

In Vitro Susceptibility of *Talaromyces Marneffe* In Malaysia: Comparison of Yeast and Mycelial Phases

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Abstract

Talaromyces marneffe is an etiologic agent of talaromycosis. It can cause serious complications and death in immunocompromised patients, particularly in acquired immunodeficiency syndrome (AIDS) patients. This infectious disease is endemic in Southeast Asia including Malaysia. To date, published reports on the antifungal susceptibility profile of *T. marneffe* is very limited. The objective of this study is to determine the minimum inhibitory concentration (MIC) of *T. marneffe* in yeast and mycelial phases in Malaysia. In the year 2020, 27 clinical strains of *T. marneffe* were received from various hospitals in Malaysia. The identification was carried out using microscopic, macroscopic and molecular methods. Following that, the susceptibility of each isolate in both yeast and mycelial form to thirteen common antifungals was performed according to the broth microdilution in Clinical & Laboratory Standards Institute (CLSI) M38 method. The antifungals tested were anidulafungin, micafungin sodium, caspofungin diacetate, 5-fluorocytosine, amphotericin B and terbinafine hydrochloride, posaconazole, voriconazole, itraconazole, ketoconazole, ravuconazole, clotrimazole and isavuconazole. The geometric mean of all antifungals other than anidulafungin, micafungin sodium, caspofungin diacetate and 5-fluorocytosine against *T. marneffe* mould (mycelial) were $>2 \mu\text{g/ml}$. However, the geometric mean of all antifungals against *T. marneffe* yeast was $<2 \mu\text{g/ml}$. Our *in vitro* data suggests promising activities of amphotericin B, terbinafine hydrochloride, posaconazole, voriconazole, itraconazole, ketoconazole, ravuconazole, clotrimazole and isavuconazole against yeast and mould phases of *T. marneffe*.

Background

Talaromyces marneffe (*Penicillium marneffe*) is a fungus that causes a lethal fungal infection known as talaromycosis [1]. The common clinical presentations of talaromycosis in Malaysian patients are weight loss, fever, cough, skin lesions, lymphadenopathy, hepatomegaly and diarrhoea [1]. It is endemic in Southeast Asia in HIV-infected patients [2]. In Malaysia, talaromycosis cases were increased from 20-25 (2010-2011) to 45-50 (2012-2014) and estimated to be further increased to 350 per year [1, 3].

The inhalation of spores was considered as the route of transmission of *T. marneffe* [4–6]. *T. marneffe* mostly causes mild and localized infections in patients with normal immunity, but it can cause severe disseminated infections in immunocompromised patients [7]. Even though *T. marneffe* is frequently detected in HIV patients; however, it also had been reported in non-HIV or immunocompromised patients recently [8–10]. The mortality rate is 75% in those with delayed diagnosis and administration of antifungal therapy [11, 12].

This pathogen is dimorphic. This fungus grows as yeast at 37°C ; while it grows as a mould at 25°C [13]. The yeast form is pathogenic as it can produce proteins or toxins that can evade the immune defence of the host [14]. The most common treatment of talaromycosis is amphotericin B [15]. In addition, itraconazole, posaconazole and terbinafine were also reported to be effective in treatment [13, 16, 17]. However, the susceptibility pattern of Malaysian isolates of *T. marneffe* is rarely reported. Therefore, in

this study, we report the susceptibility pattern of Malaysian *T. marneffe* which might be useful to the treatment of talaromycosis.

Materials And Methods

Ethical review was conducted and approved by the Medical Research and Ethics Committee, Ministry of Health of Malaysia, Malaysia (NMRR-20-207-53607).

(i) Isolate

Twenty-seven clinical isolates of *T. marneffe* on potato dextrose agar (PDA) were received from Malaysian hospitals in the year 2020. Their identities were confirmed by both macroscopic and microscopic methods. Internal transcribed spacer (ITS) region of the nuclear rDNA was amplified with PCR and detected with direct DNA sequencing to determine the species [18]. The mycelial and yeast form of *T. marneffe* were obtained as mentioned by Sar et al [19].

