Fungal Pneumonia
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Disclosures

- None (sorry)

Fungal Pneumonia

- Risk Factors
- Major Fungal Pathogens
  - Histoplasmosis
  - Coccidioidomycosis
  - Blastomycosis
  - Cryptococcosis
  - Aspergillosis
  - ? Candida

- History/Physical Findings
- Lab Findings
- Radiologic Findings
- Histologic Findings
- Pharmacologic Treatments
- Inpatient considerations
- Prevention/Patient Education
- References/Prevention of Fungal Pneumonia
Pneumonia is the leading infectious cause of death in developed countries (Lamoth F, et al, Clin Lab Med, June 2014; Restrepo F, et al, Current Opin Infect Dis, Apr 2013)

Fungi account for only a small portion of community-acquired and nosocomial pneumonias – i.e., "normal hosts".

However, fungal respiratory infections generate concern in the expanding population of immunosuppressed patients.

Fungi may colonize body sites without producing disease or they may be a true pathogen, generating a broad variety of clinical syndromes.

**Yeast**
- multiple solitary small rounded forms:
  - actively dividing, growing, and metabolizing form of the fungus.
  - Reproduction occurs via budding (or fission)
  - Examples:
    - Cryptococcus
    - Candida

**Molds**
- Interwoven filamentous forms known as hyphae
- Mass of hyphae called a mycelium (fungal ball)
- Hyphae grow by elongation of their tips
- Conidia (or spores) at the end of hyphae – metabolically inactive, likened to "seeds" looking for a good place to grow
Intro: endemic vs opportunistic fungi
- Fungal pneumonia is an infectious process in the lungs caused by one or more endemic or opportunistic fungi.

Examples of endemic fungi:
- Histoplasma capsulatum
- Coccidioides immitis
- Blastomyces dermatitidis
- Paracoccidioides brasilensis
- Cryptococcus neoformans

Examples of opportunistic fungi:
- Candida species
- Aspergillus species
- Mucor species

Intro: acquisition of fungi
- Inhalation of spores
- Inhalation of conidia
- Reactivation of a latent infection
- Hematogenous spread frequently occurs, especially in an immunocompromised host

At risk patient populations:
- Neutropenic
  - “Risk inversely related to neutrophils < 300”

- HIV/AIDS
  - F treated w/ protease inhibitors and +/- cytokine antagonists
  - “Fungi generally held in check by cell-mediated immunity”

- Solid Organ Transplant (SOT) recipients
  - -Neutropenic - ubiqitous
  - -Histoplasmosis, coccidioidomycosis depending on geography
  - -Filamentous fungi
  - -Aspergillus, mucor, rhizopus
Endemic fungi

- Histoplasma
- Coccidioides
- Blastomyces

Histoplasmosis

- Bat guano
- Chicken droppings

“Histo Belt”
Histoplasmosis

- Transmitted by airborne *Histoplasma capsulatum* spores
- Primarily affects lungs and lymph nodes
- Risk factors: contact with bird or bat droppings
- Host defense: neutrophils, macrophages
- T-lymphocytes crucial in limiting extent of infection
- Susceptibility increased with impaired cellular host defenses

LLL nodule

Thoracic Histoplasmosis
Disseminated Histoplasmosis (disease)
- Signs/Symptoms
  - Fever, fatigue, weight loss, hepatosplenomegaly
  - Cough, dyspnea for greater than 1 month
  - Recurrent pneumonia

Histoplasmosis
- Diagnostic tests
  - Urine histo ag
  - Fungal comp fix panel
  - Blood/fungal cx
  - Tissue biopsy from caseating/necrotic granulomas

Anti-fungal Agents: Histoplasmosis
- Polyenes
  - Amphotericin deoxycholate
  - Liposomal amphotericin (Ambisome)
  - Amphotericin B Lipid Complex (Ambi-cast)
- Echinocandins
  - Anidulafungin
  - Caspofungin
  - Micafungin
- Azoles
  - Fluconazole
  - Itraconazole
  - Voriconazole
- Other Agents
  - 5-Flucytosine
  - Nystatin
  - Terbinafine
Coccidiodomycosis

- Transmitted by inhalation of airborne spores of *C. immitis* or *C. posadasii*
- Infection occurs in endemic areas and is most commonly acquired in the summer/late fall during outdoor activities.
- Travelers to endemic areas are at risk for contracting the disease, which may not become clinically evident until after they have returned home.
- Infections outside of endemic areas via transport of contaminated material.

“Valley Fever”

Areas Endemic for Coccidiodomycosis

- Highly endemic
- Established endemic
- Suspected endemic

- Valley Fever in endemic areas
Coccidiodomycosis

- In most patients with coccidioidal infection, primary infection is in the lungs.
- In 60-65% of cases, infection is asymptomatic.
- In other cases:
  - Mild influenza-like illness develops 1-4 weeks after exposure.
  - Fever, sore throat, cough, headache, fatigue, and pleuritic chest pain.
  - Resolution typically occurs over several weeks (although fatigue may persist for months).
  - 95% recover without any further sequelae.
- More at risk: Filipinos, African-American

More involved presentation → constellation of fever, arthralgias, erythema nodosum or erythema multiforme, and chest pain is commonly referred to as San Joaquin Valley fever (or simply “Valley fever”) or desert rheumatism.

