Marvelous Mycology Matters

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SCACM
Michigan Meeting
Lansing Community College West Campus

September 26, 2018

Grand Valley State University
www.gvsu.edu

Presentation Objectives

1) Recognize the importance of the study of clinical diagnostic mycology.

2) Review identification of some common fungi, based upon plate and microscopic morphology.

3) Describe newer discoveries in the field of mycology

Mycology IS Important?

1) Education-"Don't need to or not important to teach mycology to MLS students"
2) World Health Organization-has no formal program on fungal infection
3) Public Health-little to no surveillance on mycology infections
   - **CDC (National level)**- Coccidioidomycosis is only notifiable fungal disease (2011- but only in <25 states)
   - **MDHHS (Michigan)**-Blastomycosis, Coccidioidomycosis, and Histoplasmosis
4) Funding for clinical mycology is low/lacking

Reportable Fungal Disease for 7 SCACM states (CDC –June 2018)

State/Disease	Blastomycosis	Coccidioidomycosis (Valley fever)	Cryptococcosis	Histoplasmosis	Other Fungal diseases
Michigan	**X**	**X**		**X**	
Illinois				X	
Indiana		X		X	
Kentucky				X	
Ohio		X			
West Virginia					
Wisconsin	X			X	

Reference: https://www.cdc.gov/fungal/diseases/coccidioidomycosis/health-professionals.html

Recognition of Importance of Fungal Disease

1) Increasing number of immunocompromised people susceptible to opportunistic fungal infection
2) New healthcare advances and practice changes enable pathogen and drug-resistant fungal disease emergence
3) Environmental (weather and climate) changes and natural disaster occurrence make conditions favorable for fungal proliferation
4) Wide geographic distribution of endemic areas where fungi live

Ten Most Significant Invasive Fungal Infections

Disease (most common species)	Location	Estimated life-threatening infections/ year at that location*	Mortality rates (% in infected populations)*
Opportunistic invasive mycoses			
Aspergillosis (*Aspergillus fumigatus*)	Worldwide	>200,000	30–95
Candidiasis (*Candida albicans*)	Worldwide	>400,000	46–75
Cryptococcosis (*Cryptococcus neoformans*)	Worldwide	>1,000,000	20–70
Mucormycosis (*Rhizopus oryzae*)	Worldwide	>10,000	30–90
Pneumocystis (*Pneumocystis jirovecii*)	Worldwide	>400,000	20–80
Endemic dimorphic mycoses*†			
Blastomycosis (*Blastomyces dermatitidis*)	Midwestern and Atlantic United States	~3,000	<2–68
Coccidioidomycosis (*Coccidioides immitis*)	Southwestern United States	~25,000	<1–70
Histoplasmosis (*Histoplasma capsulatum*)	Midwestern United States	~25,000	28–50
Paracoccidioidomycosis (*Paracoccidioides brasiliensis*)	Brazil	~4,000	5–27
Penicilliosis (*Penicillium marneffei*)	Southeast Asia	>8,000	2–75

*Most of these figures are estimates based on available data, and the logic behind these estimates can be found in the text and in the Supplementary Materials. †Endemic dimorphic mycoses can occur at many locations throughout the world. However, data for most of those locations are severely limited. For these mycoses, we have estimated the infections per year and the mortality at a specific location, where the most data are available.

Reference: www.scinecetranslationalmedicine.org ; Dec 19, 2012; Vol 4 Issue 165, *Hidden Killers: Human Fungal Infections,* Gordon D. Brown, David W. Denning, Neil A. R. Gow, Stuart M. Levitz, Mihai G. Netea, Theodore C. White.

Healthcare Advances and Practice

The Spectrum of Fungi That Infects Humans

Julia R. Köhler,[1] Arturo Casadevall,[2] and John Perfect[3]

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Abstract

Go to:

Few among the millions of fungal species fulfill four basic conditions necessary to infect humans: high temperature tolerance, ability to invade the human host, lysis and absorption of human tissue, and resistance to the human immune system. In previously healthy individuals, invasive fungal disease is rare because animals' sophisticated immune systems evolved in constant response to fungal challenges. In contrast, fungal diseases occur frequently in immunocompromised patients. Paradoxically, successes of modern medicine have put increasing numbers of patients at risk for invasive fungal infections. Uncontrolled HIV infection additionally makes millions vulnerable to lethal fungal diseases. A concerted scientific and social effort is needed to meet these challenges.

CONCLUSION

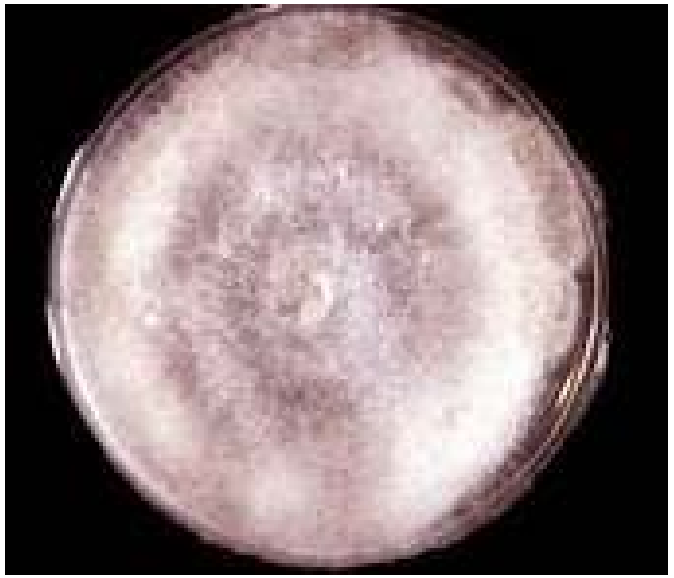
Go to:

Immunologically intact humans manifest robust defenses against fungal diseases. Recently, human social evolution produced scientific medicine, whose progress has rendered a large population susceptible to infections with fungi not considered human pathogens as recently as a hundred years ago. Human social

Reference:
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4292074/

Cutaneous Infections-2011 Joplin Tornado US (CDC)

- 18 cases (5 deaths) of serious necrotizing soft-tissue infections caused by the zygomycete *Apophysomyces trapeziformis* occurred after the 2011 Joplin, Missouri tornado

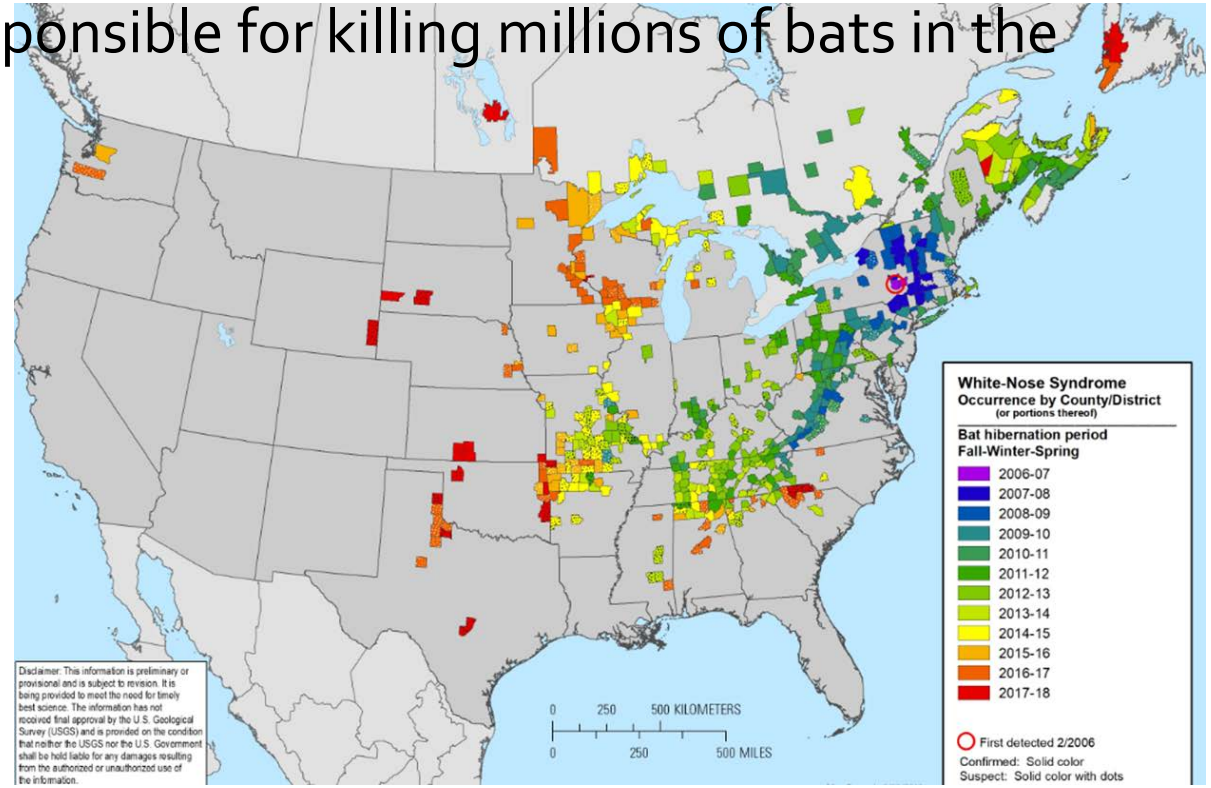


Widespread mold growth after Hurricane Katrina (2005), New Orleans, LA

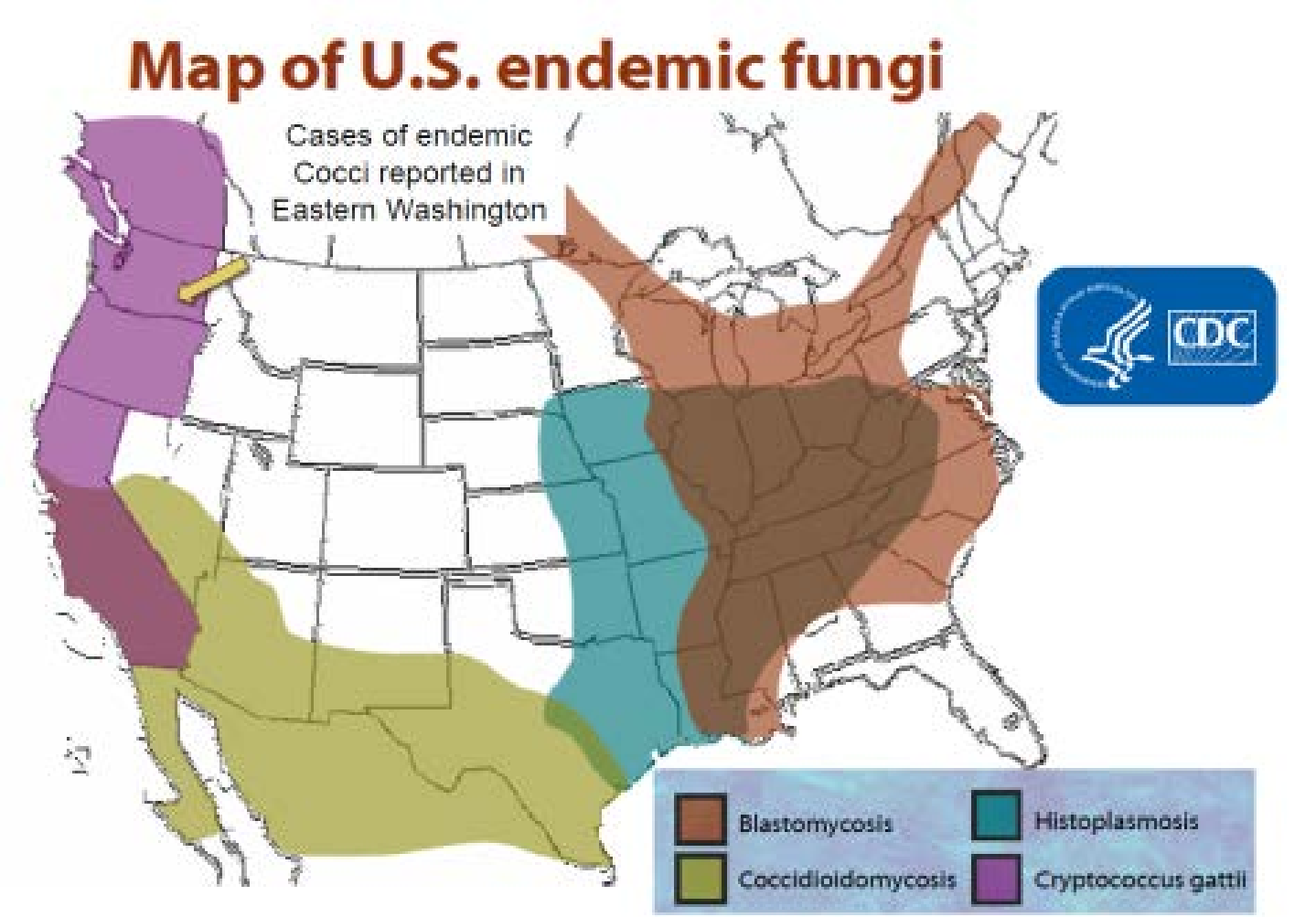
Bats and White Nose Syndrome (WNS), 2007

