

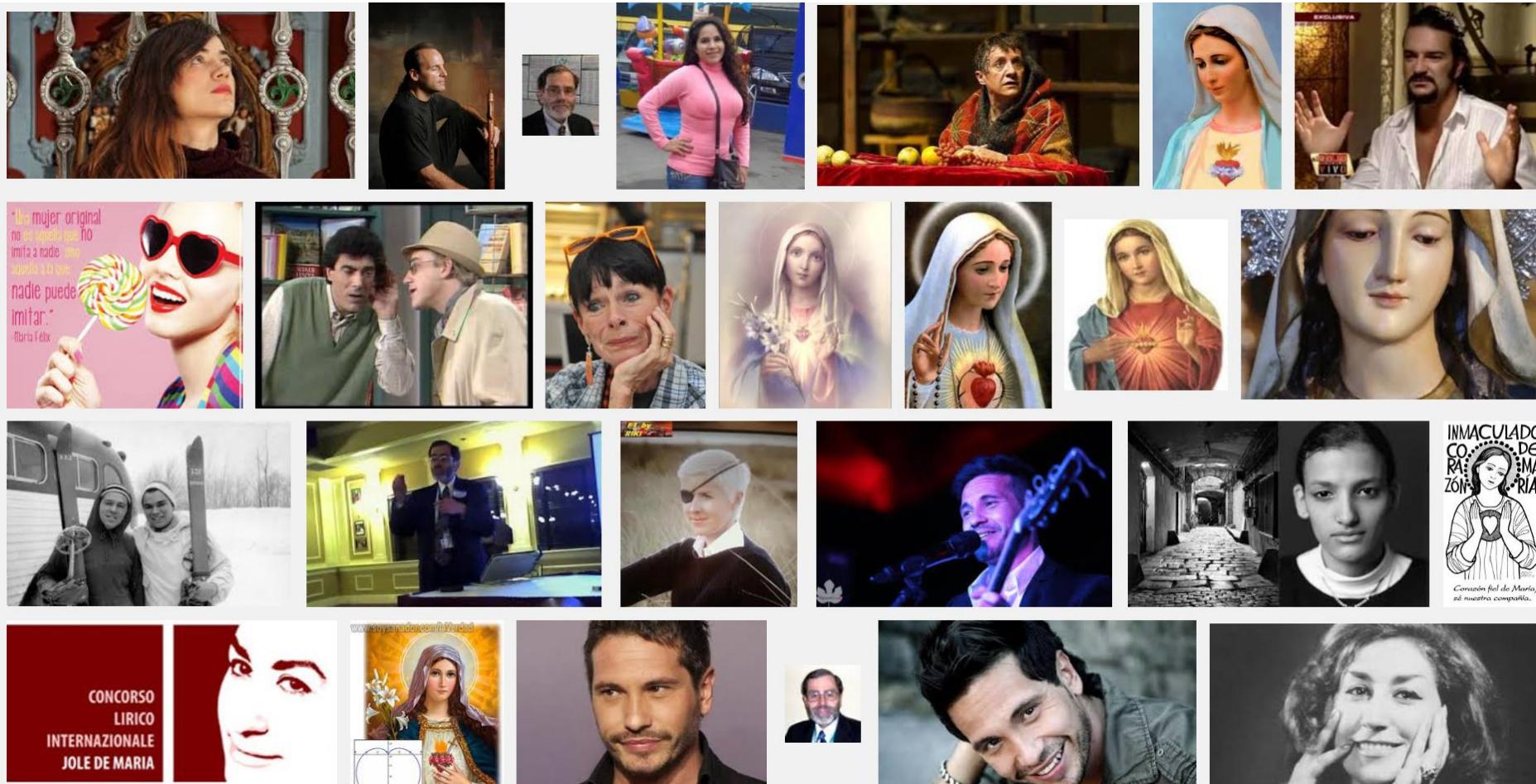
The Fungus Among Us



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University of Massachusetts Medical School

Thanks to Al DeMaria for inviting me



Google Images search of Al DeMaria

Financial Disclosure

- Below are the pharmaceutical or medical device companies from which I have received gifts or financial reimbursements for research, conferences, articles, advisory committees, consulting, speaker bureaus, travel, and regional or national meetings in the 3 years prior to this lecture.
- None



Financial Disclosures



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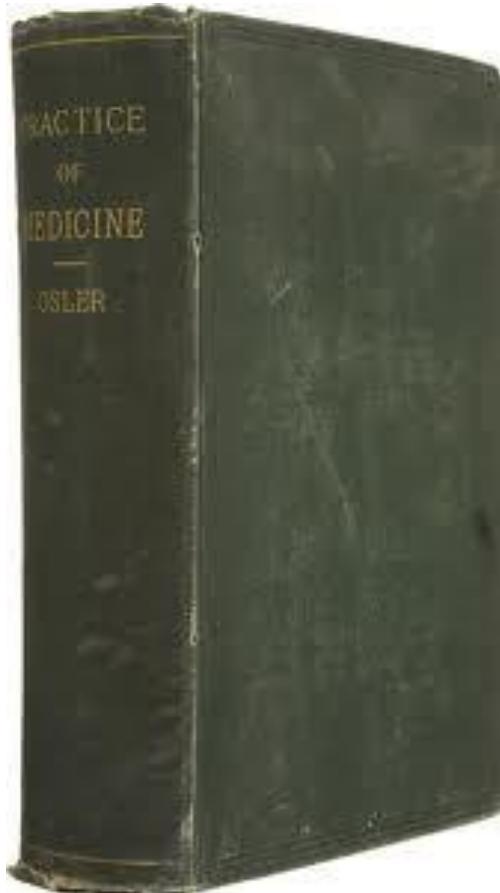
Lecture, Woman Reading
Pablo Picasso

Outline of Lecture



- Illustrative case report.
- Brief overview of fungi and antifungals.
- Emerging trends in:
 - candidiasis
 - cryptococcosis
 - aspergillosis
- Some other tidbits of info.

Osler's Textbook of Medicine



No mention of fungal diseases!!!! Why not????

Some were not recognized but mainly there were not many immunocompromised people.

(no AIDS, no steroids, no chemotherapy, no transplants, no IVs, no antibiotics).

For the most part, fungi were not considered pathogens

Case Report



Detective Case Report



Characters	Detectives	Suspects
Setting	Where does the story take place?	
Clues	Clues (in order)	Who discovered it?
1.		
2.		
3.		
4.		
*list additional clues on back if necessary		
Red Herrings	What are the distractions for the person trying to solve the mystery?	
Conclusion	What is the conclusion of the mystery?	What is the evidence that helped the detective/s crack the case?

FUNGÆMIA AND FUNGURIA AFTER ORAL ADMINISTRATION OF CANDIDA ALBICANS

W. KRAUSE

H. MATHEIS

K. WULF

FROM THE LANDESKLINIK AND THE STADT-KRANKENHAUS, KASSEL,
WEST GERMANY

Summary We have administered approximately 10^{12} cells of *Candida albicans* orally to a healthy volunteer. *C. albicans* cells were cultured from blood-samples taken after 3 and 6 hours, and from urine samples taken after $2\frac{3}{4}$ and $3\frac{1}{4}$ hours, and were found to be identical to the strain administered. There was a transient toxic reaction 2 hours after ingestion, and symptoms of fungæmia were observed up to 9 hours after the start of the test. No lasting damage resulted from the experiment. We conclude that *C. albicans* cells are capable of passing through the intestinal wall, probably by the mechanism of "persorption" and so reach the blood and urine. Since the population of *C. albicans* in the intestine was comparable to that sometimes seen after the use of broad-spectrum antibiotics, it seems likely that antibiotic-induced fungal overpopulation may also result in fungæmia.

Case

- “Volunteer” ingested 80g (10^{12}) *Candida albicans*.
- After 2h, developed fever, shaking chills, severe headache.
- Blood and urine grew *C. albicans*.
- Recovered uneventfully!

Lessons from the Case Report

- Innate defenses against fungi are strong.
- Most fungi are wimps, although some are wimpier than others.
- Compromise in host defenses turns fungal weaklings into dreaded pathogens.



#FungiGoViral!

