Fungal Infections

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Objectives:
1. Be familiar with the antifungal agents available for use
2. Recognize the major fungal pathogens involved in systemic fungal infections
3. Describe the common factors that put patients at risk for fungal infections
4. Identify the preferred antifungal agent for a given fungal infection
5. Given a clinical scenario, be prepared to develop a specific drug treatment plan for the patient

I. INTRODUCTION TO MYCOSES
A. Eucaryotic organisms
   • Filamentous molds: Tubular structures called hyphae that grow by branching and longitudinal extension to form mycelium
   o Aspergillus spp.
   o Zygomycetes (Mucor spp., Rhizopus spp., Rhizomucor spp.)
   o Dermatophytes (Tricophyton spp., Microsporum spp., Epidermophton spp.)
   • Unicellular yeasts: Usually round or oval and reproduce by budding
   o Candida spp.
   o Cryptococcus spp.
   • Di-morphic fungi: Grow in host as yeast and grow as mold in vitro
   o Histoplasma spp.
   o Blastomyces spp.
   o Coccidioides spp.

B. Cellular structure
   • Fungal organisms pathogenic to humans are nonmotile and have a rigid cell wall, usually containing chitin and polysaccharides
   • Inside the cell wall is the sterol-containing cytoplasmic (ergosterol) membrane (site affected by azole and polyene agents)

C. Reproduction
   • Form spores through mitosis and the chromosome number remains the same (anamorph or asexual state)
   • Form spores through meiosis reducing the chromosome number by half (telemorph or sexual spores)

D. Diagnosis
   • Typically based on clinical presentation and history (risk factors) and supported by serology, biopsy and culture.
   • Treatment almost always initiated based on clinical suspicion with culture confirmation +/- sensitivity data coming several days later.

E. Epidemiology
   • Pathogenic fungi include: Histoplasma capsulatum, Coccidioides immitis, Blastomyces dermatitidis, Cryptococcus neoformans
   • Opportunistic mycosis include: Candida spp., Aspergillus spp., Pneumocystis spp., Fusarium spp., Zygomycetes (Mucor spp., Rhizopus spp., Rhizomucor spp.)
   • Significant morbidity and mortality among immunocompromised individuals
   • Usually not transmitted person to person
II. SUSCEPTIBILITY TESTING

- Not routinely done (institution specific)
- Standardized methods only for *Candida* spp. and *Cryptococcus* spp. (yeasts) but not for *Aspergillus* spp. and other molds
- Difficult to correlate *in vitro* sensitivities to *in vivo* outcomes
- Most helpful for non-*albicans* *Candida* species

III. RESISTANCE

- Studied most extensively in *Candida* spp.
  - Acquired resistance (transferred from other organism or developed during therapy)
  - Intrinsic resistance (innate lack of susceptibility)
- Azole-resistant *Candida* albicans noted in AIDS patients with low CD4 counts following multiple courses of fluconazole for thrush.
- Among hospitalized patients: shift toward other resistant species like *Candida glabrata* and *Candida krusei* (greater intrinsic resistance to azoles)

IV. POLYENE ANTIFUNGAL AGENTS

A. Amphotericin

- **MOA:** Binds to ergosterol altering cell wall membrane permeability in susceptible fungi causing cell wall leaking with subsequent cell death.
- **Use:** Historically considered first-line therapy for unknown invasive fungal and mold infections thanks to its broad spectrum of activity including *Candida* spp., *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Cryptococcus neoformans*, *Aspergillus* spp., Zygomycetes, and *Sporotrix* spp.
- **Formulations:**
  - Amphotericin B desoxycholate (Fungizone®)
  - Amphotericin B Liposomal (AmBisome®)
  - Amphotericin Lipid B Complex (Abelcet®)
  - Amphotericin B Cholesteryl Sulfate Complex (Amphotec®)
- **Adverse Reactions:**
  - Infusion related toxicity (shaking chills, flushing, fever, myalgias, arthralgias, and headache) may be caused by induction of prostaglandins
  - Rare: anaphylaxis, hypokalemia, hypomagnesemia, nephrotoxicity, renal tubular acidosis, leukocytosis.
- **Monitoring Parameters:** Renal function (BUN, SCr), electrolytes (K⁺ and Mg), liver function and CBC
- **Drug Interactions:**
  - ↑ nephrotoxicity: cyclosporine, aminoglycosides
  - ↑ hypokalemia: corticosteroids, K⁺ wasting diuretics
- **Note:** Renal toxicity may be minimized by fluid boluses (500mL NaCl pre and post AmB infusion)
- **Dose:**
  - AmB desoxycholate 0.3-1.5mg/kg once daily
  - AmB Liposomal 3-7 mg/kg once daily
  - AmB Lipid B Complex 2.5-5 mg/kg once daily
  - AmB Cholesteryl Sulfate Complex 3-7.5mg/kg once daily

