

57 - Fungal Disease in Normal and Immunosuppressed Hosts

Speaker: John Bennett, MD

2020 **INFECTIOUS DISEASE BOARD REVIEW**

Fungal Disease in Normal and Immunosuppressed Hosts

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Disclosures of Financial Relationships with Relevant Commercial Interests

- None

Plan for the talk

- Endemic mycoses (dimorphic)
- Molds (hyphae): aspergillosis, mucormycosis, fusariosis
- Yeasts (round budding cells):
 - malassezia, cryptococcosis, candidiasis
- Questions

What is an endemic fungus

- Grows in certain environments as a mould and infects humans who inhale spores
- USA
 - Histoplasmosis
 - Coccidioidomycosis
 - Blastomycosis
- Overseas
 - Talaromycosis marneffei (Penicilliosis marneffei)
 - Paracoccidioidomycosis (South American blastomycosis)

All the endemic mycoses are caused by dimorphic fungi

- What's a dimorphic fungus?
- Mould in nature and in room temp culture
- Rounded form in infected tissue

Histoplasma capsulatum room temperature

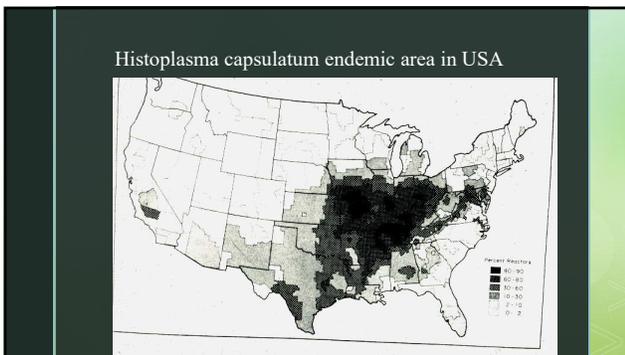
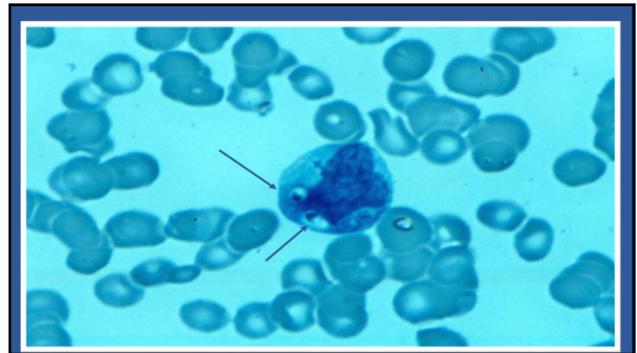
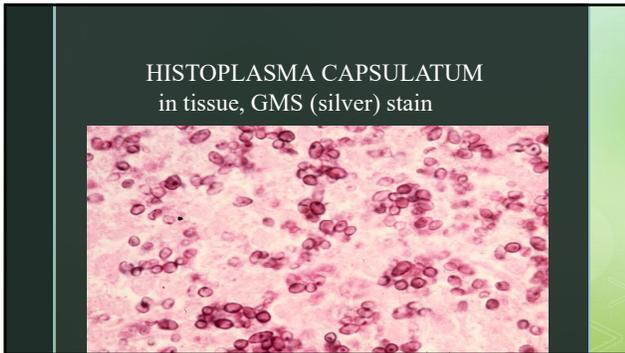


