



Talaromycosis

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Disclosure

- Research grants: Siam Pharmaceuticals, Pfizer, Janssen, Astra Zeneca, Cidara, F2G
- Speaker bureau: Pfizer, MSD, Siam Pharmaceuticals, Berlin, DCH Auriga, Biomerieux
- Consultant/advisory board: Pfizer, Gilead, MSD

Talaromycosis (Formerly Penicilliosis)

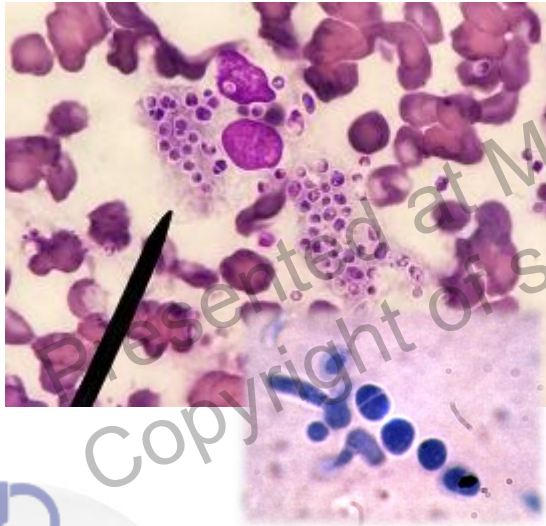
- Major fungal disease endemic in South and Southeast Asia
- Caused by a dimorphic fungus *Talaromyces (Penicillium) marneffeii*
- First isolated from a bamboo rat (*Rhizomys sinensis*) in Vietnam in 1956
- Described as a novel species *Penicillium marneffeii* by Professor Gabriel Segretain in 1959
- The first natural human case of talaromycosis (penicillois) was reported in 1973 in an American minister with Hodgkin's disease who lived in Southeast Asia
- Environmental source of infection is not known

Talaromycosis (Formerly Penicilliosis)

- Majority of cases are HIV-infected patients - 0.3% (0.1-19.6%), 4900 deaths/year
- There is a global call for talaromycosis to be recognized as a **“neglected tropical disease”**
- The incidence was projected to increase 35% from 2020 to 2025
- Highly associated with the tropical monsoon weather
- The incidence increase 30-73% during the rainy season in Thailand, Vietnam and southern China

