The Endemic Mycoses

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Objectives

- Understand the epidemiology of the endemic mycoses and how they are changing with climate change
- Understand the clinical features, diagnosis, and treatment of the endemic mycoses

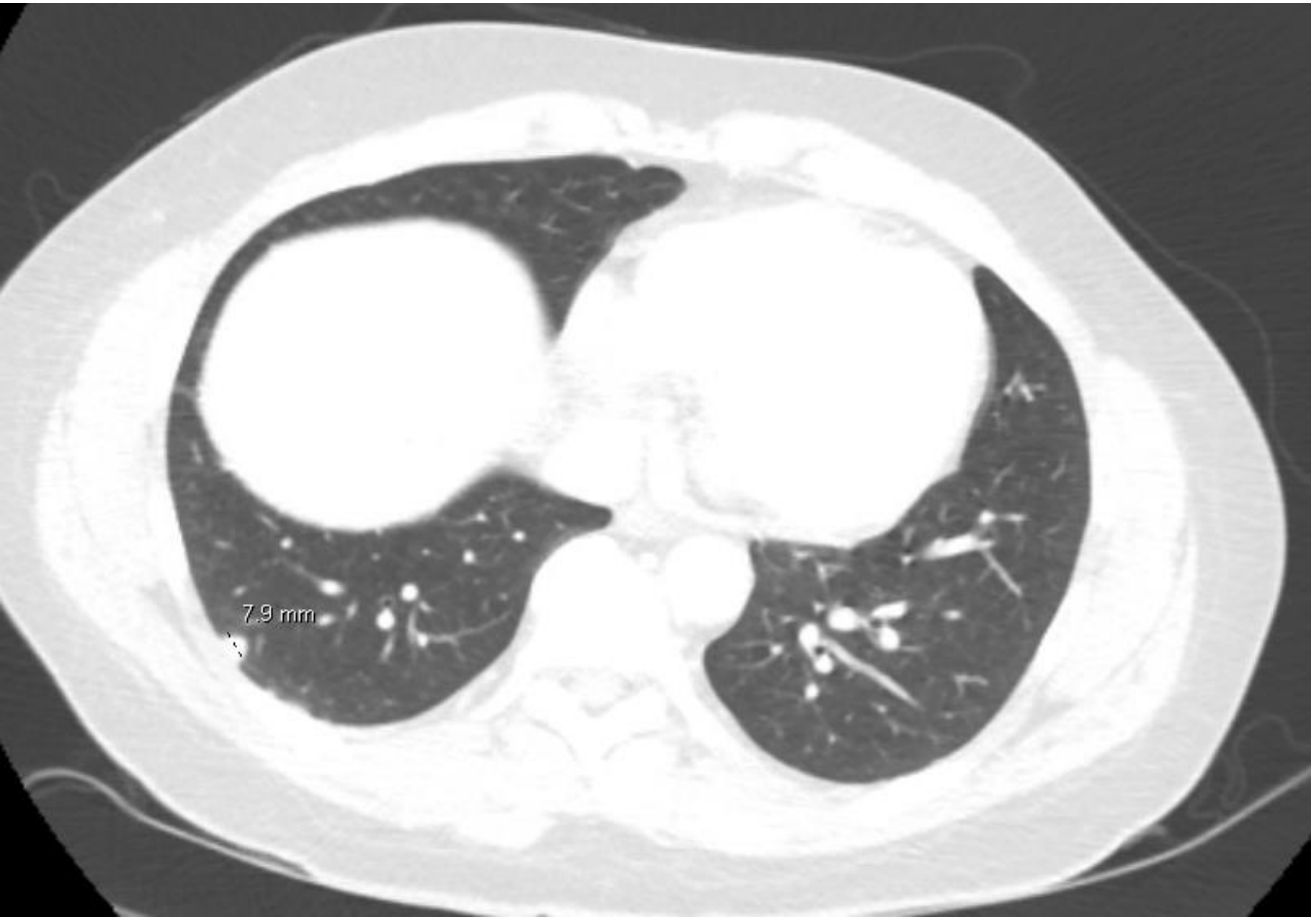
Disclosures

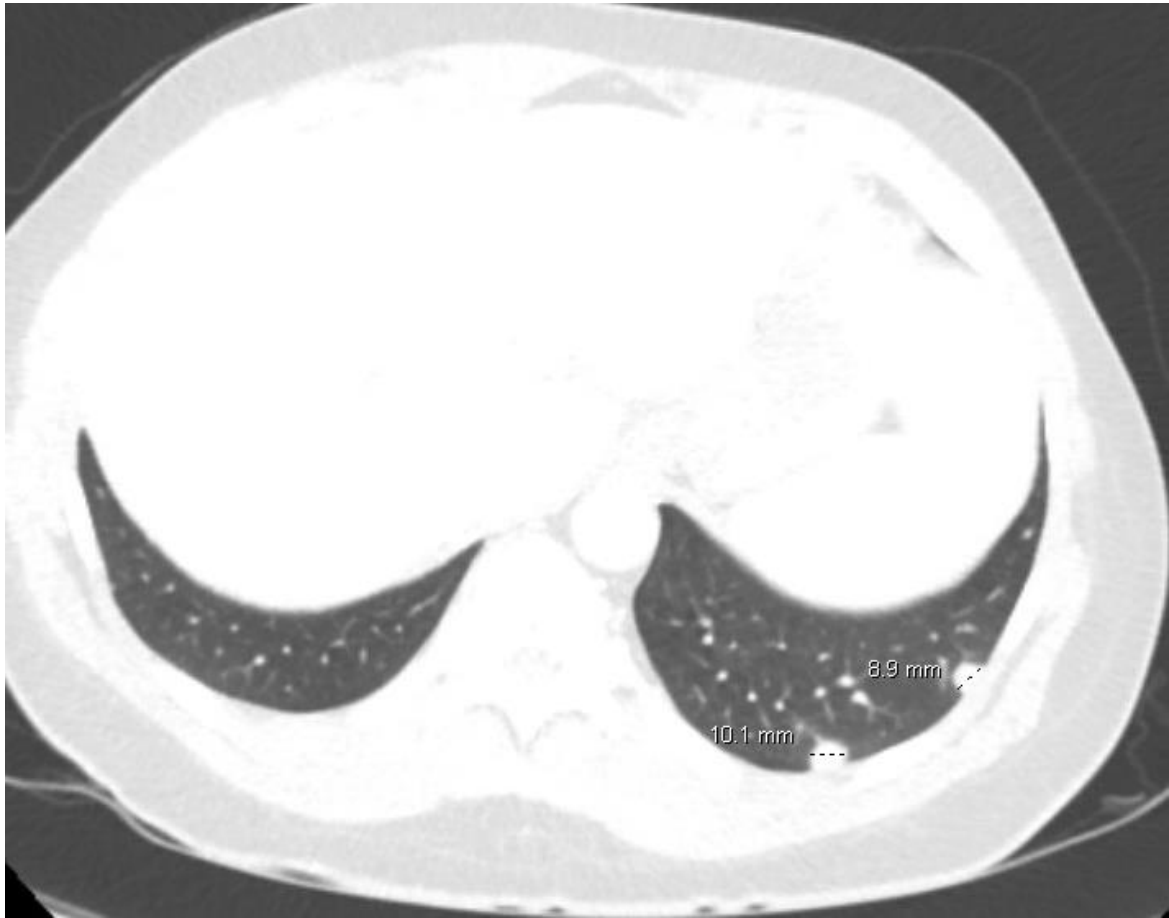
- None

The Case

- 55 year old gentleman with a past medical history of a transplanted kidney, presents with a 2 week history of fever, headache and body aches. 1 month ago went to visit family in Youngstown, Ohio. 2 weeks later both he and his wife developed headache and myalgia, but wife recovered and his symptoms continued. COVID testing at home was negative x2. 1 week ago fever and sweats developed.
- Cr up from 1.0 to 1.5, lactate 2.7, no leukocytosis, chest x-ray is clear, UA unrevealing, and comprehensive respiratory panel negative.
- Exam is unrevealing

CT

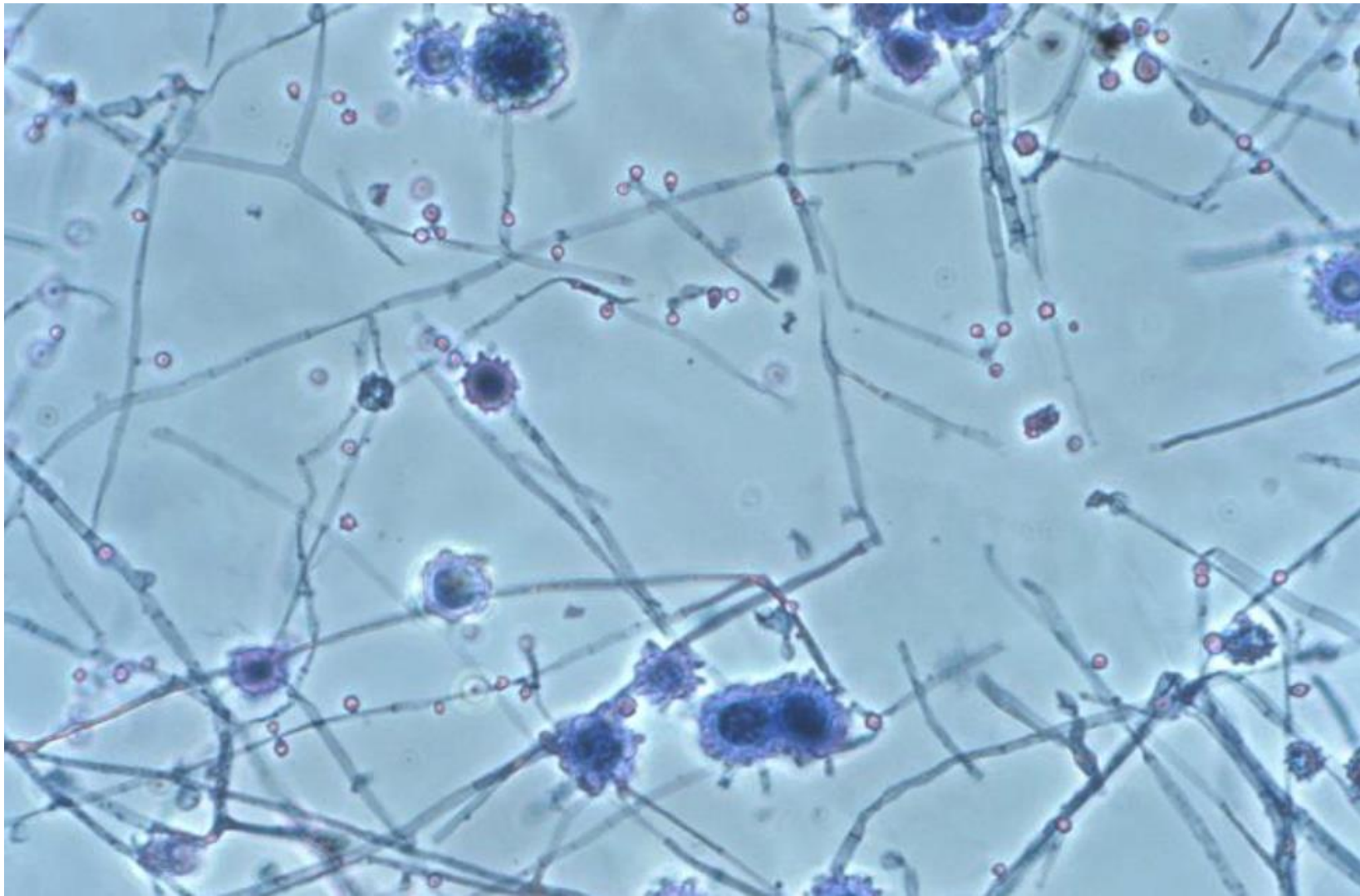




The world of fungi

- Are their own eukaryotic kingdom, along with plants, animals, protozoa, and chromista (algae to malaria)
- 1-5 million estimated fungal species
- Have a cell wall with chitin
- Over 300 species known to infect humans, especially in those who are immunocompromised
- Endemic mycoses are environmental dimorphic fungi, growing as yeasts at 37^{o} and mold at room temperature. In the US they are blastomycosis, coccidioidomycosis, histoplasmosis.

