Infectious & Tropical Diseases Unit
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ID Second Opinion - Italian Transplant Network

Micosi endemiche nell'immunodepresso

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INFEZIONI OPPORTUNISTICHE E POSSIBILITA' DI PROFILASSI IN PWH E OSPITI IMMUNOCOMPROMESSI

Progetto di Formazione PANDORA ID-25 - 24/03/2025

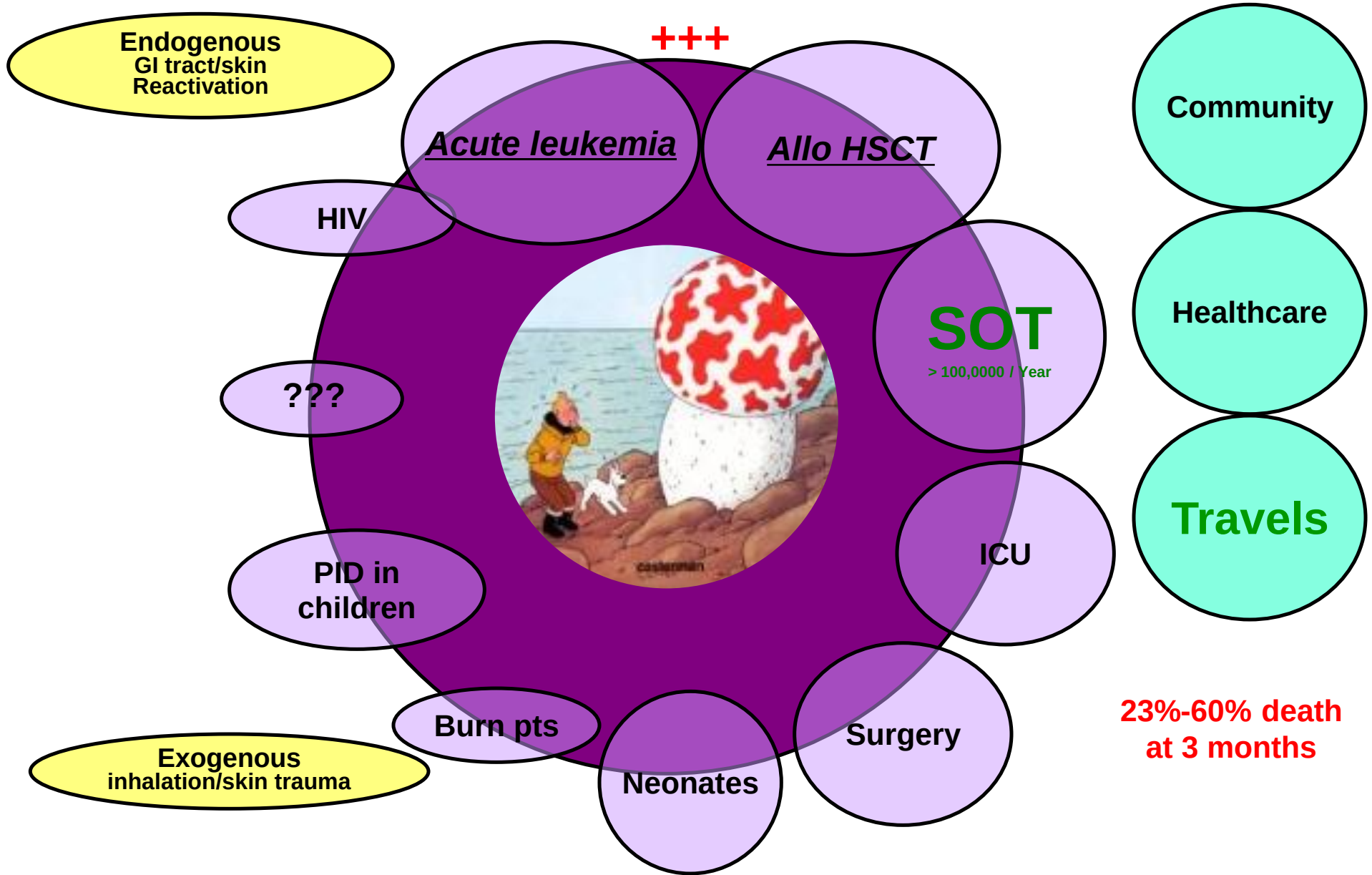
Background

- Fungal pathogens and infections are an increasing global public health concern.
- People most at risk are those with underlying health problems or a weakened immune system, such as chronic lung disease, prior tuberculosis (TB), HIV, cancer, and diabetes mellitus.
- Critically ill patients in an intensive care unit (ICU), patients undergoing invasive medical procedures and receiving broad spectrum antibiotics, and those taking immune-suppressing medicines are also at risk.
- Cases of invasive fungal disease (IFD) are rising as the at-risk population continues to expand.

Background

- Examples include patients with chronic obstructive pulmonary disease (COPD), liver or kidney disease, viral respiratory tract infections such as influenza and those with prior non-tuberculous mycobacterial infections.
- The coronavirus disease (COVID-19) pandemic has been associated with an increase in the incidence of comorbid invasive fungal infections.
- Three groups of COVID-19 associated fungal infections: aspergillosis; mucormycosis; and candidaemia, were frequently reported, often with devastating consequences.
- Finally, there is evidence to suggest that both the incidence and geographic range of fungal infections are expanding globally due to climate change

Risk Factors for IFI



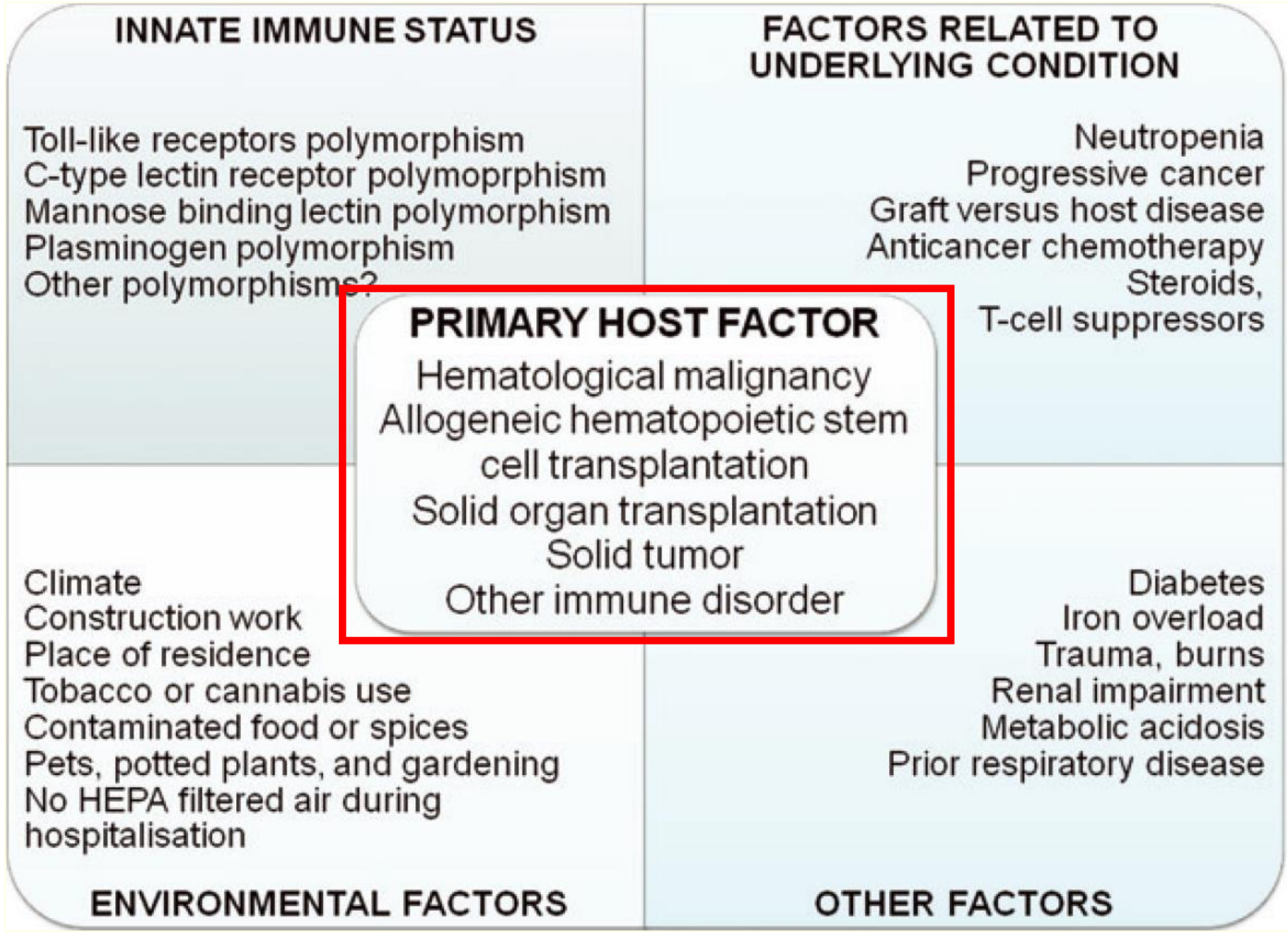
Global incidence and mortality of invasive fungal diseases

	Mean annual incidence (thousands)	Treated mortality (%)	Untreated mortality* (%)	Ratio of treated to untreated cases*	Mean estimated deaths (thousands)	Percentage of deaths attributable to fungal infection (%)	Attributable deaths (thousands)
Invasive aspergillosis in COPD	1513 (753–2272)	43–72%	>95%	1:5	1325	~80%	1060
Invasive aspergillosis in ICU	519 (208–1038)	50% (46–82)	>95%	1:3	416	~50%	208
Invasive aspergillosis in leukaemia and lymphoma, and allogeneic HSCT	27	45% (30–57)	>95%	10:1	14	~80%	11
Invasive aspergillosis (lung cancer)	57*	51%	>95%	1:4	49*	~40%	19*
Chronic pulmonary aspergillosis	1837	8%	20%	1:12	340*	60% (0–85·7)	204*
Candida bloodstream infection	626	35% (8·7–77·3)	~90%	9:1	254	~65% (21–100)	165
Invasive candidiasis without positive blood culture	939	35% (27–60)	~90%	1:5	742*	~65% (21–100)	482*
Pneumocystis pneumonia in AIDS	400	15% (0–71)	>95%	4:1	140	90%	126
Pneumocystis pneumonia not in AIDS	105	40% (8–58)	100%	1:1	74	35% (30–90)	49*
Cryptococcal meningitis	194	60% (20–70)	100%	3:2	147	80% (63–68)	118
Disseminated histoplasmosis in AIDS	71 (47–95)*	30%	100%	1:10	66*	80%	53*
Talaromycosis	19	28%	>95%	3:1	9	90%	8
Mucormycosis	211	25%	100%	4:1	84	70%	59
Coccidioidomycosis (95% USA and Mexico)	30	..	..	10:1	2	90%	2
Fungal asthma	..	..	..	1:20†	92*	50%	46*
Totals	6548	NA	NA	NA	3752	NA	2548

Data are mean (range), unless stated otherwise. COPD=chronic obstructive pulmonary disease. ICU=intensive care unit. HSCT=haematopoetic stem cell transplant. NA=not applicable. *Low-confidence estimates requiring additional study. †Refers to antifungal treatment, not standard asthma therapy.

Denning D. Lancet Infect Dis 2024 Published Online January 12, 2024

Factors influencing the risk of IFI



R.Herbrecht Ann N Y Acad Sci 1272 (2012;) 23-30

WHO fungal priority pathogens list

- Inspired by the bacterial priority pathogens list (WHO BPPL) developed in 2017, WHO has now developed the first fungal priority pathogens list (WHO FPPL).
- The WHO FPPL is the first global effort to systematically prioritize fungal pathogens, considering their unmet R&D needs and perceived public health importance.
- The WHO FPPL aims to focus and drive further research and policy interventions to strengthen the global response to fungal infections and antifungal resistance.

https://www.who.int/publications/i/item/9789240060241

WHO fungal priority pathogens list

Critical group	High group	Medium group
 *Cryptococcus neoformans*	 *Nakaseomyces glabrata (Candida glabrata)*	 *Scedosporium* spp.
 *Candida auris*	 *Histoplasma* spp.	 *Lomentospora prolificans*
 *Aspergillus fumigatus*	 Eumycetoma causative agents	 *Coccidioides* spp.
 *Candida albicans*	 Mucorales	 *Pichia kudriavzeveii (Candida krusei)*
	 *Fusarium* spp.	 *Cryptococcus gattii*
	 *Candida tropicalis*	 *Talaromyces marneffei*
	 *Candida parapsilosis*	 *Pneumocystis jirovecii*
		 *Paracoccidioides* spp.

