

Antifungals

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Mary A. Ullman, PharmD
Department of Experimental and Clinical Pharmacology
McGuire Translational Research Facility Room 4-500
ullma020@umn.edu

Objectives

- 1) Describe the reasons for the increased incidence of fungal infections
- 2) Discuss the clinical use of fungal susceptibilities
- 3) For each antifungal, be able to identify
 - a. Mechanism of action
 - b. Dosing
 - c. Key side effects and monitoring parameters
- 4) Given a patient case, be able to recommend a treatment regimen for each of the following fungal infections
 - a. Candidemia
 - b. Candiduria
 - c. Aspergillosis
 - d. Blastomycosis
 - e. Coccidioidomycosis

Fungal Basics

- 1) Dramatic increase in the number of fungal infections worldwide
 - a) Contributing factors:
 - b) Major cause of death in cancer and transplant patients
 - c) *Candida* spp. 4th most common bloodstream isolate
 - 2) Great number of issues surrounding factors involved in antifungal therapy; not as refined as antibacterial therapy
 - 3) Three groups of fungi responsible for fungal infections
 - a)
 - i) Consist of tubular structure called hyphae
 - ii) Grow by branching or expanding longitudinally
 - b)
 - i) Oval or spherically shaped unicellular forms
 - ii) Reproduce by budding
 - c)
 - i) May exist either as a mold or yeast dependent of environmental factors
 - (1) Yeast usually form causing infection in humans
 - (2) Molds usually form found growing in environment

Susceptibility Testing and Antifungal Resistance

- 1) Not routinely performed by laboratories but CLSI standards exist for *Candida* spp. and *Cryptococcus* spp.
- 2) Questions still surround correlation between *in vitro* results and *in vivo* outcomes in patients
- 3) Susceptibility testing may be useful for patients with prolonged fungemia between treated with an agent to which the fungi is presumed susceptible
- 4) Two types of resistance
 - a) Clinical resistance
 - i) Failure of antifungal agent due to other factors other than antimicrobial factors (PK/PD factors or lack of immune system)
 - b) Microbial resistance
 - i) Primary = intrinsic resistance to antifungal
 - (1) e.g. *Candida krusei* resistance to fluconazole
 - ii) Secondary = acquired resistance to antifungals
- 5) Possible for patient to respond clinically to a species that is considered resistant *in vitro* due to the effects of a person's immune system or an increased concentration of the drug at the site of infection

Antifungal agents

- 1) Three antifungal mechanisms of action
 - a) Inhibitors of the fungal cell membrane
 - i) Amphotericin B
 - ii) Azole antifungals
 - iii) Nystatin