Histoplasma



Histoplasma capsulatum

- Lives in soil, particularly soil contaminated with bird and bat guano, aka droppings
- Infection acquired through inhalation of mycelial fragments and microconidia, usually from disturbance of contaminated material. Occasionally can be from a transplanted organ

Ecology and epidemiology

- Soil based fungus in which cases have been reported from every continent except Antarctica
- Most highly endemic regions in the US are the Ohio and Mississippi river valleys
- Favorable conditions thought to require mean temperatures of 22° to 29°C, annual precipitation of 35-50 inches, and relative humidity of 67 to 87%.
- Often associated with decaying bird and bat guano. Birds do not get infected, whereas bats do shed it

Ecology and epidemiology

- Disruption of the soil by excavation or construction releases infectious elements that are inhaled and settle into the lungs
- Individuals involved in recreation or occupations that expose them to disrupted soil are at highest risk of infection
- Spelunkers, agricultural workers, construction workers, landscapers, cleaners of chicken coops, or those involved in renovation of buildings inhabited by birds or bats are at highest risk

Classic distribution of US histoplasma cases

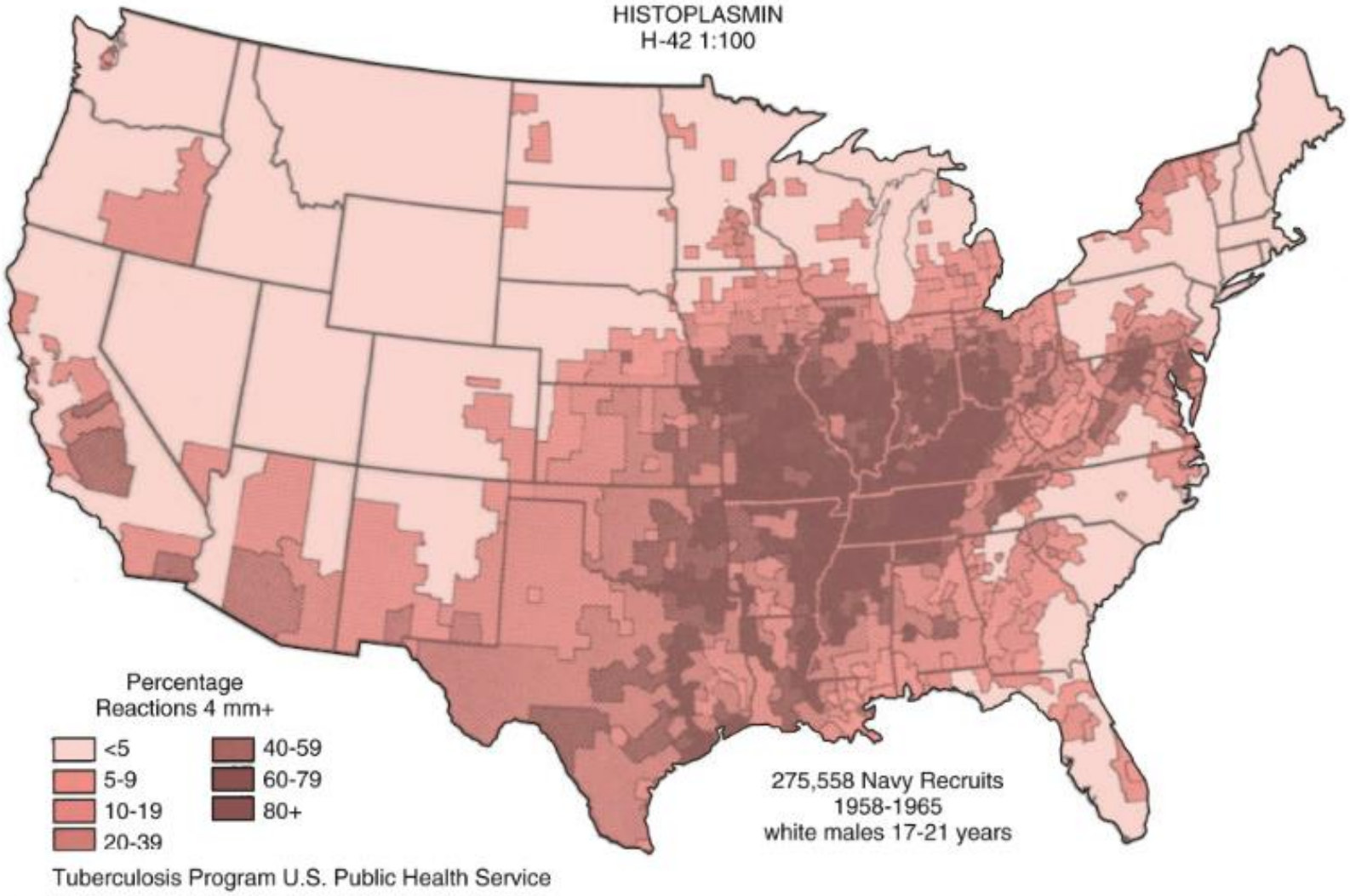
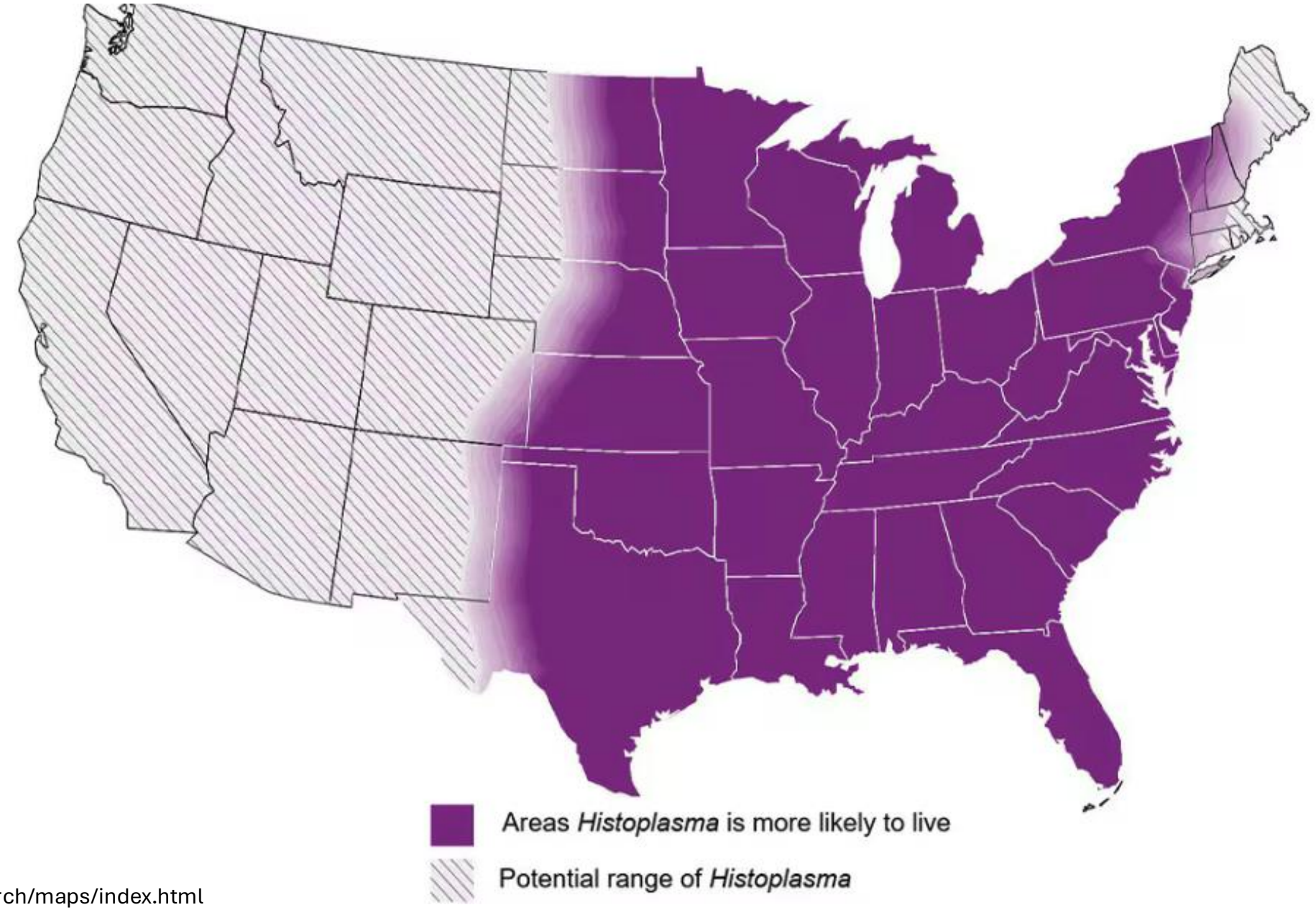


FIG. 263.1

Histoplasmin reactivity in the continental United States among naval recruits.

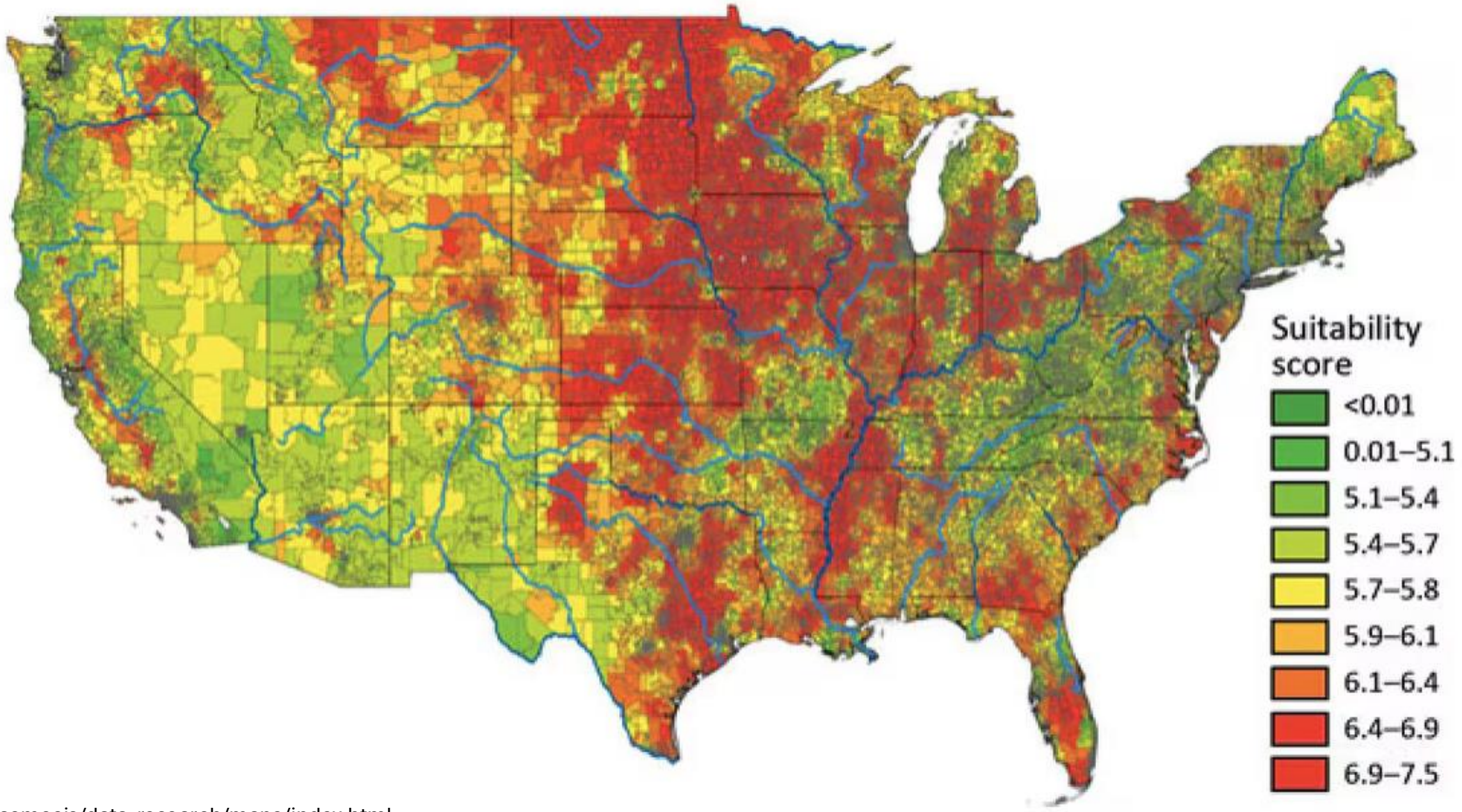
(From Edwards LB, Acquaviva FA, Livesay VT, et al. An atlas of sensitivity to tuberculin, PPD-B, and histoplasmin in the United States. *Am Rev Respir Dis* . 1969;99:1–111.)