Histoplasma capsulatum - macroconidia and microconidia UTMB MMRG 5/16/97

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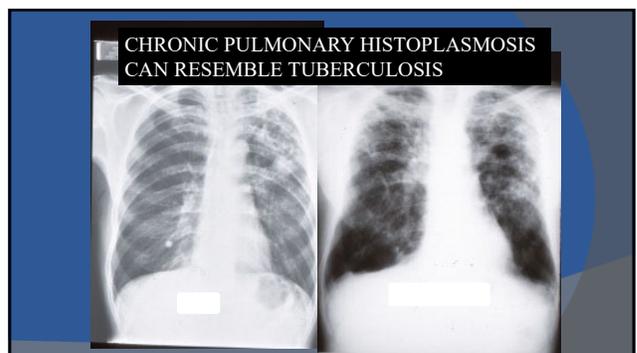
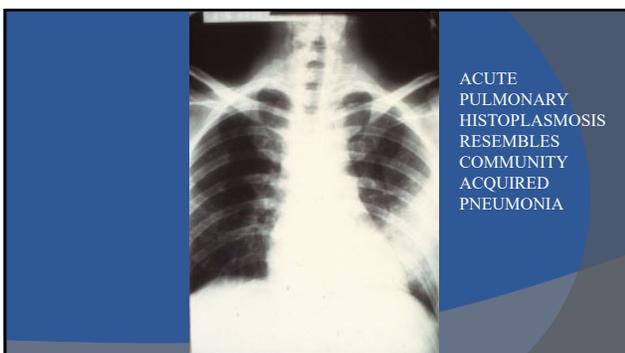
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Pulmonary Histoplasmosis

- Acute pneumonia 2 wks after exposure to dust from rich earth (digging, raking) or bat guano (caving). Antibody or antigen test. Self-resolving.
- Difficult to culture from sputum.
- Lung nodule may persist



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Disseminated histoplasmosis

- Immunosuppression, including TNF blockers, AIDS, solid organ transplant

- subacute fever, pancytopenia, hypoadrenalism, miliary lung lesions, mucosal lesions
- yeast-like cells in tissue, mold on culture
- urine antigen test usually positive

Uncommon manifestations

-endocarditis, chronic meningitis

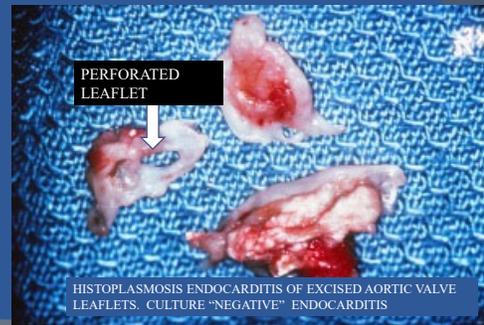
Rx: amphi B followed by itraconazole

Gingival Ulcer



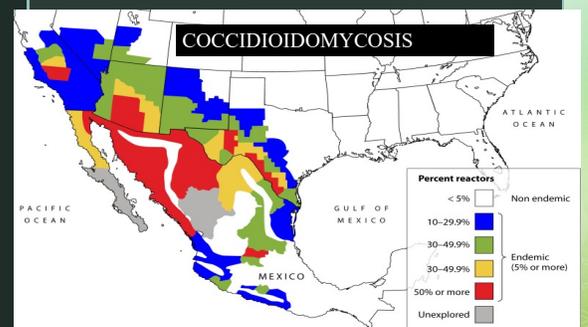
¼ CASES HAVE ORAL LESION IN DISSEMINATED HISTO

TONGUE AND PENILE LESIONS MUCOSAL LESIONS CAN RESEMBLE SQUAMOUS CARCINOMA



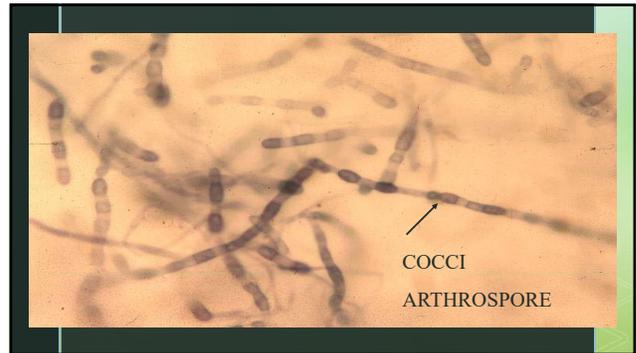
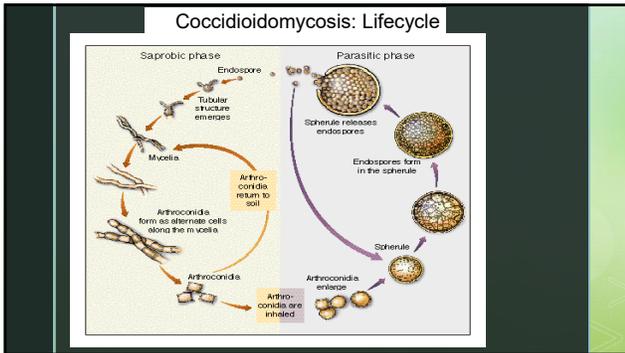
Coccidioidomycosis=Valley Fever