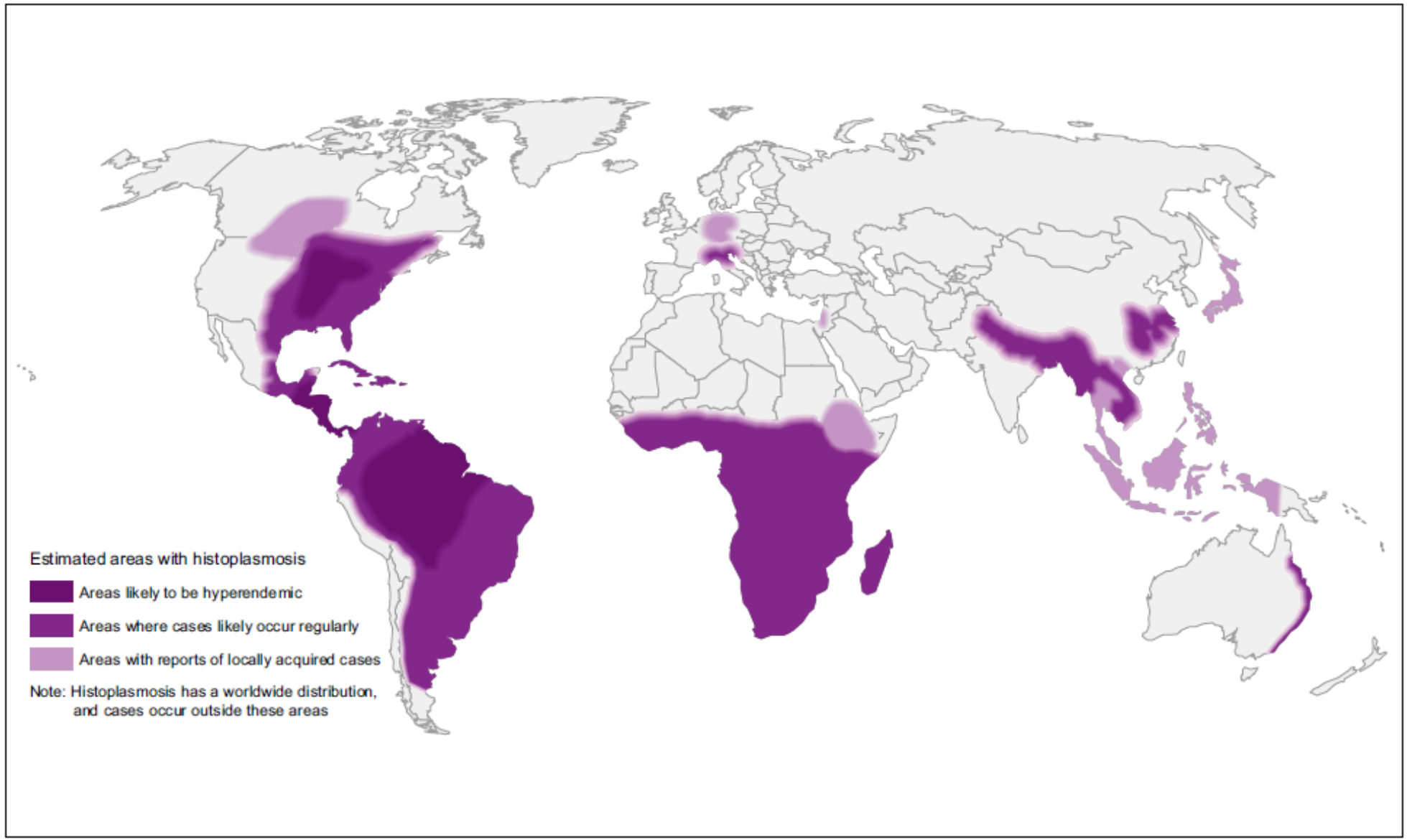
https://www.who.int/publications/i/item/9789240060241

Re-drawing the Maps for Endemic Mycoses

- Endemic mycoses such as histoplasmosis, coccidioidomycosis, blastomycosis, paracoccidioidomycosis, and talaromycosis are well-known causes of focal and systemic disease within specific geographic areas of known endemicity.
- However, over the past few decades, there have been increasingly frequent reports of infections due to endemic fungi in areas previously thought to be ‘‘non-endemic.’’
- There are numerous potential reasons for this shift such as increased use of immune suppressive medications, improved diagnostic tests, increased disease recognition, and global factors such as migration, increased travel, and climate change.

Ashraf N, et al. Mycopathologia. 2020 Oct;185(5):843-865.

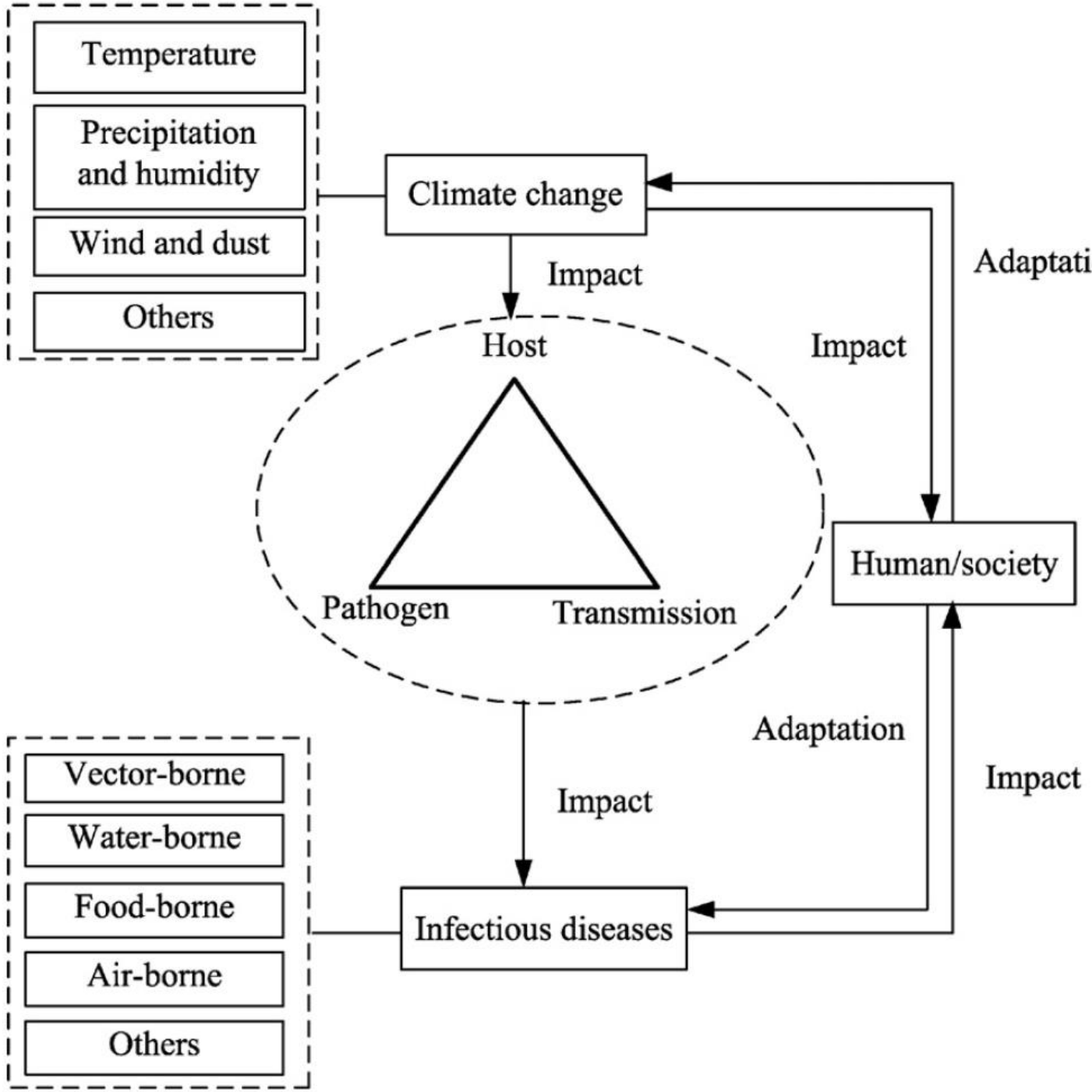
World map estimating regions most likely to have histoplasmosis based on literature review



Ashraf N, et al. Mycopathologia. 2020 Oct;185(5):843-865.

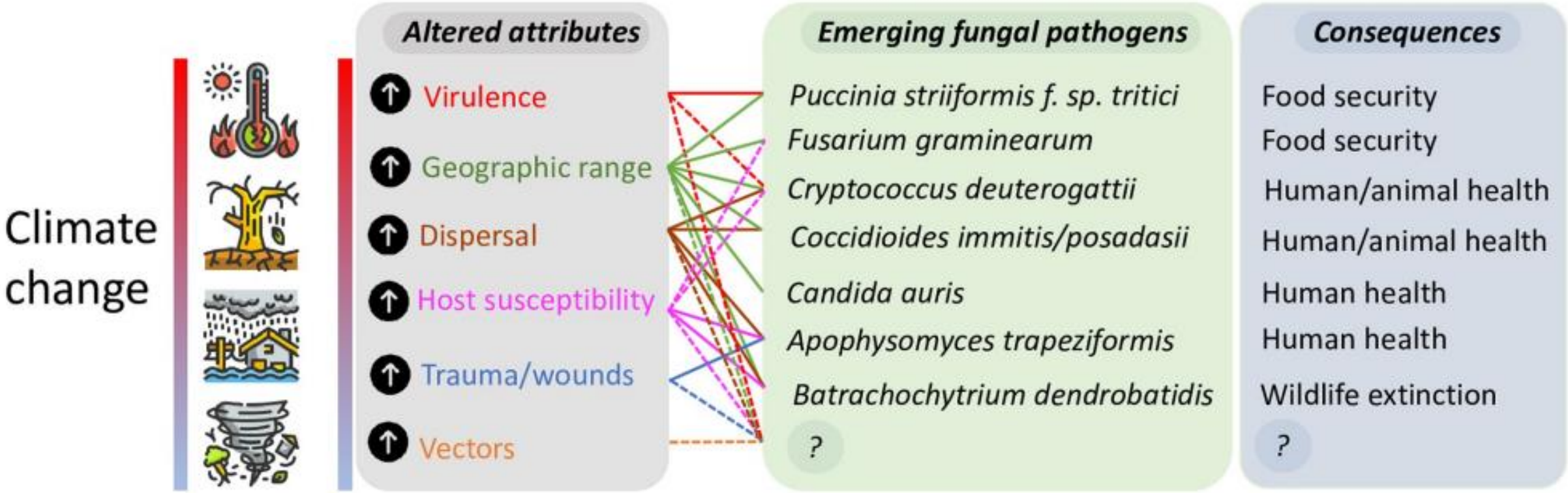
Climate change, human infectious diseases, and human society

- Effects of climate changes on infectious diseases
  - Spatial distribution
  - Annual/seasonal cycles
  - Diseases incidence and severity



Xiaoxu W, et al. Environment International 2016;86:14–23

The effect of climate change on the emergence of fungal pathogens



Nnadi and Carter PLoS Pathogens., 2021

Globalization and Infectious Diseases

- We are living in an increasingly globalized world in which people have a greater capacity for travel than at any previous time in history.
- Massive tourist movements, international migration, and increases in world commercial exchanges act as important underlying factors for the emergence and re-emergence of specific infectious diseases.
- **Migration is considered to be one of the defining global issues of the early 21st century.**
- Health professionals will become increasingly involved in the management of patients from tropical and other geographic areas where certain infections are endemic
- **Immunocompromised patients may be sentinel for new outbreaks or emerging infections**

Endemic Systemic Mycoses in Italy: A Systematic Review of Literature and a Practical Update

- The most common endemic systemic mycoses are caused by thermally dimorphic fungi.
- Among these diseases, blastomycosis, coccidioidomycosis, histoplasmosis, talaromycosis, paracoccidioidomycosis are emerging as an important cause of morbidity and mortality worldwide.
- They have a peculiar geographical distribution in most cases.
- Migratory flows and travels allow their spread also in non-endemic countries.