Current distribution map



https://www.cdc.gov/histoplasmosis/data-research/maps/index.html

Areas suitable for growth



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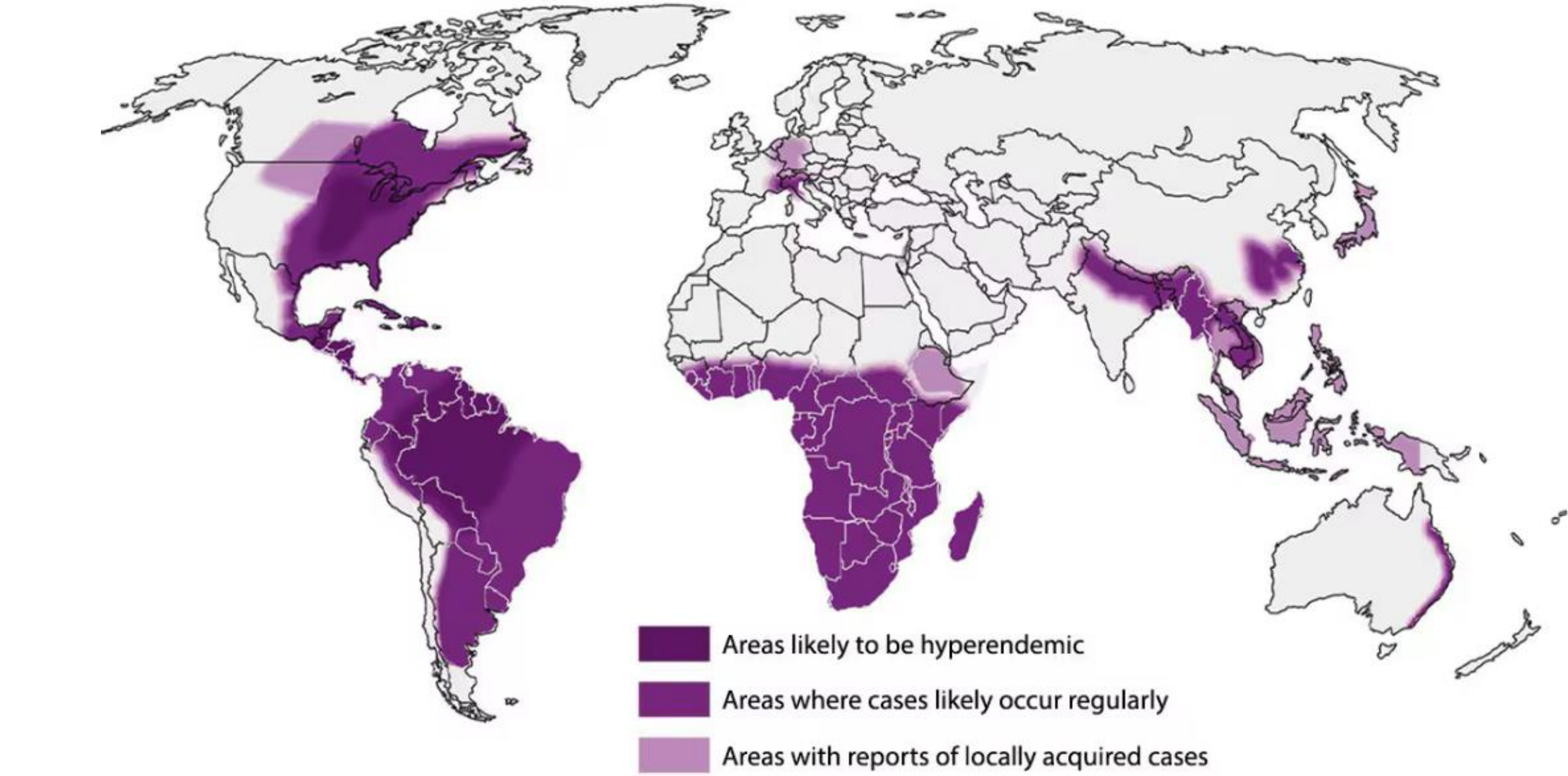
Worldwide distribution



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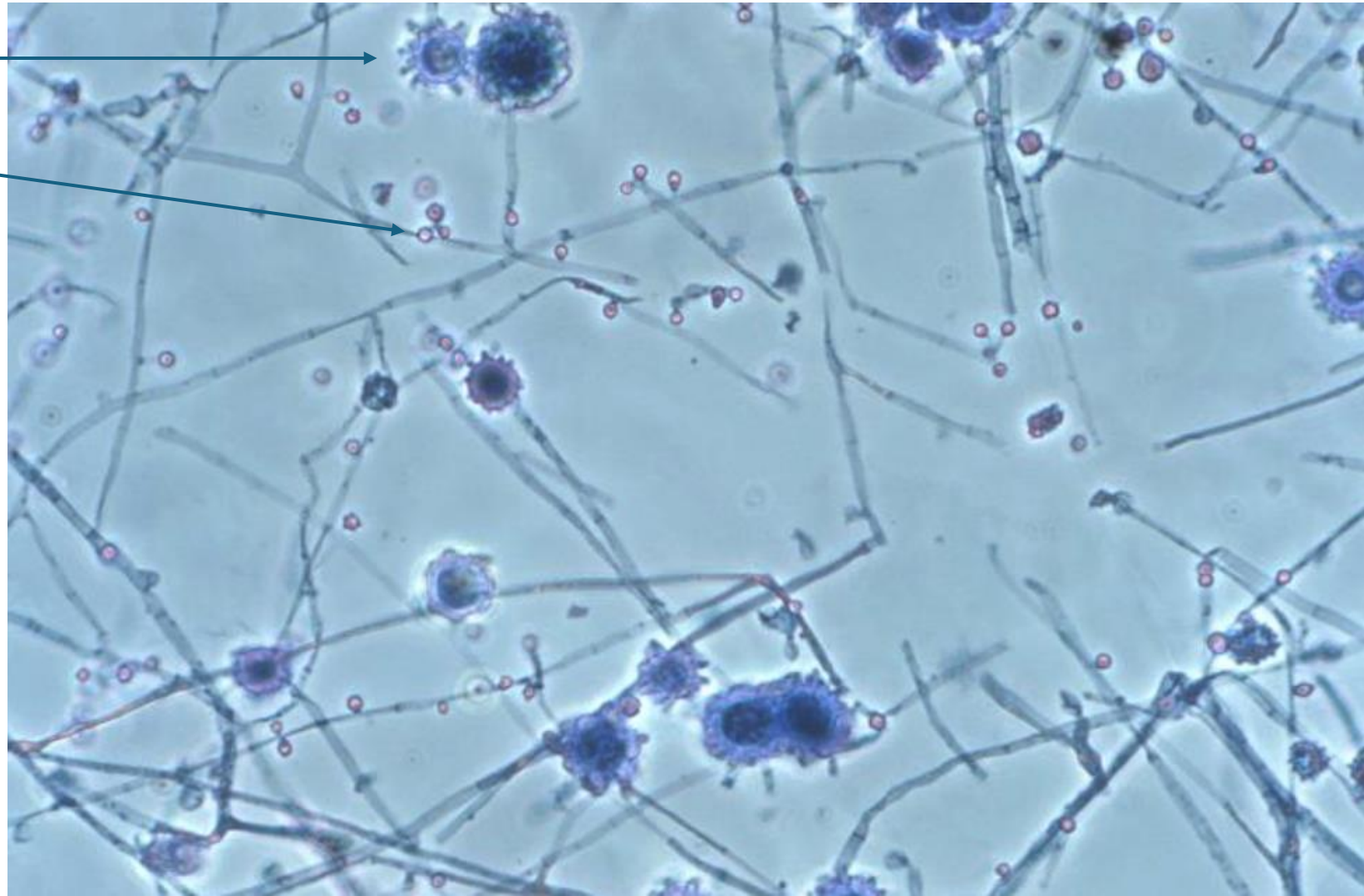
- Macroconidia
- Microconidia



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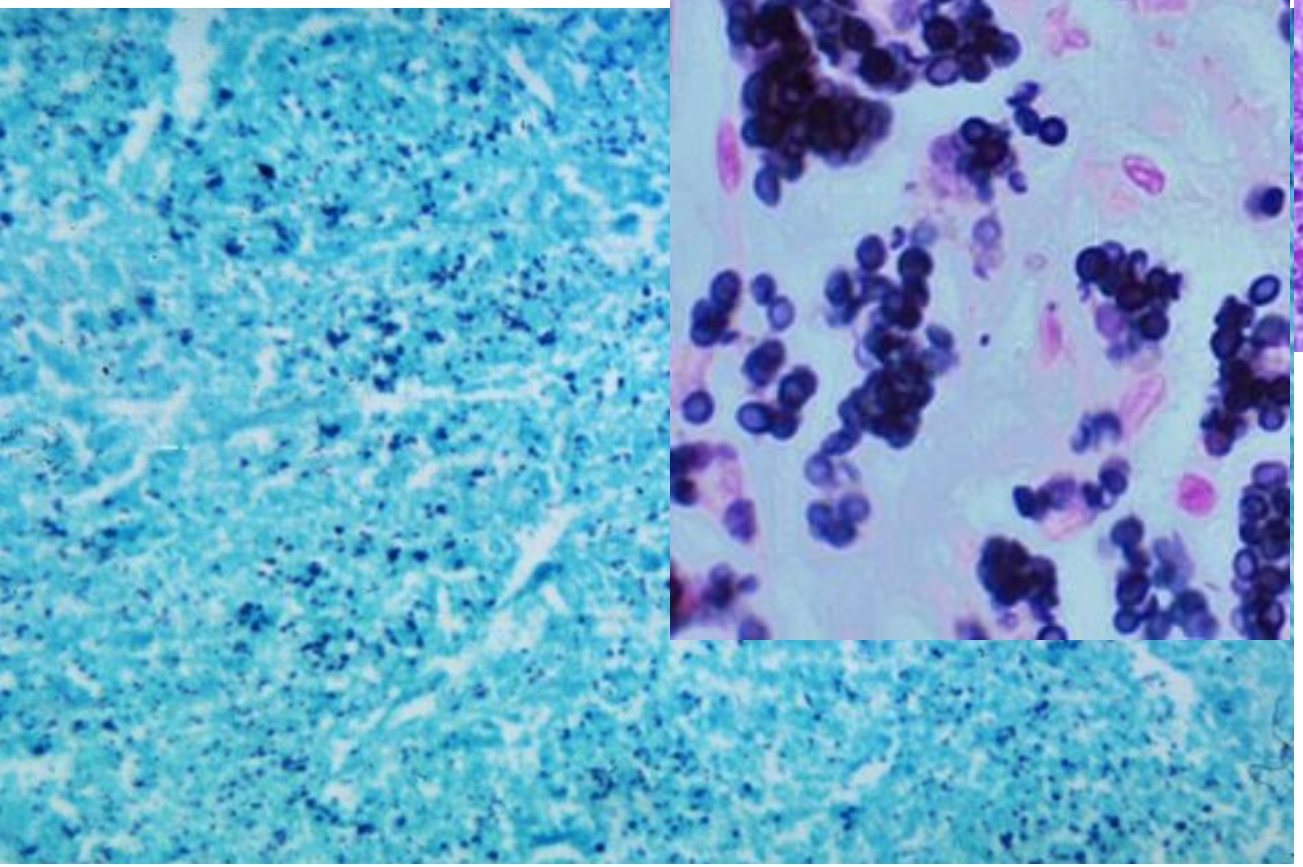
- Yeast forms – small with narrow based budding



