The Fungus
Among Us

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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

- None
Outline of Lecture

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

<table>
<thead>
<tr>
<th>Detective Case Report</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Characters</strong></td>
</tr>
<tr>
<td>Detectives</td>
</tr>
<tr>
<td>Setting</td>
</tr>
<tr>
<td>Where does the story take place?</td>
</tr>
<tr>
<td>Clues (in order)</td>
</tr>
<tr>
<td>1.</td>
</tr>
<tr>
<td>2.</td>
</tr>
<tr>
<td>3.</td>
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<tr>
<td>4.</td>
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</tbody>
</table>
| "Add additional clues if necessary."

| Red herrings         |
| What are the distractions for the person trying to solve the mystery? |
|                       |

<table>
<thead>
<tr>
<th>Conclusion</th>
<th>What is the evidence that helped the detectives crack the case?</th>
</tr>
</thead>
</table>
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$^{3/4}$ and 3$^{1/4}$ 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

<table>
<thead>
<tr>
<th>Mycosis</th>
<th># Life-Threatening cases/yr</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergillosis</td>
<td>200,000</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>400,000</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td>1,000,000</td>
</tr>
<tr>
<td>Mucormycosis</td>
<td>10,000</td>
</tr>
<tr>
<td>Pneumocystosis</td>
<td>400,000</td>
</tr>
<tr>
<td>Dimorphic (endemic) mycoses*</td>
<td>65,000</td>
</tr>
</tbody>
</table>

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

Closely related kingdoms

Fungal taxonomy
(Tree of Life)
Dear Ann Landers:

Please tell your female readers not to put their underwear in the microwave to kill the bacteria that causes yeast infections. A Utah woman scorch ed her walls and ruined her microwave when her undies burst into flames. No charge for this, Ann. Love your column.

— Appleton, Wis.

Underwear in the microwave? Holy smoke! What next? Thanks for the warning.

How much do you know about pot, cocaine, PCP, crack, speed and down dia them? For up-to-the

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

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%)

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

Candida species (% of isolates)

- albicans 54%
- glabrata 19%
- paraps. 11%
- tropicalis 11%
- krusei 2%

Crude mortality

### Susceptibility of *Candida* species

<table>
<thead>
<tr>
<th><em>Candida</em> species</th>
<th><strong>Fluconazole</strong></th>
<th><strong>Echinocandin</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><em>C. albicans</em></td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><em>C. tropicalis</em></td>
<td>S</td>
<td>S</td>
</tr>
<tr>
<td><em>C. parapsilosis</em></td>
<td>S</td>
<td>S - R</td>
</tr>
<tr>
<td><em>C. glabrata</em></td>
<td>DD to R</td>
<td>S</td>
</tr>
<tr>
<td><em>C. krusei</em></td>
<td>R</td>
<td>S</td>
</tr>
</tbody>
</table>

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).

Reboli, NEJM 356:2472, 2007
3 licensed echinocandins (therapeutic equivalents)

- Caspofungin
- Anidulafungin
- Micafungin

Note cyclic lipopeptide structure

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

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Cryptococcosis: Epidemiology

- 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.

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

Park, BJ et al.; AIDS. 23:525-530, 2009
Improving outcome in cryptococcal meningitis

- Serum CrAg screening in patients with CD4<100 in high prevalence settings.
- Measure opening pressure on lumbar puncture; repeated LPs may be needed to keep pressure <25cm H2O.
- Make antifungal drugs (amphotericin and 5-FC) 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

Immunocompromise

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

Reversible visual disturbances common

Highly photosensitizing

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

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 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.
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 IFNγ 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”