- Two species, one disease:
 - C. immitis and C. posadasii. Both serious lab hazards
- Acute pneumonia 2 wks after inhalation: arthralgias or erythema nodosum may accompany. Resolves.
- Residual nodule or thin walled cavity may persist
- Dissemination: bone, skin, chronic meningitis
- Serum and CSF serology useful. Eosinophilia in CSF.
- Rx: fluconazole. Nonmeningeal: itraconazole



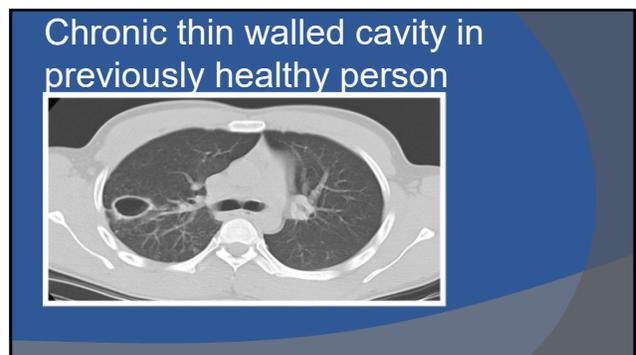
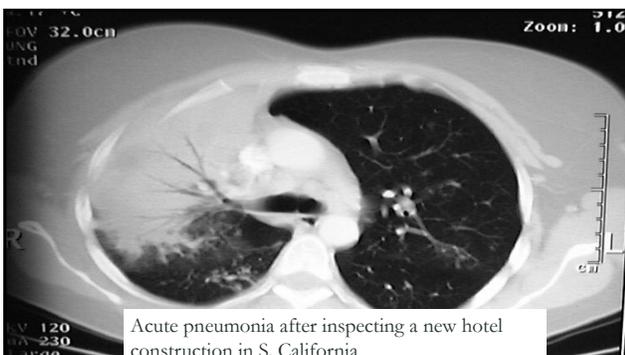
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Ethnic differences. Kern county 1937 disseminated coccidioidomycosis

Race	cases/100,000	case ratio
Caucasian	82	1.0
Mexican	284	5.4
African American	1,122	13.7
Filipino	14,550	17.5



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COCCIDIOIDES DISSEMINATES TO BONE, CNS, SKIN

NOTABLE FEATURES:
-CHRONICITY
-PUS
-**EOSINOPHILIA** (low grade)
-SLOW RESPONSE TO FLUCONAZOLE OR ITRACONAZOLE-



BLASTOMYCOSIS

BLASTOMYCES DERMATITIDIS, B. GILCHRISTII
MOLD IN NATURE, BROAD-BASED BUDDING IN TISSUE

MOIST EARTH NEAR RIVER, BEAVER DAMS.