(trending on Twitter)



The fungus among us

Mycosis	# Life-Threatening cases/yr
Aspergillosis	200,000
Candidiasis	400,000
Cryptococcosis	1,000,000
Mucormycosis	10,000
Pneumocystosis	400,000
Dimorphic (endemic) mycoses*	65,000

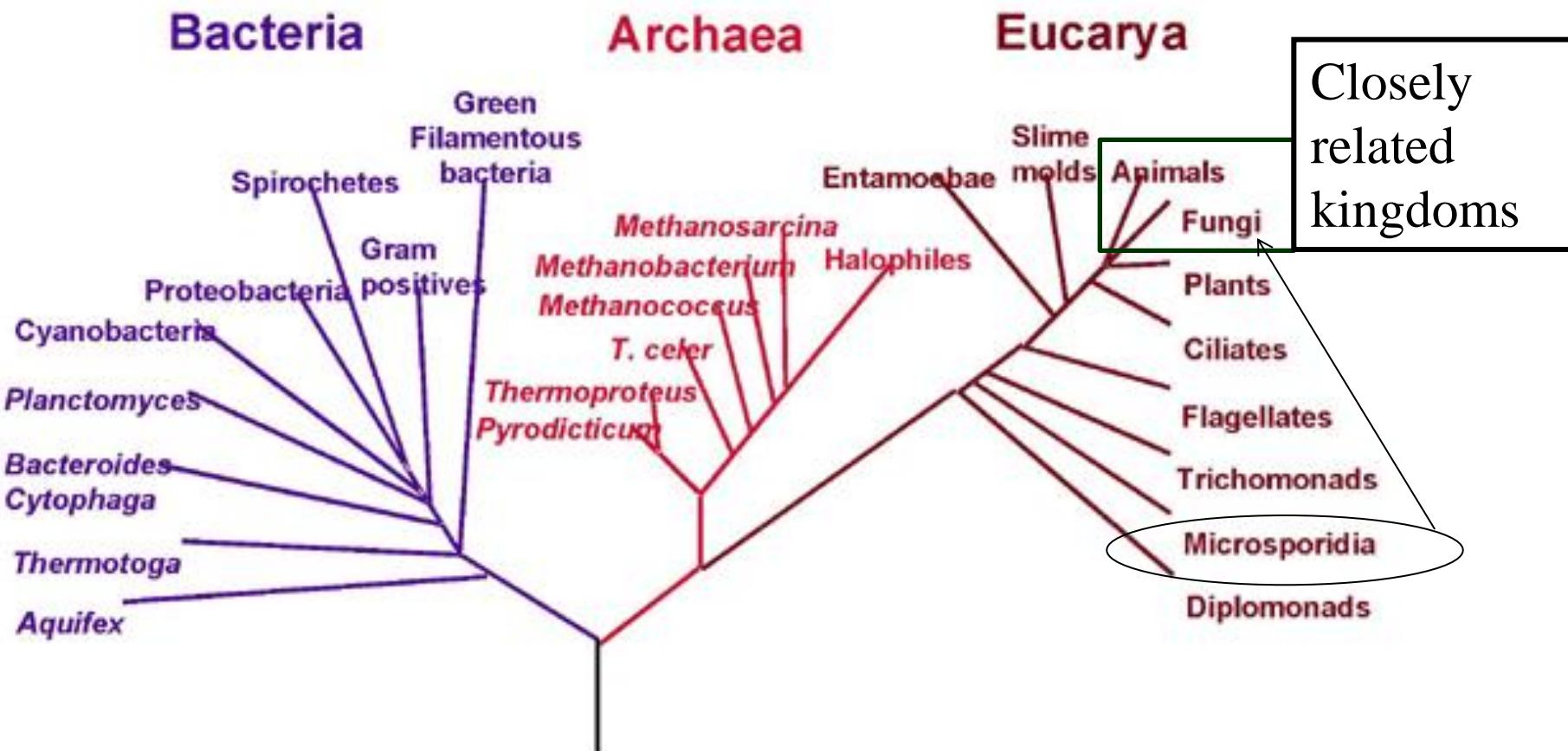


* - Blastomycosis, coccidioidomycosis, Emmonsia disease, histoplasmosis, paracoccidioidomycosis, penicilliosis, sporotrichosis

Brown, Denning, Gow, Levitz, Netea, White. Hidden Killers: Human fungal infections.
Sci Transl Med 4:165rv13, 2012



Fungal taxonomy (Tree of Life)





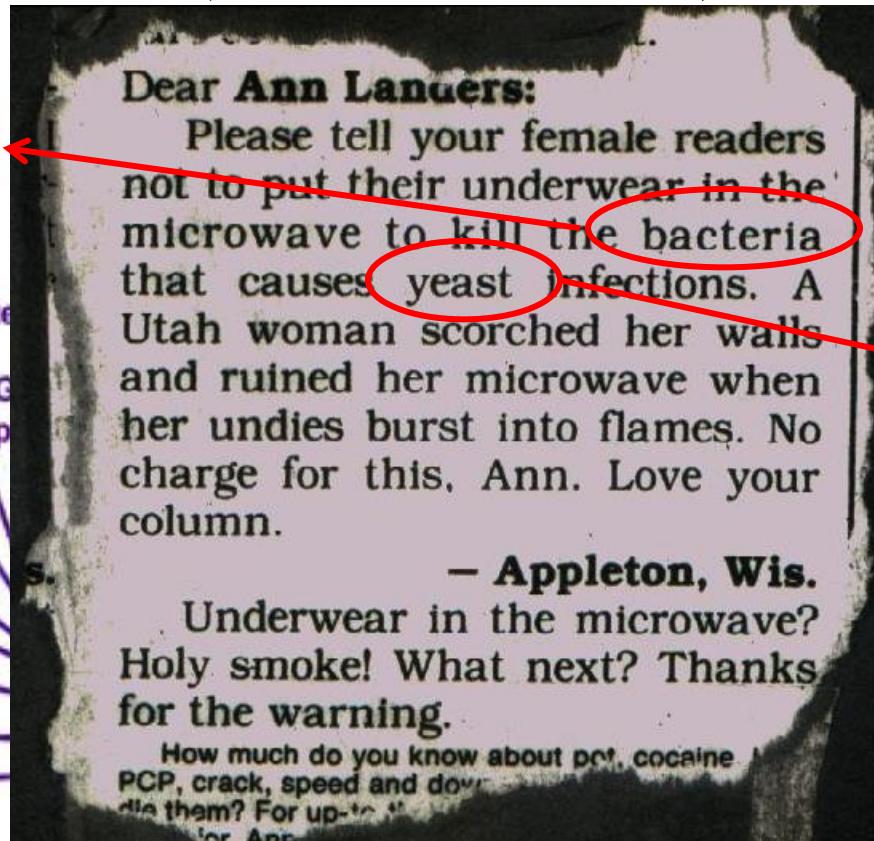
Fungal taxonomy

(Tree of Life)



Bacteria

Spirochetes
Proteobacteria
Cyanobacteria
Planctomyces
Bacteroides
Cytophaga
Thermotoga
Aquifex



ya

imals

Fungi

Plants

Ciliates

Flagellates

Trichomonads

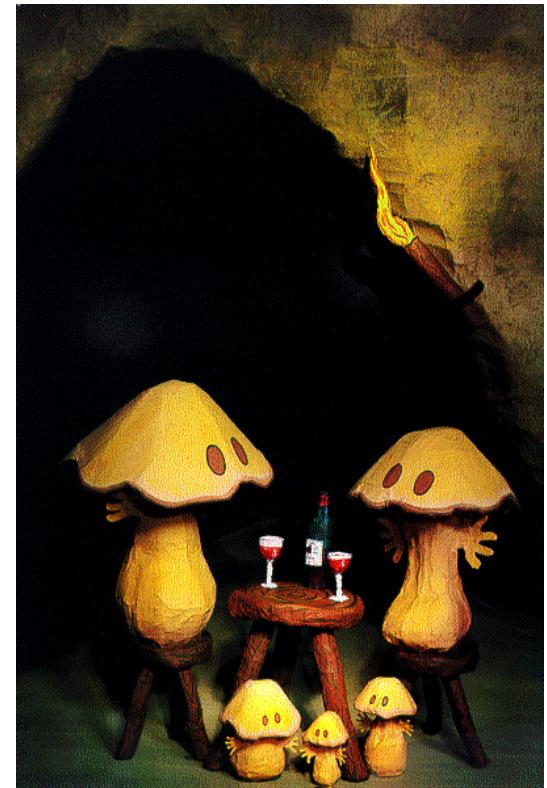
Microsporidia

Diplomonads

Closely related kingdoms

Comparison of fungi and people: Implications for Antifungal Drugs

- Because fungi and people are eukaryotic, targets for antifungal therapy are limited.
- Major targets are ergosterol (amphotericin B, azoles, terbinafine) and cell wall β -glucans (echinocandins).