- WNS is considered an emerging disease caused by *Pseudogymnoascus destructans,* a fungus found on the skin of bats. It is considered one of the worst wildlife diseases in modern times, responsible for killing millions of bats in the US and Canada

Reference: https://www.whitenosesyndrome.org/



Endemic Fungal Disease Geographic Distribution in US (CDC)



Fungal Infections and Pathogens Considered Today

- *Candidiasis*
- *Cryptococcosis*
- *Aspergillosis*
- *Coccidiomycosis*

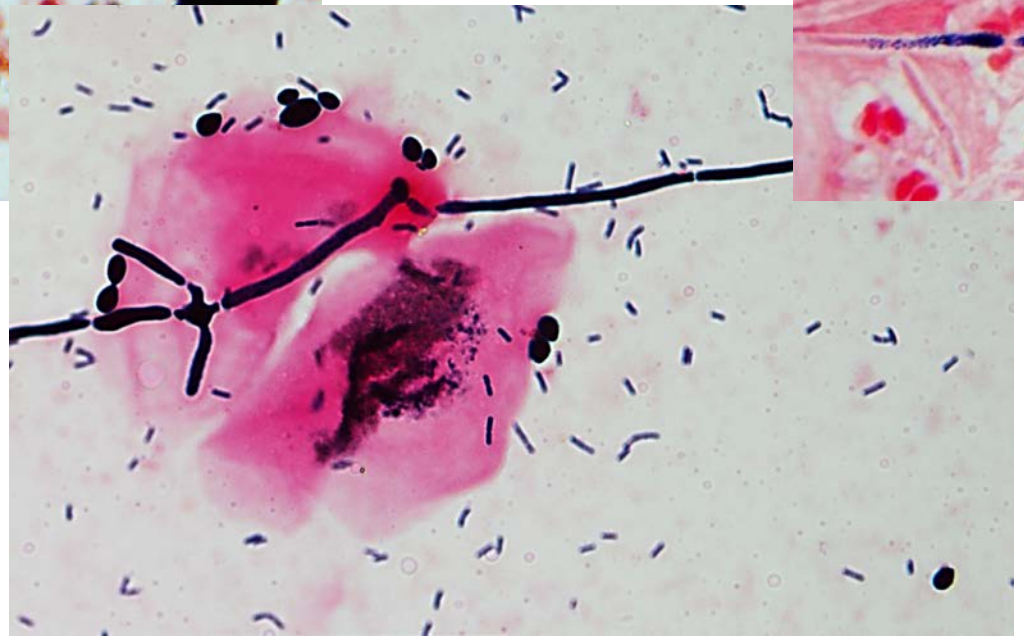
Candida Clinical Disease

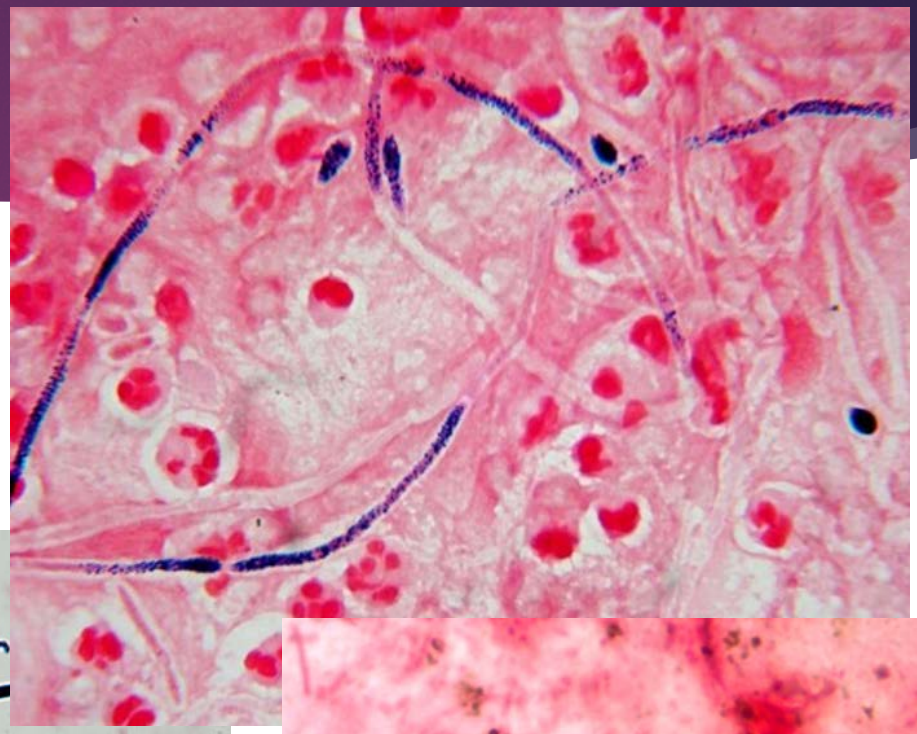
- Human infections occur with over 20 different species of *Candida*
- Commensal in gastrointestinal tract and on skin
- Opportunistic infections occur with endogenous spread of the organism from a person's own normal flora
  - Types of Candidiasis
    - **Oropharyngeal**
      - called "thrush"
      - Infection in mouth, throat, or esophagus
    - **Vulvovaginal**
    - **Invasive** (Candidemia)

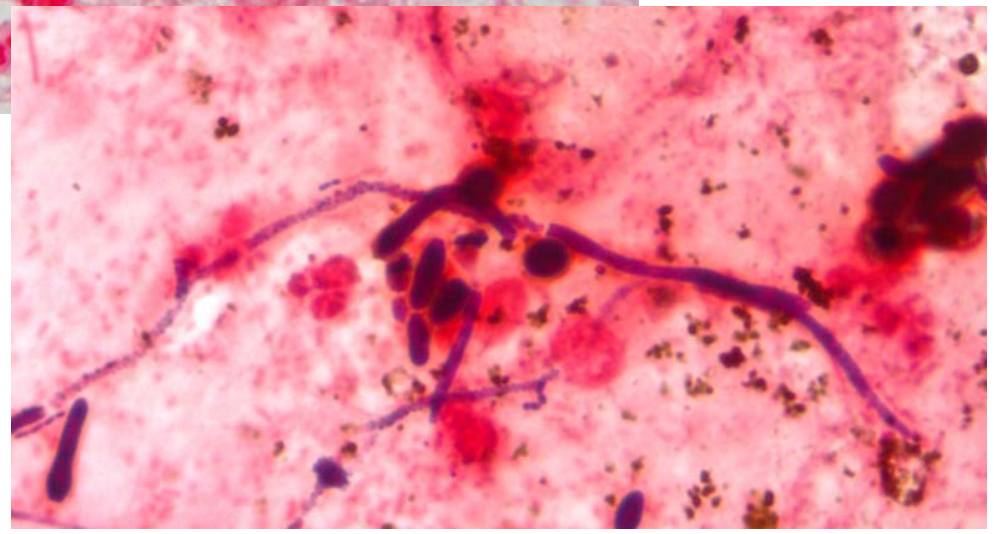
Most Common *Candida* Opportunistic Pathogens

- *Candida albicans*
- *Candida dubliniensis*
- *Candida glabrata*
- *Candida parapsilosis*
- *Candida tropicalis*
- *Candida lusitaniae*
- *Candida krusei*