B. Nystatin

- **MOA:** Binds to sterols in the fungal cell membrane altering cell wall permeability in susceptible fungi and causing leakage of cell components with subsequent cell death
- **Use:** Treatment of susceptible cutaneous mucocutaneous and oral cavity fungal infections normally caused by *Candida* spp.
- **Adverse Reactions:** Contact dermatitis, Stevens-Johnson syndrome, N/V/D, and hypersensitivity
- **Dose:** Swish and swallow 400,000-600,000 units every 6 hours.
V. AZOLE ANTIFUNGAL AGENTS

• MOA: Inhibits cytochrome P450 dependent 14-alpha lanosterol. Inhibition of this enzyme disrupts the synthesis of ergosterol, resulting in the formulation of a cell membrane with abnormal characteristics and accumulation of toxic sterol intermediates.

• Activity: Broad spectrum of activity including Candida spp., Coccidioides immitis, Histoplasma capsulatum, Blastomyces dermatitidis and Cryptococcus neoformans. Generally less activity against Candida glabrata and Candida krusei.

• Drug Interactions: Interactions with drugs metabolized by cytochrome P450

• Adverse Effects: Teratogenic

A. Miconazole (Monistat®, Micatin®)

• First systemically available imidazole antifungal agent
• Poorly soluble (castor oil vehicle)
• Adverse Reactions: Phlebitis, pruritis, N/V, chills (due to vehicle)
• Use: Topically for vulvovaginal candidiasis and superficial skin infections (available OTC)

B. Ketoconazole (Nizoral®)

• Oral imidazole (no activity against Aspergillus spp., limited activity against C. neoformans)
• Poorly soluble, needs acidic (pH<3) media
• Adverse Reactions: Dose related GI discomfort, inhibition of adrenal steroid synthesis (reversible), hepatitis, ↑ dose in men can cause gynecomastia, ↓ libido, oligospermia, azoospermia, and impotence 2° to ↓ testosterone
• Use: Topically for tinea corporis, tinea cruris, tinea versicolor and cutaneous candidiasis, seborrheic dermatitis
• Interactions: Substrate of CYP3A4
• Usual Dose: 200-400mg daily

C. Itraconazole (Sporanox®)

• Triazole antifungal with activity including Aspergillus spp., and Sporothrix spp.
• Formulations:
  o Oral Capsule
    - Needs acidic gastric pH
  o Oral Solution
    - Use cyclodextrin to ↑ solubility of drug
    - Cyclodextrin is not absorbed, but ↑ GI side effects
  o Intravenous
    - Use cyclodextrin to ↑ solubility of drug
    - Cyclodextrin ↑ risk of nephrotoxicity (limit therapy to 2 weeks)
• Adverse Reactions: Rash, edema, rare: ventricular tachycardia, torsade de pointes, hepatic toxicity, adrenal suppression, arrhythmia and alopecia
• Use: Blastomycosis, histoplasmosis, aspergillosis, onychomycosis, candidiasis, cryptococcosis and coccidioidomycosis
• Usual Dose: 200-400mg once or twice daily

D. Fluconazole (Diflucan®)

• Triazole antifungal lacking activity against Aspergillus spp.
• Formulations: IV and oral tablet, oral suspension
• Adverse Reactions: Headache, GI effects, rarely alopecia (reversible)
• Use: Prophylaxis in AIDS patients to ↓ incidence of oropharyngeal and esophageal candidiasis, cryptococcosis, and histoplasmosis
• Usual Dose: 200-400mg daily

