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Advances in diagnosis and treatment of talaromycosis in patients with AIDS

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Talaromycosis (formerly named penicilliosis) is an important invasive mycosis caused by *Talaromyces marneffei* (formerly *Penicillium marneffei*, *T. marneffei*).[1] The World Health Organization and Food and Drug Administration have recently paid increasing attention to the disease as a neglected tropical disease due to the growing burden of *T. marneffei* infection globally.[1,2] Talaromycosis is a common opportunistic disease and a leading cause of death in patients with acquired immune deficiency syndrome (AIDS) in endemic regions; moreover, it is increasingly being reported in human immunodeficiency virus (HIV)-negative individuals and outside of epidemic areas.[3,4] The mortality of talaromycosis is up to 30% in both HIV-positive and HIV-negative individuals, which is associated with late diagnosis and untimely or ineffective antifungal therapy.[5] Therefore, early diagnosis and effective antifungal treatment are critical to reduce the mortality.

Talaromycosis is endemic in southeast Asia and southern China. Given that the AIDS epidemic is not fully controlled and about 30% of HIV-positive people have low $CD4^+$ T lymphocyte count (lower than 200 cells/μL) in developing countries, the number of talaromycosis cases is increasing yearly, accounting for up to 18.8% and 16% of HIV-associated hospital admissions in Guangdong and Guangxi, China, respectively.[6,7] The main endemic regions of the disease include southern China, northern Thailand, Vietnam, northern India, etc. In China, the areas with the highest incidence of talaromycosis are Guangdong, Guangxi, Yunnan, Hong Kong, and Taiwan.[8] However, travel-related cases have been ceaselessly reported in non-endemic areas.

Although a presumptive diagnosis can be made in AIDS patients who present typically foveal rashes, the skin lesions are absent in 30% to 40% of AIDS patients, making the early diagnosis difficult merely based on the clinical characteristics. The gold-standard confirmative diagnosis depends on culture or histopathology. However, because the culture can take up to 3 to 14 days with only 60% to 75% positive rate in blood or bone marrow culture,[6,7] and the histopathological examination is less clinically accessible due to the trauma caused by tissue biopsy, it is crucial to develop novel assay methods and systematic diagnostic strategies.

Identification of *T. marneffei* is based on the morphology of colonies, conversion between mold and yeast, and microscopic morphology. For some atypical strains of *T. marneffei*, matrix-assisted laser desorption ionization time-of-flight mass spectrometry (MALDI-TOF MS) has been used for identification because it is easy to operate even by an inexperienced technician and is time-saving.[9] Nevertheless, the MALDI-TOF MS database of *T. marneffei* is still under construction. The Tzanck smear or rash biopsy is a simple and effective way of detecting *T. marneffei* infection in the skin or mucosa using Wright, Giemsa, or Gomori–Grocott methenamine stains.[10,11]

In the past few years, advances in serology have made a significant contribution to the progress of talaromycosis diagnosis. The commercial galactomannan (GM) test has been regarded as a screening and adjunct diagnostic tool with a sensitivity of 80.6%.[12] However, the specificity of the GM assay is only approximately 80% because of the cross-reactivity between *T. marneffei* and *Aspergillus*. Recently, a monoclonal-based immunoassay has been used to detect *T. marneffei* Mp1p antigen in patient plasma with a sensitivity of 82% and high specificity of 93%.[13] A number of typical applications for Mp1p are reported gradually, which shows great potential to speed up diagnosis.[14] This antigen is abundantly secreted in the blood as well as the urine of patients during infection. Testing plasma and urine together in the same patient enhanced sensitivity significantly compared with testing plasma or urine alone.[13] A commercial Mp1p antigen

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detection assay for clinical use was approved in China in 2018. In a recent study of 283 patients with AIDS, the diagnostic sensitivity, specificity, positive predictive value, and negative predictive value of Mp1p enzyme immunoassay within 3 days after admission were 72.0% (67/93), 96.8% (184/190), 91.8% (67/73), and 87.6% (184/210), respectively, which was consistent with the gold standard (kappa, 0.729) and superior to GM determination (kappa, 0.603).[15] The GM and M1p1 antigen tests have been listed as the auxiliary diagnostic methods in the Chinese AIDS diagnosis and treatment guideline in 2021.[16]