Direct smears of *Candida* in blood, urogenital, wound, and sputum cultures



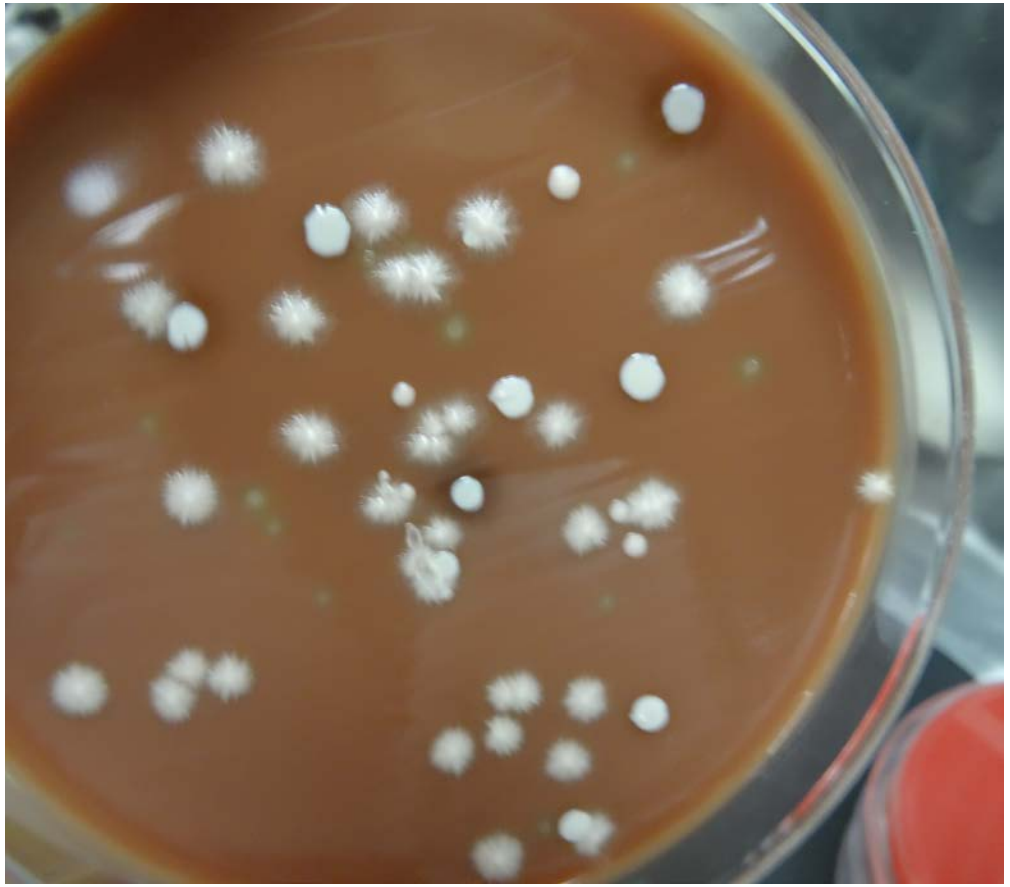


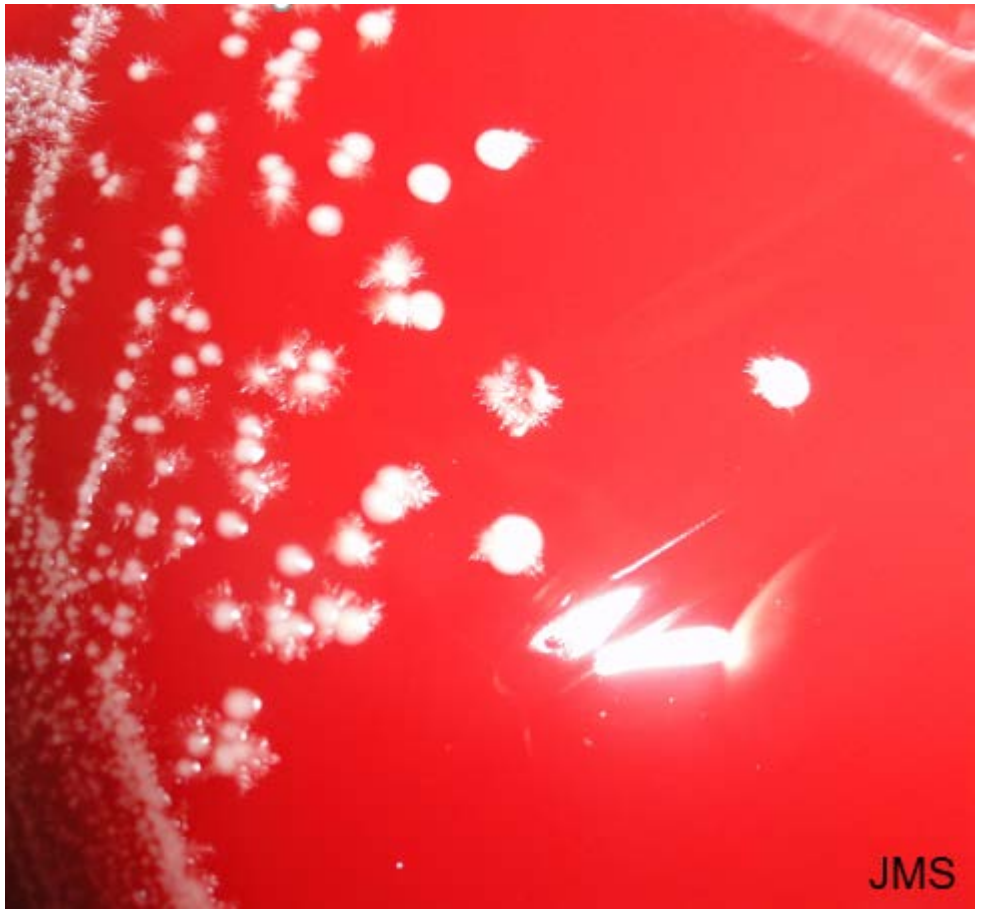


Candida Identification

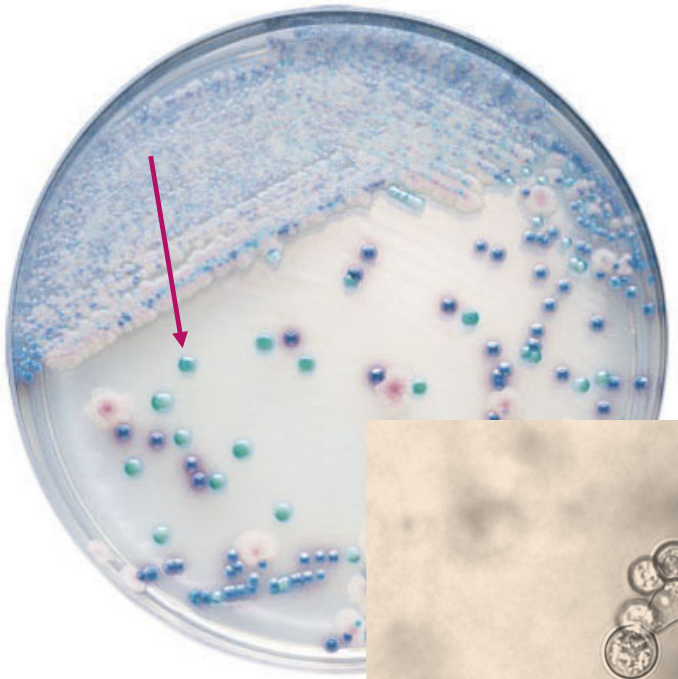
- Typical macroscopic colonial morphology
- Microscopic: **Germ tube** and appearance on **Corn meal agar**
- Biochemical characteristics-Urea, CHO assimilation (API/ Vitek)
- Rapid ID
  - Chromogenic agar is selective and differential
  - Bacticard™ Candida
- MALDI- Bruker and Vitek systems both ID yeast quicker and well (80-95% correct ID's)
- Nucleic acid: PNA FISH and film array for blood cultures

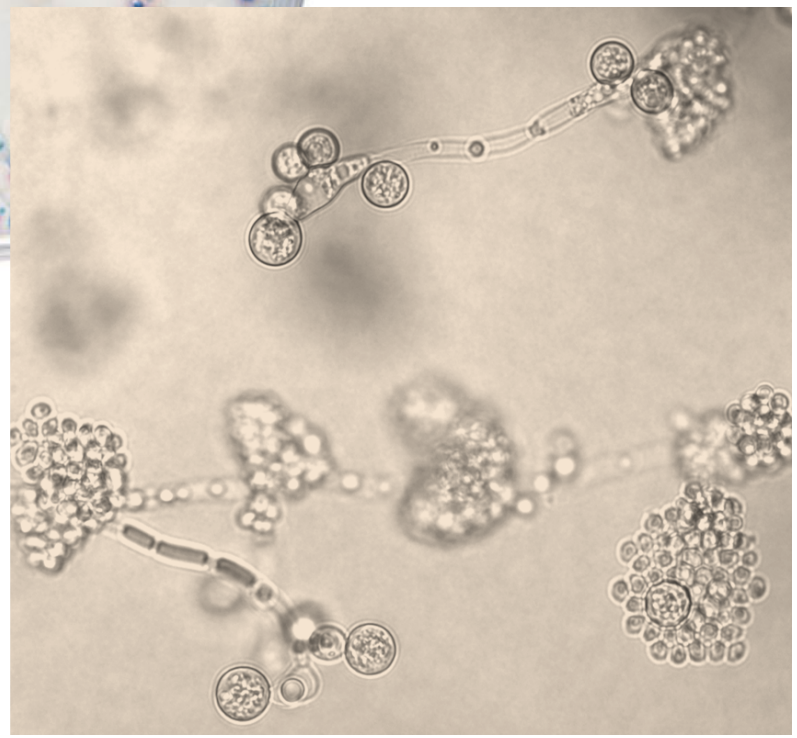
Candida albicans and characteristic "feet"





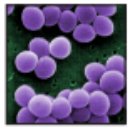
Candida albicans Identification





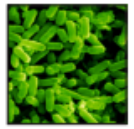
FilmArray Blood Culture Identification Panel

1 Test. 27 Targets. All in about an hour.



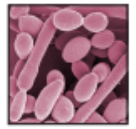
Gram-Positive Bacteria

Enterococcus
Listeria monocytogenes
Staphylococcus
Staphylococcus aureus
Streptococcus
Streptococcus agalactiae
Streptococcus pyogenes
Streptococcus pneumoniae



Gram-Negative Bacteria

Acinetobacter baumannii
Haemophilus influenzae
Neisseria meningitidis
Pseudomonas aeruginosa
Enterobacteriaceae
Enterobacter cloacae complex
Escherichia coli
Klebsiella oxytoca
Klebsiella pneumoniae
Proteus
Serratia marcescens

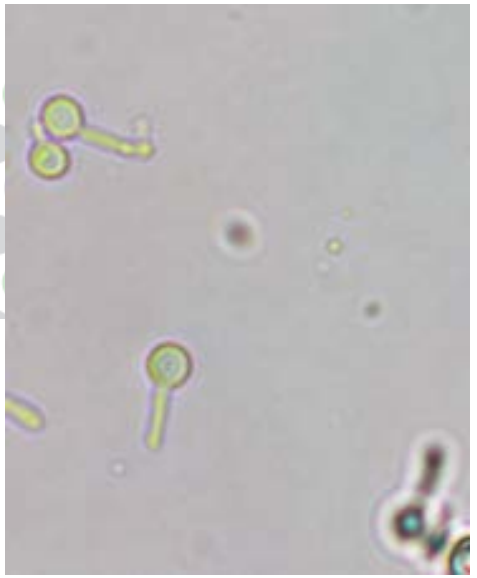


Yeast

Candida albicans
Candida glabrata
Candida krusei
Candida parapsilosis
Candida tropicalis

Antibiotic Resistance Genes

mecA - methicillin resistant
vanA/B - vancomycin resistant
KPC - carbapenem resistant



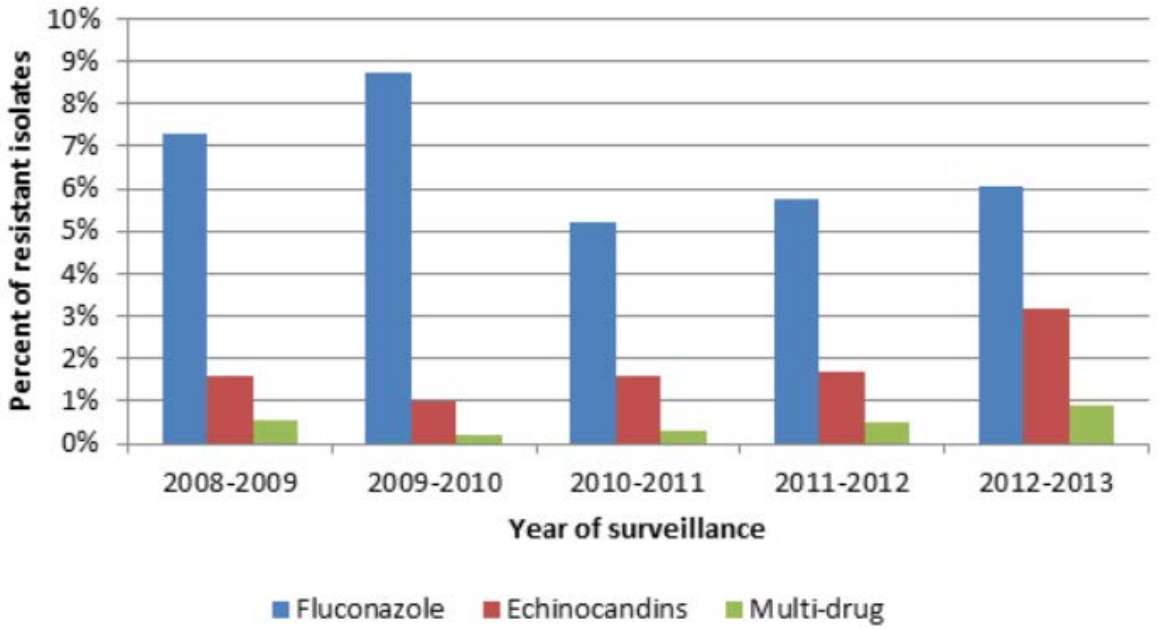
Candida Infection Treatment (CDC)

- Candidemia mortality is high, early antifungal therapy and catheter removal may help
- Echinocandins are the first choice for antifungal treatment for candidemia
- Fluconazole MICs for *C. glabrata* > *C. albicans, C. tropicalis, C. parapsilosis*
- Susceptibility testing should be performed to identify resistance and to facilitate transition to oral therapy

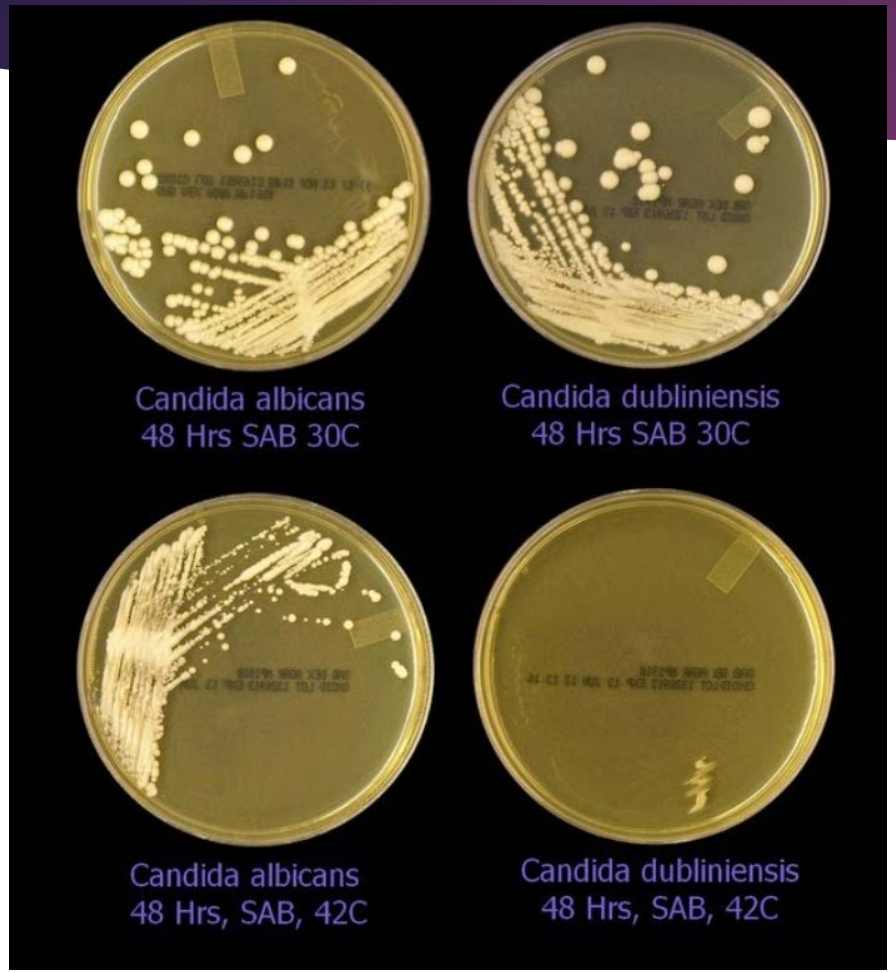
Candida Susceptibility

Candida spp.	Fluc	Echino	Ampho	5-FC
C. albicans	S	S	S	S
C. glabrata	I/R	S	S^	S
C. krusei	R	S	S^	R
C. lusitaniae	S	S	R	S
C. parapsilosis	S	S^	S	S
C. tropicalis	S	S	S	S