E. Voriconazole (Vfend®)

• Triazole antifungal with activity including Aspergillus spp., Scedosporium apiospermum, and Fusarium spp.
• Formulations: Both oral tablets and IV form in sulfobutylcyclodextrin for solubility (concern for accumulation if CrCl < 50)
• **Adverse Reactions:** Visual disturbances (dose related red/green color blindness) rare: hepatic failure, hepatitis.
• **Use:** Aspergillosis, infections caused by Scedosporium and Fusarium spp.
• **Dose:**
  o 6mg/kg IV Q12h x 2 doses followed by 4mg/kg IV Q12h
  o 200mg PO Q12h for pts > 40kg and 100mg PO for pts < 40kg
  o Don’t use IV formulation in pts with CrCl < 50 mL/min (accumulation of SBECID)

F. **Posaconazole (Noxafil®)**
• Triazole antifungal with activity against *Aspergillus* spp., *Zygomycetes* and *Candida* spp.
• **Formulations:** Oral suspension (cherry flavored)
• **Adverse Reactions:** Nausea and vomiting, rarely: QT interval prolongation and elevation of hepatic enzymes
• **Use:** Prophylaxis of invasive *Aspergillus* and *Candida* infections in immunocompromised patients
• **Dose:** 200mg (5mL) TID with meals

VI. ECHINOCANDINS
• **MOA:** Inhibit the synthesis of β(1,3)-D-glucan, an essential component of the cell wall of susceptible fungi. Highest activity in regions of active cell growth. Mammalian cells do not require β(1,3)-D-glucan, limiting potential for toxicity.
• **Activity:** The echinocandins have activity against *Candida* (fungicidal) and *Aspergillus* spp.(fungistatic), *C. neoformans* is intrinsically resistant, as are *Fusarium* spp., the Mucorales and *Trichosporon* spp. Activity against the dimorphic endemic moulds such as *Histoplasma capsulatum* and *Coccidioides immitis* is questionable.
• **Formulations:** All intravenous

A. **Caspofungin (Cancidas®)**
• **Use:** Approved for the treatment of candidemia, esophageal candidiasis and invasive aspergillosis in patients refractory to or intolerant of other antifungal therapies
• **Adverse Reactions:** Fever, phlebitis, nausea, vomiting, flushing, rash, facial swelling, pruritis.
• **Drug Interactions:** Concomitant use of cyclosporine with caspofungin is NOT recommended. Caspofungin ↓ tacrolimus concentrations.
• **Dose:** Loading dose of 70 mg IV, then 50 mg IV daily
  o Moderate hepatic insufficiency: Load with 70 mg, then 35 mg daily
  o No adjustment needed for renal insufficiency

B. **Micafungin (Mycamine®)**
• **Use:** Approved for the treatment esophageal candidiasis and for prophylaxis of Candida infections in patients undergoing hematopoietic stem cell transplantation.
• **Adverse Reactions:** Fever, abnormal LFTs, and electrolyte disturbances
• **Drug Interactions:** Micafungin ↑ sirolimus and nifedipine concentrations
• **Dose:** Esophageal candidiasis 150 mg IV daily, HSCT prophylaxis 50 mg IV daily, candidemia or invasive candidiasis 100 mg IV daily
  o No adjustment needed for moderate hepatic impairment
  o No adjustment needed for renal insufficiency

C. **Anidulafungin (Eraxis®)**
• **Use:** Approved for the treatment of esophageal and invasive candidiasis.
• **Adverse Reactions:** Abnormal LFTs.
• **Drug Interactions:** Several minor (cyclosporine, voriconazole, tacrolimus, rifampin) but none requiring a dosage adjustment
• **Dose:** Esophageal candidiasis 100 mg IV, then 50 mg IV daily, candidemia 200 mg IV, then 100 mg IV daily
No adjustment needed for moderate hepatic impairment
No adjustment needed for renal insufficiency

Diluent contains a significant amount of ethanol. Wouldn’t recommend in NICU/Peds.
Effect with metronidazole unknown.