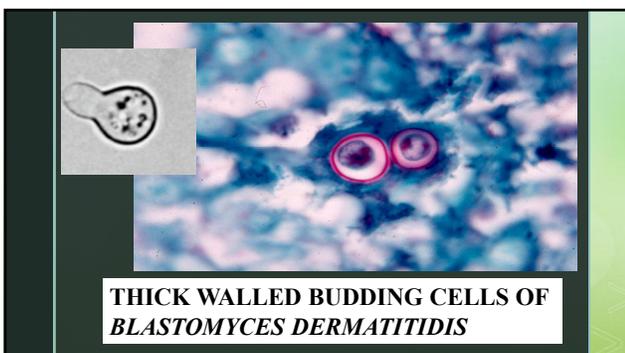
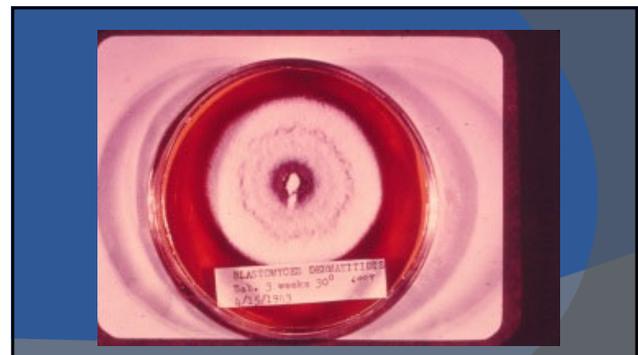
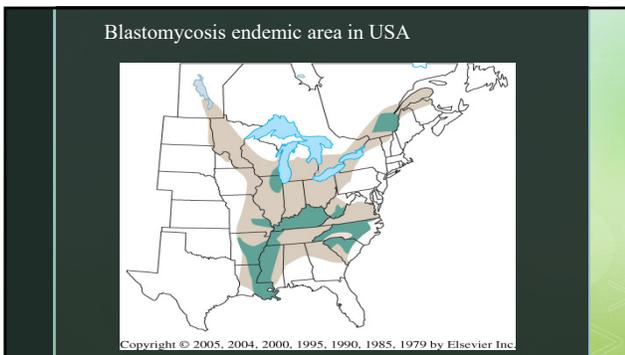
NORMAL HOST

ACUTE PNEUMONIA MAY SELF HEAL

INDOLENT, PROGRESSIVE PNEUMONIA
DISSEMINATES TO SKIN, BONE, MALE GU TRACT

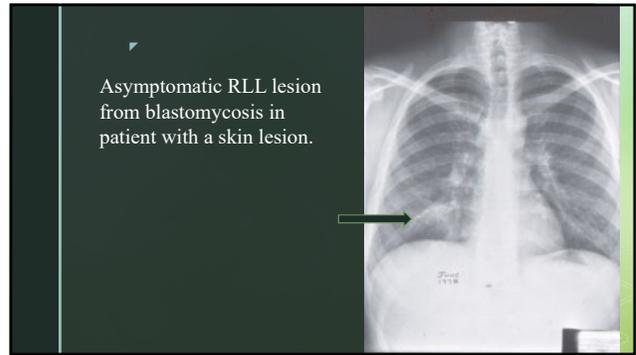
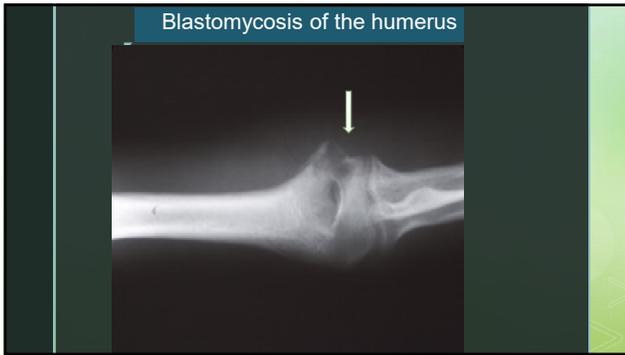
DX. CULTURE OR SKIN BIOPSY

RX: ITRACONAZOLE



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Treatment of blastomycosis

- Amphotericin if severe
- Itraconazole** 200 mg bid 6-12 months
- Fluconazole less effective
- Posaconazole: perhaps?

Paracoccidioides brasiliensis

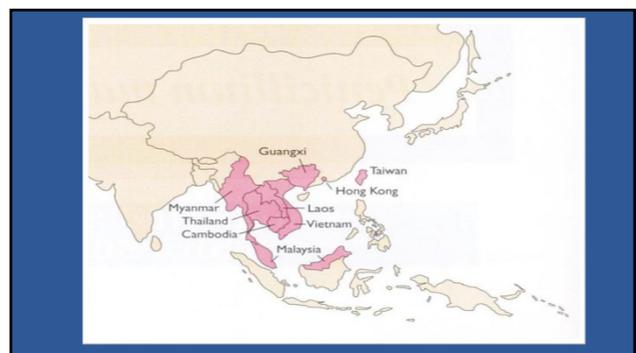
Multiply budding yeast, slow growing mold.