Antifungal menu

Licensed systemic antifungals:

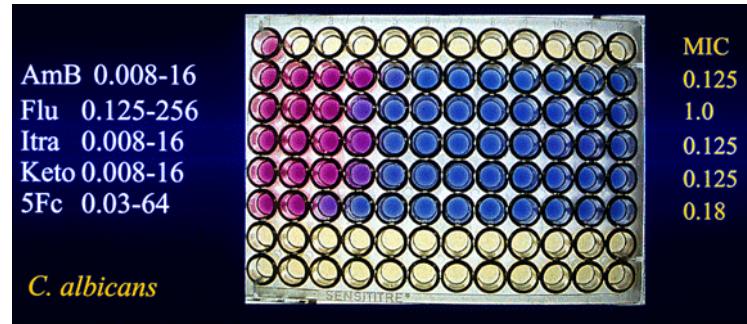
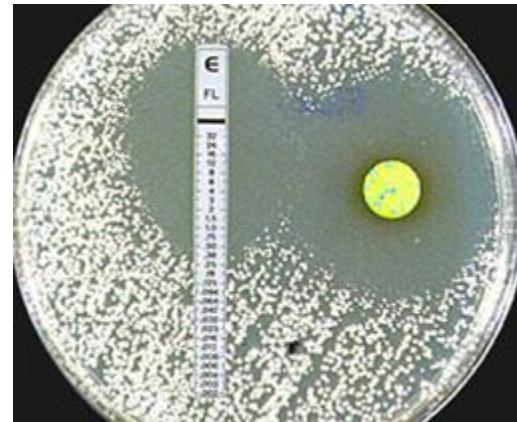
- 4 amphotericin B preparations
- 6 azoles (**ketoconazole, fluconazole, itraconazole, voriconazole, posaconazole, isavuconazole**)
- 3 echinocandins (**micafungin, caspofungin, anidulafungin**)
- 1 squalene epoxide inhibitor (**terbinafine**)
- 1 pyrimidine (**5-flucytosine**)



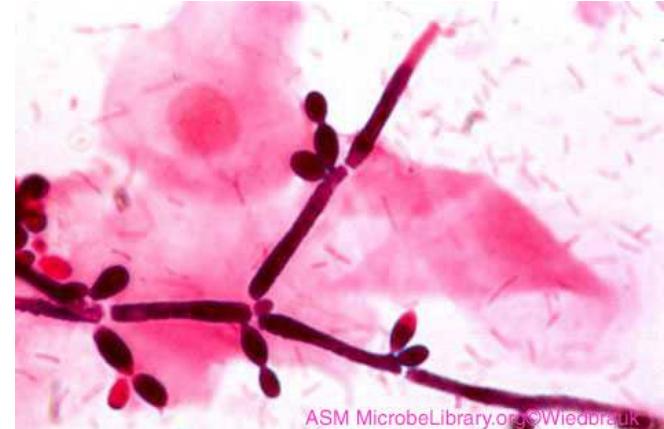
More are on their way!

Antifungal therapy

- Each antifungal drug has its own spectrum and side effect profile.
- As for bacterial infections, drugs of choice exist for specific fungal infections.
- Resistance is becoming a problem.
- Susceptibility testing to guide therapy is useful in many situations. CLSI guidelines exist for yeast but not hyphae.



Candidiasis

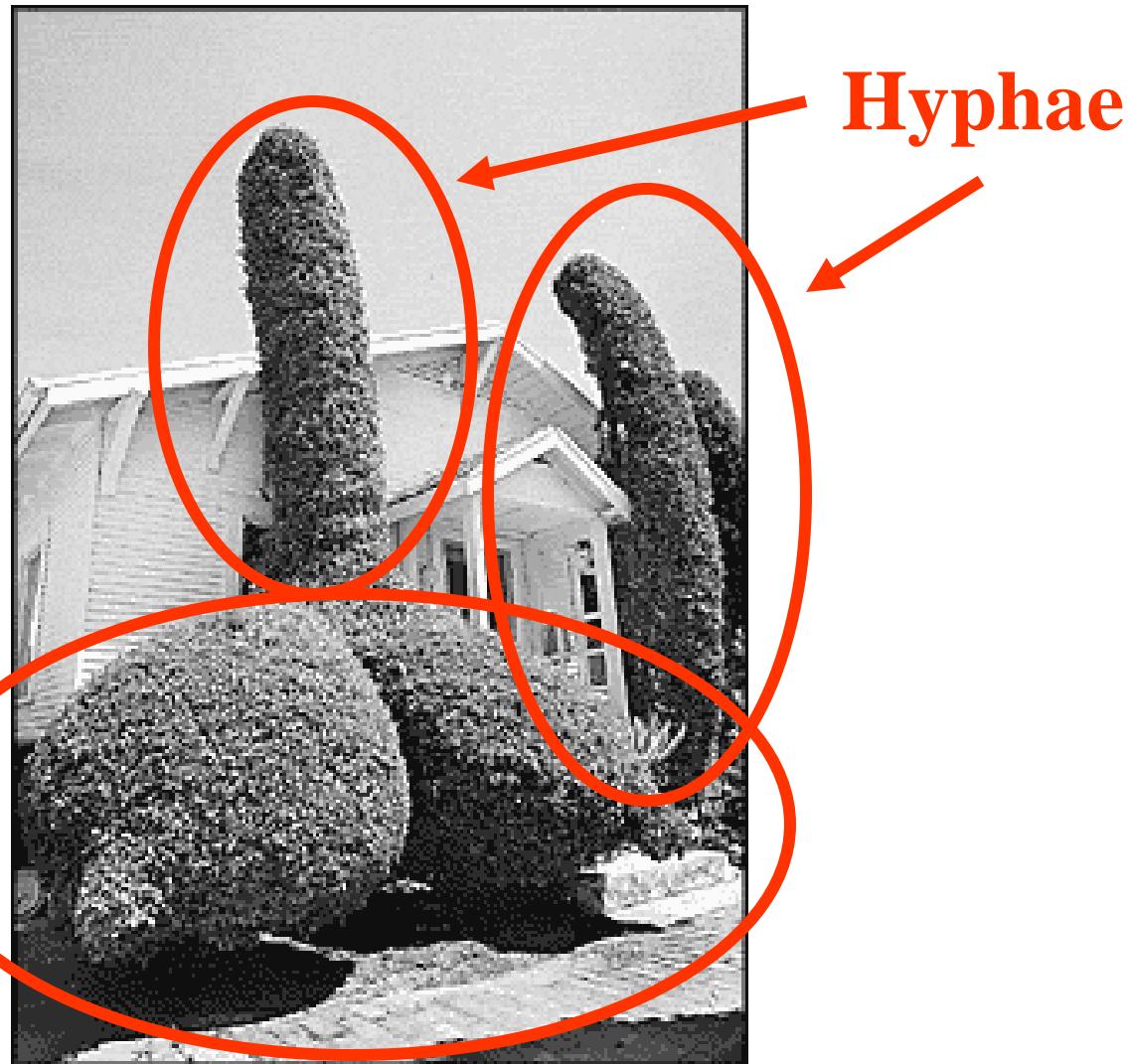


- Agents: species of *Candida*.
- Epidemiology: Colonization common. Infection ensues when host defenses break down. **Most common of the systemic mycoses.**
- Morphology: Yeasts, pseudohyphae and hyphae in tissue (except for *Candida glabrata*).

Horticulturist's vision of fungal morphology



ASM MicrobeLibrary.org/Wiedenks...