Diagnostics
- IgM/IgG serologies
- Fungal comp-fix panel
- Tissue biopsy
- CSF PCR (if meningitis w/u warranted)
- CSF/blood cultures often negative

CT Chest imaging of Coccidioides
CT Imaging advanced Coccidioides Pneumonia

Anti-fungal Agents: Coccidiomycosis
- Polyenes
  - Amphotericin deoxycholate
  - Liposomal amphotericin (Ambisome)
  - Amphotericin B Lipid Complex (Ambicet)
- Echinocandins
  - Anidulafungin
  - Caspofungin
  - Micafungin
- Azoles
  - Fluconazole
  - Itraconazole
  - Posaconazole
  - Voriconazole
- Other Agents
  - 5-Flucytosine
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  - Terbinafine

Blastomycosis
Blastomycosis

- Blastomyces dermatitidis: thermally dimorphic fungus that causes the systemic pyogranulomatous disease termed blastomycosis.
- Least common of the endemic systemic mycoses; the other, more common mycoses include histoplasmosis and coccidiodomycosis
- Lungs, and to a lesser extent, skin and bone, are the most common organs involved with this fungus.
- Hematogenous dissemination can occur

Elderly patient visited eastern Canada. He developed cough, fever, and SOB.

CXR demonstrates focal patchy opacities throughout lung fields.

Bronchoscopic biopsy: Blastomyces dermatitidis

Cutaneous Blastomycosis
Anti-fungal Agents: Blastomycosis

- Polyenes
  - Amphotericin deoxycholate
  - Liposomal amphotericin (Ambisome)
  - Amphotericin-lipid Complex (Ambicet)
- Echinocandins
  - Anidulafungin
  - Caspofungin
  - Micafungin
- Other Agents
  - 5-flucytosine
  - Nystatin
  - Terbinafine

Azoles

- Fluconazole
- Itraconazole
- Posaconazole
- Voriconazole

Other Agents

- 5-flucytosine
- Nystatin
- Terbinafine

Ubiquitous Fungi

Cryptococcus neoformans

- Attack rate 0.2 cases/million/year in normal hosts
- Pneumonia, Cryptococcal meningitis
- May present as subacute meningitis
- Responsible for:
  - Meningitis
  - Pneumonia
  - Nodular skin disease

Aspergillus sp

- Mortality of 50-85% in neutrophilic hosts
- Radiographic findings of cavitations, fungal balls
- Angio-invasive → perforations, broncho-pulmonary fistula

Case

- 50y male admitted w/ temp 106.8F (104F one day pta at home). Reported “coughing fit.” 5th hospitalization for fever, cough in past 8 months
- ROS: fever, weight loss, pulmonary congestion, “pleuritic chest pain, dyspnea”, wheezing, nausea w/ loss appetite x 2 days, generally weak
- PMH
  - COPD
  - Pneumonia Nov-Dec 2008, again in Mar 2009 → CXR showed “destroyed L upper lobe”
  - Chronic empyema/p pulvermonary wedge resection April 2009 and multiple courses of antibiotics past 8 months
Case

- PSxH
  - Pneumothorax surgery 1991 w/ R thoroscopic resection
  - LUL wedge resection Apr2009
  - Hand sx d/t trauma

- SH/FH
  - 50+ pk/yr smoking hx (started age 13). No etoh. Hx inhaled drugs in past: marijuana, cocaine, pharmaceuticals
  - Divorced, disabled accountant, lives w/ adult son
  - Mom → COPD; Dad → Emphysema
  - Brother → DM; another Brother → unknown cancer
  - No travel outside of Dallas in 15 years. No cats, 1 dog, no exotic animals

Physical Exam

- Gen: thin, debilitated male. No cardio-respiratory distress at rest.
  - T 100.3, RR 20, BP 130/82, sat 97% on RA
- HEENT: No thrush, poor dentition, retracted gums
- Neck: No carotid bruises.
- Back: Without spinal or CVA tenderness.
- Lungs: Decreased breath sounds on the left. Prior small anterolateral thoracotomy scar on the left, well healed. Thoraco-scapic biopsy scar on the right, all well healed.
- Extremities: Muscle wasting, no edema.
- Skin: no rash, eruption

Case #1

- Chem Panel
  - Na 136 K 5.2 Cl 103 CO2 26 BUN 16 Creat 0.68
  - Glu 91

- CBC
  - WBC 17.9
  - Hgb 9.1
  - Plts 661
Prominent emphysematous changes.
Left apical pleural thickening.
Air-fluid level is noted in the anterior aspect of the left hemithorax.
No effusions.
Trachea is midline.
Heart size is within normal limits.