- Acute or subacute infection in children with fever, wt loss, lymphadenopathy, hepatosplenomegaly and often lesions in skin and mucosal membranes
- Indolent infection, largely men over 30 yrs old working on farms in Latin America, presenting as lesions of the mucous membranes and skin. Asymptomatic infiltrates on chest xray. Can be latent for decades in adults
- Serodiagnosis in endemic areas. Biopsy.

A composite image showing a clinical photograph of a patient's face with skin lesions, a chest X-ray with infiltrates, a microscopic view of the yeast with characteristic 'candy ring' budding, and a map of Latin America highlighting endemic regions.

TALAROMYCOSIS

- Talaromyces marneffei
 - yeast in tissue, mold in culture
 - divides by binary fission, no budding
- Thailand, South China**
- Bamboo rats
- AIDS, normal children
- Skin lesions, lymph nodes, liver, spleen, bone
- Diagnosis: Methenamine silver stain of skin or other tissue. Blood culture
- Treatment: ampho B then itraconazole.



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Now on to the KILLER MOLDS

The book cover features the title "WHAT IS MOLD AND HOW DOES MOLD GROW THE ULTIMATE GUIDE" in white and red text on a black background. To the right of the text is a cartoon illustration of a black, fuzzy mold character with large white eyes.

Aspergillus Pneumonia

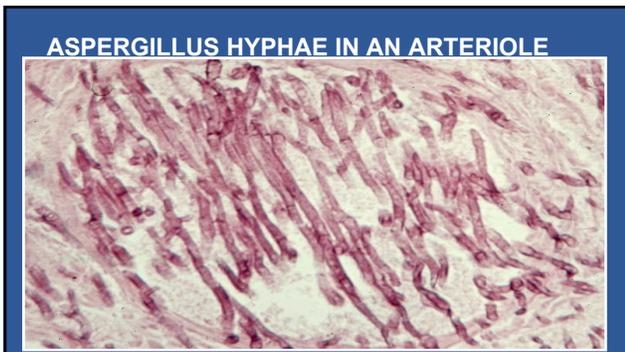
Sudden onset of a dense, well circumscribed lesion in a neutropenic patient should suggest a mould pneumonia, most commonly aspergillosis but mucormycosis gives same CT findings: **halo sign** early, crescent sign later

Septated hyphae invade blood vessels, infarct tissue.

Galactomannan useful in CSF, BAL, blood

- False positives
- False negatives with azole prophylaxis

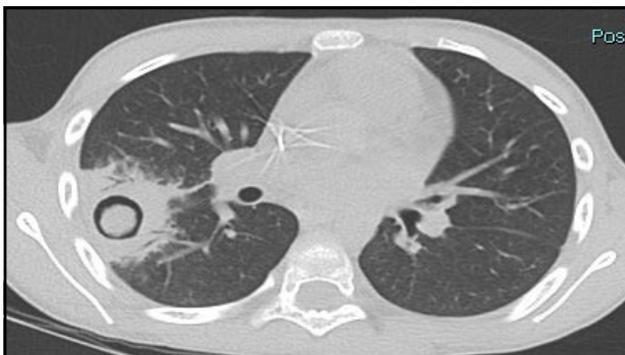
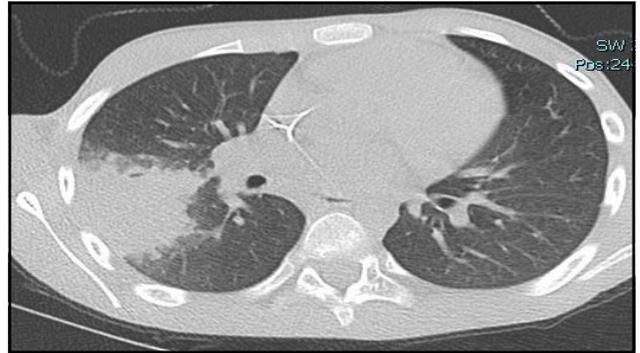
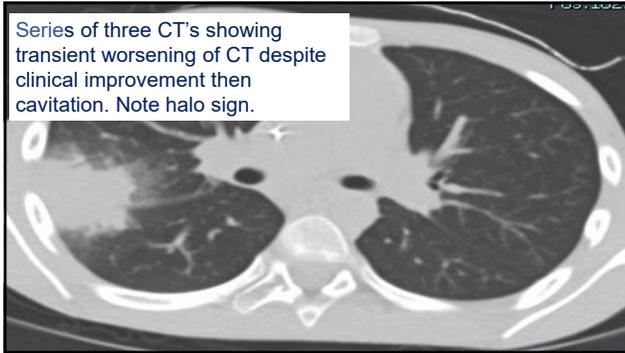
Rx. voriconazole, isavuconazole, amphotericin B