Fluc = fluconazole, Echino = echinocandins (caspofungin, micafungin), Ampho = amphotericin, 5-FC = flucytosine, S = Susceptible, I = intermediate or susceptible dose dependent, R = resistant, ^ = elevated MICs



Candida albicans versus *Candida dubliniensis*



Org/Test	*Candida albicans*	*Candida dubliniensis*
42-45º growth/SDA	Positive	negative
Germ tube	Positive	Positive
Fluconazole	Usually susceptible	Increased resistance
Biofire Film array	Detected	Not detected
Corn meal agar	B, P, C (single, terminal)	B, P, C (often clusters)
Urea	Negative	Negative

Reference: http://thunderhouse4-yuri.blogspot.com/2009/12/candida-albicans.html

Candida auris-Emerging Pathogen (EID)

- Discovered in 2009
- Rare in US, BUT is increasing rapidly
- Causes **serious invasive infection** in hospitalized patients
- Found in **blood** and wounds, urine, sputum, and other non-invasive sites
- May be missed or **misidentified**
- Only reportable in 3 states (Tennessee, Utah, and Wyoming) (CDC)

- **All confirmed isolates of *C. auris* should be reported to local and state public health officials and to CDC at candidaauris@cdc.gov.**

Candida auris-Emerging Pathogen (EID), CDC Recommendations for Healthcare Facilities

1) Put patient in contact precautions
2) Observe strict hand hygiene
3) Eradication is difficult-can live on surfaces for months, use same room cleaning as for *C. difficile* (quaternary compounds not effective)
4) Screen patients for colonization
5) May be resistant to all 3 classes of antifungal agents, including echinocandins
6) Before 2009, never isolated from natural environment and not known to be human colonizer


COMMENTARY

The Unexpected and Troubling Rise of *Candida auris*

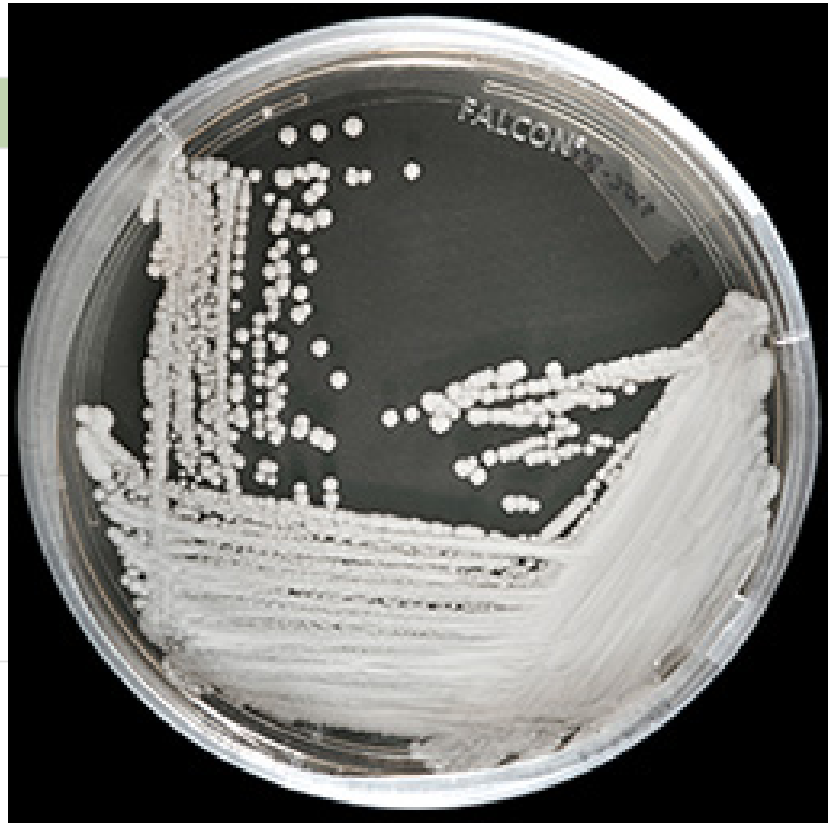
Tom Chiller, MD

DISCLOSURES | August 24, 2017

EDITORIAL COLLABORATION Medscape & CDC

Colonies of *Candida auris*, CDC

Identification Method	Organism *C. auris* can be misidentified as
Vitek 2 YST	*Candida haemulonii* *Candida duobushaemulonii*
API 20C	*Rhodotorula glutinis* (characteristic red color not present) *Candida sake*
BD Phoenix yeast identification system	*Candida haemulonii* *Candida catenulata*
Microscan	*Candida famata* *Candida guilliermondii** *Candida lusitaniae** *Candida parapsilosis**

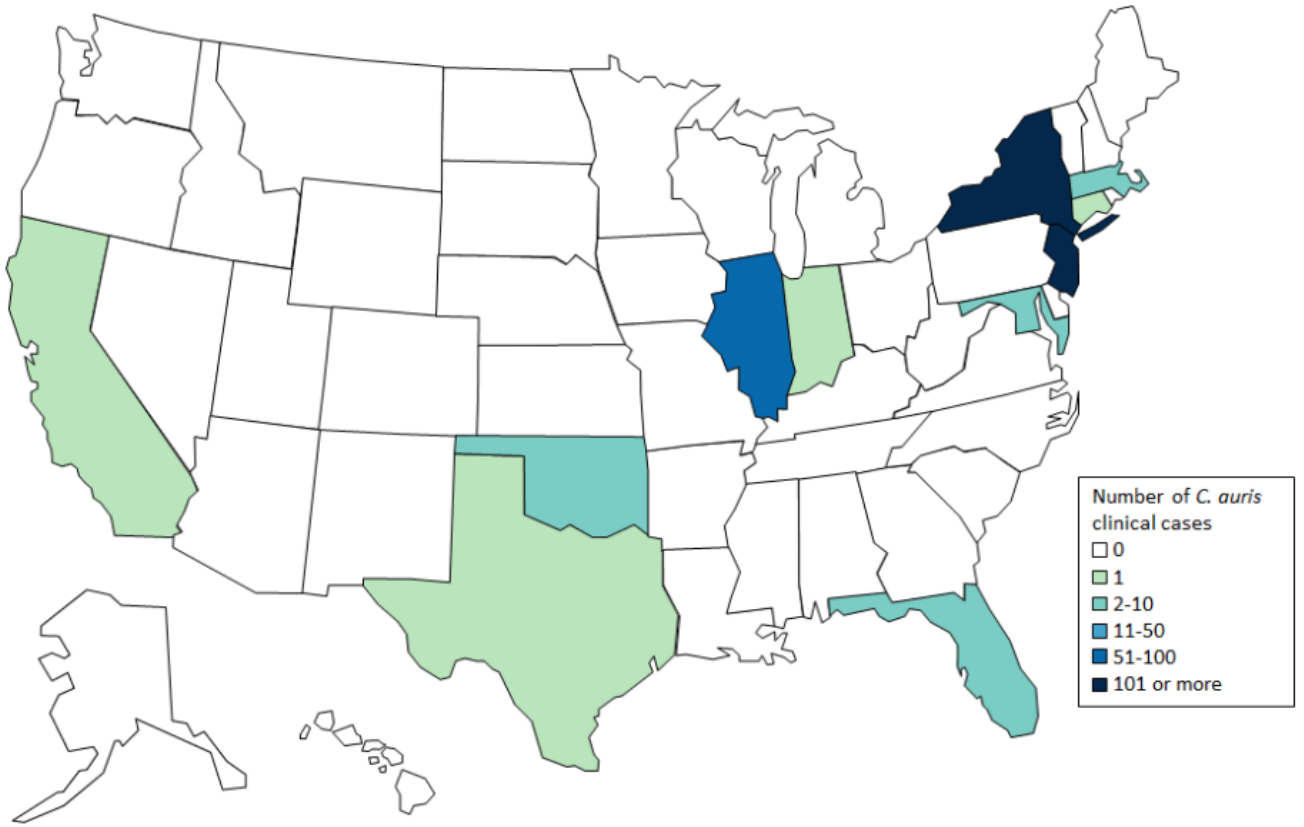


Tracking of *Candida auris*, CDC

Table: Clinical cases of *Candida auris* reported by state, United States, as of July 31, 2018

State	Number and type of clinical *Candida auris* cases reported	
	Confirmed	Probable
California	1	0
Connecticut	1	0
Florida	3	0
Illinois	51	4
Indiana	1	0
Maryland	3	0
Massachusetts	7	0
New Jersey	82	22
New York	209	4
Oklahoma	2	0
Texas	1	0
TOTAL	361	30

U.S. Map: Clinical cases of *Candida auris* reported by state, United States, as of July 31, 2018



Cases are categorized by the state where the specimen was collected. Most probable cases were identified when laboratories with current cases of *C. auris* reviewed past microbiology records for *C. auris*. Isolates were not available for confirmation. Early detection of *C. auris* is essential for containing its spread in healthcare facilities.

Antifungal Treatment of *Candida auris*, CDC

Class/Drug	Tentative MIC Breakpoints (µg/mL)	Comment
Triazoles		
Fluconazole	≥32	Modal minimum inhibitory concentration (MIC) to fluconazole among isolates tested at CDC was ≥256; isolates with MICs ≥32 were shown to have a resistance mutation in the *Erg11* gene, making them unlikely to respond to fluconazole.
Voriconazole and other second generation triazoles	N/A	Consider using fluconazole susceptibility as a surrogate for second generation triazole susceptibility assessment. However, isolates that are resistant to fluconazole may respond to other triazoles occasionally. The decision to treat with another triazole will need to be made on case-by-case basis.
Polyenes		
Amphotericin B	≥2	Recent pharmacokinetic/pharmacodynamic analysis of *C. auris* in a mouse model of infection indicates that under standard dosing, the breakpoint for amphotericin B should be 1 or 1.5, similar to what has been determined for other *Candida* species. Therefore, **isolates with an MIC of ≥2** should now be considered resistant. If using Etest for amphotericin B and an MIC of 1.5 is determined, that value should be rounded up to 2.
Echinocandins		
Anidulafungin	≥ 4	Tentative breakpoints are based on the modal distribution of echinocandin MICs of approximately 100 isolates from diverse geographic locations.
Caspofungin	≥ 2	
Micafungin	≥ 4	

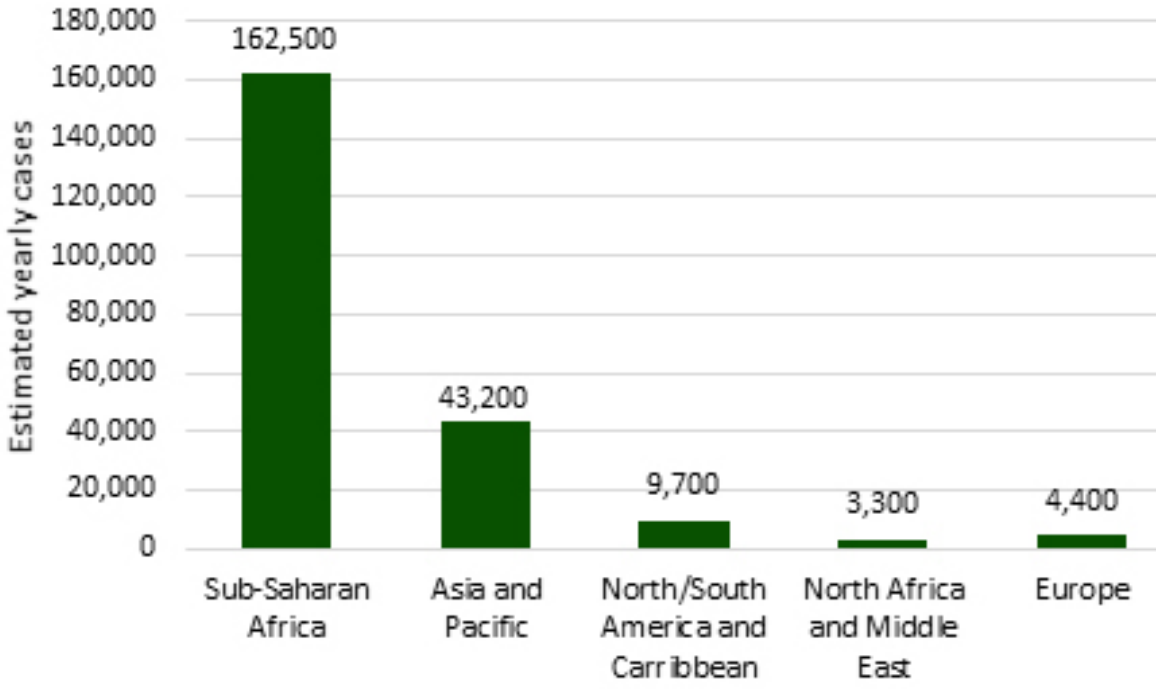
Cryptococcosis

- *Cryptococcus neoformans* is found worldwide in environment
- Infection occurs via respiratory route with inhalation of the fungus
- Clinical picture depends on the yeast strain and immune status of the host, with rare infections in healthy individuals
- Infection is often subclinical or can be latent or symptomatic
- Infection can present as **pneumonia-like illness**, with cough, fever, chest pain, and weight loss symptoms
- *C. neoformans* also has a predilection for CNS and can disseminate and cause **meningoencephalitis**