(ii) Clinical & Laboratory Standards Institute (CLSI) methods

Since no existing guidelines were available for susceptibility testing of *T. marneffe*, the minimum inhibitory concentration (MIC) was performed according to the broth microdilution in CLSI M38 [20]. The antifungals tested were the echinocandin anidulafungin, micafungin sodium, caspofungin diacetate, 5-fluorocytosine, amphotericin B and terbinafine hydrochloride, posaconazole, voriconazole, itraconazole, ketoconazole, ravuconazole, clotrimazole and isavuconazole. Each microdilution well contained 100 µl of antifungal. The final concentrations of antifungals were ranged from 0.0313 to 16.0 µg/ml for each antifungal.

Following that, 100 µl of diluted inoculum suspension was added to the well. The inoculum sizes for yeast and conidia mould were 0.4×10^4 to 5×10^4 colony-forming unit (CFU)/ml. The mould mixture was then incubated at 25°C for 96 h while the yeast mixture was incubated at 37°C for 72 h [13].

(iii) Quality control

Each test included two reference strains; *A. flavus* ATCC 204304 and *A. fumigatus* ATCC 204305 to ensure that the MIC obtained was within the reference range.

(iv) Data analysis

A descriptive analysis was performed using geometric mean (GM) values. For each antifungal test, the MIC₅₀ and MIC₉₀ were calculated. MIC₅₀ was defined as 50% of the isolates were inhibited; whereas MIC₉₀ is the MIC at which 90% of the isolates were inhibited. Comparisons between results from the yeast and mycelial phases were evaluated by the Wilcoxon test using SPSS 20.0. *P*-values less than 0.05 were considered statistically significant.

Results

T. marneffe was initially isolated from blood (n=23), pleural fluid (n=1), tracheal aspirate (n=1) and skin biopsy specimen (n=2). All samples were obtained from HIV-infected patients and their common clinical manifestations were fever and cough.

The geometric mean of MIC, MIC₅₀ and MIC₉₀ of *T. marneffe* are listed in Table 1. Most of the MICs were fallen within the expected range for each antifungal. In addition, triazoles were found to have lower MIC against most of the strains as compared with echinocandins.

The antifungals which demonstrated active against both mycelial and yeast phases of *T. marneffe* were terbinafine hydrochloride, posaconazole, voriconazole, itraconazole, ketoconazole, ravuconazole, clotrimazole and isavuconazole as their geometric mean of the MIC were <0.10 µg/ml. However, the GM MICs of anidulafungin, micafungin sodium, caspofungin diacetate for the mycelial forms of *T. marneffe* strains were more than 10 times higher than their yeast forms.

In addition, the geometric mean of MICs of anidulafungin, micafungin sodium, caspofungin diacetate, 5-fluorocytosine, amphotericin B, terbinafine hydrochloride and clotrimazole against mycelial form were higher than those recorded for the yeast form. However, comparison between results of anidulafungin ($p=0.002$), micafungin sodium ($p= 0.012$), caspofungin diacetate ($p= 0.011$), 5-fluorocytosine ($p= 0.047$), amphotericin B ($p=0.049$) and terbinafine hydrochloride ($p=0.005$) against yeast and mycelial phase of *T. marneffe* was statistically significant.

Table 1
Minimum inhibitory concentrations (MIC) of 27 clinical isolates of *Talaromyces marneffe* in yeast and mycelial phases to antifungal drugs

Antifungal	GM of MIC (µg/ml)		MIC ₅₀ (µg/ml)		MIC ₉₀ (µg/ml)	
	MF	YF	MF	YF	MF	YF
Anidulafungin*	4.55	0.22	8	0.03	32	4
Micafungin sodium*	6.03	0.20	32	0.03	32	32
Caspofungin diacetate*	2.33	0.13	4	0.03	16	4
5-fluorocytosine*	3.39	0.76	32	0.5	32	32
Amphotericin B*	1.63	0.35	1	0.06	32	32
Terbinafine hydrochloride*	0.09	0.05	0.06	0.03	0.25	0.06
Posaconazole	0.05	0.05	0.03	0.03	0.13	0.03
Voriconazole	0.04	0.06	0.03	0.03	0.03	0.03
Itraconazole	0.06	0.06	0.03	0.03	0.25	0.25
Ketoconazole	0.05	0.05	0.03	0.03	0.13	0.13
Ravuconazole	0.05	0.06	0.03	0.03	0.13	0.25
Clotrimazole	0.07	0.06	0.03	0.03	0.25	0.13
Isavuconazole	0.05	0.05	0.03	0.03	0.06	0.03

GM: geometric mean; MF: mycelial form; MIC: minimum inhibitory concentration; YF: yeast form. * indicates P < 0.05 for the difference between the MIC values relative to the phases of *T. marneffe*.