Verena Zerbato, et al. Mycopathologia (2023) 188:307–334

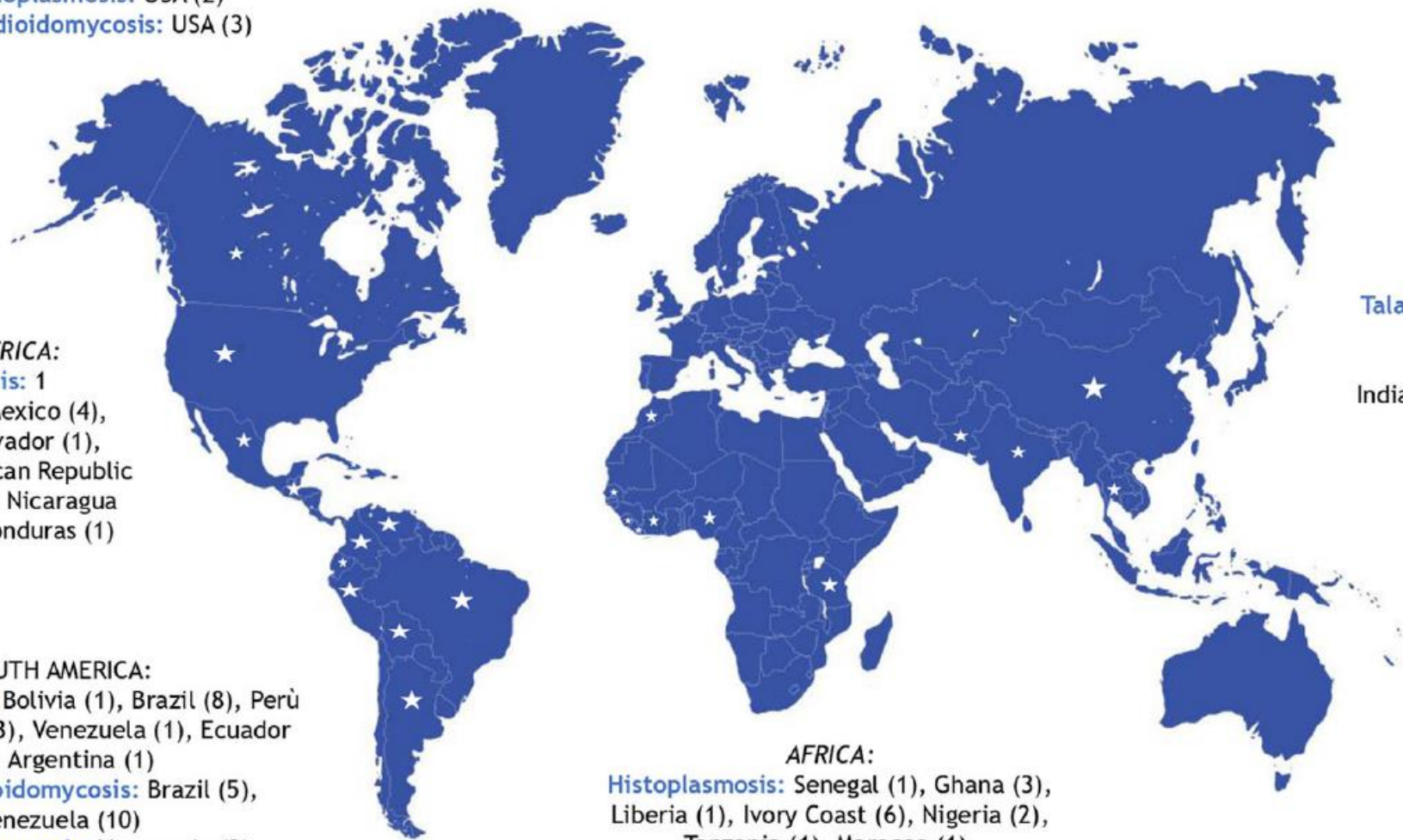
Endemic Systemic Mycoses in Italy: A Systematic Review of Literature and a Practical Update

- We conducted a systematic review on endemic systemic mycoses reported in Italy from 1914 to nowadays. We found out:
  - 105 cases of histoplasmosis,
  - 15 of paracoccidioidomycosis,
  - 10 of coccidioidomycosis,
  - 10 of blastomycosis and
  - 3 of talaromycosis.
- Most cases have been reported in returning travelers and expatriates or immigrants.
- **Thirtytwo patients did not have a story of traveling to an endemic area.**

Verena Zerbato, et al. Mycopathologia (2023) 188:307–334

Endemic Systemic Mycoses in Italy: A Systematic Review of Literature and a Practical Update

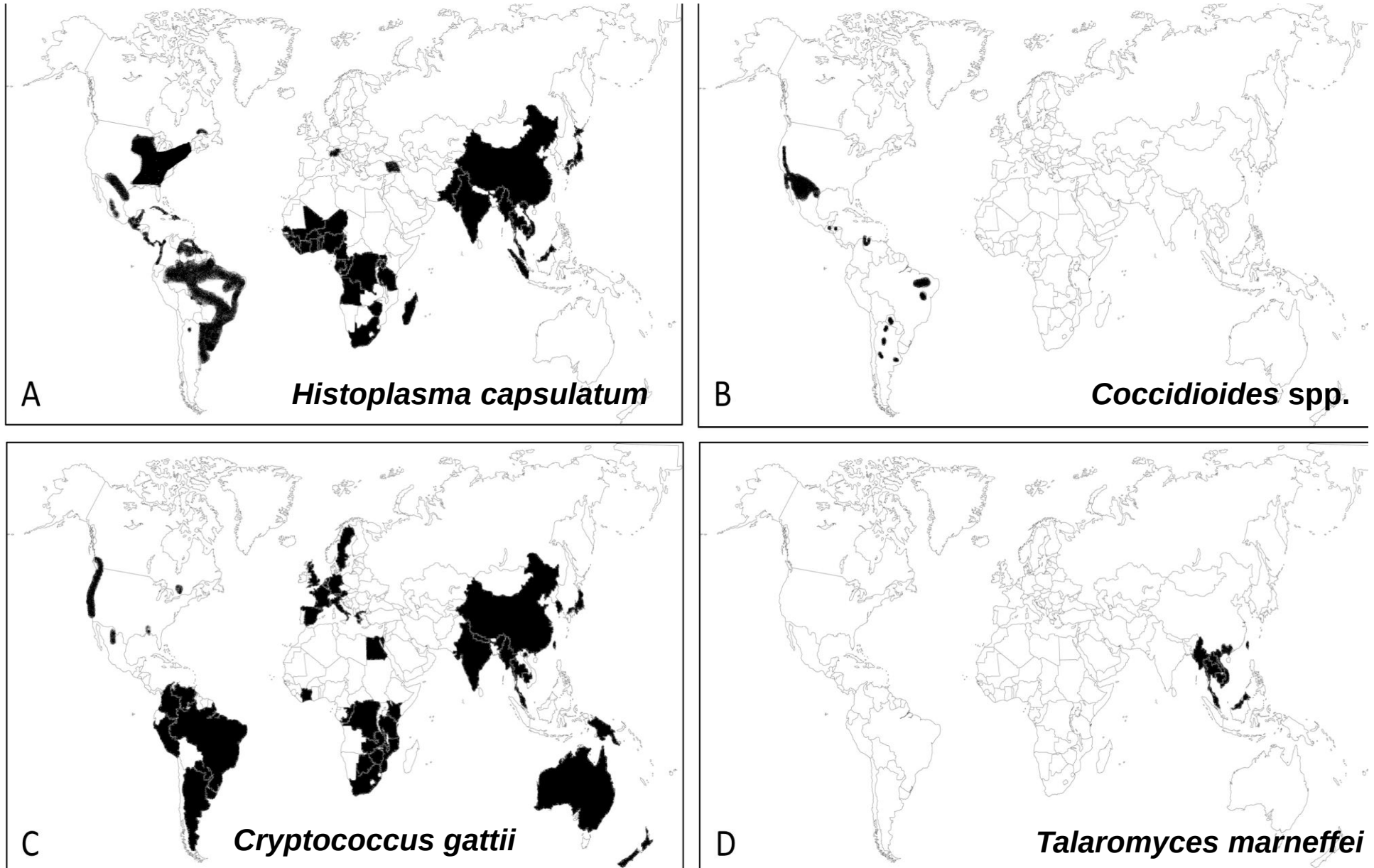
Countries of infection acquisition



Verena Zerbato, et al. Mycopathologia (2023) 188:307–334

Immunocompromised SOT and worldwide fungal risk

Lortholary O *et al*. CID 2013



HISTOPLASMOSIS

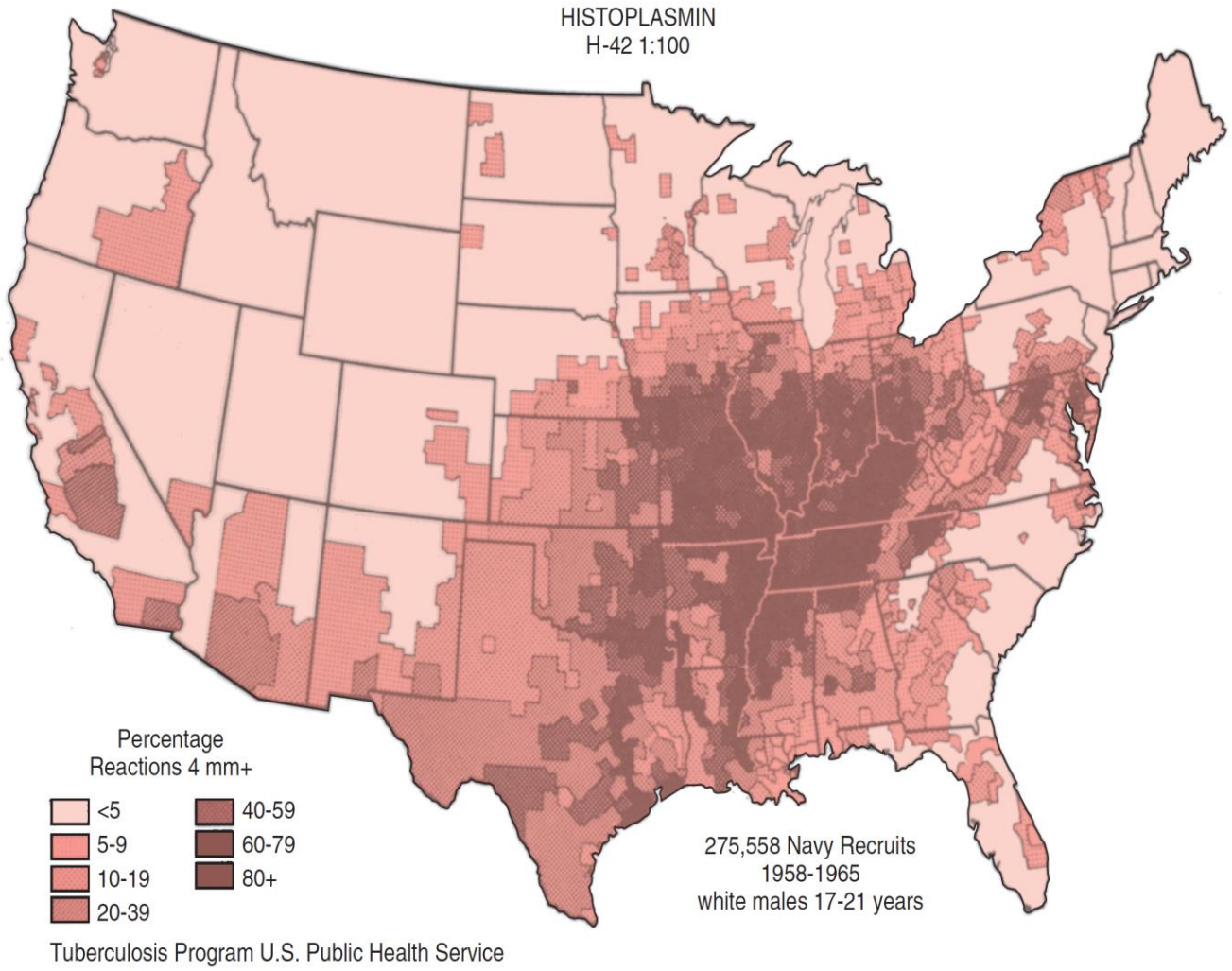
Definition

- Histoplasmosis is the most frequent cause of fungal respiratory infection and has a broad spectrum of clinical manifestations ranging from a self-limited, acute, influenza-like illness to a progressive disseminated infection that is life threatening.