Cryptococcosis

- Worldwide see 220,000 cases of cryptococcal meningitis/year
- US incidence is estimated at 0.4-1.3 cases/100,000, with a case fatality rate of 12%
- Rates are high enough in HIV positive patients that screening for cryptococcal infection may be warranted

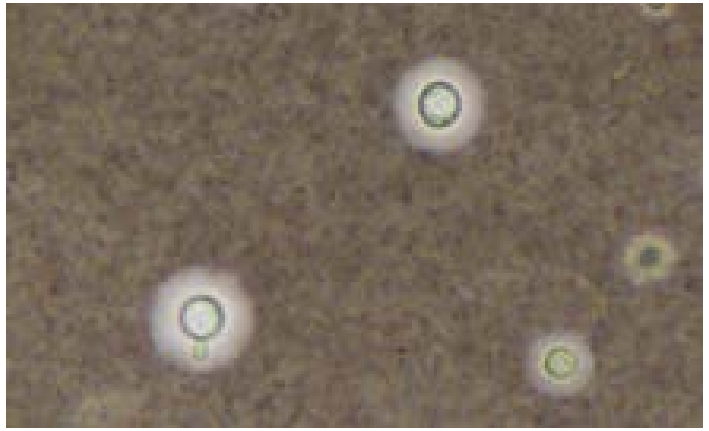
Figure 1: global burden of HIV-related cryptococcal meningitis

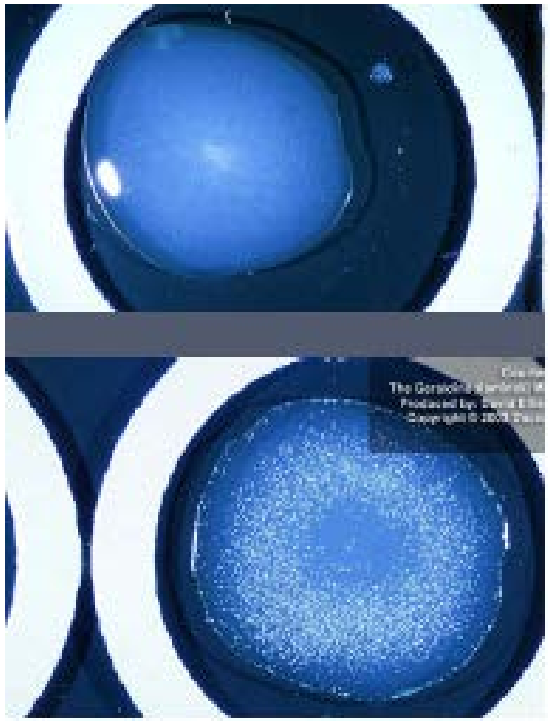


Adapted from R Rajasingham et al., Lancet Infectious Diseases 2017.

Lab Diagnosis of Cryptococcosis

- India Ink
- Culture
- Antigen detection-CSF or serum
  - Latex agglutination
  - Enzyme Immunoassay
  - Lateral flow assay (IMMY)





Comparison of *C. neoformans and C. gattii*

Org/characteristic	*Cryptococcus neoformans*	*Cryptococcus gatti*
Patient population	Mainly compromised	Immunocompetent and compromised
Geographic distribution/natural habitat	Worldwide	Tropics, EID in Pacific Northwest US (Oregon, Washington, and California) and Canada
Clinical disease progression	Pneumonia, CNS dissemination	Higher rate of cryptococcoma formation in lungs and brain/assoc. with neurological sequelae
Case Fatality Rate	12%	13-33%
Anti-fungal drug susceptibility guidelines	CLSI	None, being evaluated; may have higher MIC's for some antifungal agents

Differentiation of *C. neoformans* and *C. gatti*

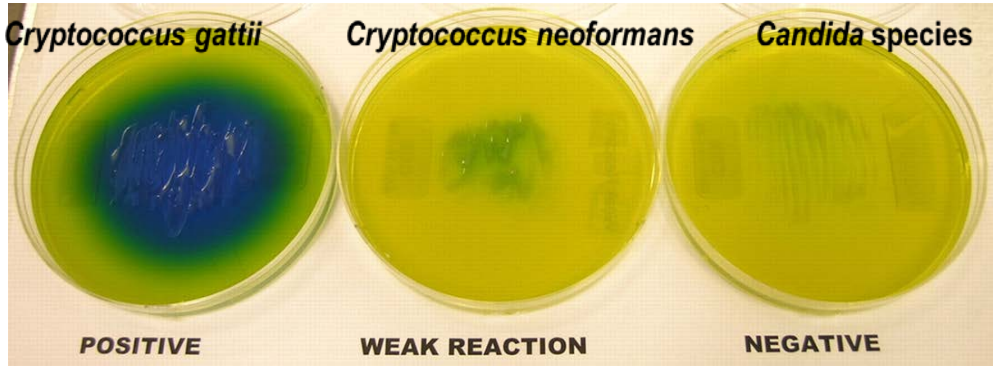
- Use glycine as sole carbon and nitrogen source in the presence of canavanine
- Can use Canavanine glycine bromothymol blue agar (CGB)

(+) = *Cryptococcus gatti* (blue)

(−) = *Cryptococcus neoformans*

Cryptococcus Identification

Species	Urea	Birdseed	Caffeic Acid	CGB
C. neoformans	+	+	+	-
C. gattii	+	+	+	+
Other species	+	-	-	-



CDC A-Z INDEX

EMERGING INFECTIOUS DISEASES®

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Research

Non-*cyp51A* Azole-Resistant *Aspergillus fumigatus* Isolates with Mutation in HMG-CoA Reductase

Daisuke Hagiwara[1], Teppei Arai[1], Hiroki Takahashi, Yoko Kusuya, Akira Watanabe✉, and Katsuhiko Kamei

Author affiliations: University of Tsukuba, Tsukuba, Japan (D. Hagiwara); Chiba University, Chiba City, Japan (D. Hagiwara, T. Arai, H. Takahashi, Y. Kusuya, A. Watanabe, K. Kamei)

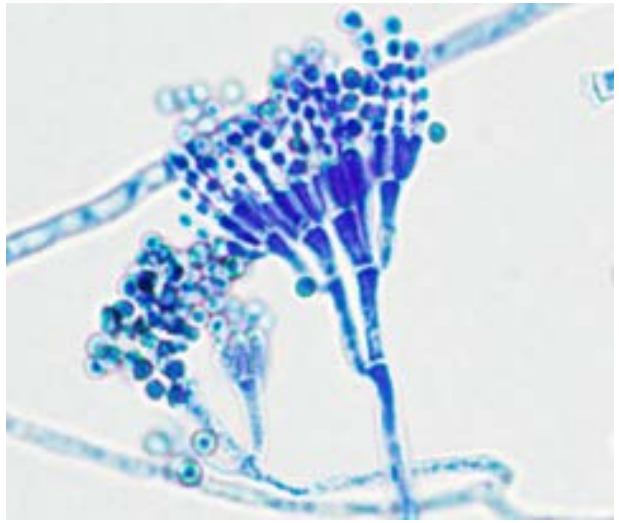
Suggested citation for this article

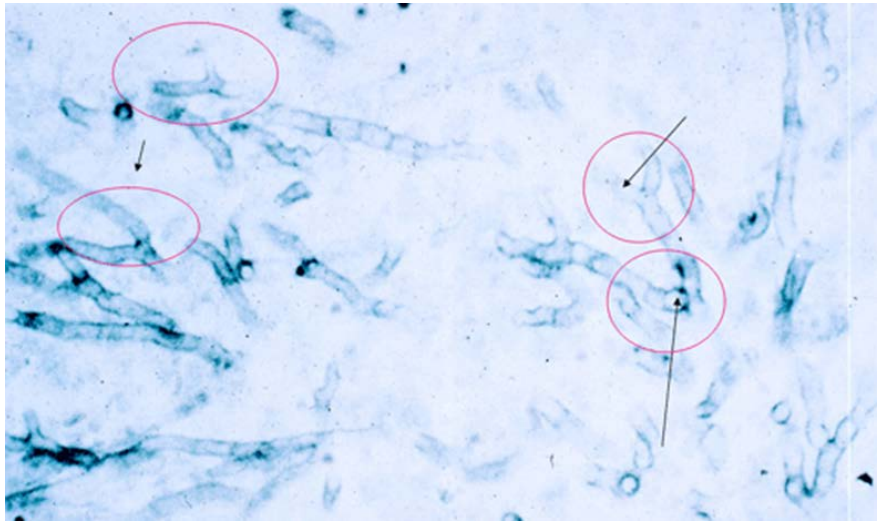
Abstract

The recent increase in azole-resistant *Aspergillus fumigatus* is a global concern. Identifying the mutations that confer azole resistance is essential for developing novel methods for prompt diagnosis and effective drug treatment. We screened *A. fumigatus* clinical isolates for novel mutations conferring azole resistance. We compared the genomic sequences of susceptible and resistant isolates without mutations in *cyp51A* (non-*cyp51A*) and found mutations in *hmg1* and *erg6* involved in ergosterol biosynthesis. We also found the novel mutations in these genes in azole-resistant isolates with different genetic backgrounds. The resistant isolates with mutations in *hmg1* showed increased intracellular ergosterol levels compared with susceptible isolates. This finding supports the concept that the ergosterol level is a determinant for resistance to any class of azoles. Multiple isolates with increased resistance to azole possessed a mutation in *hmg1*, indicating that this mutation is widely present in non-*cyp51A* azole-resistant *A. fumigatus*.