VII. FLUCYTOSINE (5-FC)
- **MOA:** Flucytosine is a fluorinated pyrimidine analog of cytosine. 5-FC rapidly enters the cell and is deaminated into 5-fluorouracil (an antimetabolite), which then inhibits DNA synthesis by incorporation into RNA and competitive inhibition of thymidylate synthetase.
- **Adverse Effects:** GI discomfort, elevation of hepatic enzymes, BUN, SCr, leucopenia, anemia, thrombocytopenia, enterocolitis
- **Use:** Generally used for treatment of cryptococcosis, candidiasis and chromomycosis, although is not the drug of choice for any infection due to inferior activity to AmB
- **Drug Interactions:** AmB-induced renal dysfunction may ↑ flucytosine accumulation and myelosuppression.
- **Dose:** 50-150 mg/kg/day PO in 4 divided doses
  - Extend the dosing interval as renal function declines
- **Note:** Should not be used as a single agent due to the rapid development of resistance.

VIII. FUNGAL DISEASES
A. Candida Infections
- **Epidemiology**
  - > 150 species (yeast), but only nine are regarded as frequent pathogens for humans
  - Pathogenic species include: *C. albicans*, *C. guilliermondii*, *C. krusei*, *C. parapsilosis*, *C. tropicalis*, *C. pseudotropicalis*, *C. lusitaniae*, *C. glabrata*.
  - *C. albicans* is normal flora on the skin, female genital tract and the entire GI tract
  - Candidiasis: mucocutaneous or systemic infection (candiemia, endocarditis, peritonitis, CNS infection, etc.)
- **Pathophysiology**
  - GI tract or indwelling IV catheter
  - Dissemination can result in infection of single or multiple organs
- **Presentation** (disseminated)
  - Can be indistinguishable from sepsis of bacterial origin (most common), fever, tachycardia, tachypnea, chills.
  - Intermittent fevers and only ill when febrile
  - Progressive deterioration of condition without fever
- **Treatment of candidemia** (disseminated)
  - **Fluconazole 400-800 mg/day IV or PO for 14 days after last (+) blood culture**
    - Voriconazole IV or PO for 14 days after last (+) blood culture
      - 6mg/kg IV Q12h x 2 doses followed by 4mg/kg IV Q12h
      - 200mg PO Q12h for pts > 40kg and 100mg PO for pts < 40kg
    - Caspofungin 70 mg IV, then 50 mg IV daily
    - AmB (conv) 0.6-1 mg/kg/day IV for 14 days after last (+) blood culture
    - AmB (lipid) 3-5 mg/kg/day IV for 14 days after last (+) blood culture
  - Use echinocandin if:
    - suspect *C. krusei* or *C. glabrata*
    - hemodynamically unstable
    - previous (recent) azole exposure
    - patient is neutropenic
  - **Remove all intravascular catheters!**
- **Treatment of mucocutaneous candidiasis**
  - **Oral**
    - Clotrimazole 10mg 5 times daily
    - Nystatin 200,000 – 400,000 units 5 times daily
    - Fluconazole 100-200 mg PO daily
• Treat 7-14 days after clinical improvement
  o Esophageal
    • Fluconazole 100-200 mg PO daily
    • Itraconazole 200 mg PO daily
    • Treat 14-21 days after clinical improvement

B. Cryptococcosis

• Epidemiology
  o Caused by encapsulated soil yeast Cryptococcus neoformans (pigeon droppings)
  o ↑ incidence in recent past 2° to ↑ number of immunocompromised patients and HIV patients
  o Disease usually involves the CNS

• Pathophysiology
  o Polysaccharide capsule allows organism to resist phagocytosis
  o Cell-mediated immunity important in host defense against infection
  o CNS infection due to lack of immunoglobulin and complement

• Presentation
  o 1° infection usually lung: cough, SOB, and rales that generally resolve spontaneously
  o Disease may remain localized to lung or disseminate (CNS)
  o Cryptococcal meningitis-headache, fever, N/V, mental status changes