Talaromyces marneffe

Skin scrape
Binary fission yeast



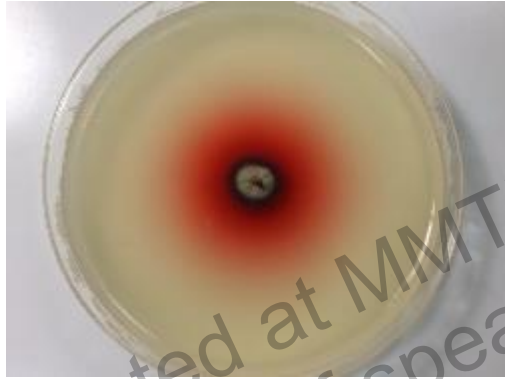
Bone marrow study



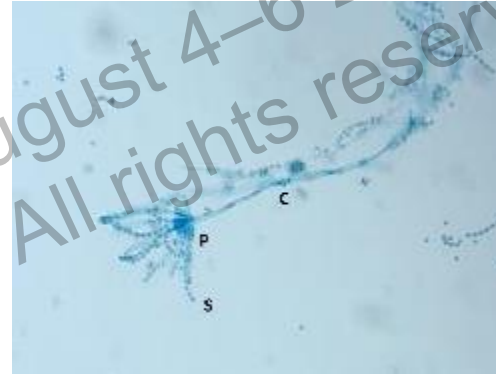
Blood culture
Septate hyphae



Talaromyces marneffe



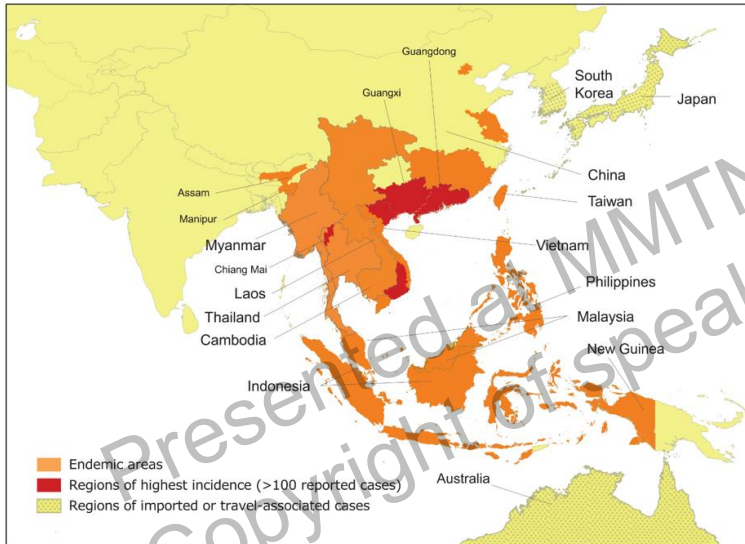
Culture on SDA showed velvety yellow-green or gray-green colony with diffusible red pigment in the culture medium



Septate hyphae with branched or unbranched conidiophores (C) with secondary branches phialides (P) grouped in brush-like clusters at the end of conidiophores are arranged in whorls; bearing unbranched chains of smooth or rough, and round to ovoid phialoconidia (S)



Talaromycosis: An Emerging Threat in Asia

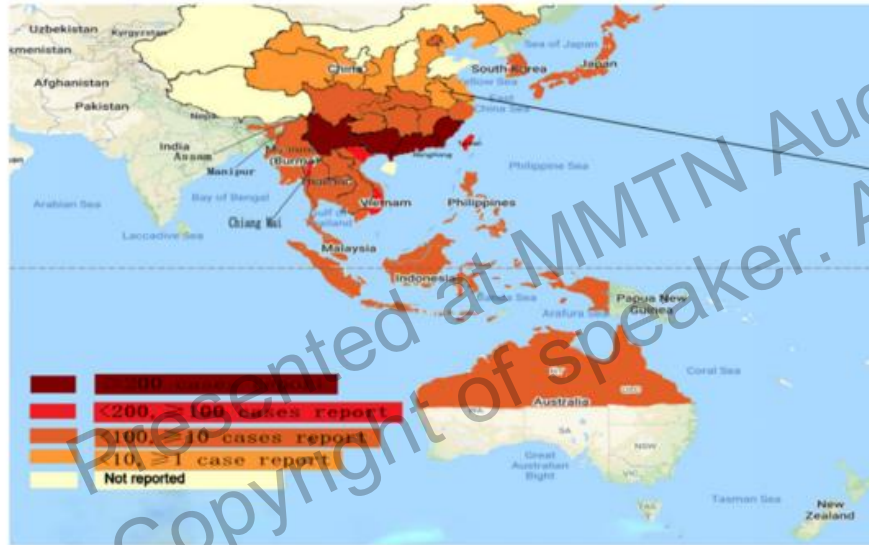


188,000 cases reported in 33 countries in 2018 (highest in China, Thailand and Vietnam)

The endemic regions : Northern Thailand, Southern China, Vietnam, Northern India, Hong Kong, and Taiwan and other 21 provinces and cities have reported cases in China

Travel-related : non-endemic areas such as Australia, Belgium, France, Germany, Japan, the Netherlands, Oman, Sweden, Switzerland, Togo, the United Kingdom, and the USA

Talaromyces: An Emerging Threat in Asia



Clinical Manifestation of Talaromycosis in AIDS

Disseminated infection presented with

- Prolonged fever
- Weight loss
- Lymphadenopathy
- Hepatosplenomegaly
- Fungemia (common in patients with AIDS)
- Skin lesions