Aspergillus versus Penicillium

- Both are classified as hyaline or **moniliaceous fungi** where **the** septate hyphal filaments are without pigment in the cell wall and cause **hyalohyphomycosis**
- Presence of **septate hyaline hyphae with dichotomous branching** in direct exam
- *Aspergillus* has large vesicle and *Penicillium* has "penicillus arrangement"



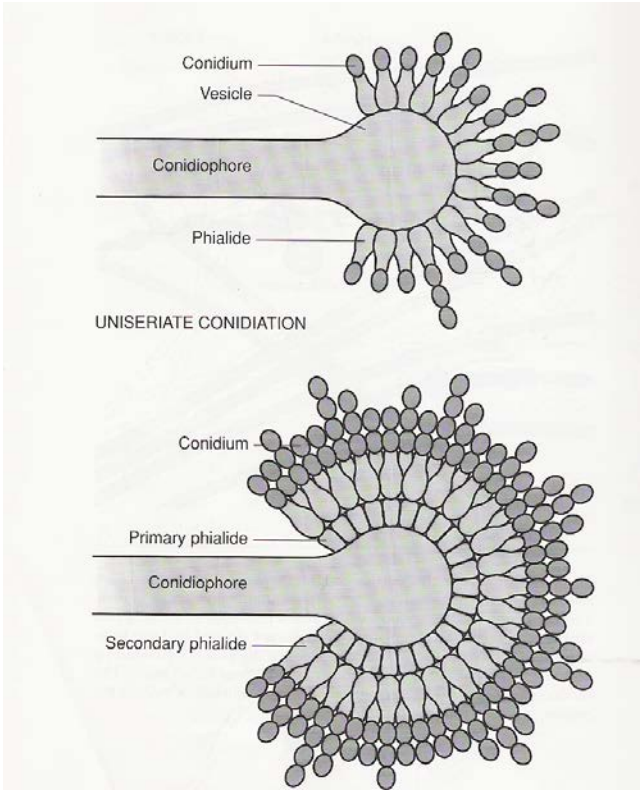


Aspergillus

- Organism is ubiquitous in the environment
- Aerosol generation (hospital construction) is a major contributing factor to infection
- Significance in culture determined by presence in more than one site, repeat cultures, or correlation with clinical picture
- *Aspergillus* is the second most common fungal pathogen requiring hospitalization (2nd to *Candida* infections)

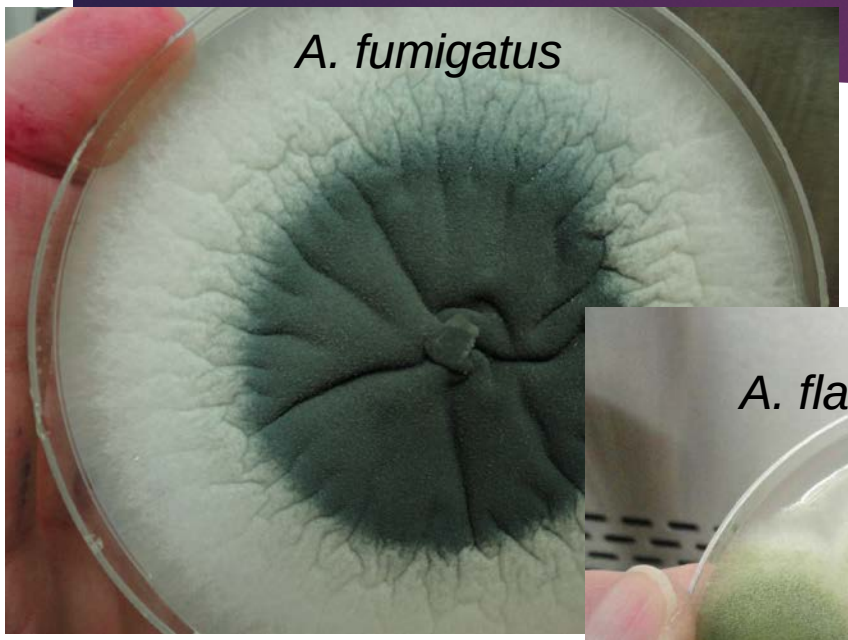
Macroscopic and Microscopic Characteristics of *Aspergillus*

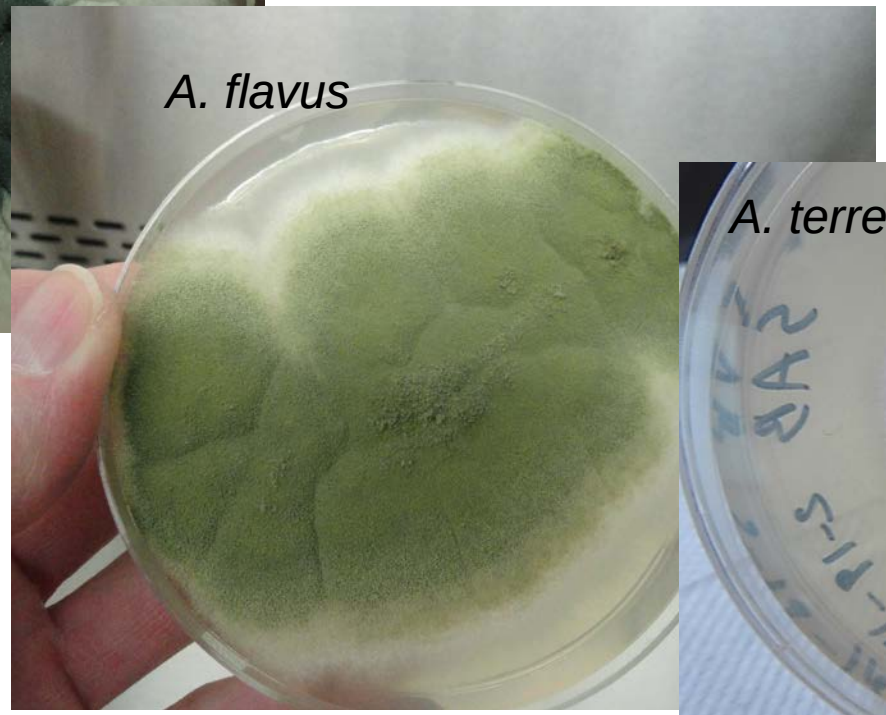
Organism	Macroscopic		Microscopic		
	Surface	Reverse	Conidiophore	Phialides	Vesicle
Aspergillus fumigatus	Blue-green to gray	White to tan	Short (<300um), smooth, colorless or greenish	Uniseriate	Round, columnar head
Aspergillus flavus	Yellow-green	Gold to reddish brown	Long, colorless, rough	Uniseriate/ biseriate	Round, radiate head
Aspergillus niger	White with Black	White to yellow	Long, smooth, colorless or brown	Biseriate	Round, radiate head
Aspergillus terreus	Cinnamon to brown	White to brown	Short, (<250um), smooth and colorless	Biseriate	Round, compactly columnar head

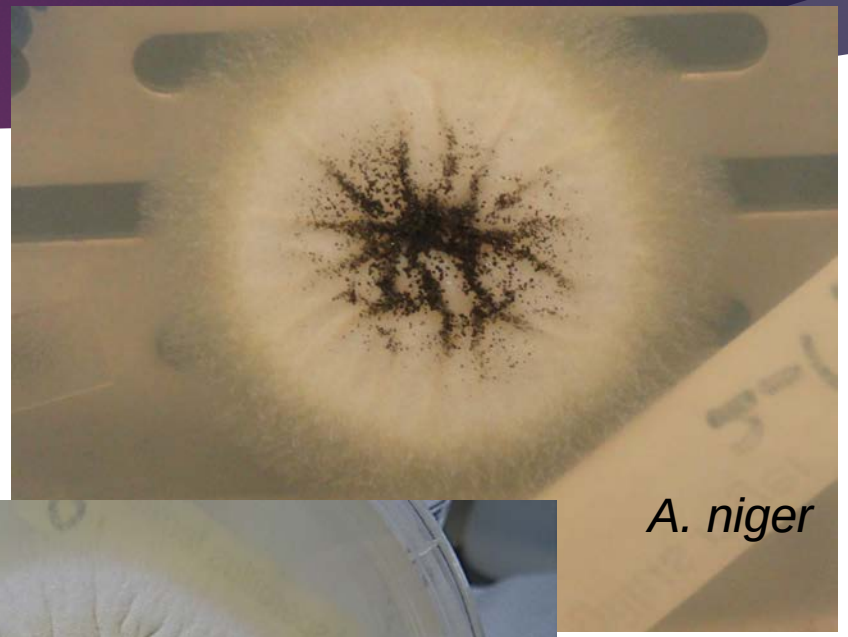


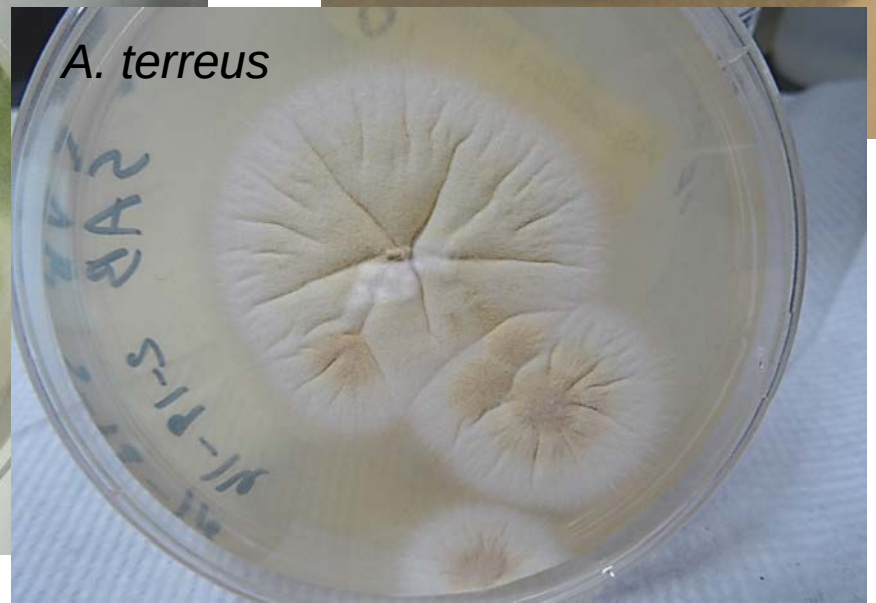
Uniseriate = one row of phialides
Biseriate = two rows of phialides