Additional studies – Case #1
- HIV -tive
- Hela urine ag -tive
- Crypto serum ag -tive
- Fungal Panel (basso, coccidiodes, helo, crypto) -
- Serum Galactomannon (aspergillus ag) -tive
- AFB/fungal blood cultures -tive
- Sputum cx (routine, anaerobic, AFB, fungal) -tive
- Nocardia -tive

Chest CT
- diffuse emphysematous changes throughout
- LUL mass
- LUL cavitory lesion
- Air-fluid levels
Hospital Course
- Surgical exploration/irrigation of the infected L pleural space with left latissimi-dorsal muscle flap closed by CVTS.
- Surgical cultures: *Aspergillus* sp
- Rx:
  - Voriconazole, long-term
  - Wound care
  - Smoking cessation (not)

Anti-fungal Agents: *Aspergillus* sp
- Polyenes
  - Amphotericin B deoxycholate
  - Lipid formulations (AmBisome, Abelcet)
- Echinocandins
  - Anidulafungin
  - Caspofungin
  - Micafungin

- Azoles
  - Fluconazole
  - Itraconazole
  - Posaconazole
  - Voriconazole

- Other Agents
  - 5-flucytosine
  - Terbinafine

Cryptococcosis
- Distribution worldwide in soil.
- Increased incidence over 20 yrs d/t AIDS, expanded use of immunosuppressive drugs.
- C. neoformans causes 3 types of human infections:
  - Cutaneous (wound) cryptococcosis
  - Pulmonary cryptococcosis, and
  - Cryptococcal meningitis.
Cryptococcosis

- Cryptococcus neoformans is an encapsulated yeast.
- 1894 → Busse, a pathologist, first described the yeast in a paper he presented to the Greifswald Medical Society. Busse isolated the yeast from the tibia of a 31-year-old woman.

Serious infections develop in patients with defective cell-mediated immunity. These account for >75% of cases:
- AIDS
- Organ transplantation
- Patients with reticuloendothelial malignancy
- Patients undergoing corticosteroid treatment
- Sarcoidosis
- Not seen frequently in neutropenics or in IgG deficiencies
Cryptococcosis

- Up to 7% of patients with AIDS will develop cryptococcal infections.
- 20% 3 month mortality rate of acute cryptococcal meningo-encephalitis in AIDS.

Cryptococcosis

- Cryptococcal pneumonia usually result (rather than cause) of disseminated disease (i.e. meningo-encephalitis).
- Symptoms of cryptococcal infection of the lung include:
  - Fever, weight loss, malaise
  - Pleuritic chest pain
  - Cough, Wheezing
  - Hemoptysis (sometimes)

Cryptococcosis

- Diagnostic tests:
  - Serum cryptococcal ag
  - CSF cryptococcal ag
  - Difficult to grow in culture
  - Fungitell will be negative
    - Cryptococcus produces very low levels of (1→3)-β-D-glucan
**Fungitell Assay**

- The Fungitell Assay is an FDA-cleared, highly sensitive, rapid diagnostic test that detects (1→3)-beta-D-glucan which is a cell wall constituent of most medically important fungi including Candida, Aspergillus, Pneumocystis.
- but NOT Cryptococcus

**Cryptococcosis**

- **Treatment**
  - Liposomal Amphotericin + 5-flucytosine x 2 weeks followed by Fluconazole 400mg IV → po daily maintenance.
  - Duration of Fluconazole
- Depending upon degree of immune suppression, need for long-term chronic Rx in AIDS → CD4 > 200 for 6m

**Anti-fungal Agents: Cryptococcosis**

- Polyenes
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So, what about Candida?

Candida in the ICU

- Ventilator-associated pneumonia (VAP) remains the leading cause of nosocomial infection in the ICU despite increasing efforts to reduce it.
- No gold standard routine method to diagnose Candida pneumonia → the most accepted method relies on lung histology.
- "no single case of candida pneumonia was found among the 232 patients autopsied, even in those (n = 77) with pre-mortem positive samples for Candida spp and histological signs of pneumonia" Meersman et al, Intensive Care Med, 2009
- C. albicans was the most common species identified (85%)
- Overall rate of Candida colonization in the whole population (taking into account those without pneumonia at autopsy) was high, 33%

Deterrence/Prevention

Immune-compromised host

- Avoid travel, work in endemic areas
- BMT, cancer chemoRx:
  - avoid gardening, cleaning, agitating debris
  - avoid potted plants, flowers, fresh fruit/veg
Summary: Fungal Pneumonia
In-patient Considerations
- Watch for rapidly progressive fever in at-risk patients
- Diagnostic w/u
  - AFB/fungal blood cultures
  - Fungal complement fix panels (serum, CSF)
  - Urine histo ag
  - Serum crypto ag
  - Serum galactomannan (aspergillus ag)
  - Fungal Comp Fix Panel
  - Radiography: CXR, CT-Chest
  - Bronch + TISSUE IS THE ISSUE

Fungal Pneumonia
In-patient Considerations
- In severe neutropenics, rapid progression of fungal PNA and dissemination (e.g., aspergillosis) requires high degree of suspicion
- Consider empiric anti-fungal therapy
- Correct neutropenia
- Rapidly taper/withdraw immuno-suppressive drugs
- Correct hypoglycemia, acidosis

Thanks
References