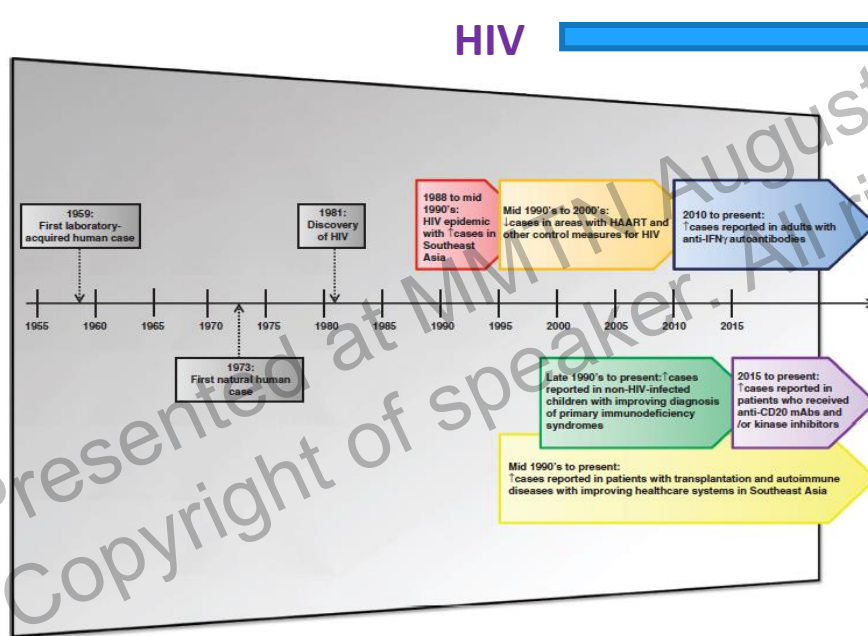


- Multiple discrete lesions
- Dome-shaped, skin-colored papules on erythematous base
- Central umbilication

Diagnosis of Talaromycosis

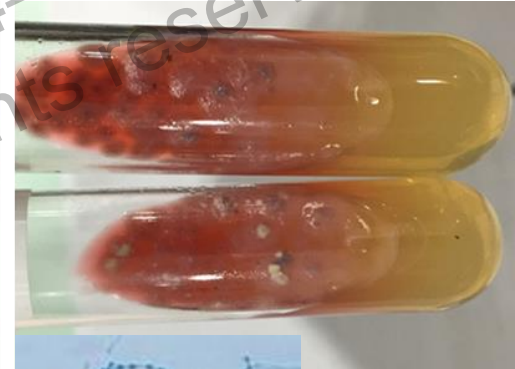
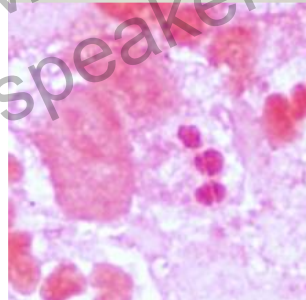
- Fungal culture from blood or other clinical samples
- Antigen detection (Mp1p) is highly accurate, inexpensive, does not require sophisticated equipment
 - A commercial antigen detection assay was approved in 2018 in China for clinical use
- A number of qPCR assays, based on specific *T. marneffe* regions
 - High specificities (100%) in whole blood or plasma samples, but sensitivity ranges from 70% to 86%

Changing in Epidemiology of Talaromycosis



- Adult-onset immunodeficiency (IFN-gamma autoantibodies)
- Transplantation
- Novel targeted therapies
- Primary immunodeficiency