Macroscopic Characteristics of *Aspergillus* species

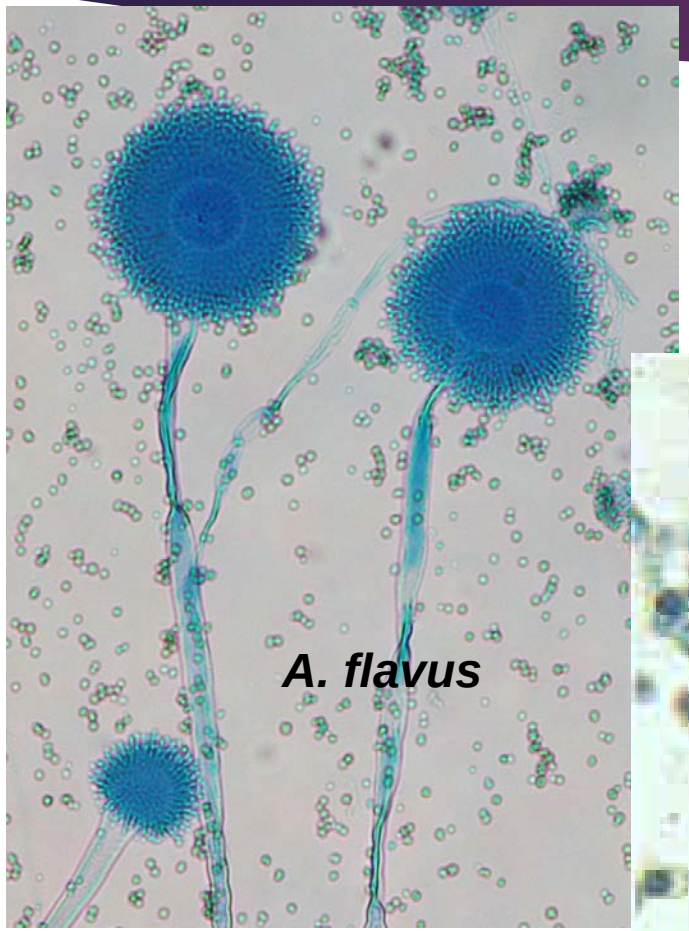




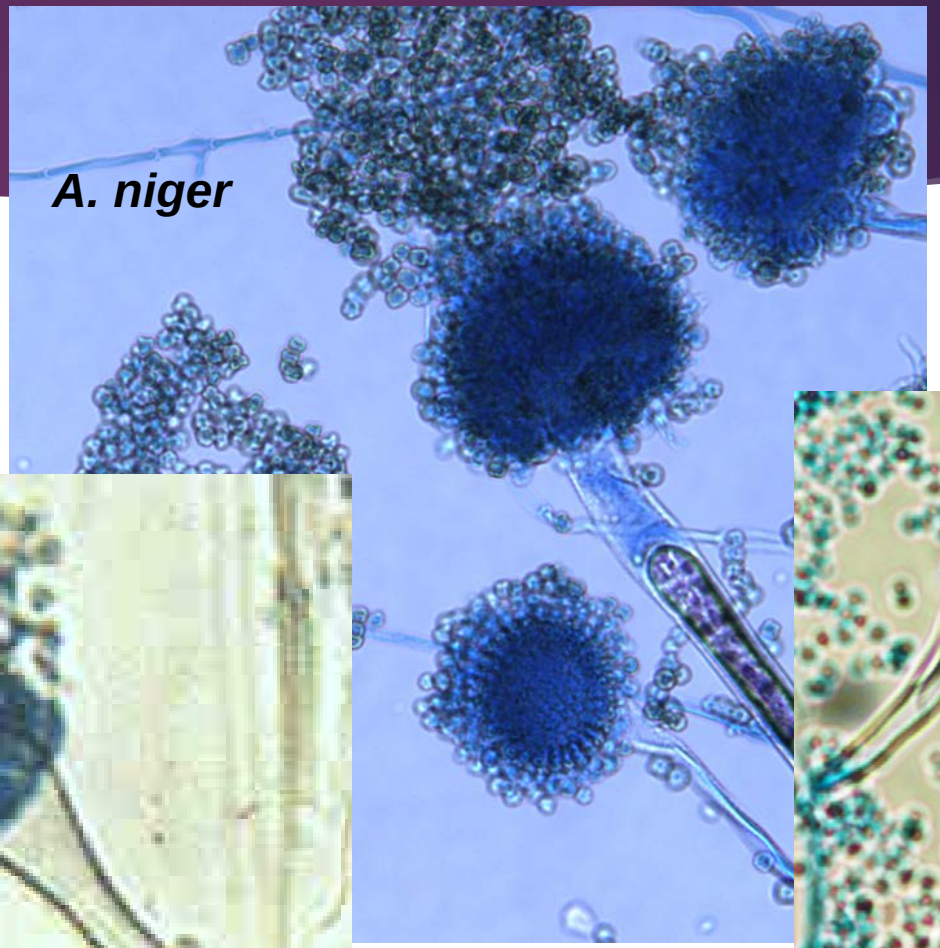




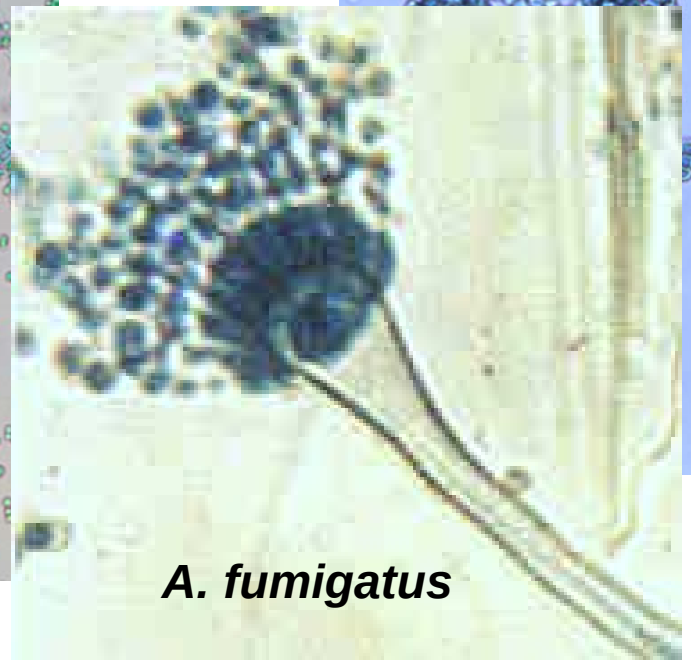
Microscopic Appearance of *Aspergillus* species



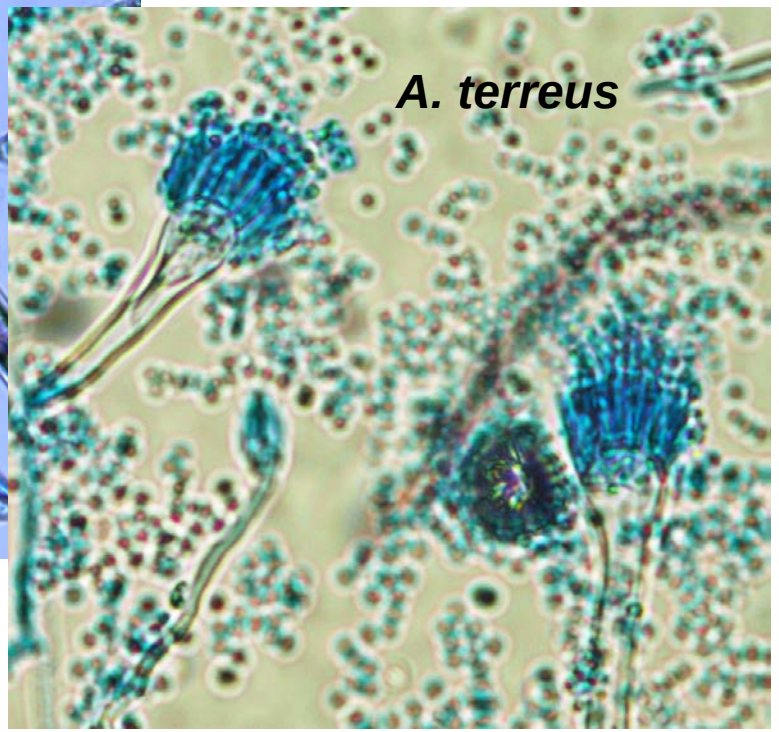
A. flavus



A. niger



A. fumigatus

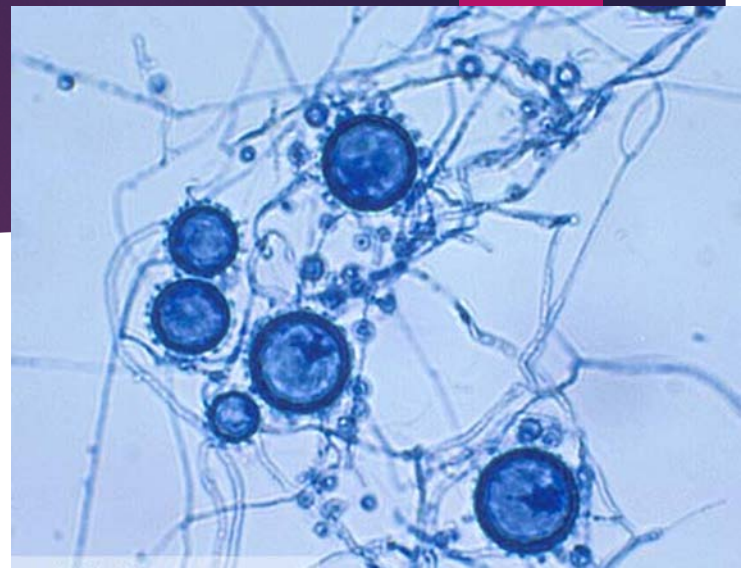


A. terreus

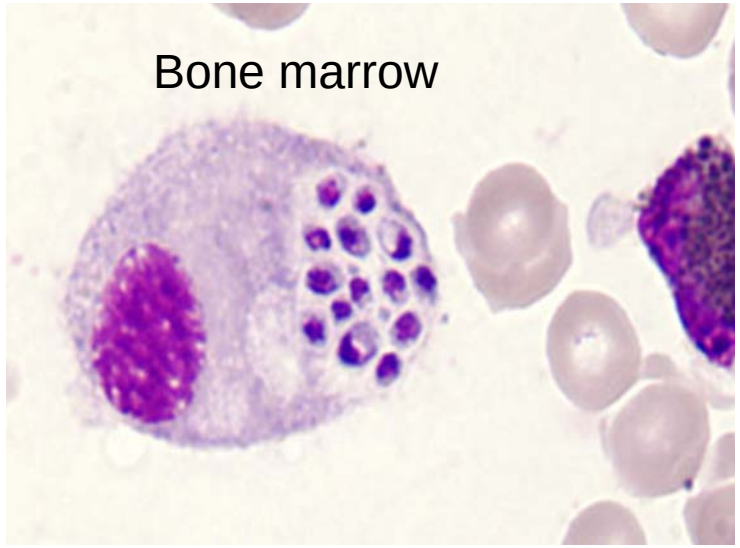
Primary Systemic Fungal Pathogens in US

- Previously known as “Dimorphic fungi”
- Typically display two growth phases based on incubation temperature
  - **Yeast (or spherule**) phase-37^{o}C, found in specimen
  - **Mould** phase-hyphae observed from cultures incubated at 25-30^{o}C
    - *Histoplasma capsulatum*
    - *Blastomyces dermatitidis*
    - *Coccidioides*

Histoplasma capsulatum



- Acquired via inhalation of conidia from soil containing bird or bad guano
- Called “Darling’s disease”
- Usually self-limiting, can cause pulmonary, ocular, or disseminated infections



- **MOULD**-has hyphae with conidiophores that support 8-16 µ diameter, round **tuberculate macroconidia** and/or non-tuberculate, smooth macroconidia

- **YEAST** phase- small, 2-4 µ diameter single budding narrow base budding yeast cells

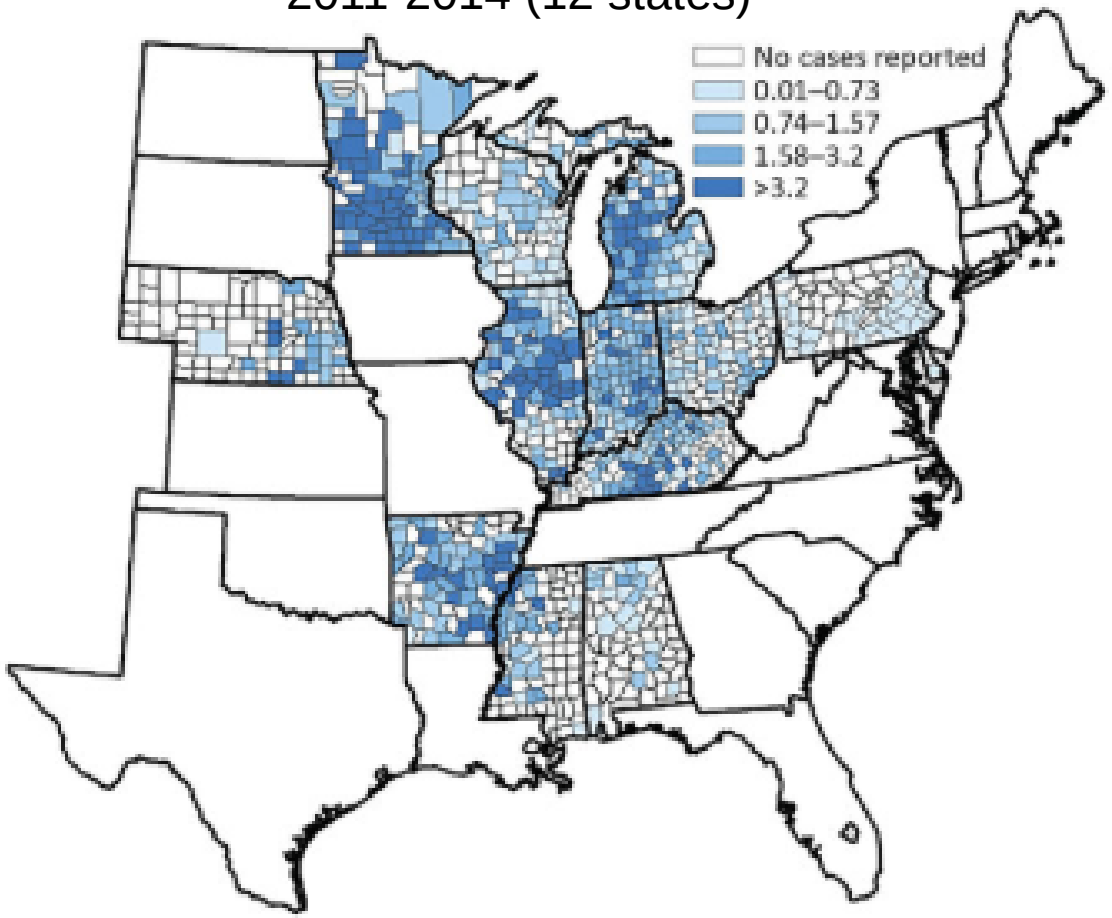
Histoplasma capsulatum Confirmation (MDHHS)

- Isolation of *H. capsulatum* from a clinical specimen or histopathology ID of yeast in tissue or sterile body fluid
- ≥ 4-fold rise in *H. capsulatum* serum complement fixation antibody titers
- Detection in serum of H band or M band seroconversion (after documented previous missing M band) by *H. capsulatum* immunodiffusion antibody test
- PCR demonstration of *H. capsulatum*-specific nucleic acid in a clinical specimen
- Michigan had 130 cases reported in **2012**

Test	Disseminated Histoplasmosis	Acute or Subacute Pulmonary	Chronic Pulmonary
Antigen (urine)	92%	25% (subacute) and 75-80% (acute diffuse)	14%
Culture	85%	15%	85%
Histopathology	43%	9%	17%
Serology	71%	98%	100%

Histoplasma capsulatum Surveillance (MDHHS)

2011-2014 (12 states)