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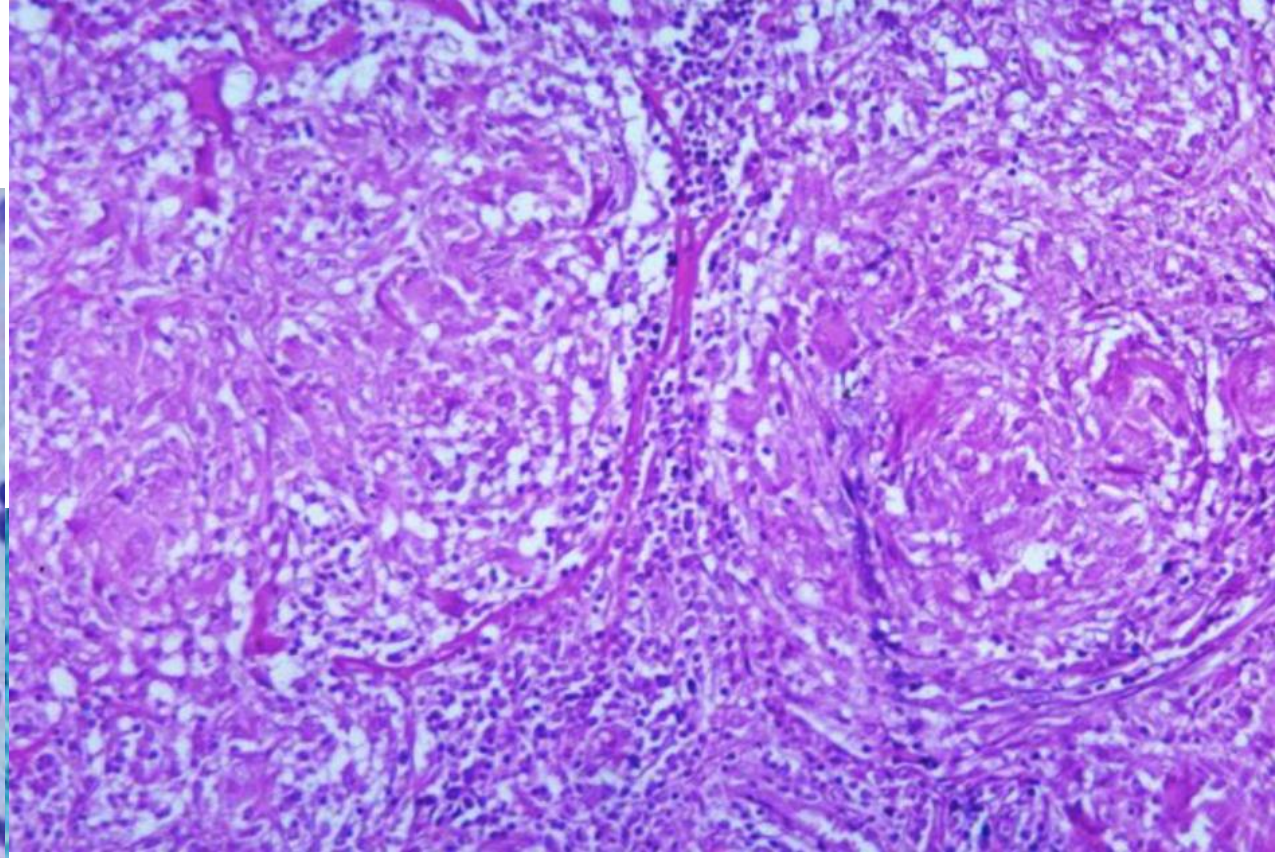


https://phil.cdc.gov/Details.aspx?pid=3142

https://www.adelaide.edu.au/mycology/mycoses/dimorphic-systemic-mycoses#histoplasmosis

Risk factors for disseminated disease

- HIV/AIDS
- Organ transplant recipients
- Immunocompromised
- Infants
- Adults 55 years and older

- Cellular immunity essential for control of disease, especially TNF-α

Clinical Diseases

- Asymptomatic pulmonary
- Symptomatic pulmonary
- Acute diffuse pulmonary
- Chronic pulmonary
- Progressive disseminated

Acute primary infection

- >90% asymptomatic or unrecognized
- Usually mild influenza-like illness and don’t seek medical attention (or asymptomatic)
- Incubation period 7-21 days (usually symptoms before 14 days)
- High fever, headache, nonproductive cough, chills, and chest pain. Less frequently malaise, myalgias, fatigue
- Symptoms usually resolve in 10 days
- In 6% rheumatologic conditions like arthralgias, erythema nodosum, erythema multiforme. Women > men

Acute primary infection

- Crackles in the lung
- Rarely hepatosplenomegaly (may eventually get calcifications in spleen and liver)
- Imaging with patchy pneumonitis that eventually calcifies, hilar lymphadenopathy
- Usually normal leukocyte counts, but can be high or low
- Transient increase in serum alkaline phosphatase

Complications of primary histoplasmosis

- Pericarditis – occurs in 6%; many report respiratory illness within prior 6 weeks; rarely develops tamponade; usually not due to direct invasion but rather to inflammation in adjacent lymph nodes
- Histoplasmoma – mass lesion of chronic inflammation, may eventually develop concentric rings of calcification or a central calcified core
- Mediastinal granuloma and fibrosis – massive enlargement of lymph nodes (8-10 cm) from granulomatous inflammation; can occasionally directly impinge on airways; while healing retraction takes place that can cause post-obstructive pneumonia, hypoxia, bronchiectasis, constrict the esophagus or superior vena cava.
- Pulmoliths/lithoptysis

Chronic Pulmonary Histoplasmosis

- Cavitary and non-cavitary chronic disease
- Cavitary – associated with smoking and COPD; low grade fever, productive cough, dyspnea, weight loss; hemoptysis is rare
- Non-cavitary – cough, weight loss, fever and chills; biggest difference between cavitary is that positive cultures are unusual

Progressive disseminated histoplasmosis

- 1:2000 cases of histoplasmosis
- Risk factors age, immunosuppression
- Pre-HAART HIV: present in 25% of AIDS patients in an endemic area, hence why it was considered an AIDS-defining opportunistic infection
- 3 types: acute progressive, subacute progressive, chronic progressive

Progressive disseminated histoplasmosis

Acute progressive

- classically occurred in infants, but now more common in severely immunocompromised, especially AIDS and hematologic malignancies
- abrupt onset with fever, malaise, weight loss, cough, diarrhea, hepatosplenomegaly, lymphadenopathy, oropharyngeal ulcers in <20%; anemia, leukopenia, thrombocytopenia, elevated ALP and ALT
- fatal without treatment
- Acute progressive in AIDS patients – up to 20% have CNS involvement; rashes; chorioretinitis. Up to 30% have a clear chest x-ray

Progressive disseminated histoplasmosis

- Subacute progressive – more indolent, fever and weight loss, hepatosplenomegaly, oropharyngeal ulcers (usually deeper and more likely to be confused for malignancy), more mild cytopenias; focal lesions in CNS (chronic meningitis, mass lesion, cerebritis), adrenal glands, GI tract (ulcers), and endovascular structures (aortic valve and mitral valve endocarditis)
- Chronic progressive – usually in previously healthy adults; chronic and mild; malaise and lethargy, low grade fever in <30%, oropharyngeal ulcer which is well circumscribed, indurated, deep, and painless in 50%; hepatosplenomegaly in 33%; goes on for years but without treatment ultimately results in death

Diagnosis

- Fungal cultures (remember to tell the micro lab if suspecting histoplasmosis)
- Urinary and serum antigen, positive in up to 90% of those with progressive disseminated disease, positive in 80% for moderate to severe acute pulmonary if both samples taken
- Galactomannan can be positive
- (1,3) β- d- glucan can be positive
- PCR
- Complement fixation

Treatment – Acute Pulmonary Histoplasmosis

- Most do not need treatment
- If not improving after 1 month, or hypoxemia, treat
- Itraconazole for 6-12 weeks
- If on mechanical ventilation, liposomal amphotericin until improvement, then itraconazole to complete 12 weeks; steroids can be given for up to 14 days

Cavitary Pulmonary Histoplasmosis

- Treat all, including those who are asymptomatic
- Itraconazole for 12-24 months
- Relapses occur in up to 20%, especially those with thick-walled cavities
- Can consider amphotericin or surgical resection

Acute Progressive Disseminated

- Life-threatening disease: Liposomal amphotericin B, followed by itraconazole once improved for 12 months
- Non-life-threatening disease, itraconazole, for 12 months
- AIDS patients: life-long suppression with itraconazole
- Immunosuppressed: relapse common, may need life-long suppression with itraconazole

- Subacute and Chronic Progressive: as often occurs in those with intact immune systems, treatment is effective – 12 months of itraconazole

Meningitis

- Liposomal amphotericin followed by itraconazole for at least a year
- CSF should have normal glucose and no detectable CSF antigen at the end of therapy.
- Relapse rates in 50%

