chemical or surgical nail avulsion of infected nails and continued with a systemic antifungal may be a reasonable treatment option<sup>15)</sup>. Precautions for factors such as diabetes, peripheral vascular diseases and occlusive footwear may predispose patients to fungal foot diseases. Increased awareness is necessary to diagnose patients who have lived in or visited endemic areas since migration of untreated cases may cause possible spread in a similar manner to other dermatophyte infections.

**Microsporum spp. tinea capitis**

Tinea capitis is one of the most common fungal infections in children. Infection by anthropophilic species may result in a spread among close contacts. *M. canis* is the most common causative agent of tinea capitis in Thailand in about a third of patients, although occasionally *M. ferrugineum* may cause outbreaks in overcrowded communities. *T. tonsurans* and *T. mentagrophytes* are the next common pathogens,

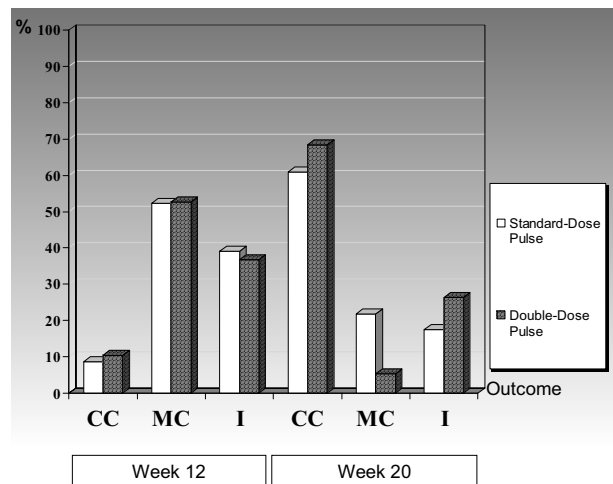


Fig. 4. Results of the comparative study (standard-dose pulse vs. double-dose pulse terbinafine) in the treatment of *Microsporum* spp. tinea capitis. (CC = complete cure, MC = mycological cure, I = improvement)

each found in approximately 15-20%. The duration of therapy using continuous terbinafine therapy for tinea capitis due to *Trichophyton* spp. has generally been 4 to 6 weeks, although more recent studies suggest that in some cases shorter duration of 1 or 2 weeks may be sufficient<sup>16-18)</sup>. The duration and effectiveness of treatment with various systemic antifungals may in part be dependent upon the causative organism. With *M. canis* and some ectothrix organisms, the response to treatment may be less compared to tinea capitis due to endothrix organisms<sup>17, 19, 20)</sup>. When encountering such organisms, dosage regimen may have to be altered but the appropriate duration of treatment remains to be determined.

Terbinafine pulse therapy has been reported to be effective and safe in the treatment of tinea capitis<sup>21, 22)</sup>. However, no standard regimen has been recommended with regard to the number of pulse or dosages administered. A recent study comparing two regimens of (1) standard-dose pulse, and (2) double the standard-dose pulse terbinafine given 7 days monthly for 2 consecutive months showed that two pulses of terbinafine were effective in treating most *Microsporum* spp. infections (Fig. 4)<sup>23)</sup>. Moreover, there was no statistical difference ( $p > 0.05$ ) in the cure rates between standard and double-dose pulsed therapy at week 12 (60.9% vs. 63.1%) or at week 20 (82.6% vs. 73.7%), respectively. However, the effective cure rates were significantly higher at week 20 than at week 12 in both groups (82.6% vs. 60.9% and 73.7% vs. 63.1%, respectively), probably reflecting the benefits of sustained tissue concentration and

the lipophilic properties of terbinafine. None of the patients had received topical or systemic corticosteroids to reduce inflammation, and in those individuals who had inflammatory tinea capitis, the improvement in clinical score was slower than in patients with non-inflammatory scalp infection. Permanent scarring was noted in one patient who initially had a severe clinical presentation. These findings suggest that kerions may be managed in the same manner as non-inflammatory tinea capitis, although appropriate antibiotics should be administered if secondary bacterial infection is present. Clinical severity at the initial pre-treatment appraisal is a major predictive factor for scarring. There was no statistical difference in the failure rate or ineffective cure rate between either groups. Patients who had positive potassium hydroxide staining or organism culture at the end of follow-up were given an additional pulse of terbinafine (at the same dose as the first two pulses). All were mycologically cured by the end of 4 weeks after the additional third pulse. Retrospective evaluation showed that patients who subsequently turned out to be treatment failures at week 20 had less than 50% clinical improvement with persistent positive potassium hydroxide staining and organism culture at week 8. Thus, evaluation at this stage may be clinically useful in determining which subjects might need additional therapy in the form of a third pulse.