T. marneffei can be detected in blood samples of patients using several quantitative reverse-transcription polymerase chain reaction (qRT-PCR) assays, which show specificity near 100% and sensitivity equal to blood cultures at approximately 70%.[17,18] Although qRT-PCR demonstrates a number of benefits, including high specificity, accuracy, and being quantifiable, it is difficult to promote the method for the need for high-quality DNA for PCR, unavailable from patients' blood or other samples.[18] Recently, the metagenomic next-generation sequencing (mNGS) technology has been developed beyond the research realm and has started to mature into clinical applications. One of its major advantages is its ability to detect all pathogens. The first case of fungal infection diagnosed by mNGS was reported in 2014. Since then, a few cases of *T. marneffei* diagnosed by mNGS have been described in the literature, one of which was a central nervous system infection.[19]

Thus far, there are no definite minimum inhibitory concentration (MIC) cutoff values for *T. marneffei*, but the drug sensitivity results are still of certain guiding significance for clinical practice. There have been four studies on the MIC value of *T. marneffei* isolates against echinocandin, amphotericin B, and azoles *in vitro* in the past decade [Table 1]. The MICs of all echinocandins were very high, while the MICs of posaconazole, itraconazole, and voriconazole, as well as those of amphotericin B, were comparatively low. Notably, fluconazole had a higher MIC than other azoles and exhibited particularly weak activity against some isolates.[20-23]

Amphotericin B has always been the first recommendation for the induction treatment of talaromycosis in the national guidelines of China,[16,24] and voriconazole could be used as an alternative to amphotericin B if the patient cannot tolerate induction therapy with amphotericin B. Itraconazole is usually applied as consolidation therapy after the induction therapy. A randomized controlled trial conducted by Thuy in five Vietnam hospitals in 2017 to compare amphotericin B and itraconazole for the treatment of talaromycosis, demonstrated that amphotericin B was superior to itraconazole as the initial treatment for talaromycosis.[25] A retrospective real-world observational study from Guangdong, China, also revealed that the application of amphotericin B alone or combined with azoles can result in better prognoses than azoles alone.[9]

Voriconazole had been proven to be an effective, well-tolerated treatment option for talaromycosis.[26-28] In a prospective multicenter cohort study, 410 HIV-infected patients diagnosed with talaromycosis received induction treatment with either amphotericin B deoxycholate intravenously or voriconazole. In terms of all-cause mortality rate, induction therapy using voriconazole had a similar efficacy with amphotericin B deoxycholate in HIV-infected patients with talaromycosis.[27] Moreover, another retrospective study from Guangxi, China, indicated that voriconazole is an effective and safe induction antifungal drug for HIV-associated disseminated talaromycosis.[28]

Most guidelines recommended that antiviral treatment (ART) should be initiated within 1 to 2 weeks after effective antifungal treatment for talaromycosis, with weak evidences.[16,24] In 2021, one multicenter randomized controlled study from China evaluated the optimal timing of ART initiation for patients presenting with AIDS-related talaromycosis. A significantly lower mortality rate during the 48 weeks was observed in the early ART group (the median period from antifungal therapy to ART initiation was 11 days) when compared to the deferred ART group (the median period from antifungal therapy to ART initiation was 21 days).[29]

Talaromycosis has been continuously threatening immunodeficient patients globally, urgently requiring rapid diagnostic and more effective treatment methods. MALDI-TOF MS, Mp1p antigen detection, and mNGS have been shown to have the potential for early diagnosis. Amphotericin B is still the most effective drug for talaromycosis, and voriconazole is the alternative for its safety and effectiveness.

Table 1: The antifungal drug sensitivity tests of *Talaromyces marneffei* reported in the past decade.

			MIC range/geometric mean MIC (μg/mL) for agents							
Location	Year	Number	Amphotericin B	Itraconazole	Voriconazole	Posaconazole	Fluconazole	Anidulafungin	Micafungin	Caspofungin
Guangxi[20]	2013	25	0.125–2.000/0.653	0.031–0.500/0.110	0.004–0.250/0.040	NA	1.000–16.000/4.072	NA	NA	NA
Hongkong[21]	2016	57	NA	0.002–0.004/NA	0.016–0.063/NA	0.001–0.002/NA	NA	2.000–8.000/NA	NA	NA
Guangzhou[22]	2018	189	≤0.120–1.000/0.501	≤0.015–0.030/0.024	≤0.008–0.060/0.016	≤0.008–0.060/0.013	1.000–32.000/4.074	2.000–≥8.000/NA	>8.000/NA	2.000–≥8.000/NA
Southern China[23]	2021	32	0.031–1.000/1.915	≤0.016–0.031/0.016	≤0.016–0.030/0.045	≤0.016/0.016	NA	NA	NA	0.250–32.000/1.354

MIC: Minimum inhibitory concentration; NA: Not applicable.

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