- b) DNA inhibitors
 - i) Flucytosine
 - c) Inhibitors of cell wall biosynthesis
 - i) Echinocandins
- 2) Antifungal therapy often uses several antifungals during the course of therapy, but hardly in combination
- a)
- 3) Amphotericin B
- a) MOA: Binds sterols in fungal cell membrane → change in membrane permeability → cell leakage → death
 - b) Therapy of choice for many infections, including in pregnancy
 - i) Broad spectrum of activity
 - c) Multiple formulations available due to attempts to limit infusion-related toxicities and nephrotoxicity
 - d) Dosing
 - i) Dependent on formulation
 - (1) Amphotericin B deoxycholate (Fungizone®) 0.25 – 1 mg/kg/day
 - (2) Amphotericin B Cholesteryl Sulfate complex (Amphotec®) 3 – 7.5 mg/kg/day
 - (3) Amphotericin B Lipid Complex (Abelcet®) 3 to 6 mg/kg/day
 - (4) Amphotericin B Liposome (AmBisome®) 3 to 6 mg/kg/day
 - ii) Should be adjusted in renal dysfunction
 - e) Adverse reactions
 - i)
 - (1) Avoid by premedicating with antihistamines, antiemetics, anti-inflammatories
 - (2) Thrombophlebitis can be avoided by slowing infusion rate
 - (3) Rigors associated with infusion should be treated meperidine
 - ii)
 - (1) May be avoided by pre-infusing with 500mL NS
 - iii) Electrolyte imbalances (esp. K^+ , Ca^{2+} , Mg^{2+})
 - iv) Leukocytosis
 - f) Drug interactions
 - i) Increased nephrotoxicity: cyclosporine, aminoglycosides
 - ii) Increase hypokalemia: corticosteroids, potassium wasting diuretics
- 4) Flucytosine
- a) MOA: Converted to 5-fluorouracil in fungal cells → noncompetitive inhibitor of thymidylate synthetase → inhibition of DNA synthesis
 - b)
 - c) Dosing : 50 – 150 mg/kg/day ÷ 4 as PO dose
 - i) Adjust in renal dysfunction
 - d) Adverse reactions
 - i)
 - ii) Hepatotoxicity
 - iii) Renal dysfunction
 - iv) N/V/D
 - v) Enterocolitis
 - e) Drug interactions
 - i) Increased flucytosine concentrations seen when used in combination with amphotericin B in patients with renal dysfunction
- 5) Echinocandins
- a) MOA: Inhibition of beta (1,3)-D-glucan synthesis, an important cell wall component in susceptible fungi, i.e. *Aspergillus*, *Candida*, *Histoplasma* (*in vitro*)
 - b) Three available agents
 - i)
 - (1) FDA approved indications: Invasive, refractory aspergillosis; candidemia; esophageal candidiasis; disseminated candidiasis; empiric therapy for neutropenic fever
 - (2) Dosing: 70 mg IV x 1 loading dose, 50 mg IV qday
 - (a) Dose adjust in hepatic insufficiency by decreasing daily dose (after load) to 35 mg qday
 - (3) Adverse reactions : fever, phelibitis, shivering, headache, hypokalemia, rash, N/V, facial swelling (treat with antihistamine)
 - (4) Drug interactions: Cyclosporine (contraindicated), tacrolimus (decreased concentrations)

ii)

- (1) FDA approved indications: Candidemia; Candidiasis prophylaxis in hematopoietic stem cell transplantation; esophageal candidiasis, disseminated candidiasis
- (2) Dosing
 - (a) Treatment: 100 – 150 mg/day IV
 - (b) Prophylaxis: 50 mg/day IV
 - (c) No dosage adjustments needed in renal or hepatic dysfunction
- (3) Adverse reactions: N/V/D, headache, phlebitis, rash, fever, rigor, anemia, leucopenia, neutropenia, renal impairment
- (4) Drug interactions: Increased sirolimus and nifedipine concentrations

iii)

- (1) FDA approved indications: candidemia; esophageal candidiasis; intra-abdominal and peritoneal disseminated candidiasis
- (2) Dosing
 - (a) Candidemia and disseminated candidemia: 200 mg IV load x 1, followed by 100 mg IV qday
 - (b) Esophageal candidiasis: 100 mg IV load x 1, followed by at least 50 mg IV qday
 - (c) No dosage adjustments needed in renal or hepatic dysfunction
- (3) Adverse reactions: Hypokalemia, diarrhea, abnormal LFTs
- (4) Drug interactions: Cyclosporine increases anidulafungin concentrations

6) Azole antifungals

- a) MOA: Inhibits fungal sterol synthesis → 14 alpha-methyl sterol aggregation → fungistatic effect
 - i) Spectrum of activity includes *Candida* spp., *Coccidioides immitis*, *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Cryptococcus neoformans*
 - b)
 - c) A number of agents available in this class
 - i) Ketoconazole (imidazole)
 - (1) Poorly soluble, needs acidic media
 - (2) Previously widely used oral agent, but now primarily used as a topical agent due to decreased toxicities with newer agents, and drug interactions
 - (3) Dosing: 200 – 400 mg PO
 - (4) Adverse reactions: GI discomfort (dose-related), hepatitis, inhibition of adrenal steroid synthesis → gynecomastia, decreased libido, oligospermia, azospermia, impotence
 - (5) Drug Interactions: CYP3A4 substrate
 - ii) Fluconazole (triazole)
 - (1) Frequent use in treatment and prophylaxis of susceptible fungal infections, especially meningitis due to good CNS penetration
 - (2) Dosing
 - (a)
 - (b) Dosages range from 100 – 800 mg/day
 - (i) More serious infections usually treated with higher doses
 - (c)
 - (3) Adverse reactions: N/V, increased LFTs, headache
 - (4) Drug interactions: CYP 3A4, CYP 2C19 substrate
 - iii) Itraconazole (triazole)
 - (1) Also has activity against *Aspergillus* spp.
 - (2) Three different formulations
 - (a) Oral Capsule
 - (i) Needs acidic gastric pH
 - (ii)
 - (b) Oral solution
 - (i) Contains cyclodextrin to increase drug solubility (not absorbed but increased GI side effects)
 - (ii)
 - (c) IV formulation
 - (i) Also contains cyclodextrin to increase drug solubility (increased risk of nephrotoxicity so limit use to 2 weeks)
 - (ii) Should not be used in patients with CrCl < 30 mL/min
 - (3) Dosing
 - (a) Typically 200 to 400 mg qday ÷ 1 – 2 doses