Epidemiology

- The fungus is typically found in **the midwestern and southeastern United States** and in **Central and South America**. Cases of histoplasmosis have been reported from every continent except Antarctica. *H. capsulatum* is a soil-based fungus that has been isolated from many regions of the world and is most often associated with river valleys; the most highly endemic region is the **Ohio and Mississippi River Valleys**

Histoplasmin reactivity in the continental United States among naval recruits



Edwards LB, et al. Am Rev Respir Dis. *1969;99:1-111.*

Spectrum of *Histoplasma capsulatum* human diseases

MANIFESTATIONS	ACUTE PULMONARY DISEASE	ACUTE CAVITARY PULMONARY DISEASE	DISSEMINATED DISEASE
Clinical	Often asymptomatic	Fever, productive cough, chest pain	Fever, weight loss, hepatosplenomegaly, hematologic disturbances*
Immunologic			
Positive skin test	>90%	70%-90%	30%-55%
Lymphocyte transformation	+++	+ to +++	±
Antibody to *Histoplasma capsulatum*†	25%-85%‡	75%-95%	70%-90%
Antigenuria	20%‡	40%	60%-90%
Pathologic			
Positive culture from lungs	<25%	5%-70%	50%-70%
Histology	Caseating and noncaseating granulomas, few yeasts, giant cells	Noncaseating granulomas, interstitial fibrosis, necrosis, yeasts, cavities, few to moderate yeasts	Diffuse macrophage proliferation, abundant few giant cells

AFRICAN HISTOPLASMOSIS

- In Africa, the classic *H. capsulatum* var. *capsulatum* coexists with *H. capsulatum* var. *duboisii.*
- The yeast form of the latter is typically much larger, with a diameter up to 15 µm, and has a thicker wall. The mycelial form of both is indistinguishable.
- The pathogenesis of this fungus is presumed to be inhalation from the soil, although a primary pulmonary infection has not been demonstrated. Cutaneous inoculation is certainly an alternative mode of acquisition of the infection.
- Only a few hundred cases have been reported, but most cases have been reported from **Uganda, Nigeria, Zaire, and Senegal**. Cases in other African countries and a case in India have also been reported.
- The clinical picture associated with infection by H. capsulatum var. *duboisii* is distinctly different from that caused by *H. capsulatum* var. capsulatum. **Skin and skeleton** are the most frequent organs affected by this pathogen.

Treatment of Histoplasmosis

INFECTION SITE	DISEASE SEVERITY	TREATMENT
Lung		
Acute	Mild-moderate	None or itraconazole 200 mg 3 times daily for 3 days followed by 200 mg twice a day for 6-12 wk.
	Moderate-severe	Lipid-formulated amphotericin B, 3-5 mg/kg, or deoxycholate amphotericin B, 0.7-1 mg/kg, daily for 1-2 wk followed by itraconazole 200 mg 3 times a day for 3 days followed by 200 mg twice a day for a total duration of 12 wk. For children, itraconazole 5-10 mg/kg or deoxycholate amphotericin B, 1 mg/kg daily.
Chronic cavitary		Itraconazole 200 mg 3 times a day for 3 days followed by twice daily for at least 1 yr and as long as 2 yr.
Disseminated*		
	Acute	Lipid-formulated amphotericin B, 3-5 mg/kg, or deoxycholate amphotericin B, 0.7-1 mg/kg, daily for 1-2 wk followed by itraconazole 200 mg 3 times a day for 3 days followed by 200 mg twice a day for at least 12 mo. For children, deoxycholate amphotericin B (1 mg/kg) daily for 4-6 wk or 2-4 wk followed by itraconazole 5-10 mg/kg daily. Total duration = 3 mo.
	Chronic	Itraconazole 200 mg 3 times a day for 3 days followed by 200 mg twice a day for at least 1 yr. Serum levels should be monitored to ensure adequate concentrations.
Central nervous system		Liposomal amphotericin B, 5 mg/kg daily for 4-6 wk followed by itraconazole administered as above for at least 1 yr and resolution of symptoms and negative cerebrospinal fluid antigen.
Mediastinal		
	Lymphadenitis	No treatment. If symptomatic (e.g., dysphagia), itraconazole 200 mg twice daily for 12 wk. Corticosteroids (60 mg with a rapid taper) may be used to diminish lymph node size.
	Granuloma	Same as lymphadenitis. Corticosteroids are not necessary.
	Fibrosis	Surgical intervention with stents. Antifungals are not useful.
Rheumatologic	Arthralgias, etc.	Nonsteroidals
Pericarditis		Nonsteroidals or corticosteroids. If the latter, treat with itraconazole (200 mg × 3 for 3 days and then once a day) until corticosteroids have been discontinued.
Endocarditis/ Endovascular		Surgical removal of the valve combined with lipid-formulated amphotericin B, 5 mg/kg daily for 6 wk. Lifelong suppression may be considered in some who are not surgical candidates with itraconazole 200 mg once or twice a day.

Prophylaxis of Immunocompromised Persons

- For immunosuppressed patients who have a high risk of acquiring histoplasmosis from the environment because of their work or their residence, **itraconazole, 200 mg/day**, is useful.
- Such patients would include those with AIDS whose CD4 cell count is less than 150/µL or those who require potent immunosuppressive therapy.
- In the former group, prophylaxis with itraconazole reduced the incidence of infection by more than twofold.
- Another indication for prophylaxis in immunosuppressed patients would be for those residing in areas that have a high incidence of infection, as defined by at least 10 cases/100 patient-years.

Coccidioidomicosi

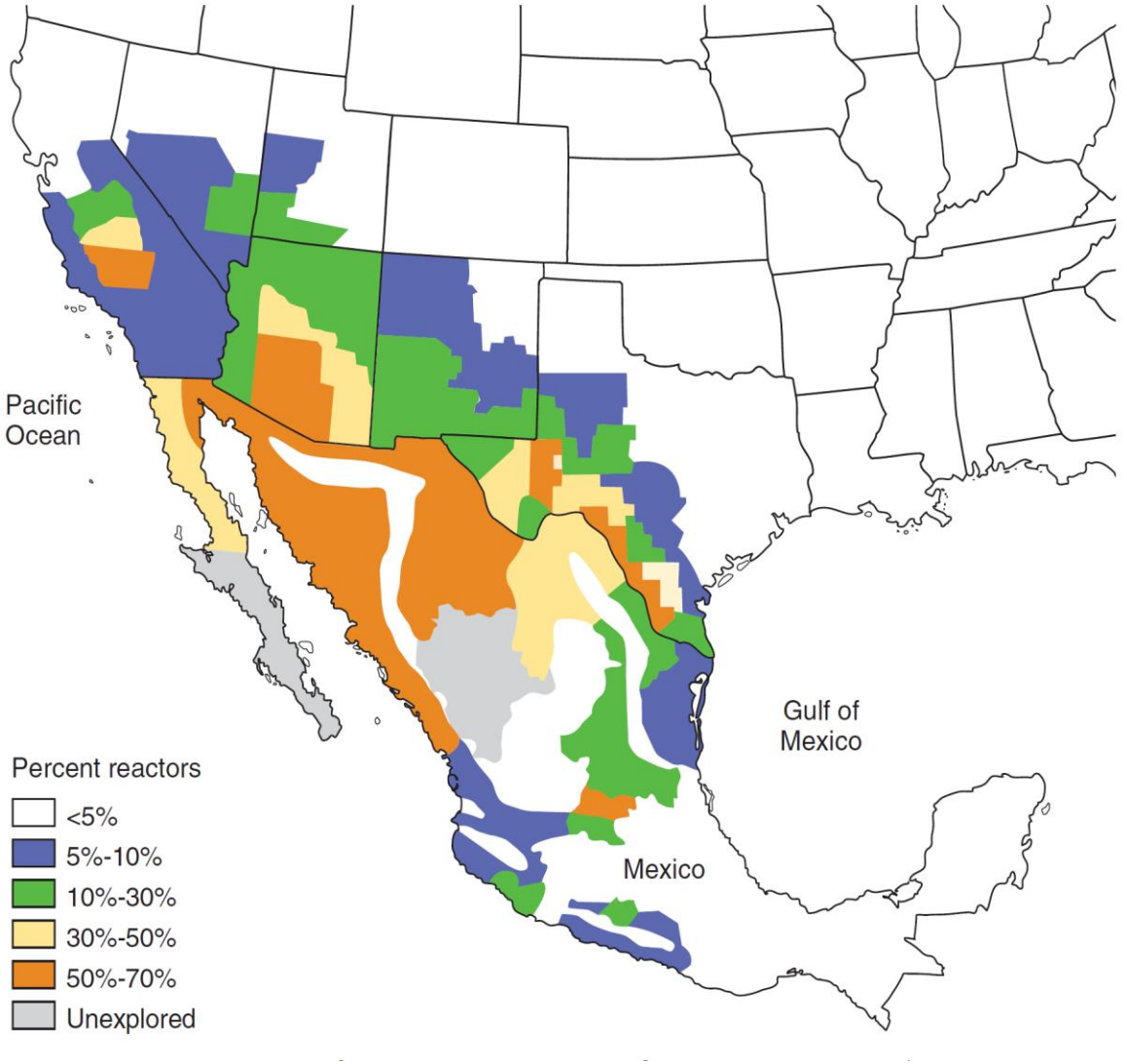
Definition

- The dimorphic fungi, *Coccidioides immitis* and *Coccidioides posadasii*, cause a systemic fungal infection, coccidioidomycosis, also known as San Joaquin Valley fever.

Epidemiology

- Coccidioidomycosis is endemic to arid regions of the Western Hemisphere.
- Approximately 150,000 new U.S. infections occur annually with **60% originating in Arizona and 30% in California**. Of these, 50,000 produce significant illness.
- Infections most frequently occur during dry seasons, and the incubation period until first symptoms ranges from 1 to 3 weeks.
- The most common illness is a **community-acquired pneumonia**, lasting weeks to months whether treated or not with antifungal agents.

Dermal hypersensitivity mapping of the endemic intensity of coccidioidomycosis



Nguyen C, et al. **Clin Microbiol Rev.** ***2013;26:505-525.***

MANAGEMENT OF COCCIDIOIDOMYCOSIS

The three components of managing coccidioidal infections are

1. assessment of the need for intervention,
2. selection of antifungal agents for patients who would benefit from treatment, and
3. choice of surgical procedures for debridement and reconstruction of destructive lesions.

Antifungal Treatment Options

- Of the several commercially available oral azole antifungal drugs, **fluconazole has become the most frequently prescribed for uncomplicated coccidioidal pneumonia**. No clinical studies exist to guide the optimal dose or duration of fluconazole or other antifungal therapy for persons with primary pulmonary coccidioidomycosis.
- If treatment of early uncomplicated coccidioidal infection is instituted, the usual dose for adults is **400 mg daily**. Some experts would recommend **800 mg daily**. The duration is not certain, although many experts would recommend a **treatment duration ranging from 3 to 6 months or longer**, depending on the clinical response. Treatment can be discontinued when the patient's signs, symptoms, and inflammatory markers have resolved, and serologies and radiographs have stabilized. Complete serological resolution is not necessary to discontinue medications.

Antifungal Treatment and Outcome of 71 Solid Organ Transplant Recipients With Coccidioidomycosis

Antifungal Treatment Strategy	No. Treated	No. Survived	% Survival
No treatment	8	2	25
AmB alone	17	5	29
AmB with concurrent azole	9	3	34
Amphotericin followed by azole	12	10	83
AmB plus azole, either sequential or concurrent (not specified)	5	5	100
Azole alone	15	13	87
Echinocandin alone	1	0	0
Multiple sequential agents including AmB and azoles	3	3	100
Surgical excision alone	1	1	100
Total	71	42	59

Paracoccidioidomycosis

- Paracoccidioidomycosis (PCM) is caused by *Paracoccidioides brasiliensis*, which contains four different phylogenetic lineages (S1, PS2, PS3, and PS4). A new species, *Paracoccidioides lutzii*, has been recognized within *P. brasiliensis* and also causes PCM.
- These fungi are restricted to **Latin American countries** in unknown habitats.
- The largest endemic areas are found in **Brazil**.
- Most patients are males and work (or have worked) in agriculture within the endemic areas.
- Two progressive disease forms exist:
  1. acute/subacute in children, adolescents, and immunocompromised individuals and
  2. chronic in adults at least 30 years of age.