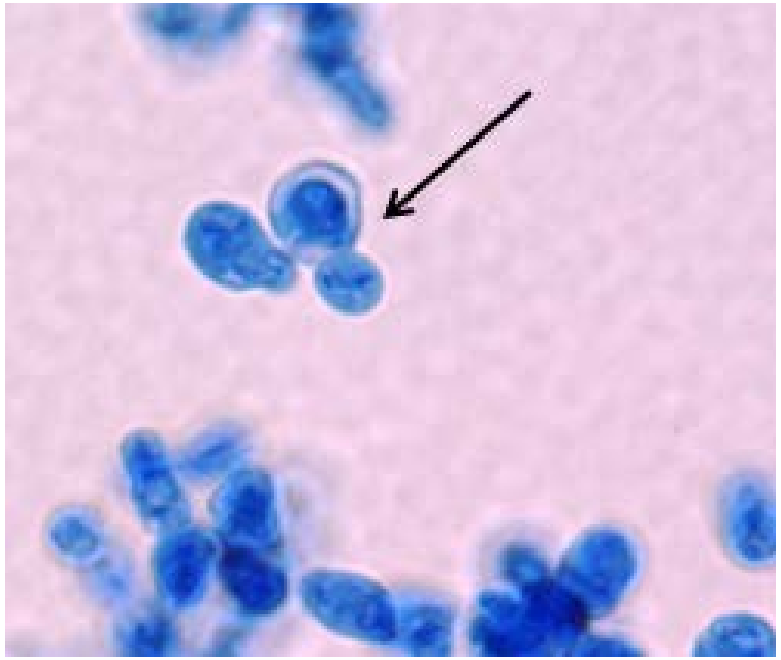
Blastomyces dermatitidis

- Acquired via inhalation of airborne conidia or cutaneous infection via traumatic implantation
- Found endemic in Ohio and Mississippi River valleys, the Great Lakes, and the Saint Lawrence River
- May comprise Two species-***B. dermatitidis*** and ***B.gilchristii***
- Coccidioidomycosis is also called: “San Joaquin Valley fever”, “Valley fever”, or “desert rheumatism”
- 50% of cases are asymptomatic, incubation is 3 weeks to 3 months, and clinical presentation is non-specific
- 2012: 13 cases reported in Michigan

Blastomyces dermatitidis Microscopy

- **MOULD**-develops **pyriform**, one-celled conidia, 2-10 µ in diameter, attached directly on the hyphae or by short conidiophores (is not diagnostic)

- **YEAST-**broad based buds and thick cell walls and round, globose shape are characteristic (resemble matryoshka dolls)



Blastomyces dermatitidis Laboratory Diagnosis

- Antigen detection using e**nzyme immunoassay** methods are used on urine or serum, or BAL
- **Immunodiffusion** and **Complement Fixation are available but have low sensitivity and specificity**
- **Culture and Microscopy**-gold standard (AccuProbe, GenProbe, Inc can be used to confirm)
- **Polymerase Chain Reaction-**only experimental

Coccidioides species

- Acquired via inhalation of airborne arthroconidia
- Found most predominantly in southwestern US
- Two species-***C. immitis*** (mainly California) and ***C. posadasii*** (Arizona, Texas, Mexico and S. America) are recognized, but clinical differentiation has not been documented
- Coccidioidomycosis is also called: “San Joaquin Valley fever”, “Valley fever”, or “desert rheumatism”
- Only 40% of cases are symptomatic and primarily self-limiting
- 5-10% of cases lead to chronic pulmonary disease or 1% may disseminate to bones, joints, or meninges
- Climate change may impact distribution of this organism in future
- 2012: 33 cases reported in Michigan

Number of Reported Coccidioidomycosis cases, 1998-2015 (CDC)

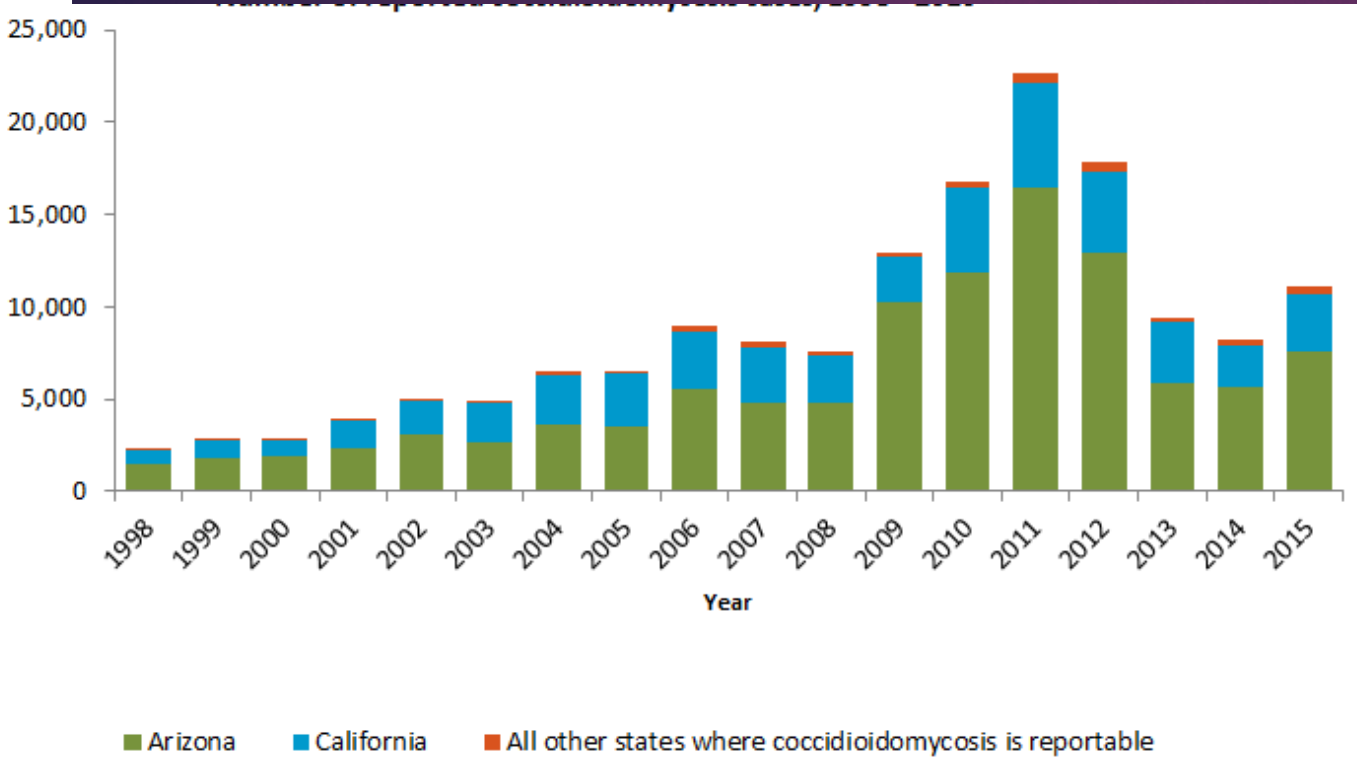
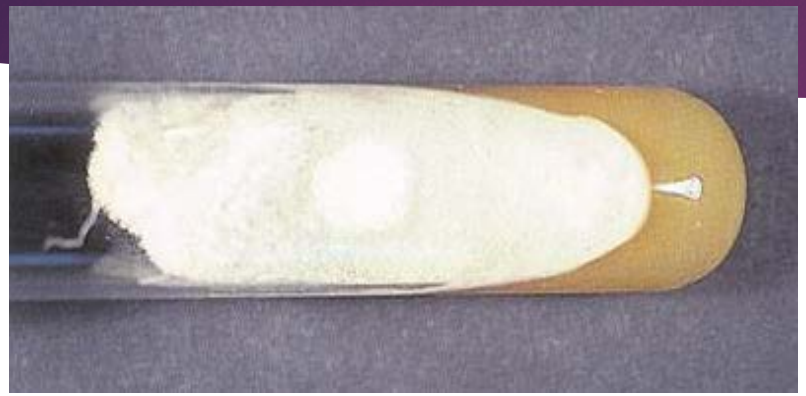
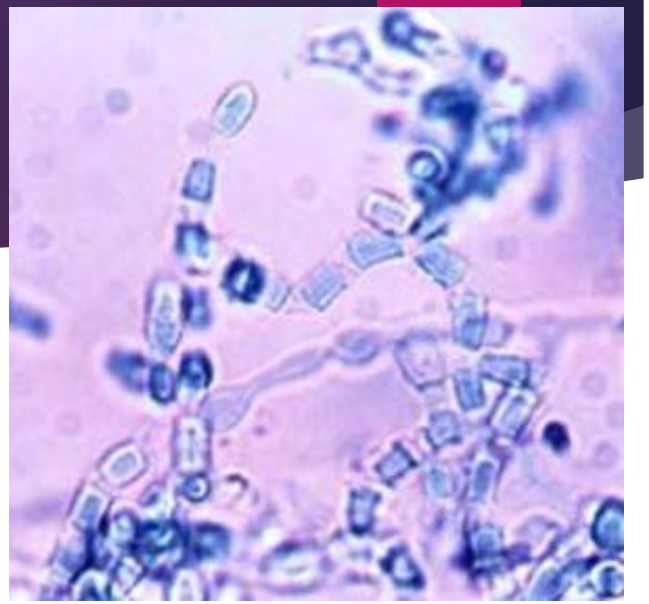


FIGURE 1. Persons attending the world championship of model airplane flying — Lost Hills, California, October 2001

Photographed by: Joe Mekina

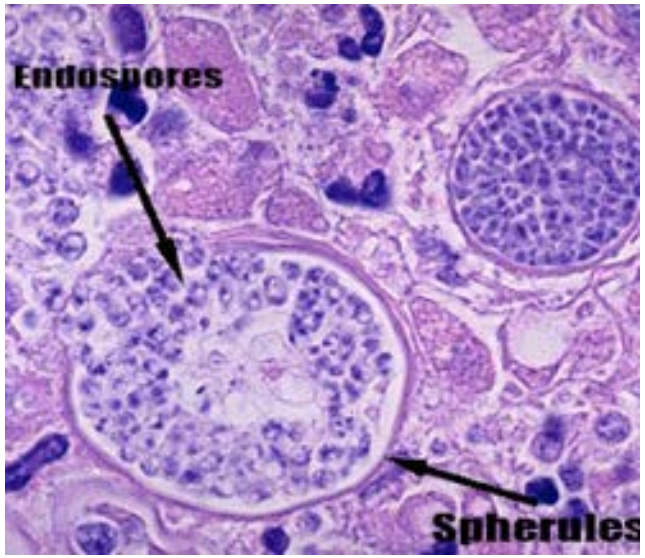
Coccidioides immitis and C. posadasii





- **MOULD**-develops rapidly, see thick walled hyphae or arthroconidia that are **barrel-shaped**, with alternating **disjunctor cells**

- **NO YEAST** phase- arthroconidia develop in tissue, sputum or body fluids into round **spherules** (up to 80 µm) which contain endospores



Diagnosis of *Coccidioides* species

- Coccidioidomycosis is most often diagnosed using serology:
  - Two **enzyme immunoassay** methods are available:
    - Premier ® Coccidioides EIA – Meridian Bioscience, Inc.
    - Coccidioides Antibody Enzyme Immunoassay – Immuno Mycologics, Inc. (IMMY)
  - **Immunodiffusion** is used for IgM antibodies; and **Complement Fixation** detects IgG antibodies (disease severity assessment)
- **Culture and Microscopy**
- **Urinary antigen** detection for diagnosis in immunocompromised patients
- **Polymerase Chain Reaction**:
  - GeneSTAT.MDx Coccidioides – DxNA, LLC –FDA approved for LRT specimens
  - Other pending

Fungal Disease Awareness: Think Fungus!

Think Fungus: Fungal Disease Awareness Week

Fungal Disease Awareness Week is October 1–5, 2018. CDC and partners have organized this week to highlight the importance of recognizing serious fungal diseases early enough in the course of a patient's illness to provide life-saving treatment. Some fungal diseases go undiagnosed and cause serious infections in people in the United States and around the world, leading to illness and death. Increased awareness about fungal diseases is one of the most important ways we can improve early recognition and reduce delays in diagnosis and treatment. A key clue to when a sick person may have a fungal infection is that he or she is being treated with medications for other types of infection but does not get better.

We encourage healthcare providers and their patients to "**Think Fungus**" when symptoms of infection do not get better with treatment.

Join us in sharing information to increase awareness in your community about fungal diseases. The quicker doctors can diagnose the right illness, the quicker a patient can be treated the right way.

Thanks
Questions?

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