• Treatment
  o Pulmonary Disease
    • Immunocompetent host with pulmonary disease can use fluconazole monotherapy
    • Fluconazole 400 mg/day IV or PO for 2-6 months
    • AmB (conv) 0.5-0.8 mg/kg/day until clinical response then fluconazole as above
  o CNS Disease
    • AmB 0.7-1 mg/kg/day and flucytosine 100 mg/kg/day (induction) then,
    • Fluconazole 400 mg/day (consolidation) for 8 weeks
    • Therapy should then be continued thereafter with fluconazole 200 mg/day until immune reconstitution takes place.
  o Length of therapy (suppression) in immunocompromised patients is much longer (years – lifetime)

C. Aspergillosis

• Epidemiology
  o Ubiquitous mold from soil, water, decaying vegetation, moldy hay and organic debris
  o > 300 species but most common pathogens include: A. fumigatus, A. flavus, and A. niger

• Pathophysiology
  o Inhalation of airborne conidia small enough to reach the alveoli or paranasal sinuses
  o Conidia remain viable for several months in dry locations
  o Phagocytes (neutrophils, monocytes, macrophages) are the 1° host defense system against invasive disease
  o Neutropenia and corticosteroid use are the most common predisposing factors

• Presentation
  o Superficial infection: ear, skin, or appendages
  o Aspergilloma (fungus ball): sinus or lung
    • Usually in sinus tissue (intertwined Aspergillus hyphae matted with fibrin, mucus, and cellular debris)
    • Pulmonary aspergillomas (look like cotton balls on X-ray)
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- **Invasive:**
  - Prolonged neutropenia (leukemia, BMT)
  - Rare in normal hosts
  - Lung most common, followed by CNS, liver, spleen, heart, GI tract and pericardium
  - Invasion of blood vessels cause thrombosis with resultant infarction, necrosis and dissemination to other tissues

- **Diagnosis** (difficult)
  - Biopsy / Culture
  - Serologic tests to detect antibody production usually not very helpful
  - Often an empiric diagnosis

- **Treatment**
  - Surgery (debridement is essential for sinusitis)
  - Colony stimulating factor if neutropenic
  - Moderate disease
    - Voriconazole 6 mg/kg IV X 2 doses, then 4 mg/kg IV Q12 hours; can switch to PO once patient is stable/able.
  - Severe disease
    - AmB (liposomal) 5-10 mg/kg/day
  - Salvage
    - Combination voriconazole or AmB PLUS caspofungin 50 mg daily
  - Duration of therapy is dependent on patient specific factors, disease state, immune status etc. and may range from weeks to months.

**D. Pneumocystis carinii**

- **Epidemiology**
  - Traditionally classified as a protozoan, although more recent evidence suggests closely related to fungi
  - Distributed worldwide

- **Pathophysiology**
  - Transmission airborne
  - Nonimmunocompromised patients asymptomatic, reactivation or significant infections occurs in the immunocompromised

- **Presentation**
  - *Pneumocystis carinii* pneumonia (PCP)
    - Fevers, chills, dyspnea, dry cough
    - AIDS patients – indolent onset and symptoms for several weeks
    - Non-HIV patient may present with fever and malaise with no respiratory symptoms
  - Extrapulmonary *Pneumocystis*
    - Rare, usually pulmonary
    - Retinal, lymph nodes, liver, spleen, thyroid, ear lesions, skin lesions, and mastoiditis

- **Diagnosis**
  - Induced sputum for *P. carinii*
  - Bronchoalveolar lavage (BAL)
  - Chest X-ray

- **Treatment**
  - Trimethoprim/sulfamethoxazole 15mg/kg/day IV divided Q8h for 14-21 days
  - Pentamidine 4 mg/kg once daily for 14-21 days
  - Atovaquone 750 mg Q12 for 21 days

- **Prophylaxis**
  - TMP/SMX DS 1 tablet 3 times/week
  - Dapsone 100mg PO daily
  - Atovaquone 1500 mg PO daily
E. Histoplasmosis