Paracoccidioidomycosis: Clinical Manifestations

- In the acute/subacute form, a severe disease, there is fever, weight loss, lymphadenopathy and hepatosplenomegaly. Multiple skin and mucosal lesions occur in half of the cases.
- In the chronic form, there are pulmonary infiltrates on chest radiographs (>90% of the cases) and lesions in mucous membranes and skin. Adrenal lesions with adrenal insufficiency are common.
- Specific diagnosis is usually late due to confusion with other more prevalent diseases (e.g., tuberculosis). **Lack of physicians' awareness is a problem**.
- In tissues, granuloma formation is an important clue to diagnosis and can resemble sarcoidosis. Budding yeast cells are found in lesions.

Paracoccidioidomycosis: Treatment

- Itraconazole is the treatment of choice for most patients, at 200 to 400 mg/day for 9 to 12 months.
- Amphotericin B deoxycholate is reserved for severe cases, at 1 mg/kg/day until achieving a 2-g total dose. This should be followed by oral medications.
- Trimethoprim-sulfamethoxazole (TMP-SMX) is given as TMP, 160 to 240 mg, and SMX, 800 to 1200 mg per day for 12 to 24 months, depending on disease severity.
- Regular follow-up observations (clinical, laboratory oriented) are mandatory.

Antifungal Therapy for Paracoccidioidomycosis

ANTIFUNGAL PRESCRIBED (ADMINISTRATION ROUTE)	MINIMAL TREATMENT DURATION BASED ON ORGAN INVOLVEMENT*	DOSE	ADVERSE EFFECTS	RESPONSE (%)	RELAPSES (%)
TMP-SMX (PO/IV)	Minor: 12 mo Moderate: 18-24 mo	*Adults* TMP: 160-240 mg/day SMX: 800-1200 mg/day Divided into two doses per day *Children* TMP: 8-10 mg/kg SMX: 40-50 mg/kg Divided into two doses per day	Leukopenia Hypersensitivity-reactions, such as rash	80	20
Amphotericin B deoxycholate (IV)	Until patient improves and can be treated by the oral route Achieve a total dose of 2 g†	1 mg/kg/day	Nephrotoxicity Hypokalemia Nausea/vomiting Fever Anemia	70	25
Ketoconazole (PO)	9-12 mo	200-400 mg/day	Hormonal alterations Increase in hepatic enzymes Nausea/vomiting	90	11
Itraconazole (PO)	6-9 mo	*Adults* 600 mg/day for 3 days; continue 200 mg/day *Children (<30/kg and >5 yr)* 5-10 mg/kg/day	Nausea/vomiting ↑ Hepatic enzymes Drug interactions	94-98	3-5
Voriconazole (PO/IV)	6 mo	Initial dose: 400 mg each 12 hr for one day, then 200 mg each 12 hr Diminish the dose to 50% if weight is <40 kg	Visual alterations ↑ Hepatic enzymes Skin rash Photosensitivity Hallucinations Periostitis	88	No data

PENICILLIOSIS MARNEFFEI

- *Penicillium marneffei*, recently renamed *Talaromyces marneffei* is a thermally dimorphic fungus that causes lifethreatening disseminated infection (penicilliosis marneffei) in a geographically distinct area of the world.
- Endemic to **Southeast Asia**, *P. marneffei* infection was extremely rare before the AIDS epidemic: fewer than 30 cases had been described since the first human infections in 1959 and 1984.
- Between 1984 and 2004, more than 6000 *P. marneffei* infections were diagnosed in Thailand.
- Infection with *P. marneffei* has a limited geographic distribution, affecting persons residing in or those who have visited Southeast Asia or southern China.
- Endogenous cases have been reported from Myanmar (Burma), Hong Kong, Indonesia, Laos, Malaysia, Singapore, Taiwan, Thailand, Vietnam, and the Guangxi province of China.

PENICILLIOSIS MARNEFFEI: CLINICAL MANIFESTATIONS

- Patients typically present with a chronic illness averaging 4 weeks in duration associated with low-grade fever, weight loss, and one or more skin lesions.
- Apart from the skin lesions, disease is quite similar in presentation, course, and treatment to that of acute disseminated histoplasmosis.
- The most common clinical characteristics are fever, malaise, anemia, leukocytosis, weight loss, and, in 60% to 70% of patients, skin lesions.
- Fungemia, generalized lymphadenopathy, and cough are reported in more than half of patients. Subcutaneous and mucosal lesions, diarrhea, colonic lesions, hepatomegaly with or without splenomegaly, hemoptysis, osteoarticular lesions, and pericarditis have also been described.
- Mortality of higher than 80% has been reported in a series of 21 HIV-infected persons with *P. marneffei* meningitis.

PENICILLIOSIS MARNEFFEI: TREATMENT

- Successful treatment of disseminated infection has been reported with amphotericin B with or without the addition of flucytosine.
- Therapy with itraconazole has also been successful, as has voriconazole in smaller series.
- Although no randomized comparative studies have been performed, the failure rates in a study of 86 HIV-infected patients were as follows:
  - 8 of 35 patients (22.9%) taking amphotericin B;
  - 3 of 12 (25%) taking itraconazole;
  - and 7 of 11 (63.6%) taking fluconazole.
- Excellent response (97.3%) was achieved with a regimen of intravenous amphotericin B for 2 weeks (0.6 mg/kg/day) followed by oral itraconazole for 10 weeks (200 mg twice daily) in 74 HIV-infected patients.
- Secondary prophylaxis in HIV-infected patients with itraconazole (200 mg once daily) has been suggested to prevent relapse.

CASE REPORT

WILEY mycoses Diagnosis, Therapy and Prophylaxis of Fungal Diseases

First-in-man observation of *Talaromyces marneffei*-transmission by organ transplantation

Frederik Hermans[1] | Sien Ombelet[2,3] | Karlien Degezelle[4] | Dries Testelmans[1] | Dirk E. Van Raemdonck[5,6] | Geert M. Verleden[1,7] | Eric K. Verbeken[8] | Pascal Van Bleyenbergh[1] | Katrien Lagrou[2,3] | Robin Vos[1,7]

***Mycoses* 2016; 1–5**

First-in-man observation of *Talaromyces marneffei*-transmission by organ transplantation

- A 61-year-old, Belgian Caucasian male underwent a bilateral lung transplantation in May 2015 for smoking-related emphysema.
- The donor was a 71-year-old, Belgian Caucasian male, without medical antecedents, except arterial hypertension, who had suffered from a haemorrhagic cerebrovascular accident and became a multi-organ donor after brain death.
- Four months after transplantation, 26 days after cessation of valganciclovir and amphotericin prophylaxis, the recipient presented with fatigue, fever, oral ulcers, anorexia, diarrhoea and diffuse abdominal pain since one week.

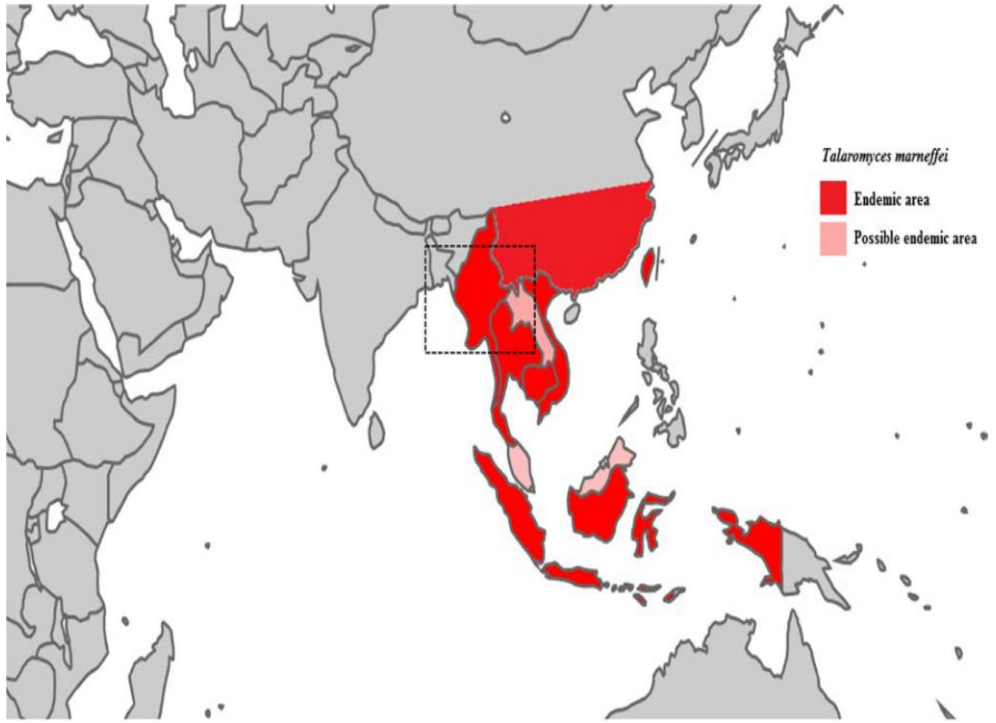
Hermans F, et al. *Mycoses* 2016; 1–5

First-in-man observation of *Talaromyces marneffei*-transmission by organ transplantation

- Surprisingly, repeated blood cultures, taken on admission and during the following days because of ongoing fever, demonstrated fungal hyphae after a median of 42.3 (30.3-83.0) hours of incubation.
- Yeast-like colonies grew upon subculture of the positive blood culture bottles on blood agar at 36.5°, while velvety, grey-green growth with a diffusing red pigment was noticed on Sabouraud agar incubated at room temperature, suggestive for *Talaromyces* species

Hermans F, et al. *Mycoses* 2016; 1–5

- *Penicillium marneffei,* recently renamed *Talaromyces marneffei* is a thermally dimorphic fungus that causes lifethreatening disseminated infection (penicilliosis marneffei) in a geographically distinct area of the world.
- *T. marneffei* is endemic in South-East Asia, but is not prevalent elsewhere.
- Most of the published cases from other regions had previously travelled to South-East Asia, notably Thailand, Vietnam, Hong Kong, Southern China, Taiwan, India, Indonesia, Cambodia or Laos.



First-in-man observation of *Talaromyces marneffei*-transmission by organ transplantation