- (4) Adverse reactions: rash, hypokalemia, diarrhea, N/V/D; rare effects include hepatotoxicity, ventricular tachycardia, torsades de pointes, neutropenia
 - (5) Drug interactions: CYP 3A4 substrate, inhibitor of intestinal P-glycoprotein
 - iv) Voriconazole(triazole)
 - (1) Also has activity against *Aspergillus* spp.
 - (2)
 - (3) Dosage
 - (a) IV: 6 mg/kg q12h x 2 doses, then 4 mg/kg q12h
 - (b) PO: 200 – 300 mg PO q12h if pt >40 kg; 100 – 150 mg PO q12h if pt ≤ 40 kg
 - (c) Do not use IV formulation if CrCl < 50 mL/min
 - (d) Adjust in mild to moderate hepatic dysfunction; do NOT use in severe hepatic dysfunction
 - (4) Adverse reactions: visual disturbances (dose related red/green color blindness), hallucinations, N/V/D, rash, rare side effects include pancreatitis, increased QTc interval, hepatitis
 - (5) Drug interactions: CYP2C19, CYP3A4, CYP2C9 substrate
 - v) Posaconazole (triazole)
 - (1) Also has activity against *Aspergillus* spp.
 - (2)
 - (3) Only FDA approved for candidiasis and prophylaxis for *Aspergillus* and *Candida* infections in severely immunocompromised
 - (4) Dosing
 - (a) Prophylaxis: 200 mg TID
 - (i) Should be taken with full meal or liquid nutritional supplement
 - (b) Treatment: 100 – 400 mg BID
 - (i) Higher doses for refractory *Candida* infections
 - (c) No dosage adjustments needed in renal dysfunction
 - (5) Adverse reactions: N/V/D, abdominal pain, rare effects include QTc interval prolongation and hepatic dysfunction
 - (6) Drug interactions: CYP 3A4 substrate
- 7) Nystatin
- a) MOA: binds to sterols in fungal cell membrane altering cell wall permeability in susceptible fungi → leakage of cell components → cell death
 - b) Typically used for oral thrush infections due to *Candida* spp.
 - c) Dosing
 - i) Swish and swallow 400,000 – 600,000 units every 6 hours
 - d) Adverse reactions include contact dermatitis, N/V/D, hypersensitivity reactions, and Stevens-Johnson syndrome

Pathogenesis and Epidemiology

- 1) Two types of fungal infections
 - a) Primary/ pathogenic fungal infections
 - i) Include histoplasmosis, coccidioidomycosis, cryptococcus, blastomycosis
 - ii) Cause infections both in healthy and immunocompromised individuals
 - (1) More severe infections in immunocompromised
 - b) Opportunistic fungal infections
 - i) Includes infections caused by *Candida albicans*, *Aspergillus* spp, *Candida glabrata*
 - ii) Only causes infections in immunocompromised individuals
- 2) Most infections acquired by accidental inhalation of conidia (formed by asexual reproduction of fungal spores)
- 3) Some fungal species are found worldwide while others are specific to a certain geographic location
- 4)
- 5) Additionally, alterations in normal flora can allow proliferation of some fungi (e.g. *Candida*), increasing likelihood of infection
- 6) Normally, fungal growth is inhibited by a number of mechanisms in the human host, mostly related to the immune system

Candidiasis and Candiduria

- 1) Epidemiology
 - a. *Candida albicans* is part of normal flora on skin, female genital tract, and GI tract
 - b. Other *Candida* spp. responsible for infection include *C. krusei*, *C. parapsilosis*, *C. tropicalis*, *C. glabrata*, and *C. lusitanae*
 - i. General susceptibilities for *Candida* infections