This study has shown that pulsed terbinafine at a higher dosage does not improve the treatment efficacy of tinea capitis caused by *Microsporum* spp. However, the data clearly demonstrated that the duration of treatment is an important factor in determining the outcome. Two pulses of standard dose terbinafine may be sufficient for treating most cases of *Microsporum* infection, although additional treatment may be needed if clinical improvement is not evident at week 8 after initiating therapy. In unpublished data, the cure rates of 6-week continuous griseofulvin were at least comparable to these of pulse terbinafine.

#### Chromoblastomycosis:

This subcutaneous fungal infection is uncommon with an average annual incidence of 3-5 patients at the Institute of Dermatology, Thailand. The most common pathogen is *Fonsecaea pedrosoi*. The problem of chromoblastomycosis is its requirement of long treatment duration with specific oral antifungals such as itraconazole or terbinafine. Combined surgical and systemic



Fig. 5. Picture shows squamous cell carcinoma presented as ulcer developing on chronic lesions of chromoblastomycosis.

therapy may improve the disease outcome. An ongoing clinical trial showed that monthly pulses of itraconazole were as effective as a continuous 400 mg/d regimen in the treatment of *F. pedrosoi* chromoblastomycosis. Preliminary results showed three out of five cases were cured after 12 pulses, 2 cases showed marked improvement at the 12<sup>th</sup> month, and 1 case recurred 8 months after treatment was stopped. Squamous cell carcinoma developed on the lesion in one patient who had had chronic chromoblastomycosis for more than 10 years (Fig. 5). If proven effective, this regimen would decrease the cost of treatment by 50%. However, more cases and longer follow-up are required to determine efficacy and relapse rate.

#### Penicillois:

*Penicillium marneffei* is an endemic, opportunistic fungus reported to be prevalent in Southeast Asia. It was first isolated from captive bamboo rats (*Rhizomys sinensis*). Penicillois is one of the most common opportunistic fungal infections among AIDS patients in Thailand. The first documented human pathogenicity was reported in 1959 that arose from accidental laboratory inoculation<sup>24)</sup>, then came successive reports of natural infection in immunocompromised patients<sup>25-27)</sup>. A 5-year incidence in northern Thailand in 1991-1996 was more than 1,500 cases.

Penicillois is uncommon among normal hosts. Most of the affected patients have underlying diseases or immune-compromised states. The most common skin manifestation is molluscum contagiosum-like or umbilicated papules. Diagnosis is by demonstration of intracellular and extracellular basophilic, spherical, oval to elliptical yeast-like

organisms (3-8  $\mu\text{m}$ ) with clear transverse fission characteristic of *P. marneffei* yeast phase. At 25°C on Sabouraud dextrose agar the mycelial phase is grown as a colony with a flattened, bluish-grey-green center with characteristic deep red pigment diffusion on the reverse side seen as early as 3 days after inoculation. Microscopic examination of the mycelia shows typical structures of *Penicillium* sp. Mold-to-yeast dimorphism can be demonstrated by subculturing onto brain-heart-infusion agar at 37°C.

Recommended treatment is based on clinical severity at the time of diagnosis. Amphotericin B is the treatment of choice in severe cases while itraconazole 200-400 mg/d may be an alternative in mild to moderately severe cases. Penicillosis is still of major concern among AIDS patients because of high morbidity and mortality. Treatment requires hospitalization or long-term prophylaxis with an expensive systemic oral antifungal which poses a financial burden to patients and the health care system. With the current use of HAART among HIV-infected patients, the incidence of penicillosis, as well as other opportunistic infections, may be declining.

In summary, superficial fungal infections remain a health problem in tropical countries. Subcutaneous mycoses, although uncommon, are a financial burden to patients in terms of treatment and long-term follow up. With AIDS prevalence and geographical endemicity of *P. marneffei* in Southeast Asia, penicillosis is still a threat, at least to patients who do not get access to proper antiretroviral therapies. With no breakthrough antifungal therapy on the horizon, perhaps new regimens or combination of antifungal drugs may need to be evaluated in well-controlled studies to improve the efficacy of treatment.

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