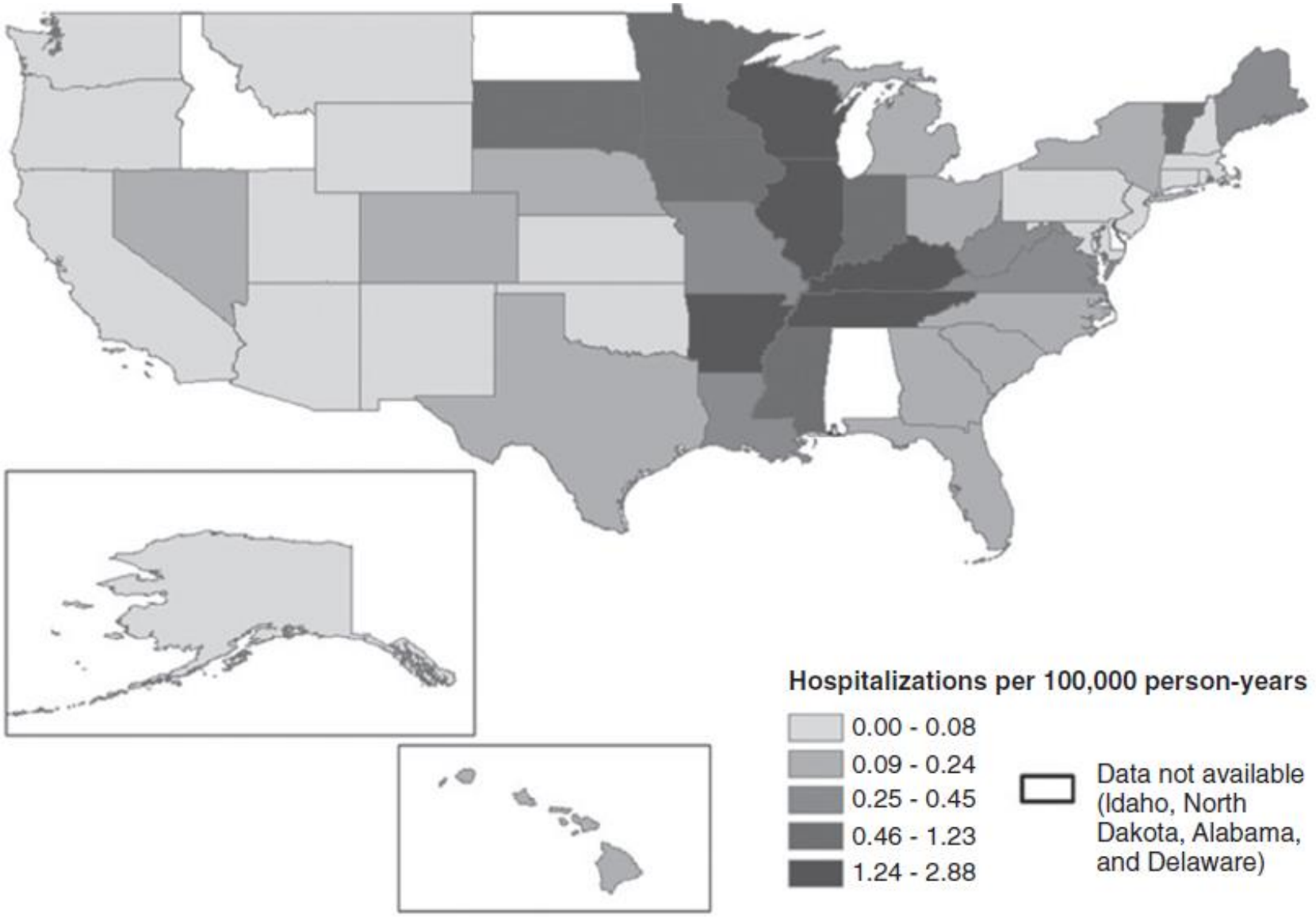
- Thorough travel history of our lung transplant recipient revealed neither travelling to an endemic region since transplantation nor any contact with people returning from South-East Asia, making *T. marneffei* infection in Belgium unlikely.
- Thus, donor-related transmission was suspected. Contact with the donor's relatives confirmed that **he had travelled to Myanmar three months before expiring**, visiting several caves, pagodas and meeting local inhabitants in rural areas during a 20-day round-trip
- Therefore, donor infection likely occurred during this trip, after which latent pulmonary *T. marneffei* infection was present, resulting in penicilliosis in our lung transplant recipient due to concurrent use of immunosuppressive therapy and cessation of antifungal prophylaxis with inhaled amphotericin-B lipid complex.

Hermans F, et al. *Mycoses* 2016; 1–5

Blastomycosis

- Blastomycosis is caused by the dimorphic fungus *Blastomyces dermatitidis*.
- Infection begins when the organism, which exists in nature in the mold or mycelial phase, is inhaled into the host's lungs and then converts to the yeast phase at body temperature.
- It is found mostly in **North America** but has been isolated rarely in disparate parts of the world.
- Both pulmonary and extrapulmonary manifestations occur, but there is often a delay in making the diagnosis because the infection can mimic a number of other more common conditions.
- The endemic area for *B. dermatitidis* is North America and **includes the states bordering the Mississippi and Ohio Rivers, the Midwestern states and Canadian provinces that border the Great Lakes, and a small area in New York and Canada along the St. Lawrence River**.
- *B. gilchristii* is more restricted geographically than *B. dermatitidis*, being found in Wisconsin, Minnesota, the St. Lawrence waterway, and western Ontario, Canada.

Map of age-adjusted blastomycosis-associated hospitalization incidence in the United States—2000-2011.



BLASTOMYCOSIS: TREATMENT

- Resolution of chronic blastomycosis without antifungal therapy is uncommon, and untreated blastomycosis has been associated with mortality rates approaching 60%.
- Thus, all patients with chronic pulmonary and extrapulmonary blastomycosis should receive antifungal therapy.
- Itraconazole, an oral triazole with broad-spectrum antifungal activity, is now considered to be the drug of choice for patients with non–life-threatening, non-CNS blastomycosis.
- Most recommend at least 6 months of itraconazole after the lesion starts to definitely improve but at least 12 months of therapy for bone infection.
- Amphotericin B remains the drug of choice for patients with severe, life-threatening or CNS disease.

INDICATION	THERAPY
Moderately severe or severe pulmonary blastomycosis or immunosuppressed patients	Liposomal amphotericin B 3-5 mg/kg or conventional amphotericin B 0.7-1 mg/kg once daily for 6-8 wk. After improvement, consider switching to itraconazole 200 mg PO twice daily.†
Pregnant	Liposomal amphotericin B 3-5 mg/kg or conventional amphotericin B 0.7-1 mg/kg once daily for 6-8 wk.
Brain abscess or meningitis	Amphotericin B as above until improved. For step-down treatment, consider itraconazole 200 mg PO 2-3 times daily, fluconazole 800 mg daily, or voriconazole 6 mg/kg for 2 doses, then 4 mg/kg q12h, IV or PO.
Mild-to-moderate pulmonary blastomycosis	Itraconazole 200 mg PO once or twice daily.†

Sporotrichosis

- *Sporothrix schenckii* sensu lato, a group of closely related species, causes sporotrichosis and are dimorphic fungi, with budding yeast in tissue and a mold in culture
- Sporotrichosis has been reported from locations around the globe, but most case reports come from the tropical and subtropical regions of the Americas.
- Treatment guidelines for sporotrichosis have been proposed.
- Due to its convenience and consistent efficacy, itraconazole at 200 mg/day has become the therapy of choice for cutaneous sporotrichosis.
- Therapy with itraconazole is given for 2 to 4 weeks beyond complete resolution of all lesions and usually requires 3 to 6 months to effect a clinical cure.
- Relapse has been observed on occasion after cessation of therapy. Should relapse develop, a higher dose of itraconazole (200 mg twice daily) may be tried.

Cryptococcosis (*Cryptococcus neoformans* and *Cryptococcus gattii*)

- There are 19 cryptococcal species with two major pathogenic species**, *C. neoformans* and *C. gattii.***

Ecology

- *C. neoformans* (serotypes A and D) found in pigeon guano to rotting trees
- *C. gattii* found in eucalyptus to coniferous trees (landscape of niche may be changing)
- Risk factors for disease (acquired immunodeficiency syndrome [AIDS], corticosteroid treatment, transplantation, cancer, monoclonal antibodies, sarcoidosis, autoantibodies to granulocyte-macrophage colony-stimulating factor, idiopathic CD4 lymphocytopenia); primarily cell-mediated immunity defect

Cryptococcus gattii Serotypes B and C

- Unlike *C. neoformans*, *C. gattii* has never been cultured from bird guano. Furthermore, there appears to be a certain geographic limitation to the occurrence of infections with this variety.
- With this knowledge base, investigators were initially able to culture *C. gattii* from vegetation around and associated with the river red gum trees (Eucalyptus camaldulensis) and forest red gum trees (Eucalyptus tereticornis) in **Australia**.
- Because these trees were exported to other areas of the world where *C. gattii* is also observed, it was reasoned that Eucalyptus species may be a vector for infection.
- However, despite the association of these trees with *C. gattii*, the ongoing outbreak of cryptococcosis on Vancouver Island, British Columbia, found that other trees such as firs, maples, and oaks may also be an ecologic niche for specific strains of *C. gattii.*

Conditions Known or Possibly Associated with Predisposition to *Cryptococcus neoformans* Infections

HIV infection
Lymphoproliferative disorders
Sarcoidosis
Corticosteroid therapy
Hyper-IgM syndrome
Hyper-IgE syndrome
Autoantibodies to GM-CSF
Monoclonal antibodies (e.g., infliximab intercept, adalimumab, alemtuzumab)
Systemic lupus erythematosus*
HIV-negative $CD4^+$ T-cell lymphocytopenia
Diabetes mellitus†
Organ transplantation*
Peritoneal dialysis
Cirrhosis

Clinical Manifestations of Cryptococcosis

Central Nervous System
Acute, subacute, chronic meningitis
Cryptococcomas of brain (abscesses)
Spinal cord granuloma
Chronic dementia (from hydrocephalus)
Lung
Nodules (single or multiple)
Lobar infiltrates
Interstitial infiltrates
Cavities
Endobronchial masses
Endobronchial colonization
Acute respiratory distress syndrome
Mediastinal adenopathy
Hilar adenopathy
Pneumothorax
Pleural effusions/empyema
Miliary pattern
Skin
Papules and maculopapules
Subcutaneous abscess
Vesicles
Plaques
Cellulitis
Purpura
Acne
Draining sinuses
Ulcers
Bullae
Herpetiformis-like
Molluscum contagiosum–like
Eye
Papilledema
Extraocular muscle paresis
Keratitis
Chorioretinitis
Endophthalmitis
Optic nerve atrophy

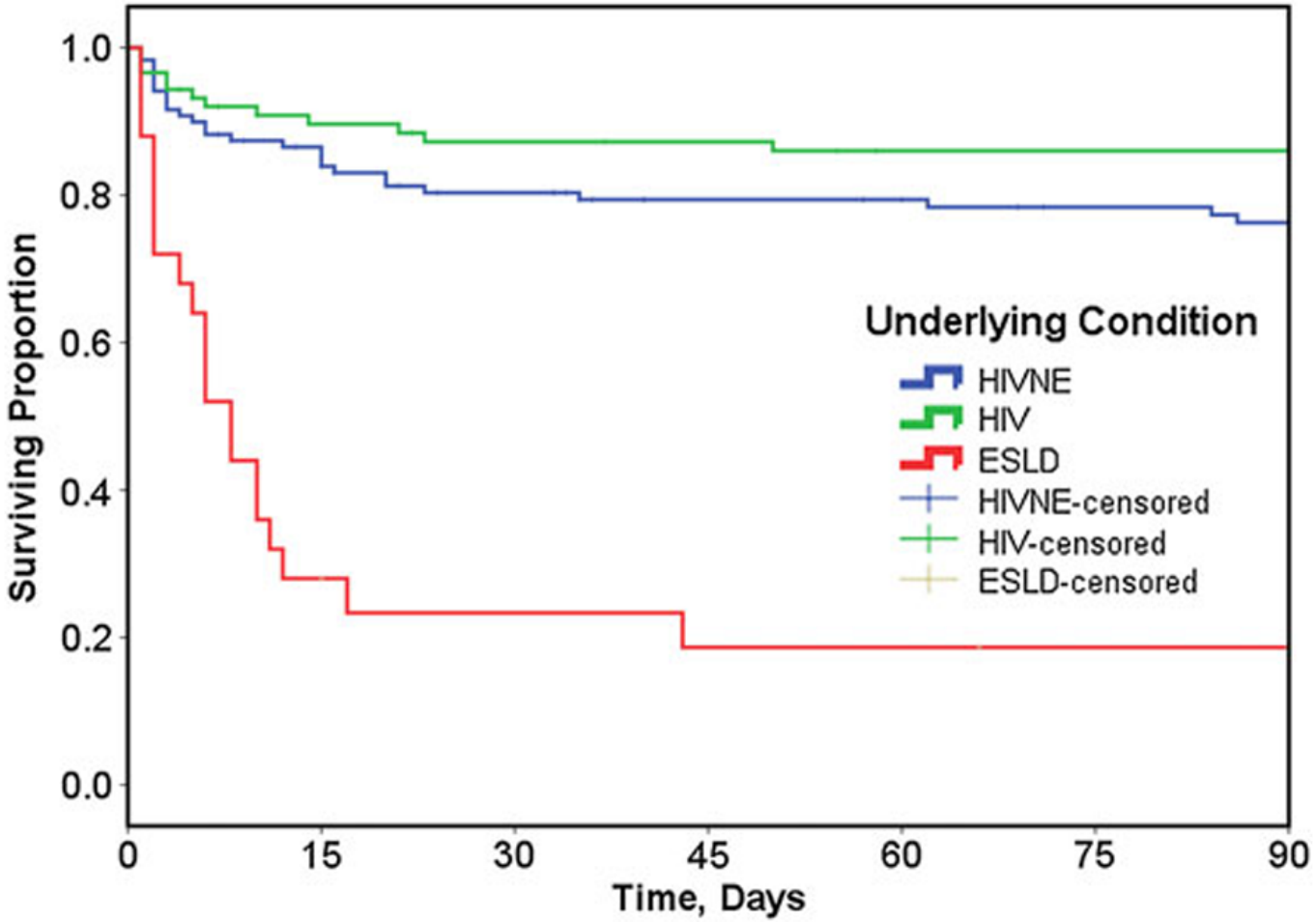
Genitourinary Tract
Prostatitis
Renal cortical abscess
Positive urine culture from occult source
Genital lesions
Bone and Joints
Osteolytic lesion (single or multiple sites)
Arthritis (acute/chronic)
Muscle
Myositis
Heart, Blood Vessels
Cryptococcemia
Endocarditis (native and prosthetic)
Mycotic aneurysm
Myocarditis
Pericarditis
Infected vascular graft
Gastrointestinal Tract
Esophageal nodule
Nodular or ulcerated lesions in stomach or intestines (may resemble Crohn's disease)
Hepatitis
Peritonitis
Pancreatic mass
Breast
Breast abscess
Lymph nodes
Lymphadenopathy
Thyroid
Thyroiditis
Thyroid mass
Adrenal Gland
Adrenal insufficiency
Adrenal mass
Head and Neck
Gingivitis
Sinusitis
Salivary gland enlargement