Budding
yeasts

Hyphae

Topiary Wars: The Revenge of the Neighbor

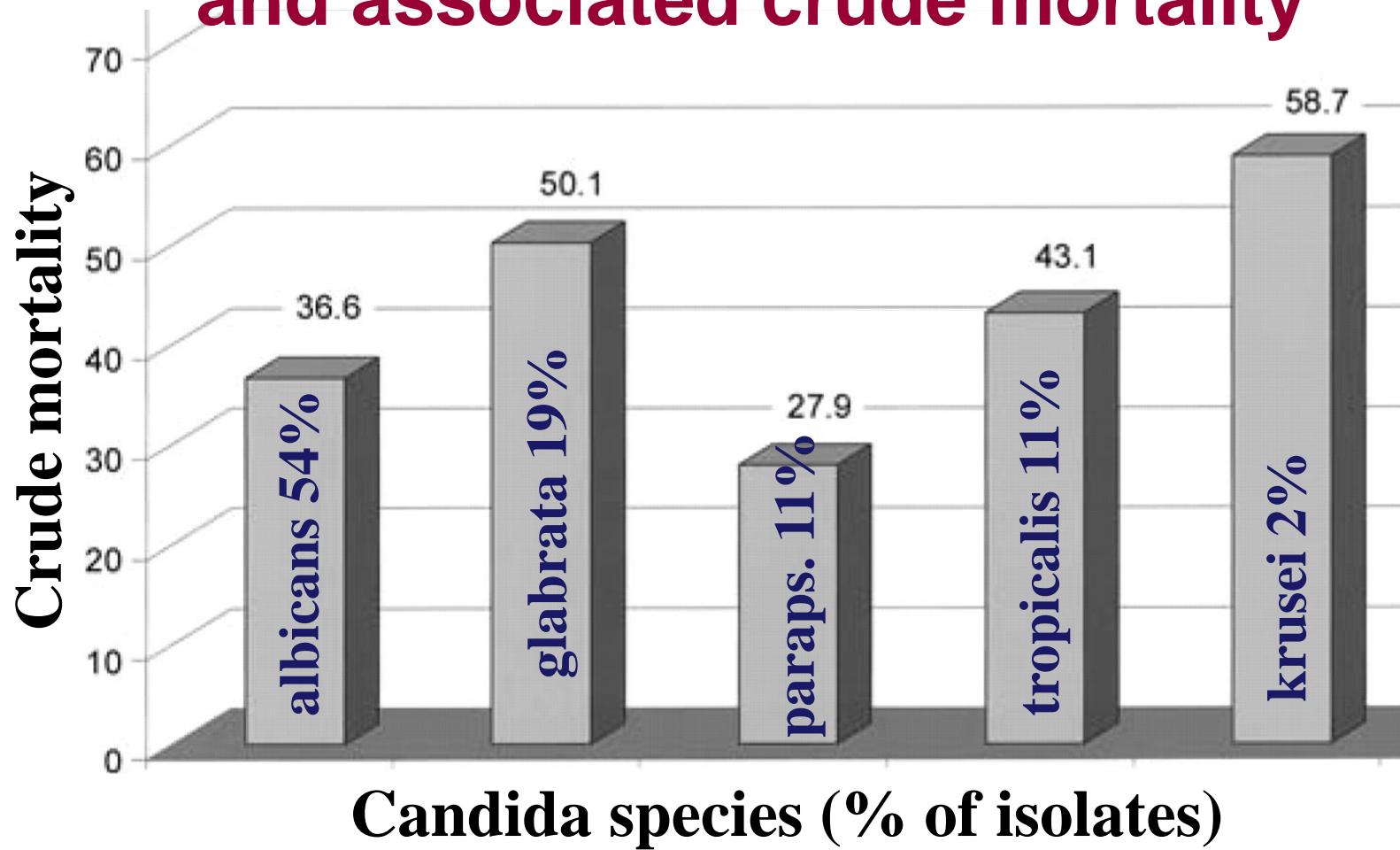


Nosocomial bloodstream infections – U.S.

- Coag-neg Staph (31%)
- Staph aureus (20%)
- Enterococci (9%)
- Candida (9%)

Wisplinghoff H et al. Clin Infect Dis.
2004;39:309-317

Distribution of *Candida* species in 1890 cases of *Candida* bloodstream infection and associated crude mortality



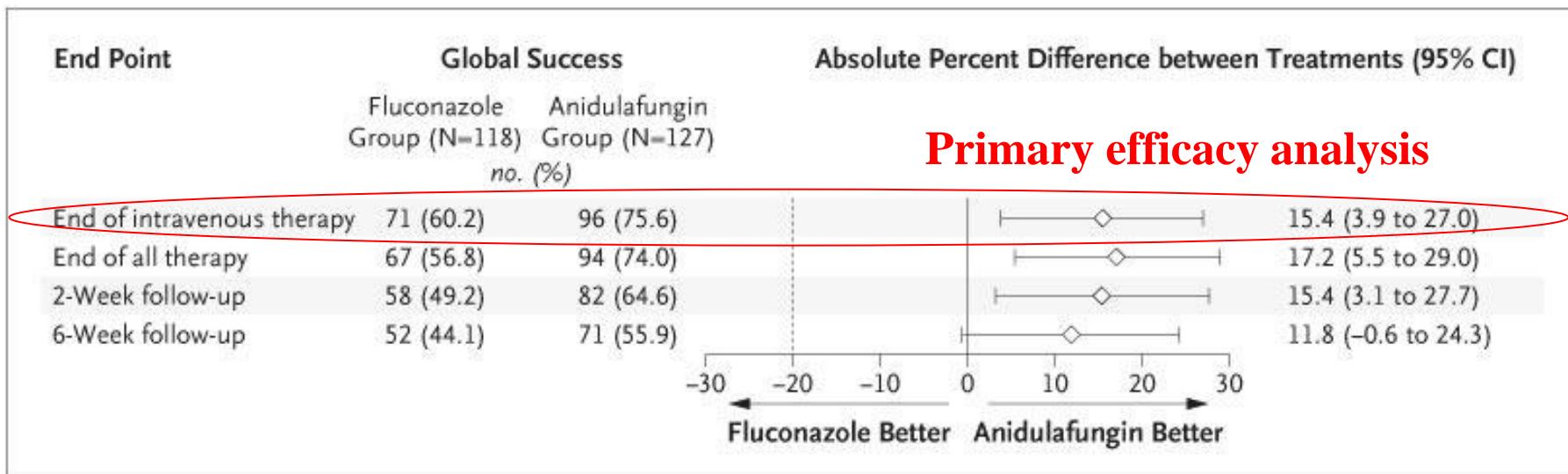
Susceptibility of *Candida* species

<u><i>Candida</i> species</u>	<u>Fluconazole</u>	<u>Echinocandin</u>
<i>C. albicans</i>	S	S
<i>C. tropicalis</i>	S	S
<i>C. parapsilosis</i>	S	S - R
<i>C. glabrata</i>	DD to R	S
<i>C. krusei</i>	R	S

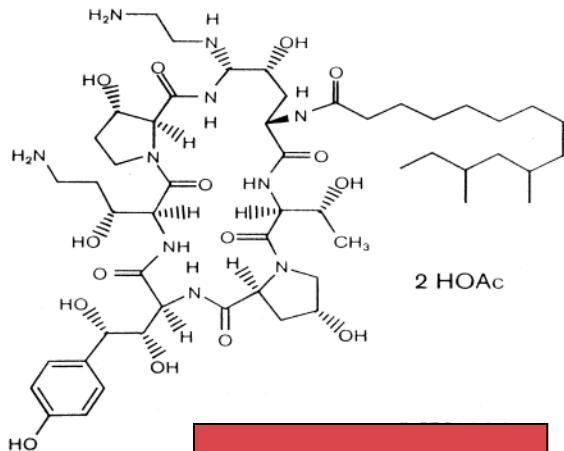
S = susceptible. DD = dose-dependent susceptible.
R = resistant.

Comparison of Echinocandins and Fluconazole for Invasive Candidiasis

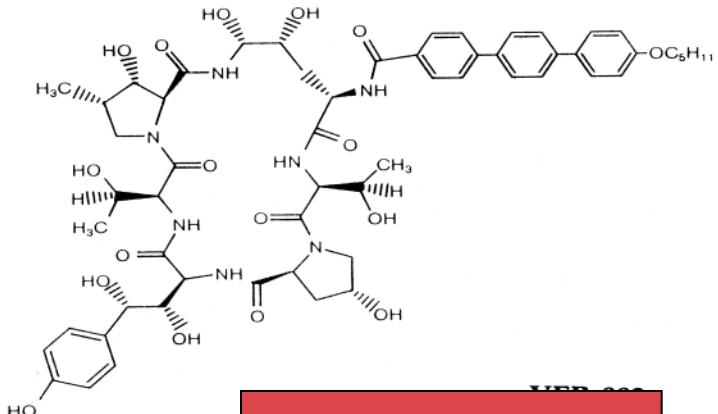
- Several studies demonstrate echinocandins are superior to fluconazole in the initial treatment of invasive candidiasis (even if the isolate is fluconazole sensitive).