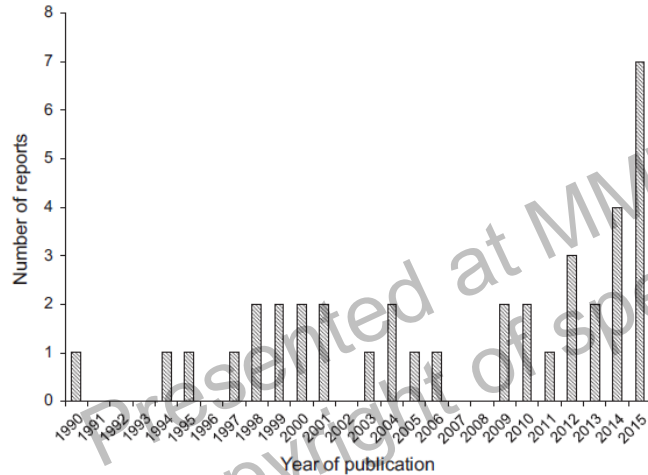
A 52-Year-Old Woman with Anti-Interferon Gamma Autoantibodies and *T. marneffe* Pharyngo-laryngitis



Talaromycosis in HIV and Non-HIV Individuals

Clinical features	Non-HIV	HIV
Skin lesions	44%	77%
Positive blood cultures	47%	77%
Delayed diagnosis	180 days	45 days
Mortality	29%	21%

Reported Talaromycosis in Non-HIV Individuals



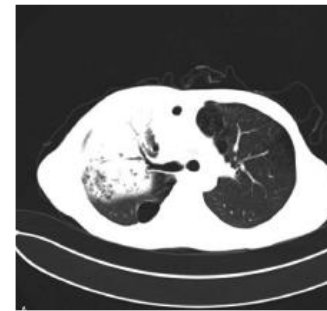
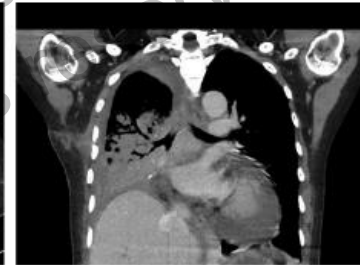
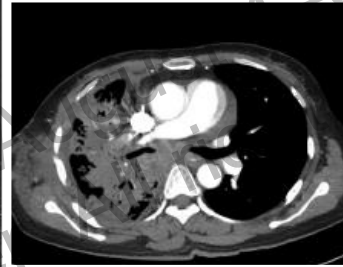
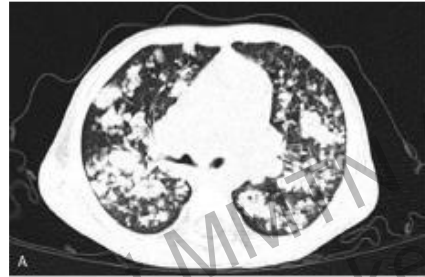
Underlying diseases:

- Adult-onset immunodeficiency (Interferon gamma autoantibodies)
- Solid organ transplant and HSCT
- Anti-CD-20
- Autoimmune diseases
- Primary immunodeficiency
- Idiopathic CD4+ lymphocytopenia
- Job's syndrome
- Diabetes mellitus
- Splenectomy
- Cancers: breast, colon, buccal

Talaromycosis in Non-HIV Individuals

- Autoimmune diseases : at least 15 case reports
 - SLE, MCTD, Sjogren's syndrome, PBC, IPT, AIHA
 - Treatment-related or disease-related
- Organ transplant
 - Kidney transplantation is the most common (>12 case reports)
 - Report in liver transplant, lung transplant, HSCT
- Novel targeted treatment
 - Rituximab (type I anti-CD20), obinutuzumab (type II anti-CD20)
 - Ruxolitinib (JAK 1 and 2 inhibitor), sorafenib (multi-kinase inhibitor)