<i>Candida</i> spp.	Fluconazole	Itraconazole	Voriconazole	Flucytosine	Amphotericin B	Echinocandins
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<i>C. albicans</i>	S	S	S	S	S	S
<i>C. tropicalis</i>	S	S	S	S	S	S
<i>C. parapsilosis</i>	S	S	S	S	S	S (to I?)
<i>C. glabrata</i>	S-DD to R	S-DD to R	S to I	S	S to I	S
<i>C. krusei</i>	R	S-DD to R	S to I	I to R	S to I	S
<i>C. lusitaniae</i>	S	S	S	S	S to R	S

(S = susceptible, S-DD = susceptible-dose/delivery dependent, I – intermediate, R – resistant) (From CID 2004; 38: 164)

2) Pathophysiology

a.

b. Risk factors for invasive candidiasis

- Neutropenia
- Lymphoreticular or hematologic malignancies
- Extensive surgery
- Immunosuppressants
- Antineoplastic agents
- Burns
- Diabetes
- Central venous catheters
- Renal failure; hemodialysis
- Immunodeficiency diseases
- TPN
- Mechanical ventilation
- High-dose corticosteroids
- Receipt of multiple antibiotics
- Prior fungal colonization

3) Clinical Presentation

a. Candidiasis

i. Can be infection in single or multiple organs, esp. kidney, brain, myocardium, skin, eye, bone, joints

1. Multiple micro- and macro-abscesses are formed

ii. Distinct signs and symptoms

1. Acute onset of fever, tachycardia, tachypnea; occasionally chills or hypotension

2. Intermittent fevers and only ill when febrile

3. Progressive deterioration with or without fever

4. Hepatosplenic manifests only as fever when patient is neutropenic

iii. Diagnosis

1. Interpretation of positive cultures from skin, mouth, sputum, feces, urine hampered by *Candida* being a commensal organism

2. Rapid presumptive identification by formation of germ tube following incubation in serum (1 – 2 hours)

a. May be hampered by some *Candida* spp. not forming germ tube and giving false negative

3. Peptide nucleic acid fluorescence in situ hybridization (PNA FISH) has a targeted DNA probe that can identify *C. albicans* from blood culture bottles in less than 2 hours

b. Candiduria

i. Usually asymptomatic

ii. Will present as typical UTI

iii. Diagnosis

1. Recovery of 10,000 organisms/ visualization of yeast and pseudohyphae from fresh midstream urine or from bladder urine by single catheterization

4) Treatment

a. Candidemia/ Disseminated Candidiasis

i. Prophylaxis

1. Generally not recommend for non-neutropenic patients except for severely ill/high-risk patients (fluconazole 400 mg qday)

2. In neutropenic patients, minimum duration during period at risk for neutropenia (fluconazole 400 mg qday, itraconazole 2.5 mg/kg PO q12, OR micafungin 50 IV qday)

3. Amphotericin B preferred for prophylaxis in certain patients at risk because of liver transplantation

ii. Delays in empiric antifungal treatment greater than 12 hours after obtaining a positive blood sample is associated with greater hospital mortality

1. For suspected fungemia, amphotericin B preferred initially in order to cover species that may not be covered by fluconazole

2. Fluconazole may be considered if

a. *Candida* colonization at multiple sites

b. Multiple other risk factors

c. Absence of any other uncorrected causes of fever

iii. Removal of intravascular catheters and implantable devices (if possible)

iv. Non-neutropenic patients

1. Minimum duration of 2 weeks after last positive blood culture

2. Azoles and amphotericin B similarly effective
3.
 - a. Dose: 6 mg/kg/day PO or IV
4. Consider alternatives if
 - a. History of recent exposure to azoles
 - b. Broader antifungal spectrum is desired
 - c. Non-*albicans* species isolated
 - d. Unstable or immunocompromised patients
 - e. Alternatives include amphotericin B or echinocandin
5. *C. krusei* infections should be treated with
6. *C. glabrata* infections should consider one of the following regimens
 - a. Amphotericin B ≥ 0.7 mg/kg/day
 - b. Fluconazole 6 – 12 mg/kg/day
 - c. Echinocandin (?)
- v. Immunocompromised patients
 1. Same as for non-neutropenic patients
 2. Also should receive granulocyte colony-stimulating factor or granulocyte-monocyte colony-stimulating factor to accelerate recovery from neutropenia
 3. Prophylaxis has shown benefits in selected populations
 - a. Allogenic bone marrow transplantation: fluconazole 400 mg day from 0 – 75 days
 - b. Hematologic malignancy: Fluconazole 400 mg qday or Itraconazole 2.5 mg/kg BID
 - c. Hematopoietic stem cell transplant: Micafungin, caspofungin, posaconazole 200 mg q8h