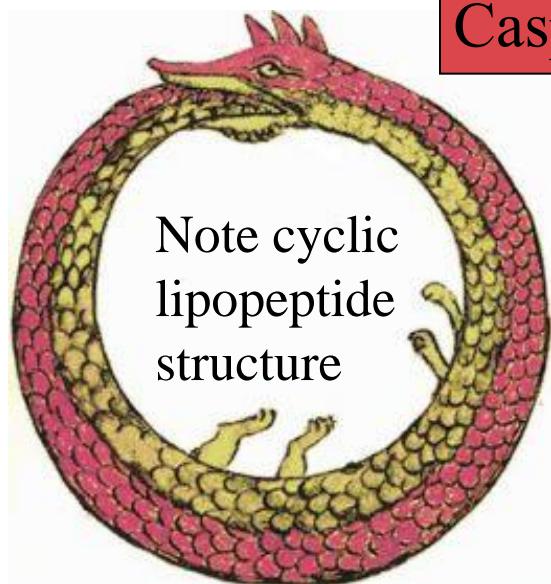
3 licensed echinocandins (therapeutic equivalents)



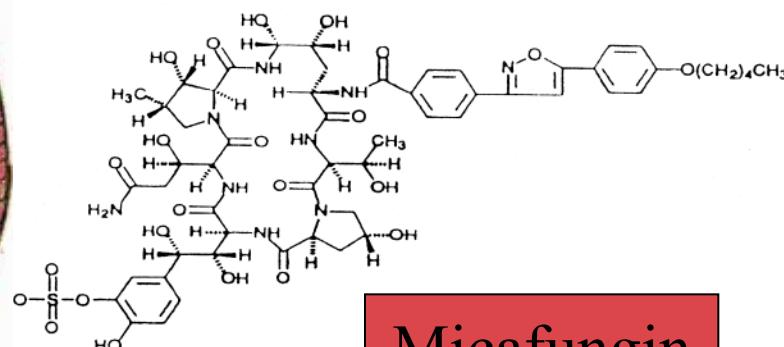
Caspofungin



Anidulafungin



Note cyclic
lipopeptide
structure



Micafungin

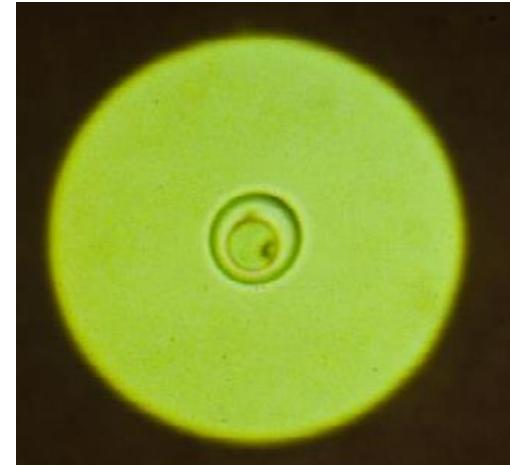


Intravenous only

What about diagnosis?

- It is estimated that about half of patients with invasive candidiasis have negative cultures.
- Isolator blood cultures do not improve yield.
- Elevated serum β -D-glucan levels in a high risk patient is highly suggestive of candidiasis (but not specific).
- T2Candida test (approved in 2014) detects amplified Candida DNA by magnetic resonance (3-5h test but around \$265).
- Other PCR tests under development.
- Antibody tests are not useful.

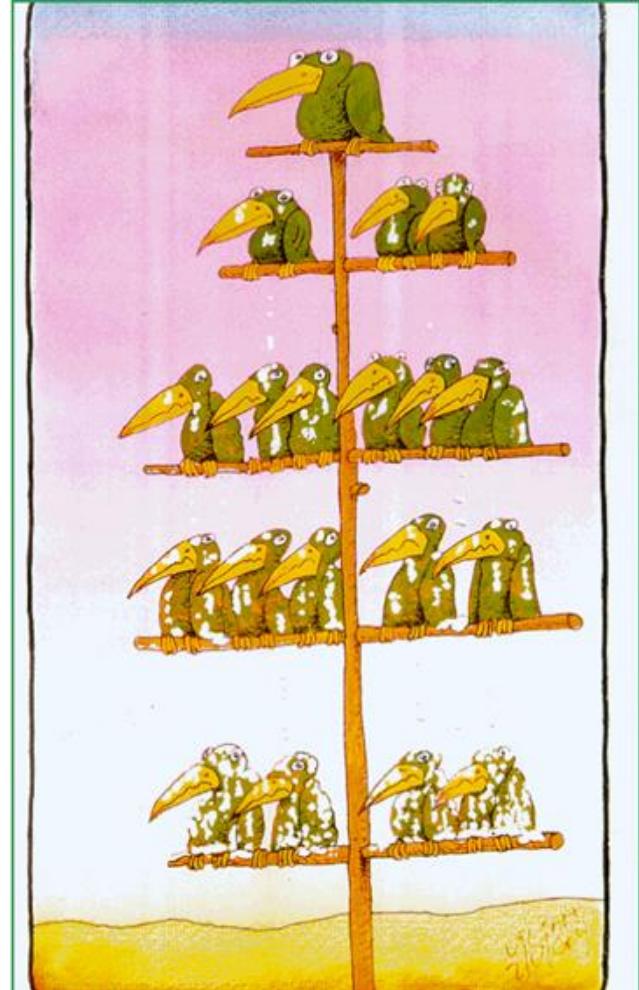
Cryptococcosis



- Agent: *Cryptococcus neoformans* and *C. gattii*.
- Only medically important fungus with a capsule.
- Capsule (cryptococcal antigen) circulates in blood and cerebrospinal fluid and is useful as a diagnostic test.

Cryptococcus: Ecology

- *C. neoformans* is found worldwide with high concentrations in soil, bird droppings, rotting wood.
- *C. gattii* has a more restricted distribution (tropical and subtropical regions, Pacific NW) and is found in association with certain species of trees.

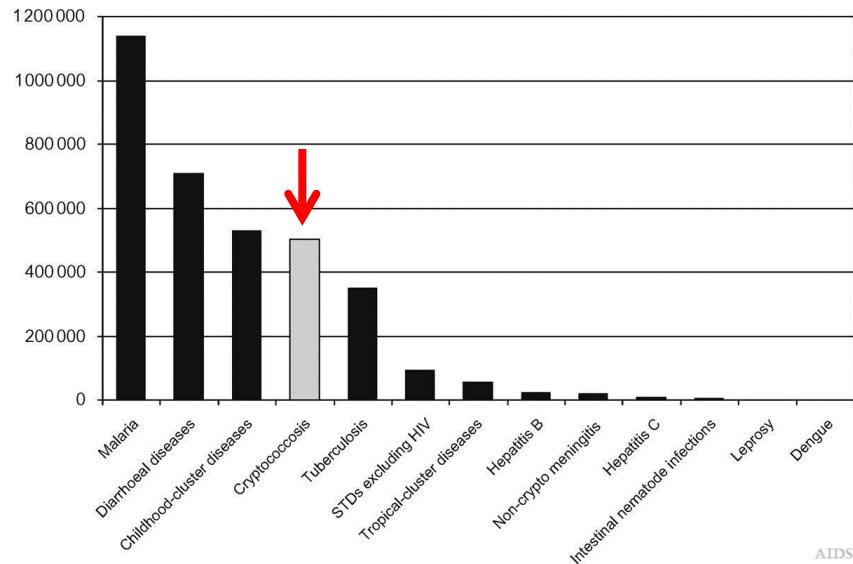


Cryptococcus: Ecology

- *C. neoformans* is worldwide, concentrated in bird droppings.
- *C. gattii* has a limited distribution in subtropical areas and is found in certain species of trees.



Cryptococcosis: Epidemiology

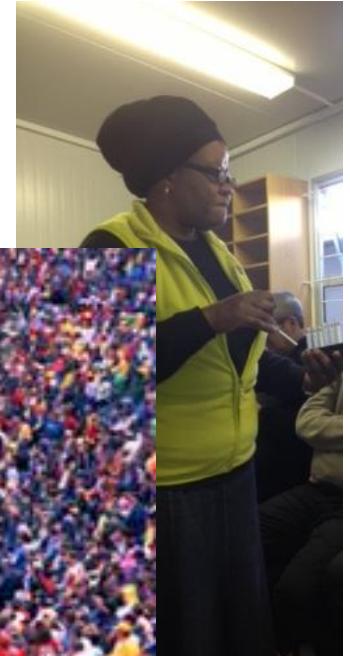


Comparison of deaths in sub-Saharan Africa due to HIV-related cryptococcosis and common infectious diseases excluding HIV, as estimated by World Health Organization.

- **Strong association with disorders of T cell immunity, particularly AIDS, immunosuppression (e.g., transplantation), lymphoma.**
- **Estimated 1 million cases/year with >500,000 deaths in persons with HIV.**
- **Incidence of ~1-5% in solid organ transplants.**

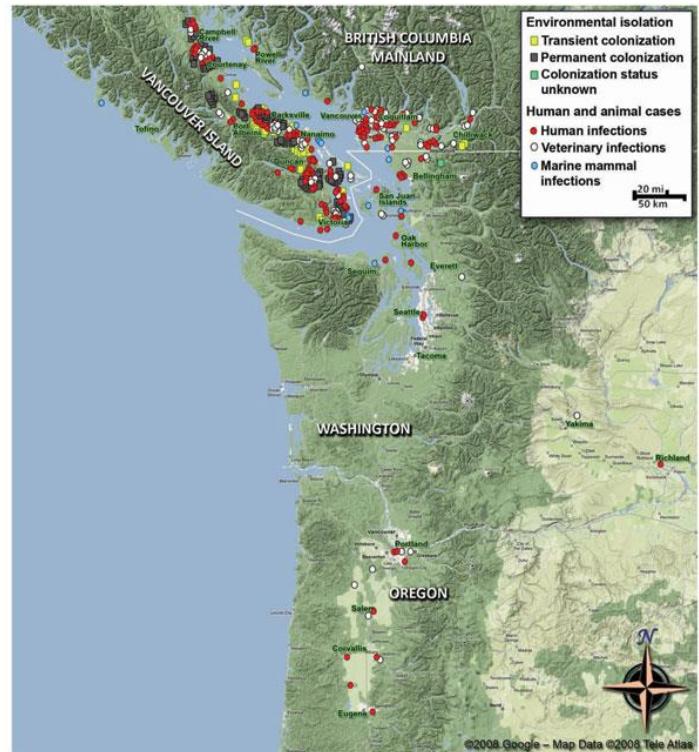
Improving outcome in cryptococcal meningitis

- Serum CD4
- Measured LPs
- Make amphotericin B (imipenem/cilastatin) available.