Thoracic CT in Non-HIV Talaromycosis - Non-specific



Talaromycosis in Non-HIV Individuals

- Many of the non-HIV-infected patients with *T. marneffei* infection were initially misdiagnosed and empirically treated as tuberculosis because both infections are endemic in Southeast Asia, have similar predisposing factors and overlapping clinical manifestations
- Non-HIV-associated talaromycosis is usually misdiagnosed as other diseases
 - Tuberculosis (80.7%)
 - Bacterial pneumonia (20.5%)
 - Lung cancer (5.1%)
 - Other diseases (5.1%)

Talaromycosis of The Musculoskeletal System



Article

Risk Factors, Clinical Characteristics, Management, and Outcomes of Musculoskeletal Fungal Infection at Thailand's Largest National Tertiary Referral Center

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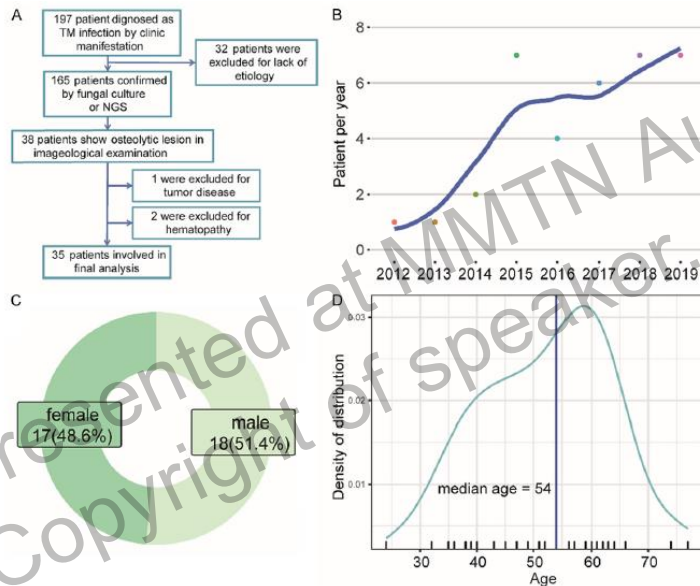
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Retrospective study 2000-2020

- Total 28 patients with fungal musculoskeletal infection enrolled
- Talaromycosis 8 out of 28 patients
- **All HIV-negative***
- There were 5 patients had **IFN gamma autoantibodies**
 - All 5 patients had pulmonary and cutaneous involvement
 - 2/5 had fungemia
 - The other 3 without IFN-gamma autoantibodies had only localized musculoskeletal infection

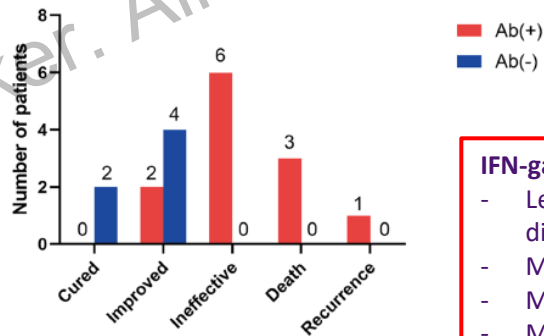
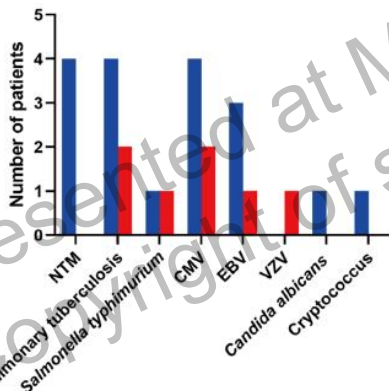
Talaromycosis with Bone Involvement in Non-HIV Individuals : China