Invasive Fungal Infections in Patients with Cirrhosis

- Infection is one of the major complications that may increase mortality in cirrhosis by 4 times and is associated with progression of disease and poor outcome.
- Bacterial infections are the most common; however, 4.0%–10.3% of cases of cirrhosis are also complicated by invasive fungal infections, mainly caused by Candida or Aspergillus, presenting as peritonitis, fungemia, and pulmonary infection.
- Notably, cirrhosis also increases the susceptibility to Cryptococcus and is reported as an independent risk factor for cryptococcosis.
- *Cryptococcus neoforman*s and *Cryptococcus gattii* are important causes of cryptococcosis.
- The respiratory tract serves as the most important portal of entry and the infection has been recognized to disseminate through the bloodstream, with the central nervous system being the most common site of dissemination.

Arvaniti V, et al. Gastroenterology. 2010 Oct;139(4):1246-56, 1256.e1-5.

Kaplan-Meier survival curve of 232 patients with cryptococcosis by underlying condition, 2002–2014.



Patients with end-stage liver disease (n=25) had the lowest survival, most dramatically expressed in the first 15 days of the infection.

Mortality was censored after 90 days because it was less likely to be related to cryptococcosis; P<.001.

Spec A, et al. Open Forum Infect Dis. 2015 Dec 15;3(1):ofv197.

Summary of cases series reporting 10 or more episodes of cryptococcosis and endemic mycosis in patients with chronic liver failure

Author, year	Fungal diseases	Number of cases reported	Main clinical manifestations	Proportion of patients that received antifungal treatment	Mortality/Follow-up
Lin, 2015[39]	Cryptococcosis	13 patients	Cryptococcemia/ meningitis	NA	75%/in-hospital
Spec, 2016[40]	Cryptococcosis	25 patients	Meningitis/pulmonary/ Cryptococcemia	72%	80%/90-days
Baddley, 2008[37]	Cryptococcosis	12 patients	Pulmonary/disseminated	NA	NA
Park, 2006[38]	Cryptococcosis	16 patients	Peritonitis	56%	87%/30-days
Singh, 2004[36]	Cryptococcosis	33 patients	Peritonitis/meningitis/ pulmonary	68%	81%/not-mentioned
Blair, 2006[43,93]	Coccidioidomycosis	9 patients	Pulmonary, liver and lung nodules, urinary, lymphadenopathy	88%	0%
Sachdev, 2007[43]	Coccidioidomycosis	2 patients	Pulmonary, cutaneous	100%	50%/5-month
Choudhary, 2016[44]	Histoplasmosis	3 patients	Fever, lymphadenopathy	NA	NA

Lahmer T, et al. Mycoses. 2022 Feb;65(2):140-151.

Cryptococcosis: Treatment recommendations – AST Guidelines 2019

Induction	Duration
CNS disease, disseminated disease, or moderate-to-severe pulmonary disease	
Preferred therapy	
Liposomal amphotericin B 3-4 mg/kg/d or amphotericin B lipid complex 5 mg/kg/d plus 5-flucytosine 100 mg/kg/d[a]	Minimum of 2 wk
Alternative therapy	
Liposomal amphotericin B 3-4 mg/kg/d or amphotericin B lipid complex 5 mg/kg/d	Minimum of 4-6 wk
Consolidation	
Fluconazole 400-800 mg/d	8 wk
Maintenance	
Fluconazole 200-400 mg/d	Minimum of 6-12 mo
Pulmonary disease	
Asymptomatic or mild-to-moderate disease[b]	
Fluconazole 400 mg/d	6-12 mo
Severe pulmonary disease, or azole use not an option	
Same as for CNS disease	

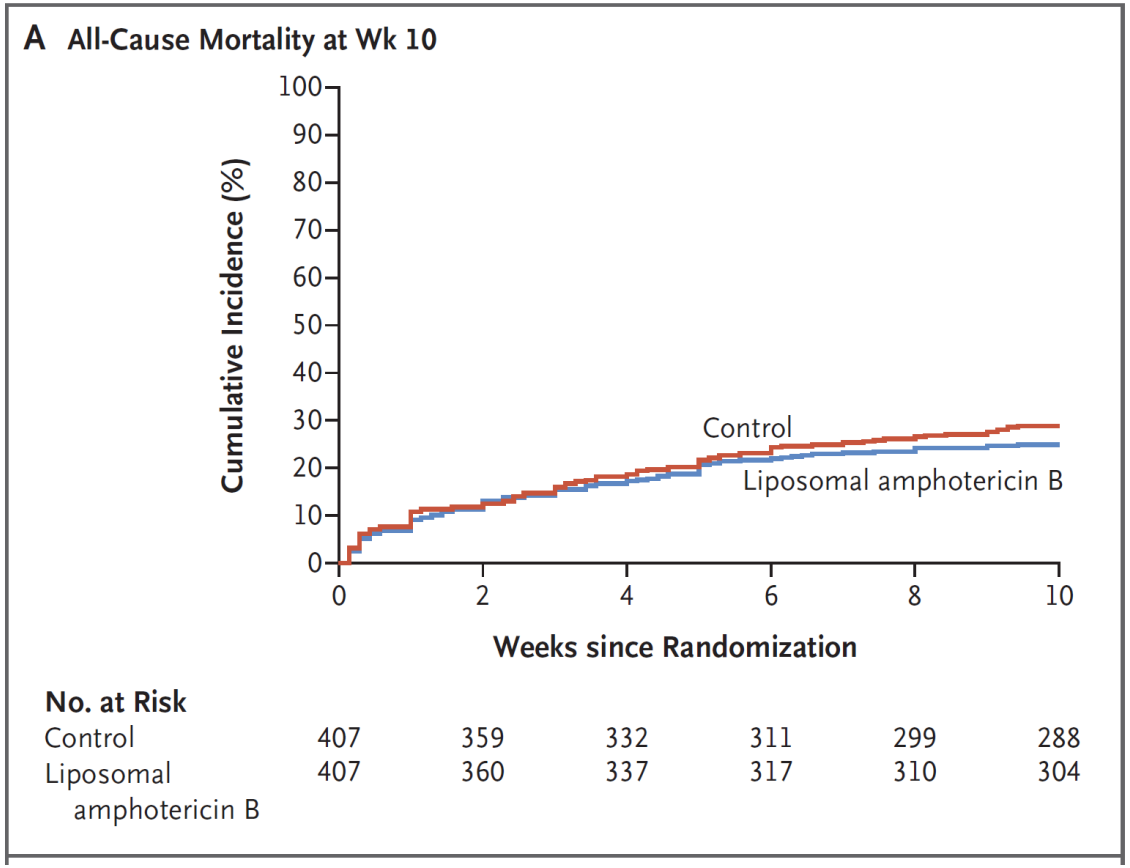
Baddley JW, Forrest GN; Clin Transplant. 2019 Sep;33(9):e13543.

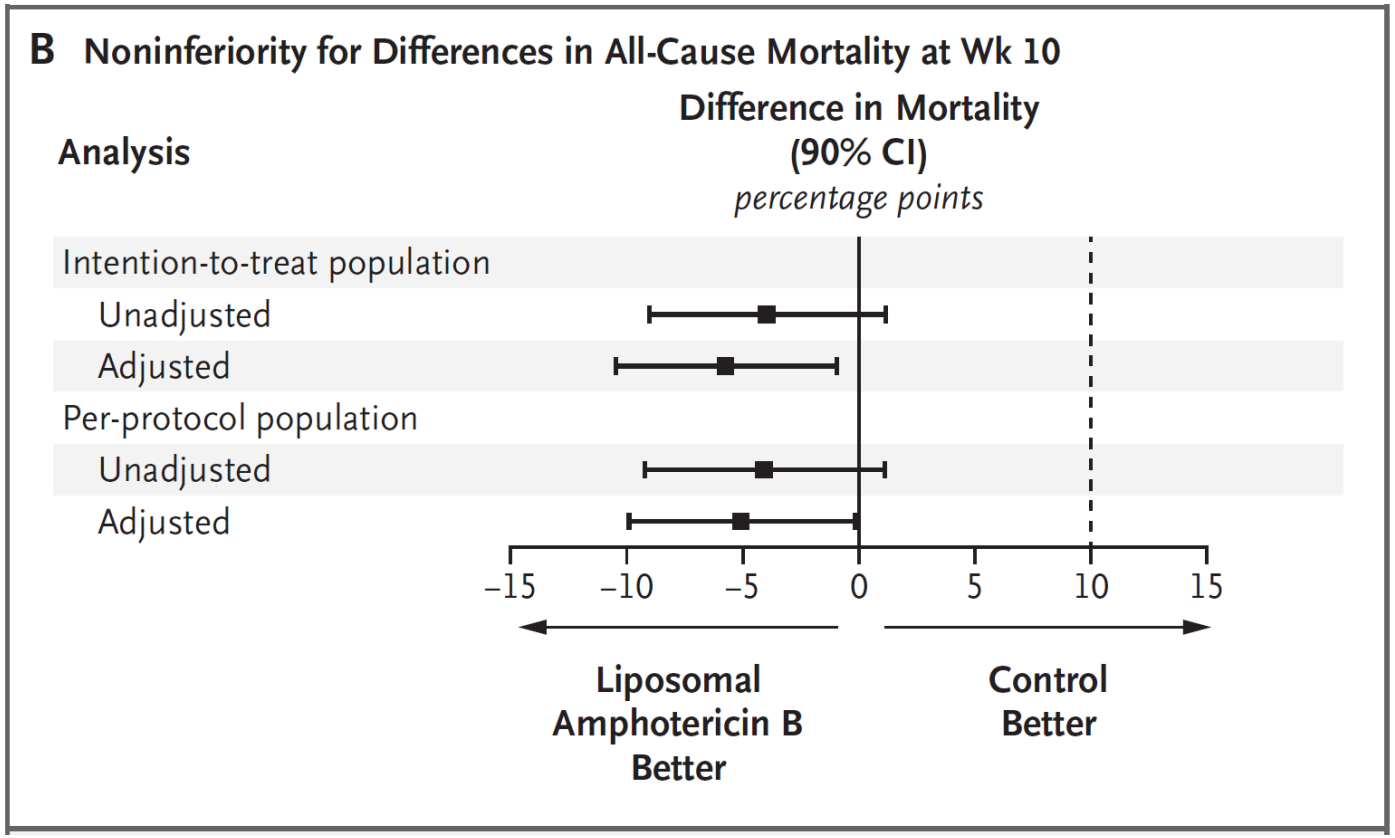
Single-Dose Liposomal Amphotericin B Treatment for Cryptococcal Meningitis

- In this phase 3 randomized, controlled, noninferiority trial conducted in five African countries, we assigned HIV-positive adults with cryptococcal meningitis in a 1:1 ratio to receive either a **single high dose of liposomal amphotericin B (10 mg per kilogram of body weight) on day 1** plus 14 days of flucytosine (100 mg per kilogram per day) and fluconazole (1200 mg per day) or the current World Health Organization–recommended treatment, which includes amphotericin B deoxycholate (1 mg per kilogram per day) plus flucytosine (100 mg per kilogram per day) for 7 days, followed by fluconazole (1200 mg per day) for 7 days (control). The primary end point was death from any cause at 10 weeks; the trial was powered to show noninferiority at a 10-percentage-point margin.
- This trial showed that a single high dose of liposomal amphotericin B given with flucytosine and fluconazole was non inferior to the current WHO recommended standard of care for cryptococcal meningitis and offers a practical treatment for the management for HIV-associated cryptococcal meningitis that is easier to administer and associated with fewer drug-related adverse effects.