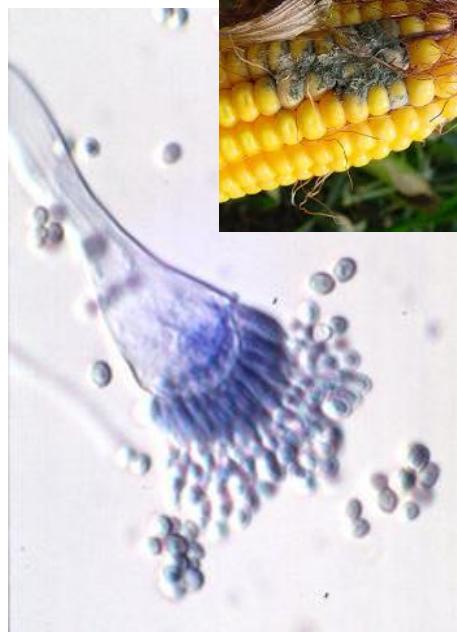


Vancouver Island *C. gattii* Outbreak

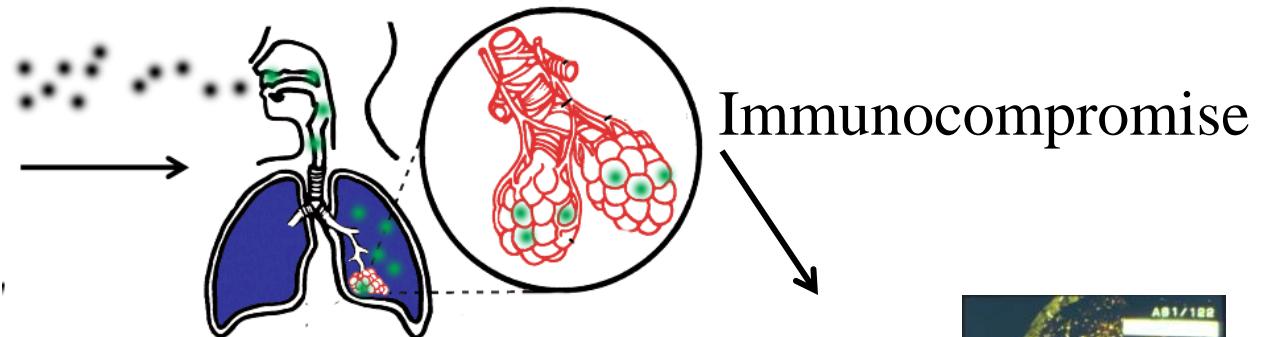
- Since 1999, >200 cases of cryptococcosis due to hypervirulent *C. gattii* on V.I.
- Spread to BC, WA and OR.
- Separate “outbreak” in CA.
- Most patients have mild or no immunocompromise.



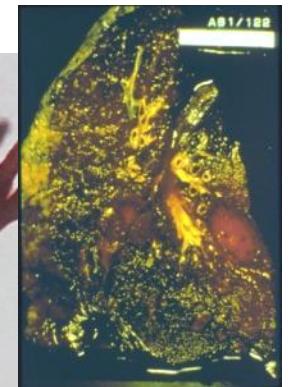
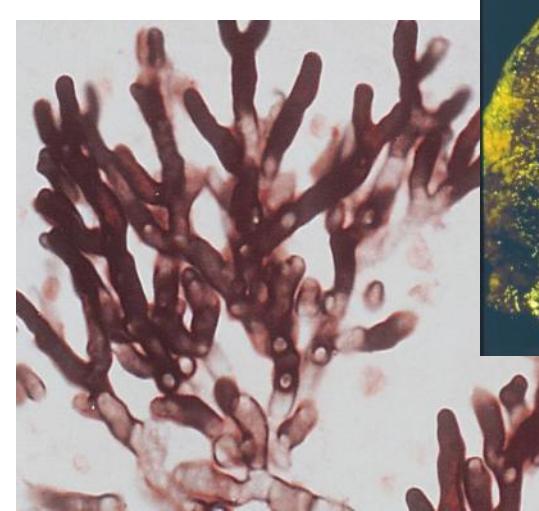
Datta, Emerging Infect Dis 2009



Aspergillus fumigatus



Mold with conidia
(spores) in the
environment



Hyphae in tissue



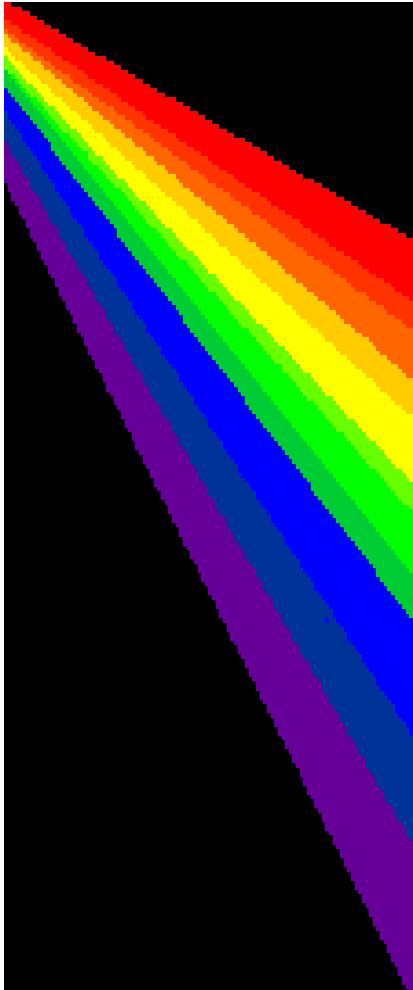
Aspergillosis



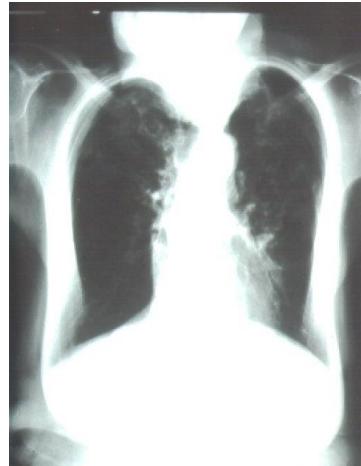
- Agent: species of *Aspergillus* (most common are *fumigatus*, *flavus*, *niger*).
- Epidemiology: ubiquitous. Most common fungus in environment.
- Estimated >200,000 life-threatening infections per year globally.