Endocarditis

- Amphotericin
- Valve removal
- Treat as for progressive disseminated

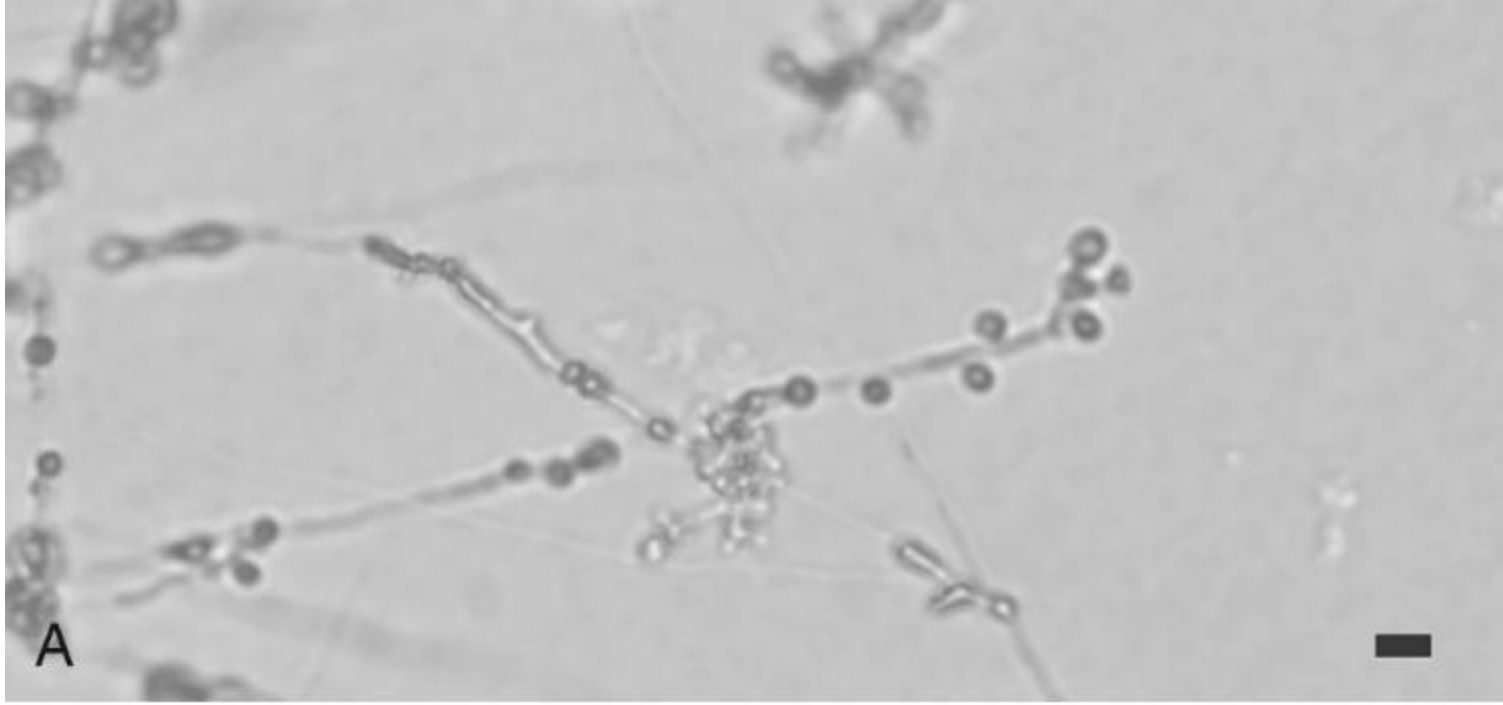
Prevention

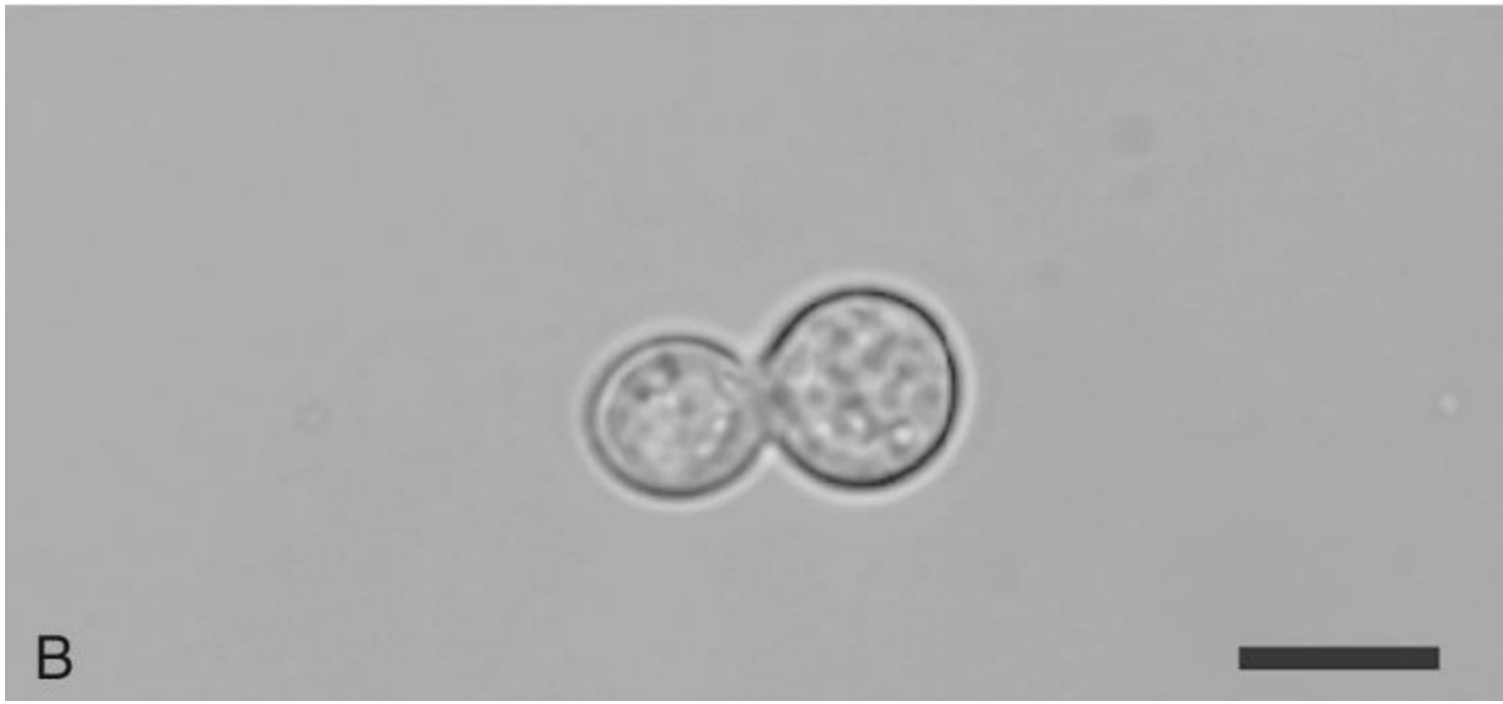
- Daily itraconazole for immunosuppressed patients at high risk from work of their environment
- Dust control and N95s – spraying 3% formalin on guano effective, but toxic.
- Vaccines being developed

Blastomycosis

Caused by

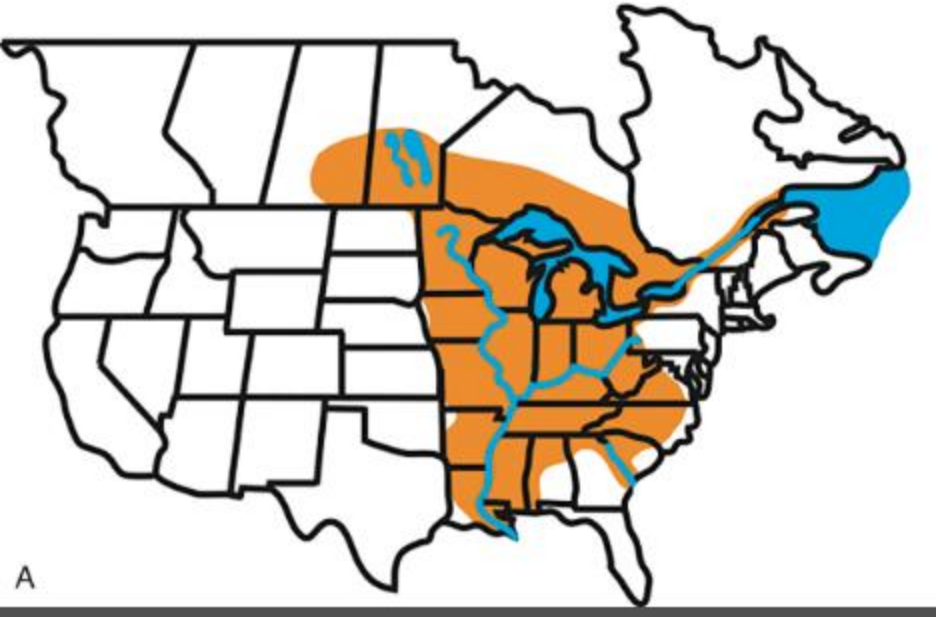
- *B. dermatitidis*
- *B. gilchristii*
- *B. helicus*





https://www.clinicalkey.com/nursing/#!/content/book/3-s2.0-B9780323482554002642

Blastomyces Geography

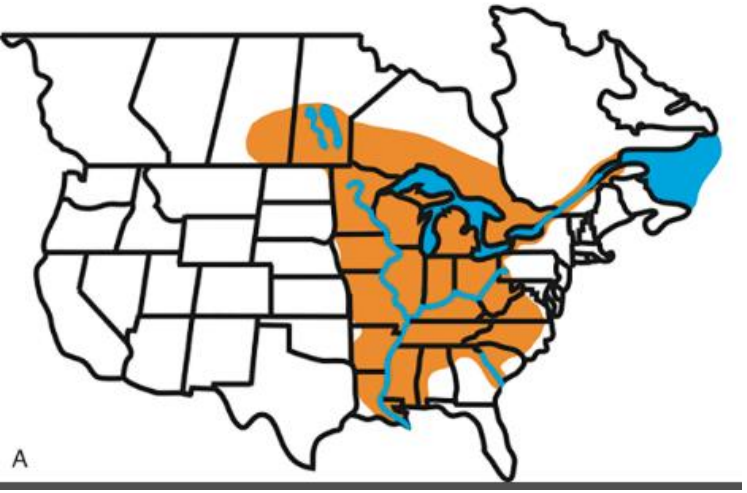


Old Map

Watershed areas for Mississippi, Ohio, Savannah, Saint Lawrence, and Nelson rivers as well as areas adjacent to the Great Lakes

Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 264, 3177-3189.e3

Blastomyces Geography

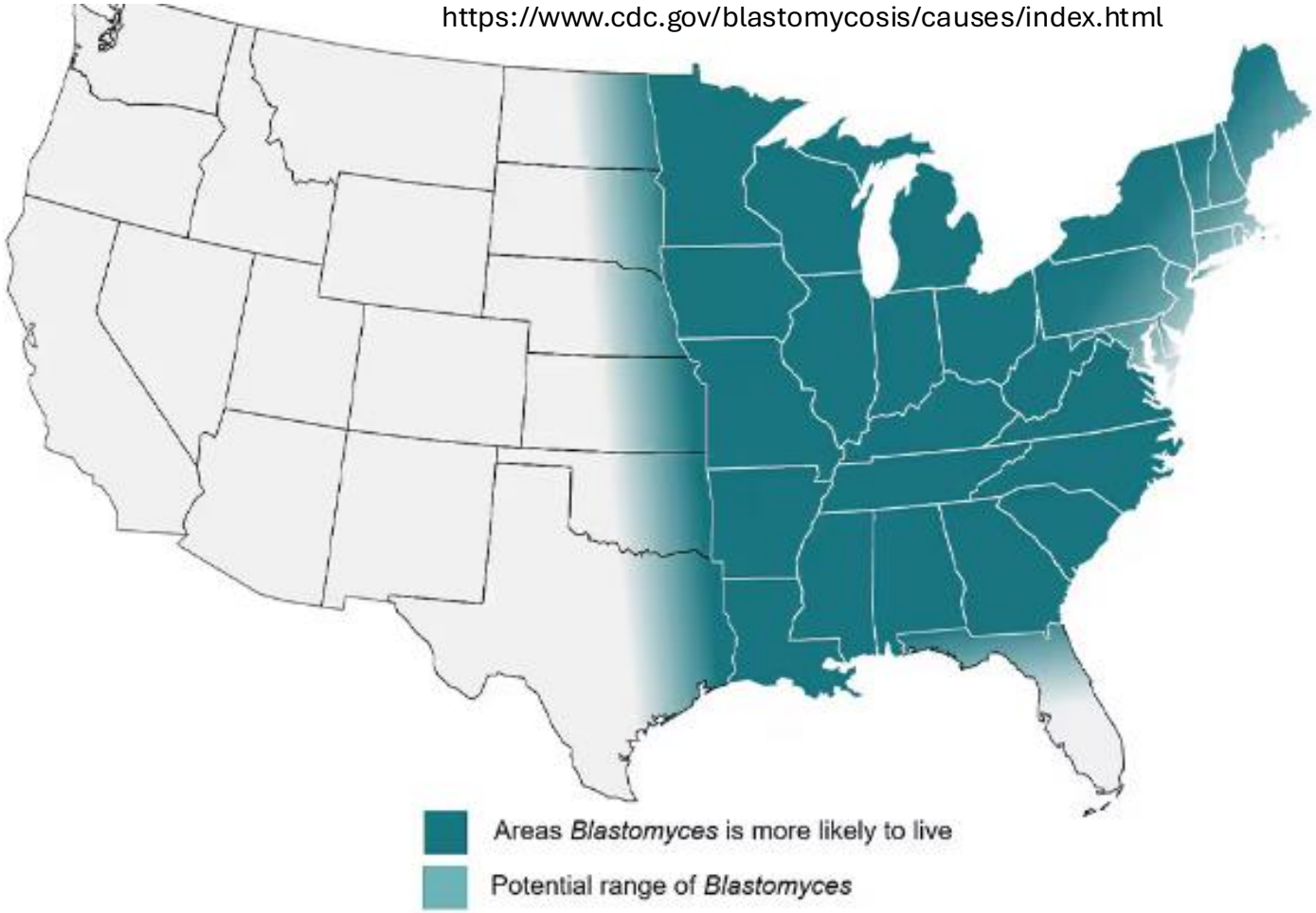


Old Map

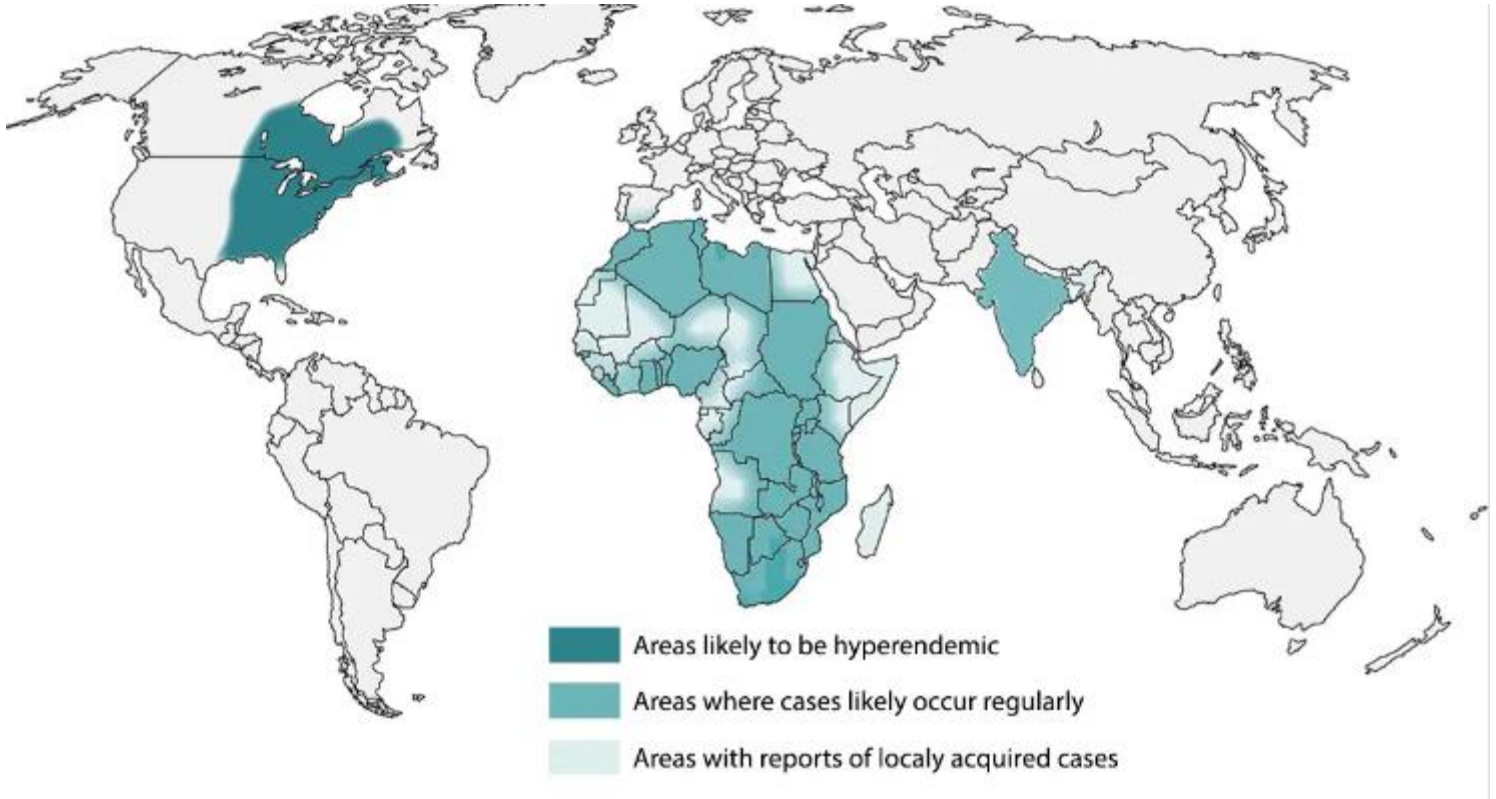
Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 264, 3177-3189.e3

New Map

https://www.cdc.gov/blastomycosis/causes/index.html



Blastomyces Geography



Blastomyces epidemiology

- Caused by breathing spores, which tend to live in soil or decomposed wood or leaves
- Risk factors: forestry, hunting, fishing by riverbanks, canoeing, tubing, hiking, beaver dam exploration, camping, construction, digging and excavating
- Pets, especially dogs, can also get blastomycosis and spread to people through bites. Canine blastomycosis incidence is 10-13x higher than human disease
- Veterinarians can also get through needlesticks

Blastomycosis clinical features

- 50% of infections are asymptomatic
- Pulmonary involvement in 91%
- Skin involvement in 18%
- Bone involvement in 4%
- GU involvement in 2%
- CNS involvement in 1%

- Incubation period of 3 weeks to 3 months
- Infections acquired usually through inhalation

Pulmonary Blastomycosis

- Acute or chronic pneumonia
- ARDS
- Cough (initially not productive but becomes productive over time), fever, chest pain, shortness of breath, weight loss, night sweats, chills, hemoptysis
- Acute pneumonia indistinguishable from community-acquired pneumonia
- Often a history of a pet dog also ill with pneumonia or having died from blastomycosis

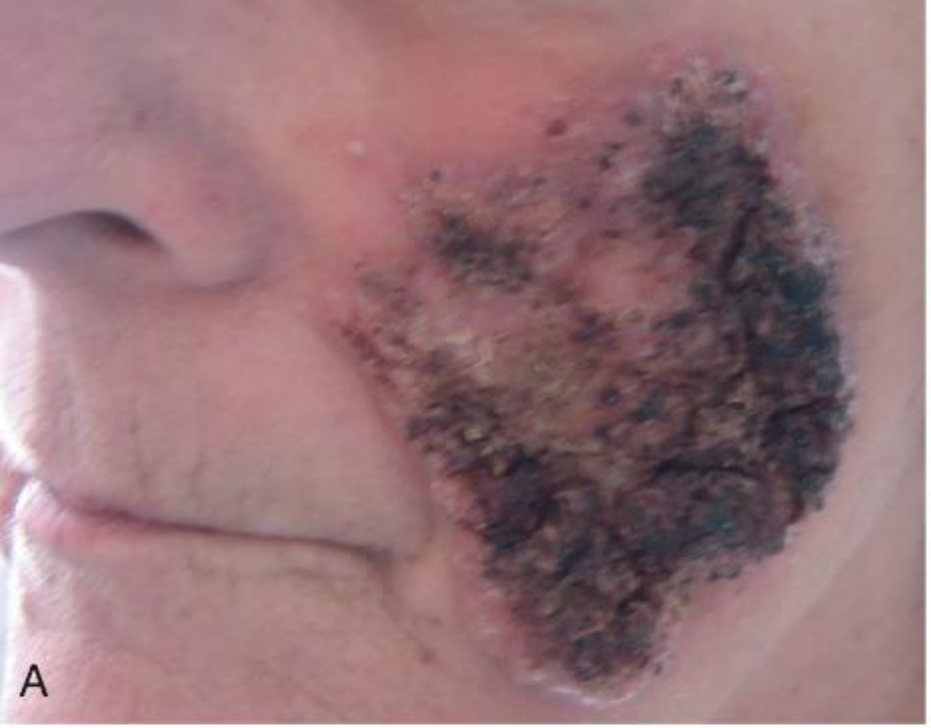
Pulmonary Blastomycosis

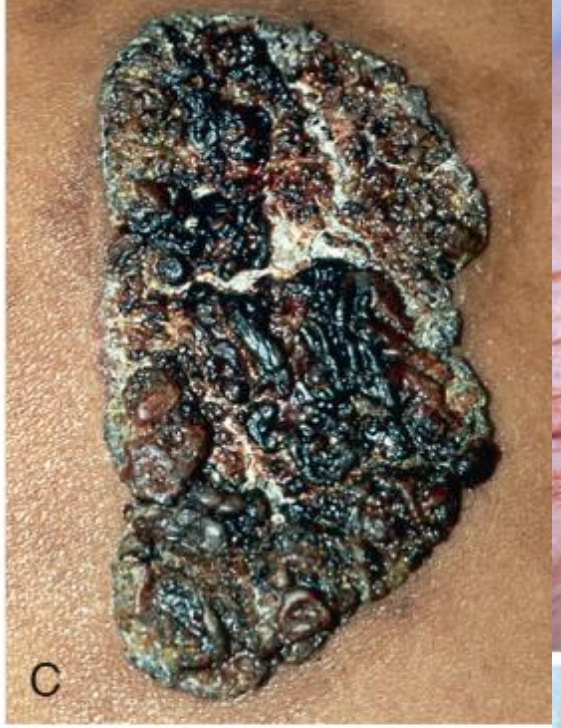
- Chest imaging shows infiltrate, masses or nodules, sometimes cavitation, tree-in-bud opacities

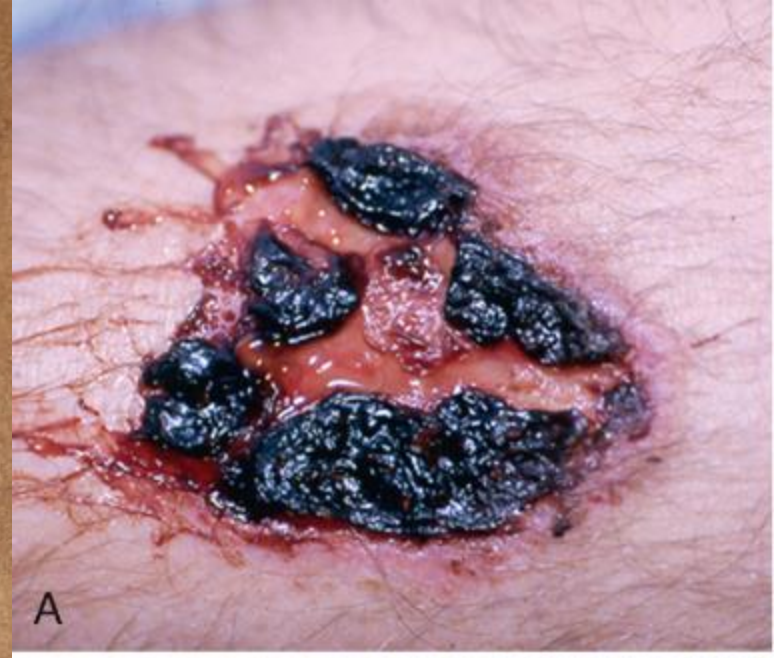
- Chronic Pneumonia – similar to TB or other fungal infections or bronchogenic carcinoma

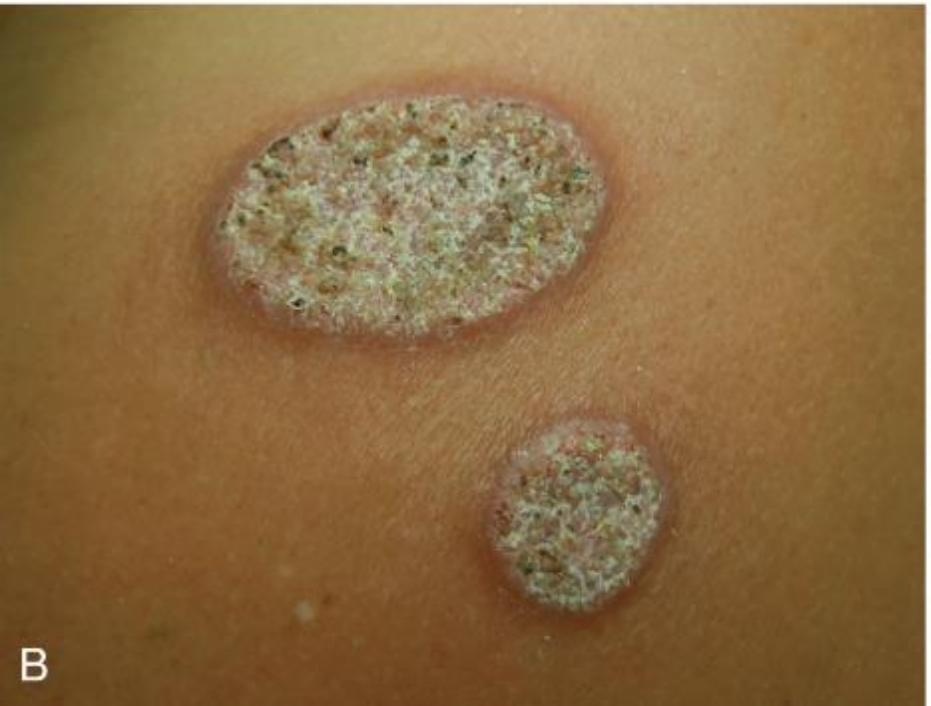
Skin Blastomycosis

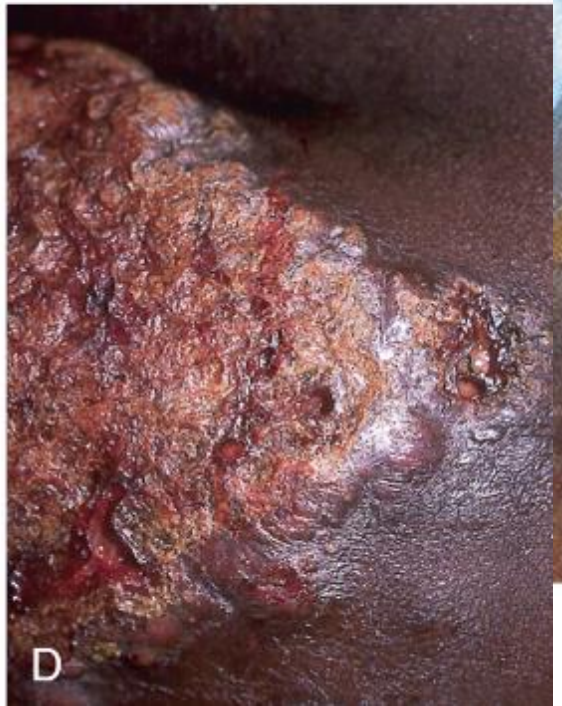
- Typically from hematogenous spread
- Verrucous lesion with irregular borders, gray to violet
- May mimic squamous cell carcinoma
- Ulcerative lesions that bleed easily, with heaped up well demarcated borders also seen
- Subcutaneous nodules also seen