- vi. Neutropenic patients
 - 1. Amphotericin B preferred in patient with suggested criteria
 - a. Fever 5 to 7 days unresponsive to antibiotics
 - b. Neutropenia > 7 days
 - c. No other obvious cause for fever
 - d. Progressive debilitation
 - e. Chronic adrenal corticosteroid therapy
 - f. Indwelling intravascular catheters
 - 2. Fluconazole and itraconazole have demonstrated equal efficacy as amphotericin B in hematologic malignancies
 - a. IV itraconazole should be used due to instability of PO formulations
 - 3. Caspofungin has also demonstrate success
 - 4. Choice of definitive therapy should rely on species identified and risk of resistance, toxicity and administration issues
 - b. Candiduria
 - i.
 - 1. Changing catheter → 20% eradication
 - 2. Removal of catheter → 40% eradication
 - ii. Asymptomatic candiduria does not require treatment
 - iii. Therapy should be used in symptomatic patients, neutropenic patients, renal allografts, scheduled urologic manipulation
 - 1.
 - 2.
 - 3. Amphotericin B IV 0.3 -1 mg/kg/day
- 5) Monitoring Parameters
- a. Antifungal therapy should not be stopped until resolution of signs and symptoms

Aspergillosis

- 1) Epidemiology
 - a. Three species responsible for most disease
 - i. *Aspergillus fumigates*
 - ii. *Aspergillus flavus*
 - iii. *Aspergillus niger*
 - b. Aspergillosis = Spectrum of diseases attributed to allergy, colonization, or tissue invasion caused by members of the *Aspergillus* genus
 - c. Ubiquitous mold that can grow well in a variety of areas
- 2) Pathophysiology
 - a. Conidia released by the fungus can remain suspended in the air for months
 - b. Acquired by inhalation of airborne conidia → alveoli or paranasal sinuses
 - c. Phagocytes are the primary host system against disease
 - i. Prolonged neutropenia = most predisposing factor for invasive aspergillosis
 - ii. Other predisposing factors include high dose/chronic glucocorticoid therapy, cytotoxic agents, recent/concurrent broad-spectrum antibiotics, chronic hepatitis, alcoholism, diabetes mellitus, leucopenia, leukemia, acute rejection of organ transplant
- 3) Clinical Presentation and Diagnosis
 - a. Lung is most common site of invasive disease
 - b. Patients will present with classic signs of pulmonary embolus:
 - c. In immunocompromised host, vascular invasion leads to thrombosis, infarction, necrosis of tissue, and dissemination to other tissues and organs in the body
 - i. If bone marrow function returns, cavitation of the pulmonary lesion occurs and infection spread halted
 - d. Diagnosis complicated by *Aspergillus* being a common commensal in GI tract and respiratory secretions
 - i. Repeated culture of *Aspergillus* AND microscopic examination provides most definitive diagnosis
 - ii. Proven aspergillosis requires histopathological documentation on infection; positive result of culture of a specimen from normally sterile site
 - iii. Probable aspergillosis requires fulfillment of criteria within 3 categories
 - 1. Host factors
 - 2. Clinical manifestations
 - 3. Microbiological evidence