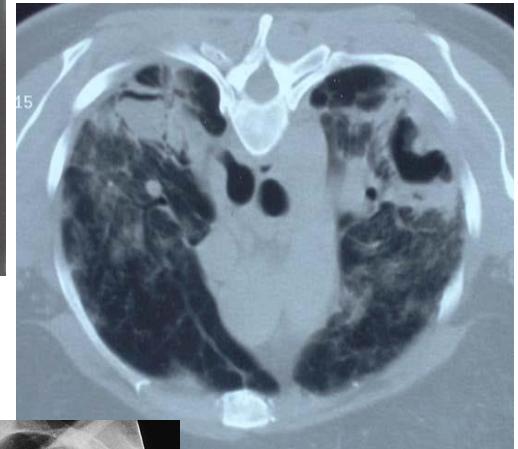
The Spectrum of Aspergillosis



Allergic



Aspergilloma →

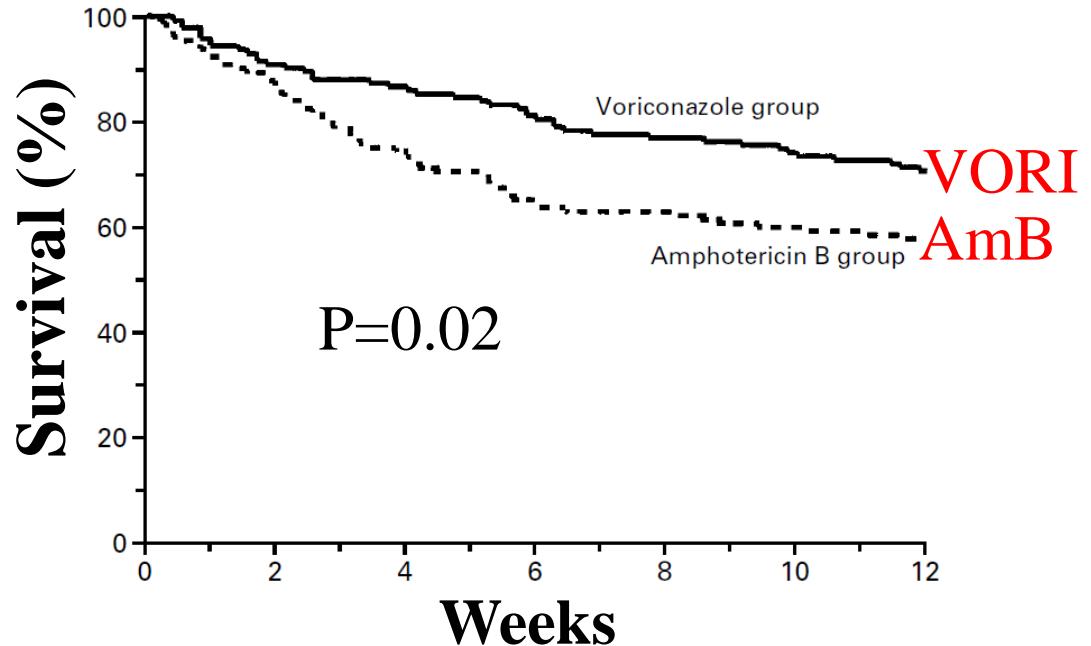


Invasive



Amphotericin B versus voriconazole for invasive aspergillosis

Landmark 2002 study
established
voriconazole as the
drug of choice for
treatment of invasive
aspergillosis.

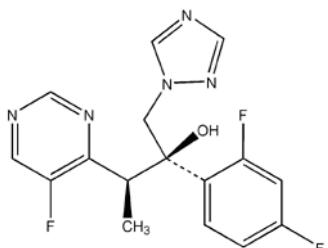


Herbrecht NEJM 347:408, 2002

Voriconazole



**Reversible
visual
disturbances
common**



**Monitoring levels
may be of value
(aim for 1.0 – 5.5)**



**Highly
photosensitizing**



**Elevated risk of
cutaneous SCC**



**No activity
against
zygomycetes
(mucorales)**

Triazole Resistance

- In parts of Europe, Africa and Asia, resistance of *Aspergillus* to triazoles has become a problem, driven by widespread agricultural use of triazole fungicides.
- Long-term triazole use in patients can also lead to resistance.
- Voriconazole failures due to resistance reported.

Bananageddon: Millions face hunger as deadly fungus Panama disease decimates global banana crop



Wheat rust: The fungal disease that threatens to destroy the world crop

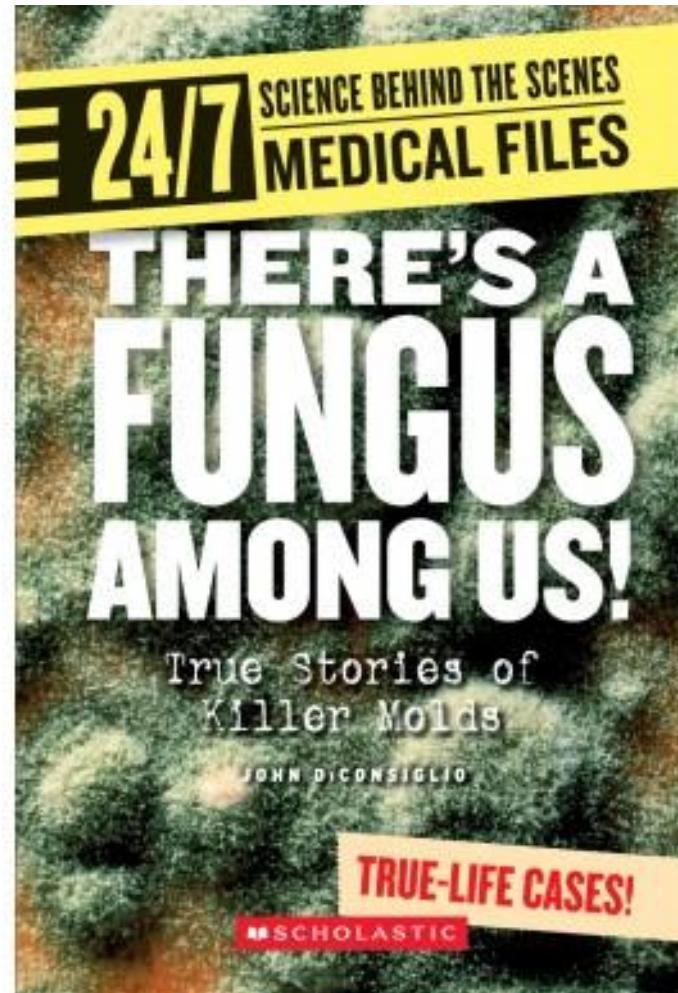


A Coffee Crop Withers: Fungus Cripples Coffee Production Across Central America



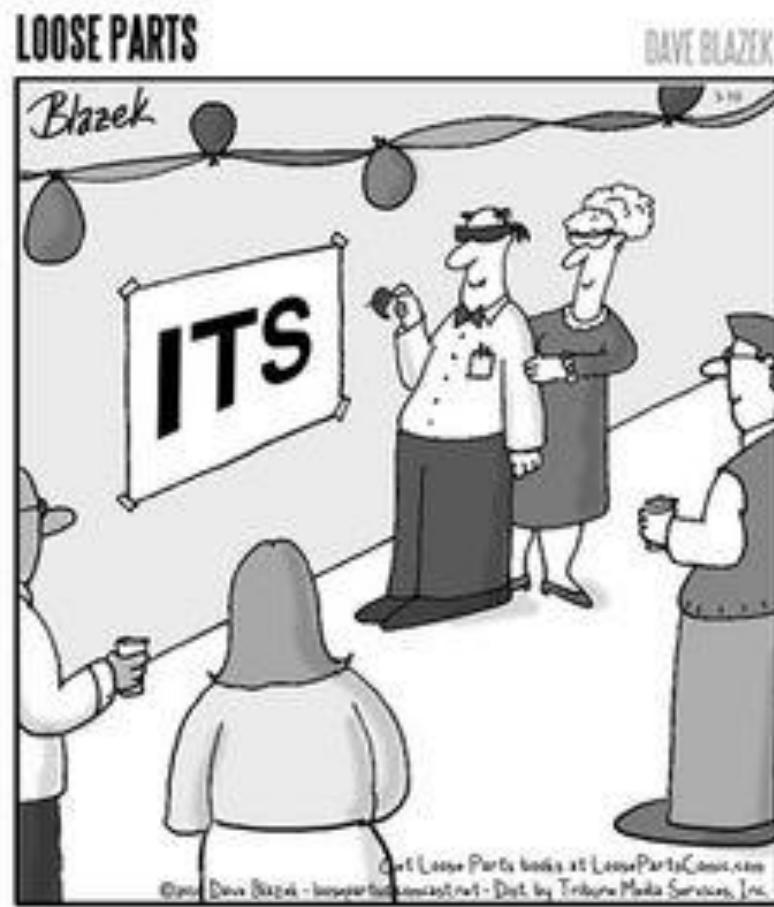
What else is new in the world of medically important fungi?

- Taxonomy
- Immunology
- New dimorphic species causing human disease.



Taxonomy Gone Wild!

- Many fungi have been renamed or divided into many species by taxonomists.
- This leads to confusion among clinicians who are used to the old names.
- Clinical microbiology labs can't keep up!



*The games get pretty crazy at
~~Taxonomists~~,
~~English teachers~~' parties.*

- *Cryptococcus*
neoformans is now *C.*
neoformans and *C. gattii*.
- *Coccidioides* is now two species.
- *Paracoccidioides* is now two species – *P. brasiliensis* and *P. lutzii*.
- *Penicillium marneffei* is now *Talaromyces marneffei*.