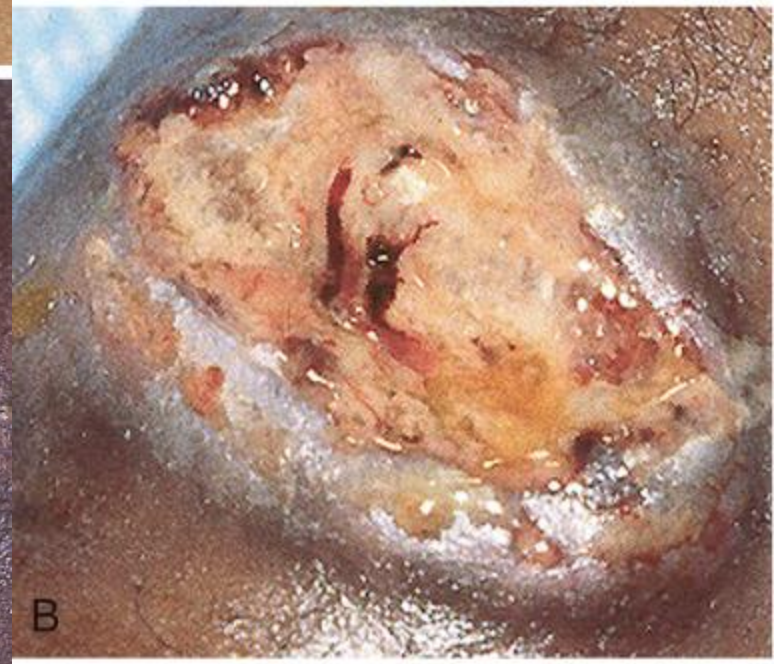












Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 264, 3177-3189.e3

Other sites

- Osteomyelitis - Pain, swelling, sinus tract formation; may be multifocal
- GU – prostatitis or epididymo-orchitis; UA with sterile pyuria; one case of male to female sexual transmission; tubo-ovarian abscess
- CNS – meningitis, brain abscess, or intracranial mass

- Immunocompromised hosts – higher risk are those with organ transplantation, AIDS, TNF-α antagonist, high dose steroids; not as common as histoplasma or coccidioidomycosis

Diagnosis of blastomycosis

- Staining of clinical specimens with broad-based budding yeast, doubly refractive cell wall

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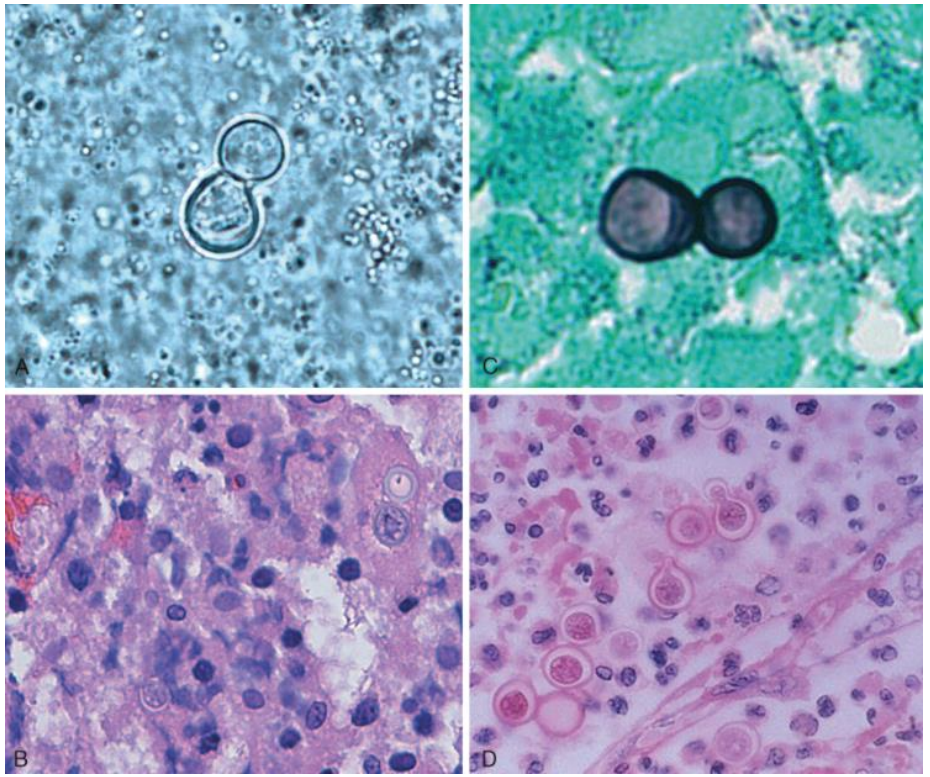


Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 264, 3177-3189.e3

Diagnosis of blastomycosis

- Staining of clinical specimens with broad-based budding yeast, doubly refractive cell wall
- Culture
- Complement fixation and immunodiffusion not very sensitive (25% and 40% respectively)
- Quantitative galactomannan antigen assay sensitivity in urine 76-93%
- (1,3) β-d glucan often negative (unlike in histoplasmosis or coccidioidomycosis)
- PCR

Mandell, Douglas, and Bennett's Principles and Practice of Infectious Diseases, 264, 3177-3189.e3

Treatment of blastomycosis

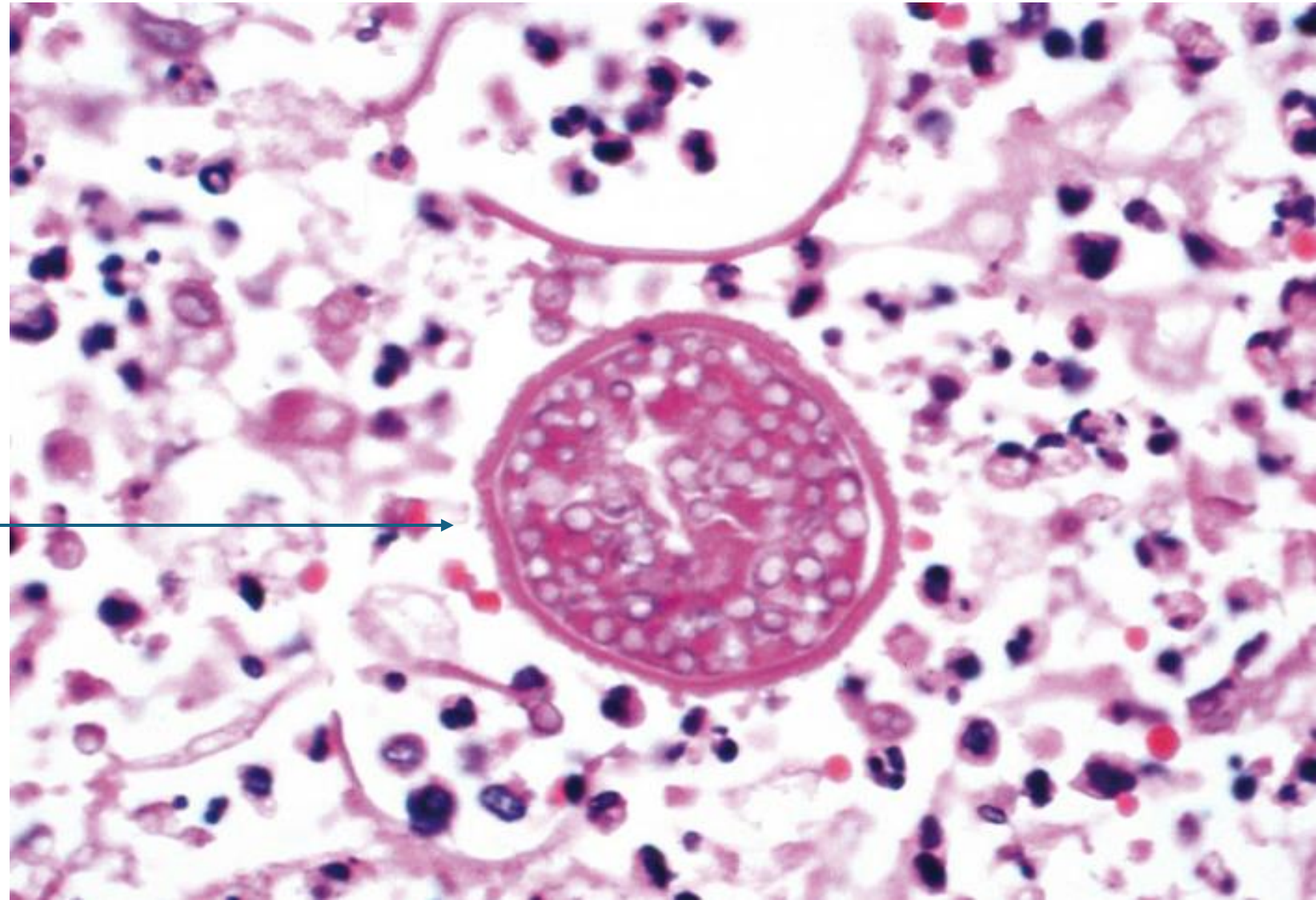
- All patients should be offered treatment
- Itraconazole drug of choice for non-CNS disease (95% cure for non-CNS disease as opposed to 64% for fluconazole)
- Mild to moderate blastomycosis treated with itraconazole for 6-12 months
- Moderate to severe treated with amphotericin B for 1-2 weeks followed by itraconazole for 6-12 months
- Immunocompromised patients – amphotericin B for 1-2 weeks followed by itraconazole for 12 months. Lifelong therapy not usually required for transplant patients, but should be continued in AIDS patients until CD4 >150
- CNS disease – amphotericin B for 4-6 weeks followed by itraconazole for at least 12 months