Site	Frequency	Percent (%)
Skull	14	45.2
Upper limb bone and pectoral girdle		
Shoulder joint	7	22.6
Clavicle	4	12.9
Scapula	3	9.7
Wrist joint	2	6.5
Humerus	2	6.5
Phalanges	2	6.5
Hand Joint	1	3.2
Trunk		
Rib	16	51.6
Lumbar vertebra	7	22.6
Thoracic spine	6	19.4
Sacrum	3	9.7
Sternoclavicular joint	2	6.5
Cervical	2	6.5
Sternum	1	3.2
Lower Extremity		
Iliac bone	8	25.8
Femur	7	22.6
Knee joint	5	16.1
Sacroiliac joint	3	9.7
Tibia	2	6.5
Ankle joint	1	3.2
Hip joint	1	3.2

Non-HIV Talaromycosis in Patients with and without IFN-gamma Autoantibodies

Variable	Univariable OR (95% CI)	P value	Multivariable OR (95% CI)	P value
White-cell count (*10 ⁹ cells/L)	1.134 (1.007, 1.277)	0.038	1.035 (0.906, 1.183)	0.610
Hemoglobin (g/L)	0.973 (0.947, 1.001)	0.057	0.985 (0.948, 1.024)	0.454
Coexisting respiratory disease	0.158 (0.035, 0.708)	0.016	0.094 (0.011, 0.809)	0.031
Pleural effusion	8.185 (1.839, 36.424)	0.006	11.162 (1.517, 82.164)	0.018
Extrapulmonary organ involvement	3.682 (0.911, 14.876)	0.067	0.469 (0.046, 4.834)	0.525



IFN-gamma autoantibodies

- Less co-existing respiratory diseases
- More pleural effusion
- More opportunistic infections
- More unfavorable outcomes

Human Non-*marneffe* Talaromycosis : Mostly in Non-HIV

Species	Hosts	Organ involvement	References
<i>Talaromyces purpurogenus</i> *	Multiple myeloma	Pulmonary	Atalay A, et al. Le Infez Med. 2016; 2: 153–157.
<i>Talaromyces amestolkiae</i> *	Acute lymphoblastic leukemia	Pulmonary	Villanueva-Lozano G, et al. J Infect Chemother. 2017; 23: 400–402.
<i>Talaromyces piceus</i>	chronic granulomatous disease	Pulmonary, ribs	Santos PE, et al. Med Mycol. 2006; 44: 749–753.
<i>Talaromyces subaurantiacus</i>	N/A	Pulmonary	Guevara-suarez M, et al. Mycoses. 2017; 60: 651–662.
<i>Talaromyces kabodanensis</i>		Pulmonary	
<i>Talaromyces minnesotensis</i>		Ear	
<i>Talaromyces rapidus</i>		Pulmonary	
<i>Talaromyces alveolaris</i>		Pulmonary	
<i>Talaromyces atroroseus</i>	HIV (2) and non-HIV (5 isolates) from Indonesia	N/A	