- e. Several diagnostic tests that detect the presence of cell wall components specific to *Aspergillus* are commercially available
 - f. Radiological features (halo sign, air-crescent sign) also facilitate diagnosis
- 4) Treatment
- a. Pharmacologic
 - i. Invasive pulmonary aspergillosis/ chronic necrotizing pulmonary aspergillosis
 1.
 - a. Continue for until lesions are resolved in immunosuppressed patients after period of immunosuppression has passed
 2. Preferred:
 3. Alternatives
 - a. Amphotericin B
 - b. Caspofungin
 - c. Posaconazole
 - d. Itraconazole
 4. Additional therapies are aimed at reducing neutropenia/immunosuppression
 - a. Addition of granulocyte colony-stimulating factor of granulocyte-macrophage colony-stimulating factor if neutropenic and not receiving as a component of cancer chemotherapy
 - b. Withdrawal/dose reductions of corticosteroids
 - ii. Invasive sinus aspergillosis
 1. Similar treatment regimens to invasive pulmonary aspergillosis
 2. May consider using amphotericin B if etiological organism is not yet known to cover zygomycosis
 3. Often used in combination with surgical resection
 - iii. Allergic bronchopulmonary aspergillosis
 1. Combination of corticosteroid and itraconazole
 2. Alternative antifungals include PO voriconazole or posaconazole
 - iv. Prophylaxis against invasive aspergillosis
 1. Recommended in
 - a. Hematopoietic stem cell transplant recipients with graft versus host disease at high risk
 - b. Patients with acute myelogenous leukemia or myelodysplastic syndrome at high risk
 2. Recommended agents
 - a. Preferred:
 - b. Alternatives
 - i. Itraconazole (PO or IV)
 - ii. Micafungin 50 mg /day
 - b. Non-pharmacologic
 - i. Surgical resection of lesions can also help in controlling aspergillosis
 - ii. Indicated for the following

<ul style="list-style-type: none"> • Pulmonary lesion in proximity to great vessels/pericardium • Infection of skin and soft tissues • Sinusitis 	<ul style="list-style-type: none"> • Invasion of chest wall from contiguous pulmonary lesion • Endocarditis • Cerebral lesions 	<ul style="list-style-type: none"> • Persistent hemoptysis from a single cavitory lesion • Osteomyelitis (debridement)
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- 5) Monitoring Parameters
- a. For pulmonary aspergillosis, serial clinical evaluation of signs/symptoms as well as CTs at regular intervals

Blastomycosis

- 1) Epidemiology
 - a. Caused by *Blastomyces dermatitidis*
 - b.
- 2) Pathophysiology
 - a. In contrast with other fungal infections, colonization does not occur
 - b. Pulmonary infection occurs by the inhalation of conidia
- 3) Clinical Presentation and Diagnosis
 - a. Difficult to differentiate from bacterial or tubercular pneumonias
 - b. Acute pulmonary blastomycosis
 - i. May be asymptomatic or self-limited disease
 - ii. Fever; shaking chills; productive, purulent cough \pm hemoptysis
 - c. Sporadic (nonepidemic) pulmonary blastomycosis
 - i. Low-grade fever, night sweats, weight loss, and productive cough
 - ii. Similar presentation to tuberculosis
 - d. Chronic pulmonary blastomycosis
 - i. Fever, malaise, weight loss, night sweats, chest pain, productive cough
 - ii. Evidence of disseminated disease usually appears 1 to 3 years after primary pneumonia due to reactivation of disease
 - iii. Frequently disseminates to skin and bony skeleton, but may also go to prostate, oropharyngeal mucosa, abdominal viscera
 - e. Most successful method of diagnosis involves direct microscopic visualization of the yeast in sputum or other respiratory specimens
 - f. Histological examination and cultures should also be used but may take up to 30 days for isolation
- 4) Treatment
 - a. Acute pulmonary disease may be self-limited but some advocate still treating to prevent extrapulmonary dissemination
 - b. Pulmonary blastomycosis
 - i. Mild to moderate disease
 - 1.
 - ii. Moderately severe – severe
 1. Lipid formulation of amphotericin B 3 – 5 mg/kg/day/ Amphotericin B deoxycholate 0.7 – 1 mg/kg/day x 1 – 2 weeks (or until improvement)
 - a. Followed by itraconazole 200 mg TID x 3 days, then 200 mg BID for total of 6 -12 months
 - c. Disseminated extrapulmonary blastomycosis
 - i. Same regimens as pulmonary blastomycosis
 - ii. Moderately severe to severe disease should be treated for a minimum of 12 months as well as osteoarticular blastomycosis
 - d. Immunocompromised patient are treated with the same regimens but should remain of lifelong suppressive therapy unless immunosuppression can be reversed.
- 5) Monitoring Parameters
 - a. Serologic response does not always correlate with clinical improvement
 - b. Guidelines suggest measuring serum levels of itraconazole after 2 weeks to ensure adequate drug exposure