Aspergillosis can resemble ecthyma gangrenosa

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MUCORMYCOSIS

- Infection acquired by inhaling spores into lung or paranasal sinus
- Rhizopus, Rhizomucor, Mucor, Cunninghamella, Apophysomyces, Saksenaea
- Broad, flexible **nonseptate hyphae**, right angle branching
- Prolonged neutropenia, desferoxamine, steroids,
- Poorly controlled diabetes mellitus
- Hyphae **invade blood vessels**, causes infarction and necrosis. May form cavity if PMN's return.
- Rx. Ampho B. Posaconazole f/u. Isavuconazole???



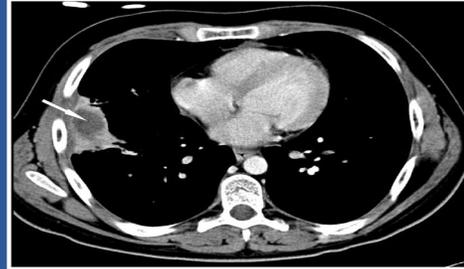
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Mucormycosis mimics cavernous sinus thrombosis following sinusitis



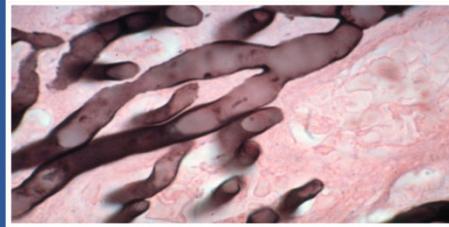
Reverse halo (Hypodense sign) in mucormycosis (and other molds???)



Fusariosis

Severely immunocompromised patients
Mold, looks like Aspergillus in tissue
Red, tender **skin** nodules
Blood culture grows mold in a third to half the patients
RX: response poor in severe neutropenia
PMN transfusions?
Fusarium solani: amphi?
Other *Fusarium* species : Voriconazole?

Fusarium hyphae. GMS stain



Scedosporiosis

- *Sc. apiospermum* (*Pseudallescheria*): hyphae and clinical disease resemble Aspergillus. Immunosuppression. Near drowning. **Ampho resistant**. Voriconazole.
- *Lomentosporium prolificans* (*Scedosporium prolificans*). Similar infection but resistant to all antifungals

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Candidiasis: testable points

- Candidemia (IDSA guidelines):
 - remove IV catheter if possible
 - dilated fundoscopic exam in first week
 - Intravitreal drug if vitritis or macular lesion
 - Candida auris: hospital transmission. Azole resistant.

Cryptococcus neoformans or *Cryptococcus gattii*

- *C. gattii* more likely to be lung, non HIV patient, S. California, Vancouver Island, overseas
- Start ARV after 2-10 wks of antifungal Rx in HIV naïve patients.
- Daily lumbar punctures for pts with opening pressure of at least 25cm and symptoms
- Antigen in serum, CSF : specific. Sensitivity variable.
- Screening for antigenemia in HIV: Africa. Fluconazole if CSF neg.