Morphology of *Talaromyces atrovirens*

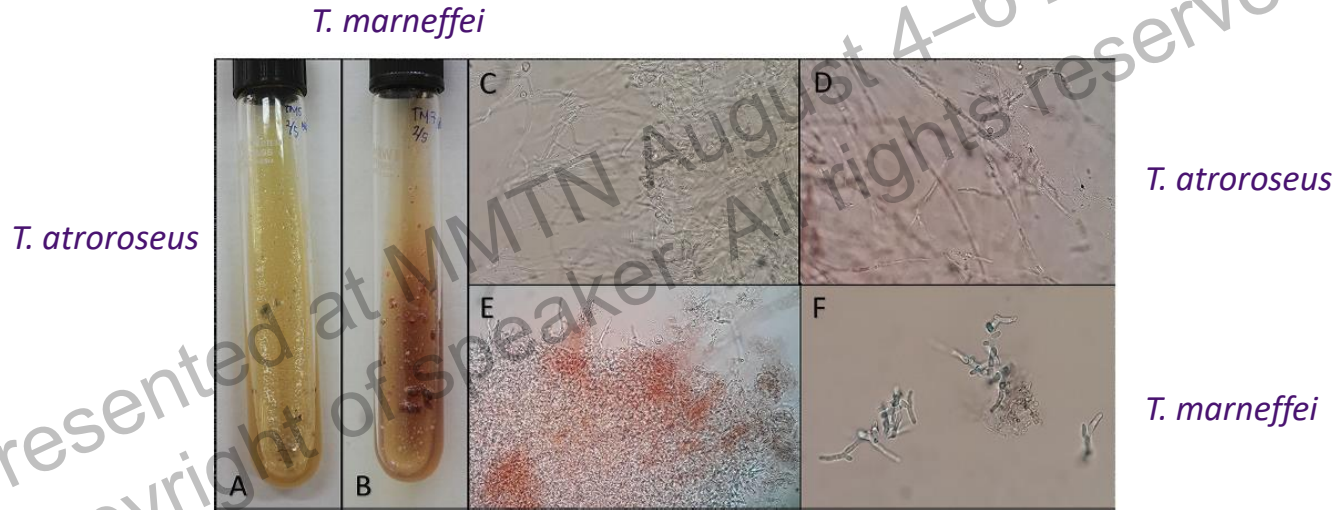


Figure 1. Morphology of the isolates at 37°C (10 days). Colony on brain heart infusion (BHI) agar representing isolates TM1-6 and TM8-10 (A); colony on BHI representing isolates TM7 (B); microscopic appearance of isolate TM5, representative for isolates TM1-6 and TM8-10 (C & D); microscopic appearance of isolate TM7 (E & F). This Figure is reproduced in color in the online version of *Medical Mycology*.

Antifungal Susceptibility Test for Non-*marneffe* *Talaromyces* (*T. atrovirens*)

Table 1. Result of antifungal susceptibility test using Sensititre™ YeastOne.

Antifungal agents	Minimum inhibitory concentration (MIC)										
	<i>T. marneffe</i>				<i>T. atrovirens</i>						Range <i>T. atrovirens</i>
	TM7	TM1&2	TM3	TM4	TM5	TM6	TM8	TM9	TM10		
Anidulafungin	4	>8	>8	>8	>8	>8	>8	>8	>8	>8	>8
Micafungin	>8	>8	>8	>8	>8	>8	0.12	>8	>8	>8	0.12- >8
Caspofungin	4	>8	>8	>8	>8	>8	0.5	>8	>8	>8	0.5- >8
5-Flucytosine	2	>64	4	8	>64	>64	0.06	32	8	8	0.06- >64
Posaconazole	≤0.008	0.5	0.25	0.25	>8	0.5	0.25	0.5	0.25	0.25	0.25- >8
Voriconazole	0.03	>8	4	8	>8	>8	0.12	>8	8	8	0.12- >8
Itraconazole	≤0.015	1	0.25	0.25	>16	0.5	0.12	0.5	0.5	0.5	0.12- >16
Fluconazole	4	>256	>256	>256	>256	>256	64	>256	>256	>256	64- >256
Amphotericin B	1	4	2	4	>8	4	0.5	2	2	2	0.5- >8

T. marneffe, *Talaromyces marneffe*.

T. atrovirens, *Talaromyces atrovirens*.

HIV

R. rattus

HIV

HIV

Non-HIV



Antifungal Susceptibility Test for *Non-marneffe* *Talaromyces*

TABLE 3 Results of *in vitro* antifungal susceptibility testing of 12 isolates of *Talaromyces* species

Species (no. of isolates tested)	Antifungal ^a	No. of isolates with antifungal MIC (µg/ml) of:											
		≤0.03	0.03	0.06	0.125	0.25	0.5	1	2	4	8	16	>16
<i>T. amestolkiae</i> (7)	CFG			2	3	1		1					
	AFG		1	3	3								
	MFG			3	2	2							
	TRB	6	1										
	PSC						2		1				4
	VRC									1			6
	ITC									1			6
	AMB				1	2	2	2					
	5FC			2	3		1		1				
	<i>T. purpurogenus</i> (5)	CFG					1				1	1	2
AFG				1	1							1	
MFG				2	1	2							
TRB		1	2	1								1	
PSC								1	1		1	2	
VRC								1	2	2			
ITC												5	
AMB								3	2				
5FC				3	2								

^a CFG, caspofungin; AFG, anidulafungin; MFG, micafungin; TRB, terbinafine; PSC, posaconazole; VRC, voriconazole; ITC, itraconazole; AMB, amphotericin B; 5FC, flucytosine.