Coccidioidomycosis (aka Valley Fever)

- 1) Epidemiology
 - a. Caused by *Coccidioides immitis*
 - b.
- 2) Pathophysiology
 - a. Initial exposure = inhalation of conidia
 - b. Conidia go through several steps of maturation to endospores that invade tissues
 - c. Acute inflammatory response in tissues \rightarrow infiltration of mononuclear cells \rightarrow granuloma formation
- 3) Clinical Presentation and Diagnosis
 - a. Half to two-thirds of infections are subclinical and confer immunity to secondary infections for most individuals
 - b. Most common clinical presentation similar to community-acquired pneumonia 1-3 weeks after exposure
 - i. Chest pain, cough, fever, occasional hemoptysis
 - c. Fatigue and arthralgias can persist for months
 - d. 5 -10% turn into chronic pulmonary infections

- e. Small percentage of infections disseminate to other parts of the body, including lymph nodes, skin, bone, meninges, spleen, liver, and kidney
 - f. Diagnosis usually involves recovery of *C. immitis* from infected tissues or secretions
 - i. Also have positive skin test within 3 weeks of onset
 - ii. Antibody production can help follow disease course
- 4) Treatment
- a. Dependent on presentation
 - b. Usually no treatment is recommended for pulmonary-related infections, but patient's symptoms should be followed for up to 2 years to ensure resolution
 - i. Treatment may be preferred
 - 1. In immunocompromised to prevent larger sequel of events
 - 2. Diffuse pneumonias
 - 3. Symptomatic patients with pulmonary nodules
 - 4. Chronic progressive fibrocavitary pneumoniae
 - c. Disseminated disease more typical in immunocompromised individuals and needs to be treated
 - d. Agents
 - i. Amphotericin B is generally preferred
 - ii. Oral azoles (ketoconazole, fluconazole, and itraconazole) are often used as initial oral therapy or may be used in patients start on Ampho B once able to tolerate PO therapy
 - iii. Fluconazole should be used in meningitis due to greater CNS penetration
 - e.
 - f. Immunocompromised patients may need to remain on lifelong secondary prophylaxis (dependent on disease course and immune status)
- 5) Monitoring
- a. Pulmonary disease
 - i. Monitor with serial physical exam, CXray or CT, serial fungal sputum culture, CF antibodies in serum
 - b. Extrapulmonary disease
 - i. Serial physical exam, imaging if appropriate, CF antibodies
 - c. Meningeal disease
 - i. Same as pulmonary disease, plus CSF CF antibodies
 - d. Obtain CF Ab titers every 6 – 12 weeks to evaluate response
 - i. Will see lag in first 1 – 2 months

Cryptococcus

- 1) Epidemiology
 - a. Caused by *Cryptococcus neoformans*
 - b. Increased incidence in recent years due to increased number of immunocompromised individuals
- 2) Pathophysiology
 - a. Infection is acquired by inhalation of the organism
 - b. Polysaccharide capsule allows organisms to resist phagocytosis
 - i. Cell-mediated immunity plays large role in host defense
 - c. Disease can remain localized in the lungs or can disseminate to other tissues (like CNS or skin)
- 3) Clinical Presentation and Diagnosis
 - a. Primary cryptococcosis
 - i. Cough, rales, and shortness of breath
 - ii. Generally resolve spontaneously
 - b. Meningitis
 - i. Non-AIDS patients tend to present with HA, fever, N/V, mental status changes, neck stiffness, visual disturbances
 - ii. AIDS patients commonly present with fever and headache
 - iii. CSF opening pressure generally elevated
 - 1. CSF fluid shows pleocytosis, leukocytosis, decreased glucose, elevated protein
 - c. Diagnosis usually relies on clinical symptoms and positive cryptococcal antigen titer (>1:8)
- 4) Treatment
 - a. Dependent on immune status
 - b. Non-immunocompromised patients
 - i. Asymptomatic individuals do not require treatment, but should be monitored for progression to CNS infection
 - ii. Cryptococcemia not involving the CNS
 - 1. Mild to moderate symptoms: Fluconazole x 3-6 months
 - 2. Severe disease: Amphotericin B
 - 3. Itraconazole also serves as an alternative for treatment