IRIS in Cryptococcosis

- Weeks or months after ARV and antifungal Rx for meningitis:
- Fever, headache, high opening pressure, seizures, cranial nerve palsies, new MRI lesions
- Key: all cultures negative.
- Dry cough, substernal pain
- Swollen nodes in mediastinum, hilum
- Rx: NSAIDS or prednisone

Beta-D glucan test

- Blood test positive in many mycoses (usually not cryptococcosis or mucormycosis)
- Many sources of false positivity
- *Pneumocystis jirovecii* also positive
- BAL beta-D glucan: sensitive for PCP but very variable



BUT FIRST 10 questions to test your knowledge

Case 1

42 yr WF with Crohn's disease taking adalimumab is admitted to a Chicago hospital because of 6 weeks of low grade fever, pancytopenia and a 10 pound weight loss. Hydrocortisone 200 mg daily was begun for low serum cortisol not responding to Cortrosyn stimulation. Micafungin was given for yeasts seen in peripheral blood smear that were not growing on routine culture.

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Question #1

The most helpful diagnostic test would be which of the following:

- A. Fungal blood culture
- B. CT of abdomen
- C. PPD
- D. Bone marrow aspirate
- E. Urine for Histoplasma antigen

Case 2

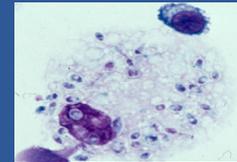
- 30 yo male business man from India presented with fever and dypnea while visiting Washington, DC
- Found to be HIV positive, with CD4 of 50.
- Diffuse infiltrate on chest xray, O2 sat of 65%, given trimethoprim-sulfa and prednisone. Failed to improve and went for BAL.



Question #2: BAL smear

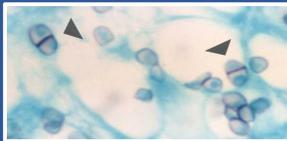
This organism usually resides in which of the following:

- A. Sandflies
- B. Desert dust
- C. Rich, moist soil
- D. Cat feces
- E. Kissing bugs



Case #3

A 45 yr old Vietnamese business man came to the US to seek medical attention for an illness of 4 weeks duration, with low grade fever, weight loss, anorexia and the recent appearance of painless skin lesions. Biopsy of the skin lesions show is shown to the right.



Question #3

Which of the following is most likely:

- A. Talaromyces marneffeii
- B. Histoplasma duboisii
- C. Fusarium oxysporum
- D. Cryptococcus gattii
- E. Paracoccidioides brasiliensis

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Case 4

35 yr male 68 days post allogeneic bone marrow transplantation for myelodysplastic syndrome, receiving methylprednisolone 500 mg for Grade III GVHD of the gastrointestinal tract developed fever, several painful, red skin nodules and a blood culture growing a mold.

Question #4

The most likely fungus is which of the following:

- A. *Scedosporium apiospermum* (*Pseudallescheria boydii*)
- B. *Scedosporium (Lomentospora) prolificans*
- C. *Apophysomyces elegans*
- D. *Fusarium multiforme*
- E. *Alternaria alternata*

Question #5

44 yr previously healthy male accountant in Washington DC presented with the acute onset of confusion that was preceded by three months of headache. Cranial MRI was normal. Lumbar CSF had an opening pressure of 350mm CSF, WBC 250/cu mm, glucose 22 mg /dl, protein 125 mg/dl and cryptococcal antigen titer 1:512. Liposomal amphotericin B was begun at 5.0 mg/kg IV daily. On the third day of treatment he complained that the room was too dark and was found to have visual acuity of hand motion only in both eyes.

Question #5

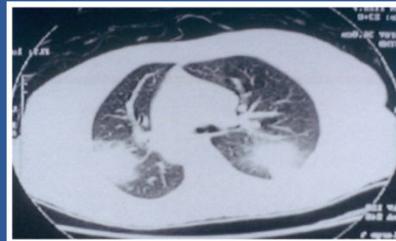
The most important next step in this patient is which of the following:

- A. start flucytosine
- B. start fluconazole
- C. Start acetazolamide (Diamox)
- D. Begin daily lumbar punctures
- E. Start dexamethasone

Case 6

39 yr old man with severe aplastic anemia and absolute neutrophil count of 25/cu mm developed the sudden onset of fever and pulmonary infiltrates not responding to five days of ceftazidime. The CT is shown in the next slide.