Jarvis Jnet al. N Engl J Med. 2022 Mar 24;386(12):1109-1120.

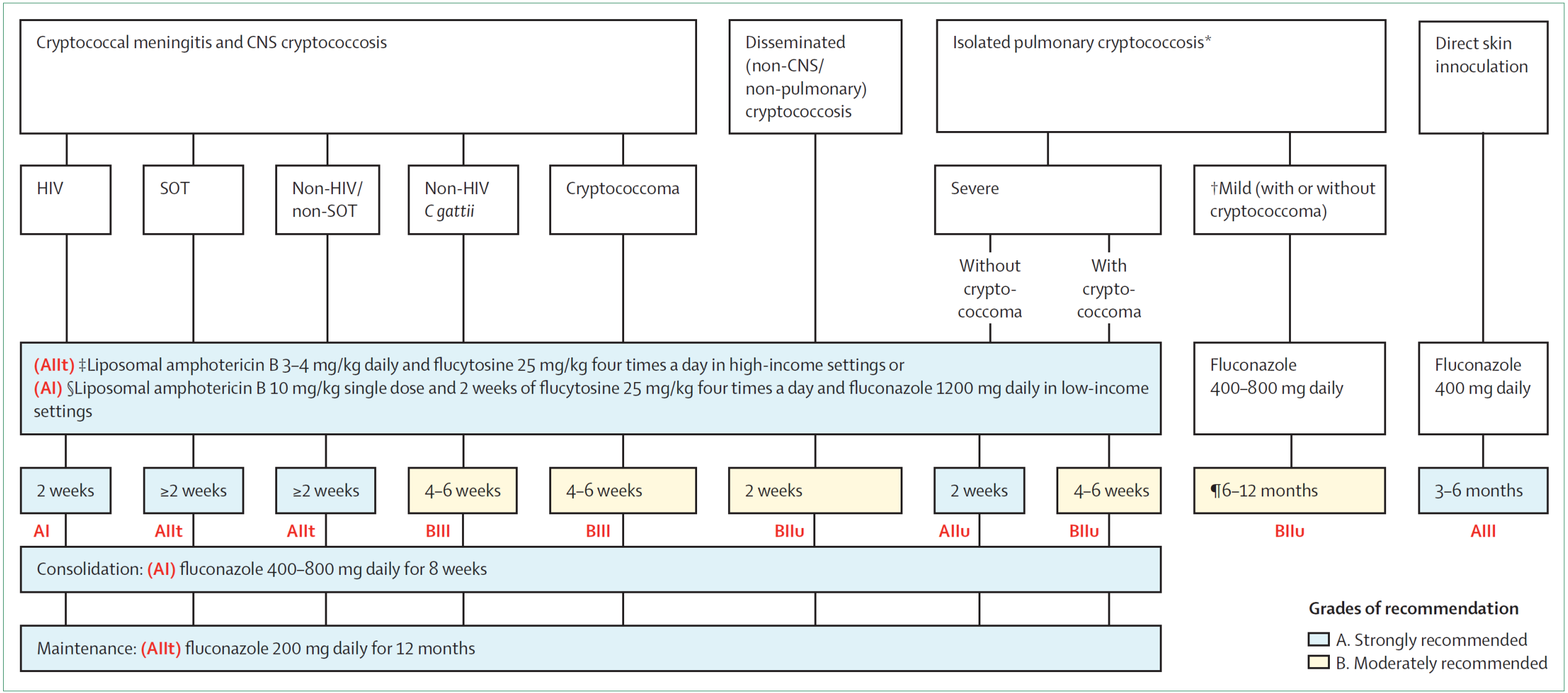
Cumulative All-Cause Mortality Up to Week 10 and Noninferiority Analysis





Jarvis J, et al. N Engl J Med. 2022 Mar 24;386(12):1109-1120.

Global guideline for the diagnosis and management of cryptococcosis: an initiative of the ECMM and ISHAM in cooperation with the ASM



Recommended first-line antifungal therapy by cryptococcosis syndrome

Lancet ID, 2024

Antifungal Treatment Recommendations for Cryptococcal Meningoencephalitis in HIV–Infected Individuals

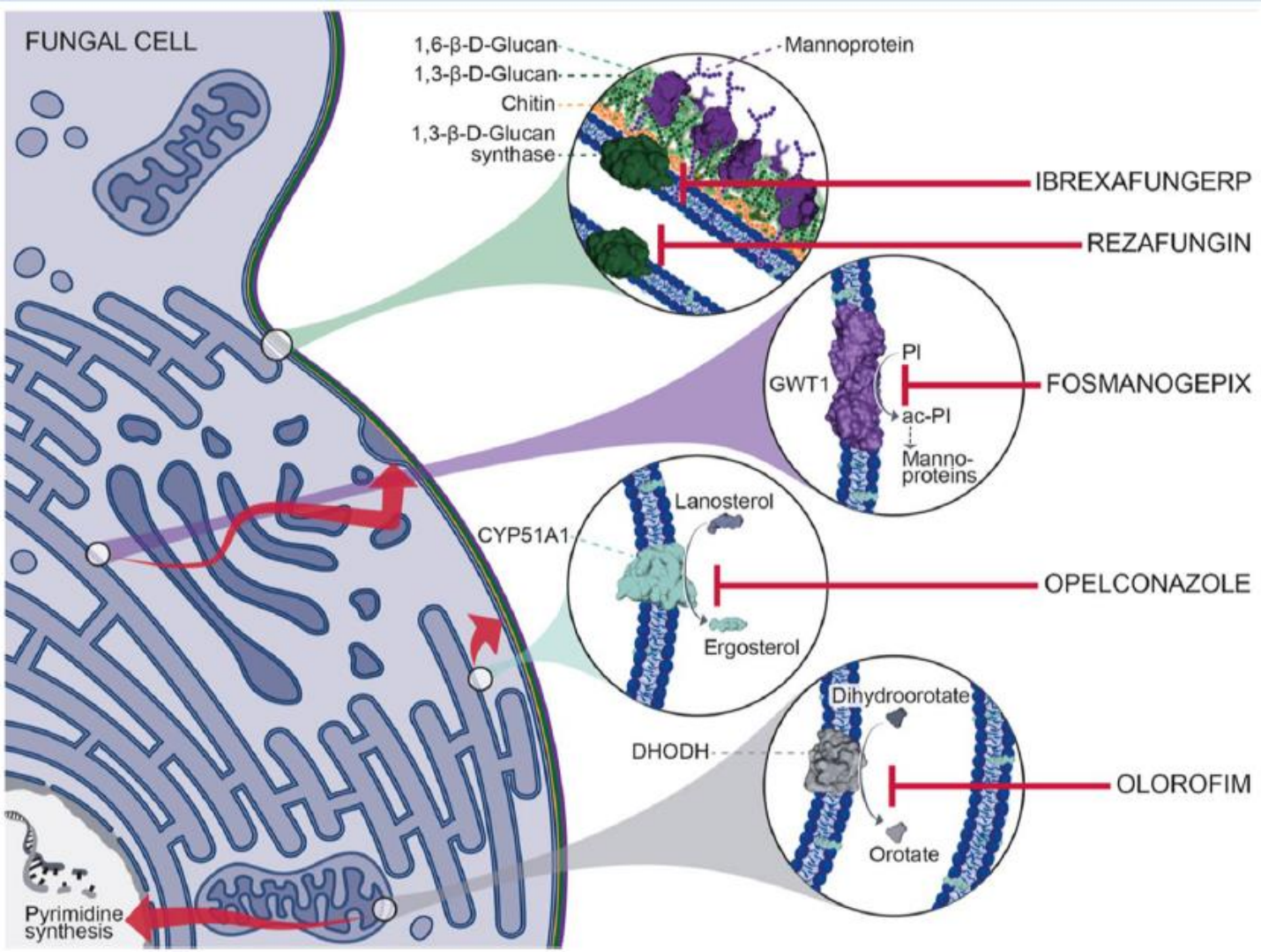
Regimen	Duration	Evidence
Induction therapy		
AmBd (0.7–1.0 mg/kg per day) plus flucytosine (100 mg/kg per day)[a]	2 weeks	A-I
Liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, with renal function concerns) plus flucytosine (100 mg/kg per day)[a]	2 weeks	B-II
AmBd (0.7–1.0 mg/kg per day) or liposomal AmB (3–4 mg/kg per day) or ABLC (5 mg/kg per day, for flucytosine-intolerant patients)	4–6 weeks	B-II
Alternatives for induction therapy[b]		
AmBd plus fluconazole	…	B-I
Fluconazole plus flucytosine	…	B-II
Fluconazole	…	B-II
Itraconazole	…	C-II
Consolidation therapy: fluconazole (400 mg per day)	8 weeks	A-I
Maintenance therapy: fluconazole (200 mg per day)[a]	⩾1 year[c]	A-I
Alternatives for maintenance therapy[b]		
Itraconazole (400 mg per day)[d]	⩾1 year[c]	C-I
AmBd (1 mg/kg per week)[d]	⩾1 year[c]	C-I

New antifungal drugs in the clinical pipeline

Agent	Phase 1	Phase 2	Phase 3	Types of Fungal Infections for Enrollment in Clinical Trials
Olorofim (F901318)	NCT05101187			Invasive aspergillosis
	NCT03583164			Invasive infections due to *Lomentospora prolificans, Scedosporium* spp., *Aspergillus*, and other resistant fungi
Rezafungin (CD101)	NCT03667690			Candidemia and/or invasive candidiasis (Completed)
	NCT04368559 (ReSPECT)			Antifungal prophylaxis in adults with allogeneic blood or bone marrow transplant
Oteseconazole (VT-1161)	NCT03562156 & NCT03561701 (VIOLET)			Recurrent vulvovaginal candidiasis (Completed)
Fosmanogepix (APX001)	NCT05421858			Candidemia and/or invasive candidiasis
	NCT04240886			Invasive infections due to *Aspergillus* or rare molds
Opelconazole (PC945)	NCT05037851			Antifungal prophylaxis or pre-emptive therapy against pulmonary aspergillosis in lung transplant
Encochleate Amphotericin B (MAT2203 or CAMB)	NCT02971007			Moderate to severe vulvovaginal candidiasis (Completed)
	NCT04031833 (EnACT)			Cryptococcal meningitis in HIV+ patients
	NCT02629419			Mucocutaneous candidiasis in patients who are refractory or intolerant to standard non-intravenous therapies
Ibrexafungerp (SCY-078) *approved for vulvovaginal candidiasis in U.S.	NCT05399641			Complicated vulvovaginal candidiasis
	NCT03672292 (SCYNERGIA)			Invasive pulmonary aspergillosis combined with voriconazole
	NCT03363841 (CARES)			Candidiasis caused by *Candida auris*
	NCT03059992 (FURI)			Invasive fungal infections in patients who are refractory or intolerant to standard therapies

Neil A. R. Gow, et al. Nat Commun. 2022 Sep 12;13(1):5352.

Mechanism of action of novel antifungal drugs



Hoenigl M, et al. Drugs. 2021 Oct;81(15):1703-1729.

Future directions

- The landscape of IFD continues to evolve.
- Although more resistant fungal infections are on the horizon, the availability of novel preparations of antifungal agents provides better opportunities in prophylaxis and treatments of IFD.
- The development of novel point-of-care fungal diagnostic tests coupled with refinements in TDM may shape the future of fungal infection management.

CONCLUSIONS

- Invasive fungal diseases are a growing public health threat worldwide
- These infections, often life-threatening and costly to treat, occur predominantly among immunocompromised hosts including hematological malignancy patients, recipients of hematopoietic stem cell transplantation or solid organ transplantation as well as critically ill patients.
- In recent years, the incidence of IFD has increased significantly, due to the growing numbers of immunocompromised patients and the marked expansion of patient groups at risk of these infections (e.g. those with trauma/surgery, pancreatitis, and diabetes mellitus).
- In particular, the rising prevalence of triazole resistant Aspergillus spp. and echinocandin-resistant Candida spp. is of major concern