Coccidioidomycosis

2 strains

- *C. immitis*
- *C. posadasii*

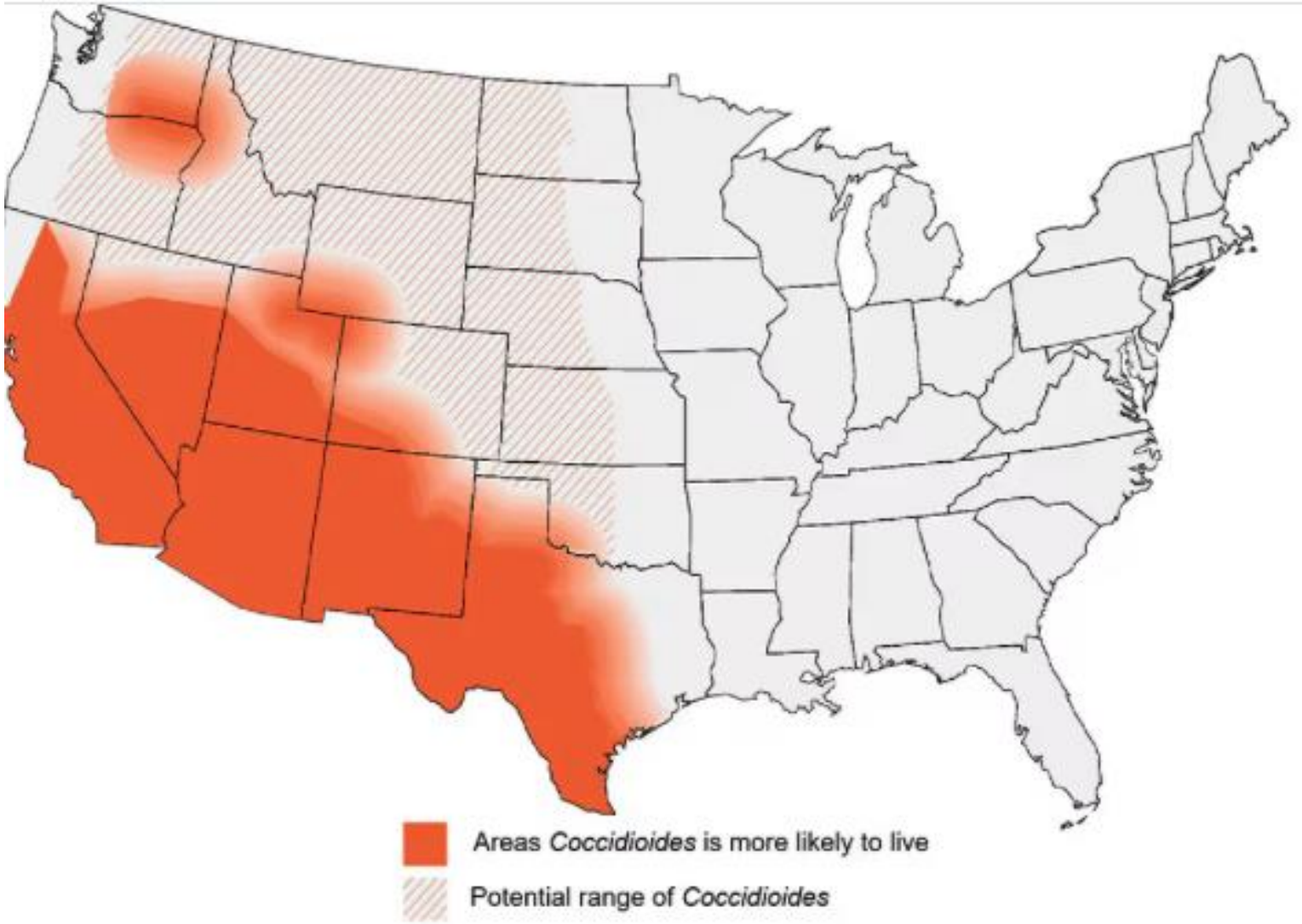
- Spherule



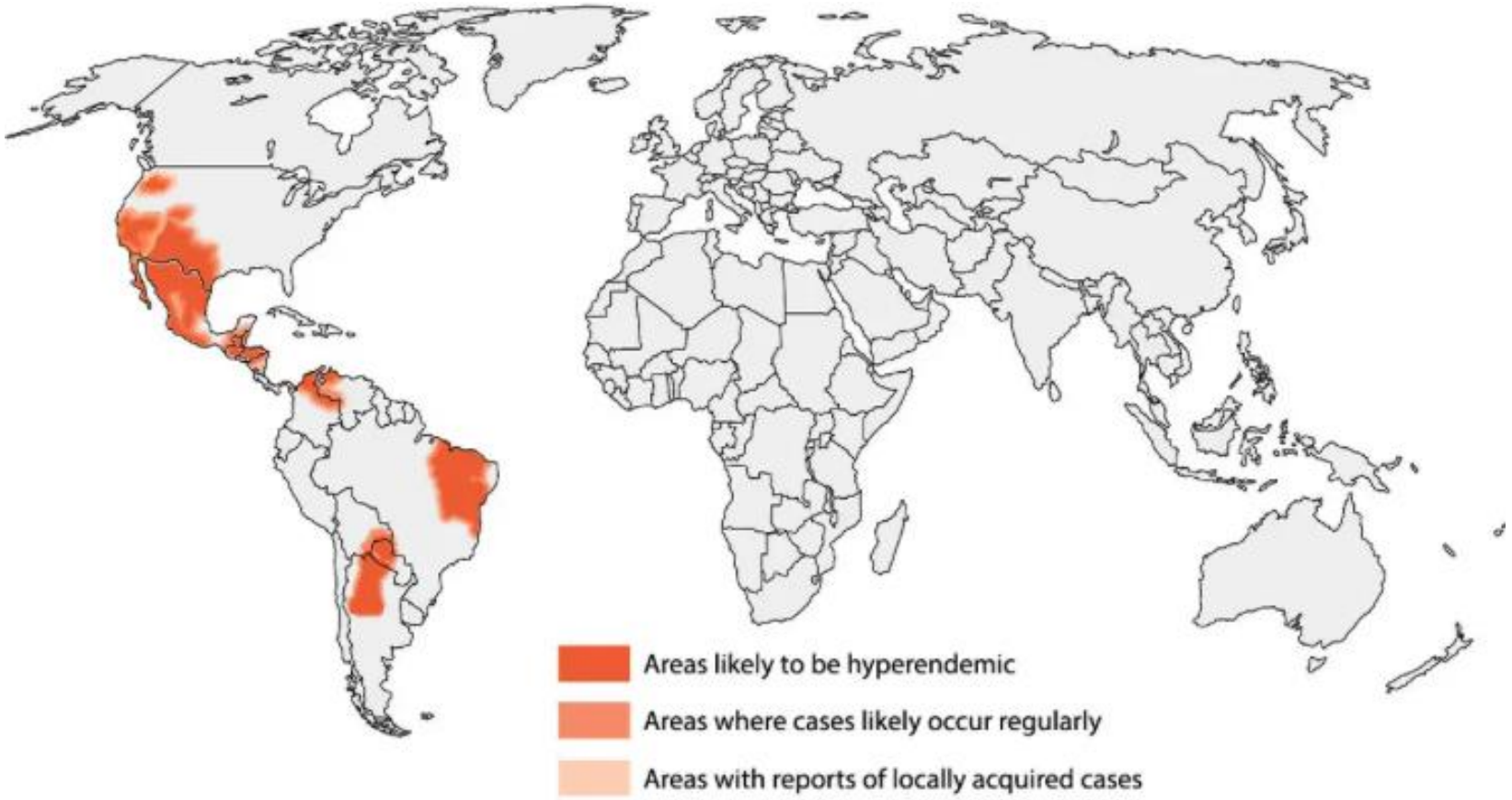
Coccidioidomycosis geography

- Old map

Coccidioidomycosis geography



Coccidioidomycosis geography



https://www.cdc.gov/valley-fever/areas/index.html

Fun facts

- 8500-year-old bison from Nebraska had evidence of *Coccidioides*
- Chance of finding *Coccidioides* in the soil is highest toward the end of winter rains, but infection rates are highest during summer months when soil is dry (and a second peak in October in Arizona after the summer rains)
- Rate of infection is thought to be 3% a year (studies from the 1950s had suggested 25-50% in Army recruits in the San Joaquin Valley)
- Epidemics described with excavation, severe dust storms, earthquakes, or military maneuvers
- Most infections result from inhaling arthroconidia
- T lymphocytes major contributor to host defense

Coccidioides clinical features

- 50-66% mild to subclinical infections
- Pneumonia, indistinguishable from community acquired pneumonia
- In Southern Arizona, up to 33% of CAP were found to be coccidioidomycosis
- Most cases are self limited
- Incubation period of 7-21 days

Early Respiratory Infection

- Cough, chest pain, shortness of breath, fever, fatigue, weight loss, headache
- Rash, erythema nodosum and erythema multiforme
- Migratory arthralgia, fever, and erythema nodosum called “desert rheumatism”
- Mild leukocytosis, elevated ESR and CRP, eosinophilia
- Chest imaging with lobar consolidation, hilar adenopathy, effusions
- Rarely respiratory failure
- Fungemia usually only in immunocompromised
- Most recover but it can take weeks to months to do so

Pulmonary Nodules and Cavities

- 4% of pulmonary infections lead to a nodule, up to 5 cm in size
- Occasionally nodules cavitate, usually thin walled
- 50% of cavities close within 2 years
- They can get fungal balls inside, either with *Coccidioides* or other molds
- Occasionally a peripheral cavity will rupture into the pleural space to cause a pneumothorax, or more often a hydropneumothorax
- Less common is pleural effusion without cavity or rupture

Chronic Fibrocavitary Pneumonia

- Pulmonary infiltrates and pulmonary cavitation
- Not associated with T-cell deficiencies, but diabetes, or smoking
- Often involves more than 1 lobe

Extrapulmonary Dissemination

- 0.5% of infections
- Immunodeficiency: AIDS, Lymphoma, SOT, high dose steroids, TNF- α inhibitors
- One study showed 2/3 of renal transplant patients who were infected developed disseminated infection
- Pregnancy, men>women, African or Filipino ancestry
- Many disseminated patients often have normal chest x-rays
- Most common site is skin
- Joints and bones, spine
- Meningitis

Diagnosis

- Pathology showing spherules
- Cultures growing *Coccidioides* (tell the micro lab when worried about this)
- EIA with reflex to complement fixation and immunodiffusion
- *Coccidioides* antigen
- PCR

- Meningitis frequently has negative cultures

Treatment

- Early uncomplicated infections – debatable to treat, if treating usually for severe symptoms or risks factors. Azole therapy, fluconazole or itraconazole for 3-6 months. Does not prevent, but may delay dissemination. Early treatment may also prevent a complement-fixing antibody response.
- Diffuse pneumonia – usually indicates either high inoculum or hematogenous spread. Treatment recommended, usually with amphotericin B for a few weeks then transition to po azole for at least 1 year. In the setting of fungemia, may need lifelong therapy
- Pulmonary Cavities – may not need treatment. Sometimes they are excised if not resolving after several years. If symptomatic, pain, hemoptysis, superinfection, usually treated with azoles indefinitely (or resection)

Treatment

- Disseminated disease (non-CNS) – azoles, often for 1 year and for 6 months after evidence of improvement has stopped, if not indefinitely. Surgical debridement may be needed
- CNS disease – fluconazole now preferred over intrathecal amphotericin B, with treatment for life. If failing fluconazole, intrathecal amphotericin B can be used

Our Case

- 55 year old gentleman with a past medical history of a transplanted kidney, presents with a 2 week history of fever, headache and body ache. 1 month ago went to visit family in Youngstown, Ohio. 2 weeks later both he and his wife developed headache and myalgia, but wife recovered and his symptoms continued. COVID testing at home was negative x2. 1 week ago fever and sweats developed.
- Cr up from 1.0 to 1.5, lactate 2.7, no leukocytosis, chest x-ray is clear, UA unrevealing, and comprehensive respiratory panel negative.
- Exam is unrevealing
- CT with scattered nodules, splenomegaly

Our Case

- BAL done
- 4 samples sent for fungal stains, all negative
- Histoplasma urinary antigen+, (1,3) beta-D glucan negative, Aspergillus antigen negative
- At 2 weeks cultures with filamentous fungi
- 4 days later returned as Histoplasma capsulatum
- Symptoms already resolving, but elected to treat with itraconazole

Why climate change is impacting human fungal disease

- Expanded ranges given warming and wetter climates
- Increased risk of dispersal with more severe weather events
- Thermoadaptation to better grow at our bodies' warmer temperatures
- *Candida auris* has been postulated to be the first new human fungal pathogen to emerge as a result of climate change, with higher temperatures favoring strains more adapted to higher salinity and temperatures (as in wetlands) that more closely approximate our bodies