Case # 6 Continued



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Question #6

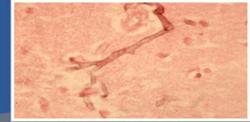
The most likely cause of his fever is which of the following:

- A. Mulch in his garden
- B. Spray from the air conditioner water tower
- C. Pigeon droppings near the air conditioner inlet
- D. Visitor with a cough
- E. Reactivation of a prior infection

Question #7

The fungus shown is best treated with a drug that has which of the following mechanisms of action

- A. binds to membrane sterols
- B. Inhibits sterol 14-alpha demethylase
- C. Inhibits glucan synthesis
- D. Blocks DNA synthesis
- E. Inhibits squalene epoxidase



Case #8

- 47 WM executive referred from Baltimore because of severe headaches, diplopia, high fever of 1 wk's duration
- 4 wks PTA: Maui resort one week
- 3 wks PTA: ranch outside Tucson 1 wk
- 2 wks PTA: back at work in Baltimore
- 1 wk: PTA: Headache began
- Exam: Temp 38.5 C. Looks ill. Photophobia, nuchal rigidity, right CN6 palsy
- CBC, Chem 7 normal. CSF : Glucose 55, Protein 58, WBC 330 (20% eos). Negative cryptococcal antigen on CSF, serum Lyme serology and RPR. MRI with contrast normal. Worsens during 2 wks ceftriaxone. CSF cultures for bacteria, fungi, tbc neg to date.

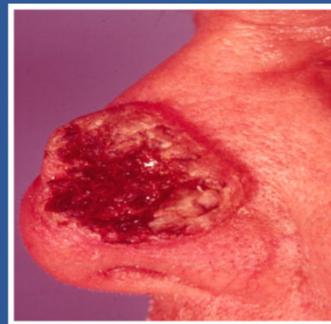
Question #8

The most helpful diagnostic test would be:

- A. CSF cytology
- B. Stool O&P
- C. Dietary history
- D. Fungal serology
- E. Leptospirosis serology

Case #9

- 55 year construction engineer living in Raleigh, North Carolina, was sent to Iraq for one month of consultation. On return, he had the slow development of a painless, crusted lesion on his nose.
- He was not aware of any preceding lesion there but had numerous insect bites over exposed areas of his body while in Iraq.
- He was otherwise in good health and was an avid rose gardener.
- Routine lab work was normal but chest xray showed an asymptomatic infiltrate.



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Question #9

The most likely source for the skin lesion and lung lesion is:

- A. Camel's hair rug he bought in Iraq
- B. Insect bite in Iraq
- C. Inhalation of soil organism from North Carolina
- D. Scratch from thorn in his garden
- E. Insect bite in USA



Case 10: What are these lesions in a recently neutropenic patient?



Question #10

Which is the most likely

- A. Bartonella henselae
- B. Candida tropicalis
- C. Fusarium oxysporum
- D. Aspergillus flavus
- E. Streptococcus anginosus

Take Home Points

- Histo: TNF α blockers. Miliary infiltrates. Addison's
- Talaromyces marneffei: SE Asia. Skin lesions. Septum in dividing cells
- Fusarium: skin nodules. Blood culture with mould
- Ecthyma gangrenosa: aspergillosis, mucor, bacteria

More take Home Points

- Aspergillosis: halo sign, crescent sign
- Mucormycosis : Can mimic cavernous sinus thrombosis. Aseptate. Ampho.
- Crypto: LP for high OP. IRIS.
- Cocci: solitary lung cavity. Eosinophilic meningitis
- Blasto: indolent skin+lung lesion
- Candida: liver, spleen lesions in neutropenics

The end.
Thanks

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