Discussion

T. marneffe has become one of the most common opportunistic pathogens in Southeast Asia, southern China and northeastern India [21]. It is a primary cause of morbidity and mortality in HIV-infected and other immunosuppressed patients who live in endemic areas including Malaysia [22]. Disseminated *T. marneffe* infection is associated with a high mortality rate in patients whose treatments were delayed [23].

Amphotericin B belongs to the polyene class of antifungals. It is fungicidal and approved by the United States Food and Drug Administration (FDA) to combat a broad range of fungal infections [24]. It was suggested to be used as initial treatment for patients with talaromycosis or severe stage of talaromycosis [25, 26]. Therefore, amphotericin B was frequently included in the susceptibility testing. The MIC of amphotericin B against yeast and the mycelial form of *T. marneffe* was typically low. However, some MIC results were reported in high value. For instance, MIC ≤2 µg/ml of yeast form was reported by both Liu et

al. [17] and Lei et al. [27]; however, MIC \geq 24 μ g/ml in yeast and mycelial form were reported by Sekhon et al. [28] and Sar et al. [19] respectively. Some of the yeast and mycelial phases of isolates in this study also showed MIC \geq 24 μ g/ml, which correlates to the results mentioned above.

Azoles antifungals can directly inhibit the enzyme lanosterol 14- α demethylase from converting lanosterol to ergosterol. This leading to the increase in the cell membrane permeability and finally lead to cell death [29]. A recent study reported talaromycosis was successfully treated with a reduced dose of itraconazole instead of using amphotericin B or voriconazole [30]. Furthermore, the use of itraconazole is frequent particularly in lower-income countries as it has better tolerability, availability, less toxicity and is economical [11, 31–33]. Several *in vitro* studies had reported its active activities against yeast and the mycelial form of *T. marneffe*. The MIC of *T. marneffe* yeast and mycelial were \leq 0.5 μ g/ml [13, 27, 34, 35]. The finding of this study also proposes that itraconazole has potential active activity against both mycelial and yeast phases of *T. marneffe* since the MIC₉₀ for both phases were <0.5 μ g/ml.

Voriconazole is a potent broad-spectrum triazole antifungal with satisfactory safety for combating various fungal infections [36]. The active activities of voriconazole against *T. marneffe* were mentioned by and Lau et al. [13] and Ouyang et al. [34] It was suggested to be used in the treatment of patients who could not tolerate amphotericin B and itraconazole [34, 37]. The MIC of voriconazole was the lowest reading compared with fluconazole, itraconazole, terbinafine and amphotericin B in Liu et al. [17] This is parallel to our study since voriconazole achieved the lowest MIC₉₀ against both phases of *T. marneffe*.

However, many patients were still died after treated with amphotericin B, itraconazole and voriconazole [8, 38–40]. In the year 2017, Lau reported that *T. marneffe* demonstrated high susceptibility against Posaconazole [13]. Posaconazole is beneficial in salvage therapy of various severe and refractory invasive fungal infections [41–43]. Similar to this study, the MIC reading of posaconazole was generally lower than 0.1 μ g/ml for both yeast and mycelial form.

Besides itraconazole, ketoconazole was suggested to be used in the treatment of mild to moderately severe talaromycosis [26]. This is due to the MIC being less than 0.5 μ g/ml from their study [26]. In addition, Kantipong and Walsh reported that the oral lesions caused by *T. marneffe* were resolved by the treatment of ketoconazole [44]. The results of the present study also supported these previous findings as the MIC₉₀ for both phases of *T. marneffe* was <0.5 μ g/ml.