• Epidemiology
  o Caused by inhalation of dust-borne microconidia of the dimorphic fungus *Histoplasma capsulatum*
  o Endemic: certain areas of North and Latin America, most disease in U.S. localized to Ohio and Mississippi river valley
  o Nitrogen-enriched soil (avian or bat guano)

• Pathophysiology
  o Soil disruption results in aerosolized conidia which reach the bronchioles or aveoli
  o After 2-3 days in lung, conidia germinate and are ingested (not destroyed) by macrophages
  o Infected macrophages migrate to other sites (mediastinal lymph nodes, spleen, liver)
  o Tissue granulomas develop over next 2-4 months
  o Over several years foci become encapsulated and calcified

• Presentation
  o Acute Pulmonary Histoplasmosis
    ▪ Majority of cases with a low-inoculum exposure to *H. capsulatum* result in mild or asymptomatic pulmonary histoplasmosis and are usually self-limiting
    ▪ Therapy may be necessary if risk of developing disseminated disease
    ▪ Symptoms: fever, chills, headache, myalgia, non-productive cough, SOB, respiratory depression.
    ▪ Rare: arthritis, erythema, pericarditis, or mediastinal granuloma
  o Chronic Pulmonary Histoplasmosis
    ▪ Opportunistic infection (structural abnormality, emphysema)
    ▪ Chronic pulmonary symptoms
    ▪ Progression of disease can occur over period of years
  o Disseminated Histoplasmosis
    ▪ Patients exposed to large inoculum and/or immunocompromised host
    ▪ Acute disseminated disease is characterized by substantial involvement of mononuclear phagocyte system and is fatal if untreated.
    ▪ Most adults with disseminated histoplasmosis demonstrate a mild, chronic form of the disease
  o Histoplasmosis in HIV-Infected Patients
    ▪ Acute form of disseminated disease
    ▪ Initial infection or reactivation of dormant foci

• Diagnosis
  o Direct exam or histologic study
  o Clinical cultures 3-6 weeks
  o DNA probe for ribosomal DNA
  o Serological: complement fixation, detection of polysaccharide capsule in urine, blood and CSF fluid
  o Bone marrow biopsy (HIV patients)

• Treatment
  o If asymptomatic, then generally no therapy
  o Moderate disease
    ▪ Itraconazole 200-400 mg PO daily
  o Severe disease (HIV patients, severe diffuse pulmonary disease, progressive disease)
    ▪ **AmB** (conv) 0.7-1 mg/kg/day
    ▪ **AmB** (liposomal) 3-5 mg/kg/day
  o Fluconazole use discouraged due to high relapse rates
  o Voriconazole and posaconazole have activity but limited evidence
  o Length of therapy will depend on type of disease and immune status of the host
F. Blastomycosis (or Paracoccidioidomycosis)

- **Epidemiology**
  - In North America caused by the dimorphic fungus *Blastomyces dermatitidis*
  - Endemic in southeastern and south central US (Mississippi and Ohio river basins) and midwestern states and Canadian provinces bordering on the Great Lakes
  - B. dermatitidis has been isolated from soil containing decayed vegetation, decomposed wood, and pigeon manure, often associated with warm moist soil of wooden areas

- **Pathophysiology**
  - Pulmonary infection by inhalation of conidia (yeast in lung)

- **Presentation**
  - Acute blastomycosis
    - Generally asymptomatic
    - Self limiting disease: fever, shaking chills, and productive, purulent cough
  - Chronic pulmonary blastomycosis
    - Fever, malaise, night sweats, chest pain, productive cough
  - Reactivation can occur in lungs or new foci (skin, bony skeleton, prostate, oropharyngeal mucosa, CNS, and abdominal viscera)
  - Disseminated disease may occur 1-3 years after pulmonary disease

- **Diagnosis**
  - Biopsy (direct microscopic visualization)
  - Culture (slow growing)
  - Serologic tests (not very specific)