- iii. CNS disease
 1. Amphotericin B IV and flucytosine $\times \geq 2$ weeks, followed by oral azole for total therapy of ≥ 8 weeks
 - a. Rapid sterilization of CNS within 2 weeks
 - b. Intrathecal amphotericin B discouraged except in very ill patients despite aggressive therapy
 2. Alternatives
 - a. Amphotericin B alone
 - b. Fluconazole \pm flucytosine
 - c. Itraconazole
 3. Suppressive therapy with fluconazole for 6 to 12 months is optional
- 5) Monitoring Parameters
 - a. Cryptococcal antigen titer can be followed during therapy to assess response to therapy

Histoplasmosis

- 1) Epidemiology
 - a. Caused by *Histoplasma capsulatum*
 - b. Endemic in Ohio and Mississippi River Valleys
- 2) Pathophysiology
 - a. Inhalation of conidia following disruption of soil containing organism
 - b. After 2 -3 days in lung, conidia ingested by macrophages
 - c. Infected macrophages migrate to other sites \rightarrow tissue granulomas
- 3) Clinical Presentation and Diagnosis
 - a. Acute pulmonary histoplasmosis
 - i. Acute, self-limited illness with flu-like pulmonary symptoms (fever, chills, HA, myalgia)
 - ii. Diffuse pulmonary histoplasmosis – diffuse radiographic involvement, hypoxia, ventilator support needed
 - b. Chronic pulmonary histoplasmosis
 - i. Opportunistic infections imposed on a preexisting structural abnormalities
 - ii. Chronic pulmonary symptoms and apical lung lesions \rightarrow inflammation, calcified granulomas, fibrosis
 - iii. Progress over period of years \rightarrow cavitation, bronchopleural fistulas, extension to the other lung, pulmonary insufficiency \rightarrow death
 - c. Disseminated histoplasmosis
 - i. “Subacute” form – focal destructive lesions in various organs, weight loss, weakness, fever, and malaise
 1. Untreated \rightarrow death in 10 months
 - ii. Most demonstrate mild, chronic form of disease
 1. Development of focal granulomatous lesions; bone marrow involvement \rightarrow thrombocytopenia, anemia, leukemia; fever; hepatosplenomegaly; GI ulceration
 - d. Diagnosis
 - i. Primary method is serologic evidence via complement fixation (CF), immunodiffusion (ID), or latex agglutination (LA)
 1. Fourfold rise in CF is indicative of re-infection
 - ii. Radioimmunoassay (RIA) measurement of IgG and IgM antibodies the most sensitive, but high number of false-positives in endemic areas
 - iii. HIV patients best diagnosis is through bone marrow biopsy and culture

- 4) Treatment
 - a. Treatment is unnecessary for mild-to-moderate acute pulmonary histoplasmosis
 - b. Moderately severe to severe acute pulmonary histoplasmosis
 - i. Lipid amphotericin B (1 – 2weeks) followed by itraconazole (10 -11 weeks) for a total of 12 weeks
 - ii. Consider adding methylprednisolone for patients the develop respiratory complications
 - c. Chronic pulmonary histoplasmosis
 - i. Itraconazole for at least 1 year, with some preferring 18 - 24 months of therapy
 - d. Disseminated histoplasmosis
 - i. Moderate to severe: Liposomal amphotericin B(1 -2 weeks) followed by itraconazole for a total of at least 12 months
 - ii. Mild to moderate: Itraconazole for a total of at least 12 months
 1. Consider monitoring blood levels
- 5) Monitoring Parameters
 - a. Resolution of radiologic, serologic, and microbiologic parameters
 - i. Antigen concentration decrease with therapy, increase with relapse
 - ii. Antigen concentration should be followed closely for relapse after treatment q3 – 6 months until negative
 - b. Improvement of signs and symptoms of infection

Resources

- 1) Carver PL (2008) Invasive Fungal Infections. Dipro JT, Talbert RL, Yee GC, et al. Pharmacotherapy: A Pathophysiological Approach (pp 1973 – 2002)
- 2) Practice Guidelines from the Infectious Diseases Society of America. Available at <http://idsociety.org/Content.aspx?id=9088>
- 3) Doctor Fungus. <http://www.doctorfungus.org/>