Terbinafine is an allylamine antifungal. It is fungicidal and able to inhibit enzyme squalene monooxygenase from synthesizing the sterol of the fungal cell membrane. As a result, the cell membrane will unable to grow and the fungus will be lysed eventually [45]. Terbinafine was one of the most effective antifungals with *in vitro* activity showing the lowest MIC values, which supports findings of other studies. Similar to our findings, McGinnis et al. reported the geometric mean of MIC for terbinafine against *T. marneffe* was as low as itraconazole [16]. Moreover, the terbinafine MIC was reported as \leq 2 μ g/ml [17]. Hence, the researchers suggested terbinafine might be effective against *T. marneffe* [16].

Echinocandin is a noncompetitive inhibitor of the formation of the enzyme 1,2- β and 1,6- β glucan synthase. It disrupts glucan and results in fungal cells being unable to maintain their shape and rigidity and hence leading to fungal cell lysis. In this study, echinocandin displayed very low activity *in vitro* against the mycelial form of *T. marneffeii*. It indicates these echinocandin antifungals might have reduced activities against *T. marneffeii*. Studies conducted by Lau et al. [13], Liu et al. [17] and Lei et al. [27] reported echinocandin was comparatively lower or no activity against *T. marneffeii* yeast and mould. In contrast, Odabasi et al. [46] reported anidulafungin exhibits potential activity against the mycelial form of *T. marneffeii* as the MIC was ≤ 2 $\mu\text{g/ml}$. However, the finding in this study indicated that echinocandin might be active against the yeast form but inactive against the mycelial form of *T. marneffeii*.

Currently, no guidelines are available for the susceptibility testing of *T. marneffeii*. Even though CLSI M38 and M27 are references for broth dilution antifungal susceptibility testing of mould and yeasts respectively; however, they have been unevaluated for *T. marneffeii* yet [20, 47]. Recent studies reported the susceptibility test using 10^4 CFU/ml yeast inocula in their studies [17, 48]. Hence, the variation of different inoculum sizes when comparing the results with mould inocula can be avoided. However, no result for *T. marneffeii* mould form was reported by them [17, 48], thus the significant differences of MIC resulting from yeast and mould were unable to be compared. Therefore, this study used the same inocula size for both phases of *T. marneffeii* to facilitate this comparison.

The growth form to be used for the test still remained unclear. Several studies reported the MIC using both mycelial and yeast form [13, 19, 26]; while others utilized the mycelial form only [35]. In the present study, some of the mycelial forms demonstrated greater MIC against antifungals. This phenomenon was also observed by Lau et al. [13] and Sar et al. [19]. This could be due to the production of red pigment, which exclusively appears when *T. marneffeii* is grown as mould. The red pigment was reported to be very important for the production of citrinin [49], where it is hepatotoxic and nephrotoxic to humans [50].

To our knowledge, this is the first study of susceptibility testing against Malaysian clinical isolates of yeast and mycelial phases of *T. marneffeii* using the CLSI method. To emphasize, this is the first study to determine the susceptibility pattern of *T. marneffeii* against ravuconazole, isavuconazole and clotrimazole. In contrast, there are several limitations to this study. The sample size of the isolate was small within the study period and thus an accurate MIC₅₀ and MIC₉₀ were difficult to be determined. In addition, the results were unable to be interpreted as susceptible or resistant as there are no official breakpoints for *T. marneffeii* according to the CLSI method. However, these results are beneficial and could contribute to limited antifungal database in Malaysia.

Conclusion

In conclusion, our data suggest all antifungals used in this study might possess potential antifungal activities against yeast *T. marneffeii*; and therefore, could be useful in the clinical management of talaromycosis. In contrast, all antifungals except anidulafungin, micafungin sodium, caspofungin diacetate and 5-fluorocytosine were shown inactive against the mycelial form of *T. marneffeii* as the

geometric means were >2.0µg/ml. More samples are required in future studies to ensure these data are reliable and useful to patients.

Declarations

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Author contribution

TXT contributed to the study design, data collection and the manuscript drafting. Material preparation and data collection were performed by TXT, NbNS, SJG and SBS. FBS conceived the study manuscript and its study design. All authors read and approved the final manuscript.

Ethics approval

This is an observational study. The Medical Research and Ethics Committee has confirmed that no ethical approval is required.

Declaration of interest

The author reports no conflict of interest.

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