- **Treatment**
  - Clinical presentation and immune status of the patient dictates therapy
  - Not all patients with pulmonary blastomycosis require treatment
  - In general, if patient is not immunocompromised and has mild to moderate disease
    - Itraconazole 200-400 mg PO daily
  - All patients with progressive pulmonary disease or with extrapulmonary disease should be treated
    - AmB (conv) 0.7-1 mg/kg IV daily
  - Regardless of therapy, must be monitored for reactivation or progression of disease for several years

G. Coccidioidomycosis

- **Epidemiology**
  - Caused by *Coccidioides immitis*, a dimorphic fungus found in southwestern and western US, Mexico and South America
  - Grows in the soil as a mold and mycelia proliferate during the rainy season
  - During the dry season, resistant arthroconidia form and become airborne when the soil is disturbed

- **Pathophysiology**
  - Inhalation into the lungs
  - Similar to histoplasmosis, an acute inflammatory response in the tissue leads to infiltration of mononuclear cells, ultimately resulting in granuloma formation

- **Presentation**
  - Range from primary uncomplicated respiratory tract infection that resolves spontaneously to progressive pulmonary or disseminated infection
  - Most cases, initially involves lungs
  - 60% asymptomatic or nonspecific symptoms that are indistinguishable for upper respiratory infection (URI)
  - Rash may appear during first few days of illness “Valley Fever”
  - Disease usually lasts a few days to weeks and resolves spontaneously without therapy, but can be fatal in immunocompromised host
Disseminated disease (<1% cases), skin, lymph nodes, bone, meninges, spleen, liver, kidney, and adrenal gland

- **Diagnosis**
  - Skin test
  - Antibody detection
  - Culture
  - Biopsy

- **Treatment**
  - **Approximately 5% of infected patients require therapy**
  - AmB generally preferred as initial therapy
  - Fluconazole, itraconazole and ketoconazole are also options
  - Fluconazole is drug of choice for meningeal disease
  - Therapy ranges from 3-6 months in duration
  - If diffuse pneumonia then several weeks of AmB then consolidation therapy with oral azole for at least one year
  - Surgical resection may be useful

**Additional Resources:**
2. Practice Guidelines from the Infectious Diseases Society of America:
Practice Cases:

TJ is a 34 year old white female who is 6 days s/p a BMT for acute myelocytic leukemia. She has been febrile and receiving vancomycin and cefipime for three days with no improvement. The team suspects that TJ has an invasive fungal infection.

Which of the following organism would be the least likely cause of infection in TJ?

A. *Candida glabrata*  
B. *Candida albicans*  
C. *Aspergillus fumigatus*  
D. *Coccidioides immitis*

TJ was started empirically on amphotericin B desoxycholate for suspected fungal infection. Which of the following is NOT a concern with amphotericin therapy?

A. Monitoring renal function (SrCr, BUN)  
B. Monitoring electrolytes (K⁺ and Mg)  
C. Monitoring for drug interaction with drug metabolized by cytochrome P450  
D. Monitoring a CBC

JB is a 45 year old white male who received a kidney transplant in 1989 for a genetic kidney disease. He presented to his community physician one week prior to admission at Fairview with fever, chills, and weight loss. He was diagnosed with a UTI and received ciprofloxacin. A week later, on admission, JB presented with altered mental status, fever, hypoxia and was diagnosed with sepsis. Urine cultures were positive for budding yeast, blood culture results are “pending”.

What organism would most likely cause a fungal UTI in JB?

A. *Candida albicans*  
B. *Candida krusei*  
C. *Cryptococcus neoformans*  
D. *Candida glabrata*

Which of the following therapies is not an appropriate choice for a fungal UTI?

A. Removal of the urinary catheter  
B. Fluconazole  
C. Bladder irrigation with amphotericin B  
D. Caspofungin

TF is a 44 year old Hispanic female with no significant medical history that works as an archeologist and just recently returned to Minnesota after spending the last six months working between two archeological dig sites in New Mexico and Missouri. She presented to her primary care physician afebrile, with a one week history of dry cough.

Based on her work history, what would be the least likely fungal organism that could cause TF’s respiratory symptoms?

A. *Blastomyces dermatitidis*  
B. *Coccidioides immitis*  
C. *Histoplasma capsulatum*  
D. *Pneumocystis carinii*