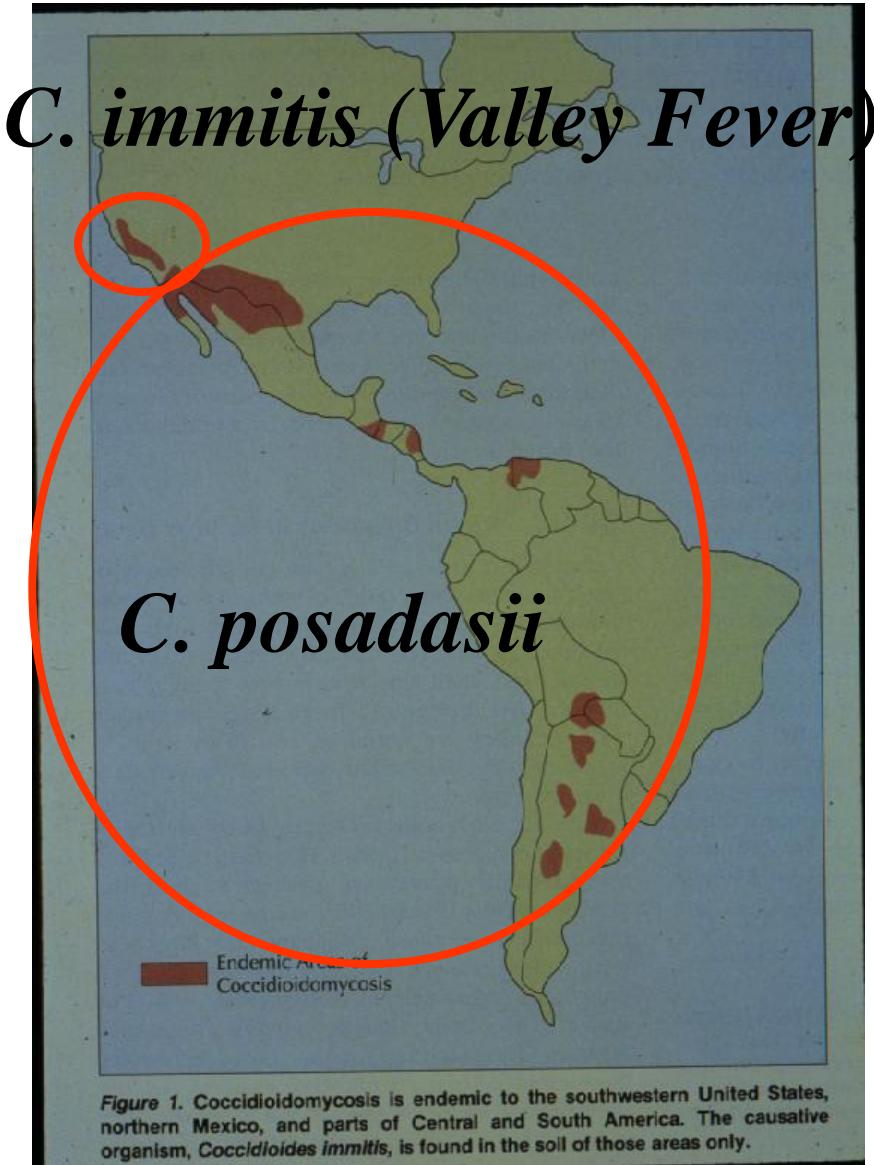
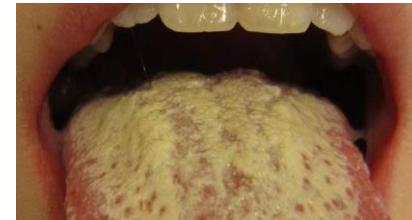


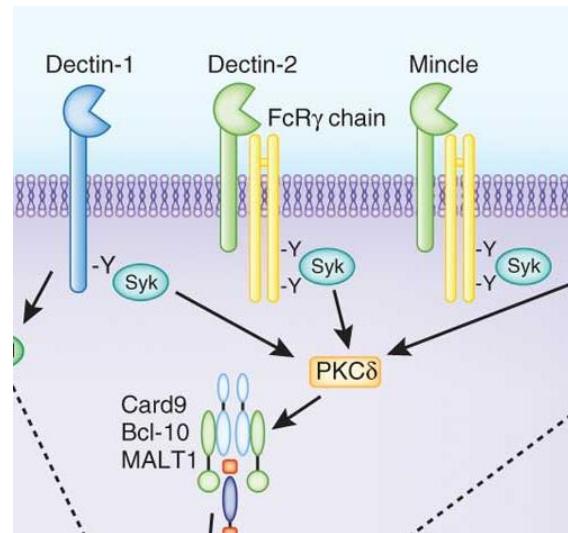
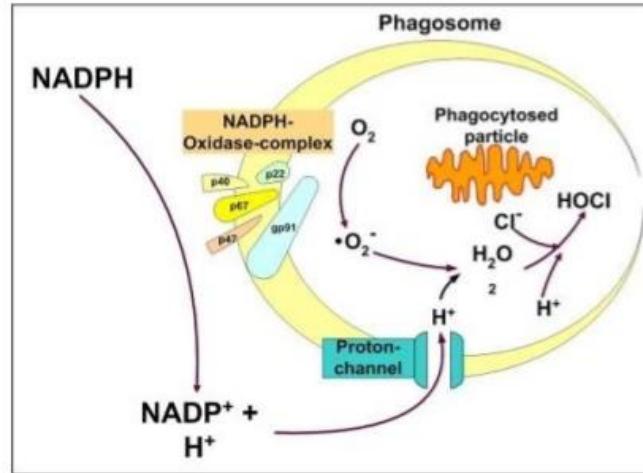
Figure 1. Coccidioidomycosis is endemic to the southwestern United States, northern Mexico, and parts of Central and South America. The causative organism, *Coccidioides immitis*, is found in the soil of those areas only.

Primary immunodeficiencies that predispose to fungal infections (partial list)



- NADPH oxidase (chronic granulomatous disease).
- Dectin-1-CARD9 pathway.
- IL-17 immunity (including gain of function STAT1 mutations and dominant-negative STAT3 mutations, both of which suppress Th17).
- Autoantibodies against IL-17a, IL-17f, IL-22 and IFN γ have also been described.

IL-17 pathways



Emmonsia pasteuriana

The NEW ENGLAND JOURNAL of MEDICINE

369:1416, 2013



A Dimorphic Fungus Causing Disseminated Infection in South Africa

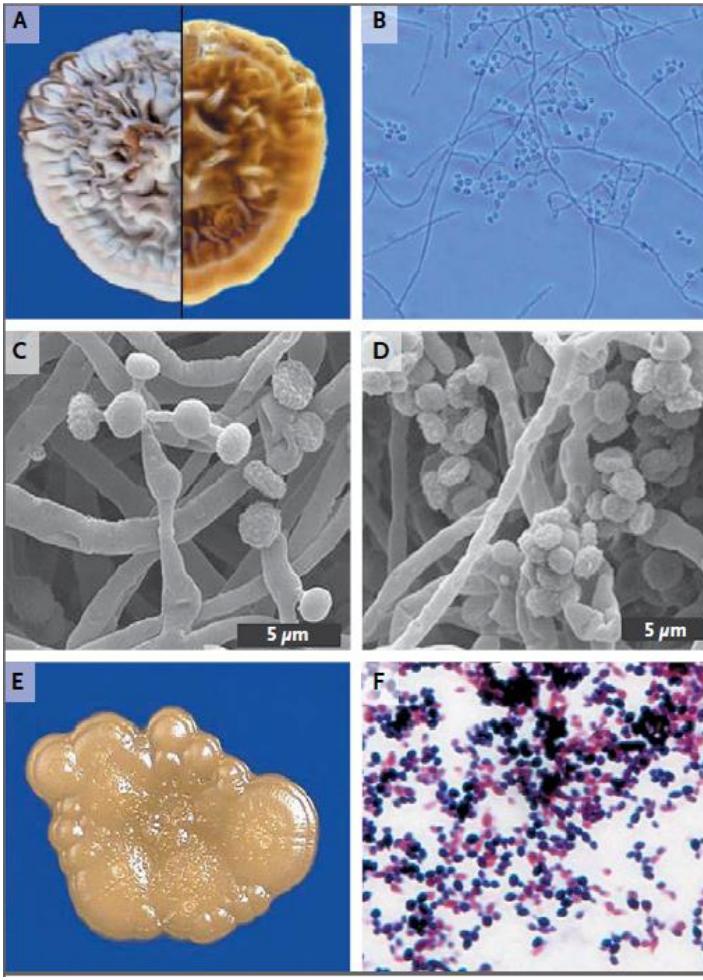
RESULTS

A total of 24 cases of dimorphic fungal infection were diagnosed, 13 of which were caused by an emmonsia species. All 13 patients were HIV-infected, with a median CD4+ T-cell count of 16 cells per cubic millimeter (interquartile range, 10 to 44), and all had evidence of disseminated fungal disease. Three patients died soon after

CONCLUSIONS

The findings suggest that these isolates of an emmonsia species represent a new species of dimorphic fungus that is pathogenic to humans. The species appears to be an important cause of infections in Cape Town.

Emmonsia pasteuriana



Most patients treated with AmB followed by itraconazole



“Apocalyptic art”



<http://strangesounds.org/2013/06/apocalyptic-art-but-how-well-the-earth-would-do-without-humanity-decor-by-johanna-martensson.html>