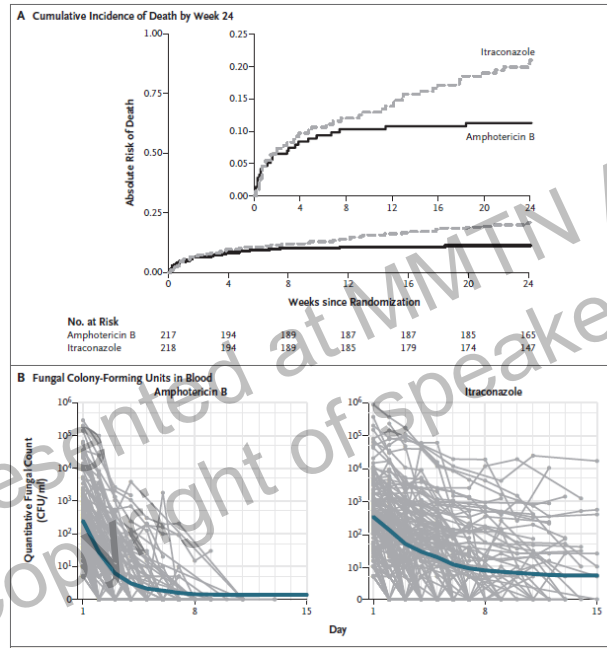
Echinocandin and terbinafine

- low MICs (Ta)
- variable MICs (Tp)

Azoles

- variable MICs

Treatment of Talaromycosis : HIV



Amphotericin B

- Lower mortality at 24 weeks (but not at 2 weeks)
- Faster clinical resolution and fungal clearance
- Lower rates of relapse and IRIS
- Higher side effects: infusion-related reactions, renal failure, hypokalemia, hypomagnesemia, and anemia

Treatment of Talaromycosis : HIV

- Multicenter, randomized controlled trial in Vietnam, induction therapy with AmB-d was superior to itraconazole with respect to mortality, blood fungal clearance, disease relapse, and immune reconstitution inflammatory syndrome
- A double-blind, placebo-controlled trial in Thailand showed that maintenance therapy with itraconazole (200 mg daily) in patients with advanced HIV disease decreased the relapse rate from 57% to 0% ($p < 0.001$)
- Primary prophylaxis with itraconazole (200 mg orally daily) reduces the incidence of invasive fungal infections (ie, talaromycosis, cryptococcosis, and oesophageal candidiasis) in HIV-infected patients with a CD4 count < 200 cells/ μ L in a randomized controlled trial in Thailand

Treatment of Talaromycosis : HIV

- Guidelines strongly recommend induction therapy with AmB. Specifically, L-AmB is preferred over AmB-d where available
- L-AmB is given at 3–5 mg/kg per day intravenously, **OR** AmB-d is given at 0.7 mg/kg per day intravenously, both for 10–14 days, followed by consolidation therapy with itraconazole (200 mg orally twice daily) for 10 weeks, followed by maintenance therapy with itraconazole (200 mg orally daily)

Summary

- The incidence of talaromycosis is increasing, especially in non-HIV individuals in Asia
- Adult onset immunodeficiency with interferon-gamma autoantibody is the newly-recognized host factor for talaromycosis
- Transplantation, autoimmune disease and immunosuppressive agents are also the risk factors
- Clinical manifestations of non-HIV talaromycosis are atypical resulting in delayed diagnosis and high mortality



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