“There’s Fungus Among Us”
2008
Kara L. Birrer, Pharm.D.
Clinical Pharmacist, Trauma/General Surgery
Orlando Regional Medical Center

Objectives
• Describe the epidemiology
• Identify risk factors for infection
• Review common fungal infections
• Discuss special high-risk populations
• Differentiate between the various antifungal agents

Patient Case - DB
• 62yom presents for Ex-lap, colonoscopy, rigid anoscopy, LOA, small bowel resection
• POD# 10 – sepsis, perc-drain RLQ
• Empiric antibiotics:
  – Zosyn 4.5g IV q6
  – Vancomycin 750mg IV q12
  – Fluconazole 800mg IV x1, then 400mg IV q24

Epidemiology
• Fungal species account for up to 25% of all healthcare-associated blood infections
• Candida spp. account for 8-15% of all bloodstream infections
• C. albicans accounts for 40-60% of the fungal infections
• Aspergillus spp. are the 2nd most common cause of fungal infections in cancer patients

Risk Factors

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<th>Immune Defects</th>
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**Diagnosis**

- Culture – single best tool
- Smear of body fluids and/or tissues
- Skin test – coccidioidin antigen
- Histopathology or special stains of biopsy specimens
- Serology – only moderately helpful

**Types of Invasive Fungal Infections**

- Yeasts
  - Candida spp.
  - Cryptococcus neoformans
- Aspergillus spp.
- Fusarium spp.
- Mucor spp.
- Other fungi

**Emerging Fungal Pathogens**

- Yeast
  - Candida spp.
  - Cryptococcus spp.
  - Trichosporon spp.
- Mold
  - Dimorphic
  - Histoplasmosis
  - Blastomycosis
  - Coccidioidomycosis
- Zygomycetes
  - Septate
  - Mucor spp.
  - Others
- Phialophoromycetes
  - Black mold
  - Dematiaceous
  - Mucor spp.
- Hyalohyphomycetes
  - Aspergillus spp.
  - Fusarium spp.
  - Paecilomyces spp.

**Yeast – Candida spp.**

- Most common fungal pathogen
- Opportunistic pathogens
- 4th most common nosocomial bloodstream infection
- Portals of entry:
  - Gastrointestinal tract
  - Central venous catheters
- C. albicans versus non-C. albicans

**Yeast – Candida spp.**

- Most common types of infections
  - Mucosal candidiasis (thrush)
  - Candida esophagitis
  - Candida pneumonia
  - Candidemia
    - 25-50% of nosocomial candidiasis
    - 20% associated with central venous catheters

**Yeast – Candida spp.**

- C. albicans = 80-90% of oropharyngeal colonization
- Also common fecal normal flora
- C. albicans & C. glabrata account for 70% of all Candida infections
- Drug of Choice (DOC): Candida spp. dependant


www.asm.org/Division/c/fungi.htm
Fungal Infections – Kara Birrer, PharmD

Yeast – Candida spp.

- At ORMC (July 2006 – June 2007 Sterile Sites):
  - 52% C. albicans
  - 48% C. non-albicans
- Other Candida spp concerns:
  - Biofilm formation on indwelling catheters
  - C. albicans resistance to fluconazole

Yeast – Candida spp. Treatment

<table>
<thead>
<tr>
<th>Candida spp</th>
<th>C. krusei</th>
<th>C. glabrata</th>
<th>C. dubliniensis</th>
<th>C. guilliermondii</th>
<th>C. lusitaniae</th>
<th>C. parapsilosis</th>
<th>C. tropicalis</th>
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<td>Echinocandin</td>
<td>Fluconazole – 1st infection</td>
<td>Echinocandin</td>
<td>Fluconazole – 2nd infection</td>
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Yeast – Cryptococcus spp.

- Cryptococcus neoformans
- Source – soil contamination with pigeon droppings
- Portal of entry – inhalation
- Primarily infects the central nervous system – meningoencephalitis

Patient Case - DB

- RLQ Abscess Cx: (results available POD#15)
  - Candida (Torulopsis) glabrata
  - Candida tropicalis
- Is the fluconazole enough? Concerns?
  - POD# 15 –
    - Discontinue fluconazole
    - Caspofungin 70mg IV x 1, then 50mg IV daily

Yeast – Cryptococcus spp.

- Nearly always associated with an immunocompromised state
  - 6-10% of HIV+ patients in the US will develop
- Treatment:
  - Amphotericin B + Flucytosine x 2 weeks
  - Followed by Fluconazole 400mg po daily x 6 weeks
**Aspergillus spp.**

- Aspergillus spp. are widespread in the environment
- Aspergillus spp. are moulds
- Air = primary route of transmission in hospitals
- *Aspergillus fumigatus* – most frequent pathogen

**Aspergillus spp. Treatment**

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<th>High Risk</th>
<th>Low Risk</th>
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<td>Neutropenia</td>
<td>Solid organ transplant</td>
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<tr>
<td>Febrile</td>
<td>Malignancy</td>
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<tr>
<td>Lung infiltrates</td>
<td>Chronic granulomatous disease</td>
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<tr>
<td>Isolation of Aspergillus in sputum cultures</td>
<td>HIV (+)</td>
</tr>
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? Start Treatment:
- **High Risk** → start empiric therapy
- **Low Risk** → await biopsy results

**Fusarium spp.**

- Ubiquitous fungus found in the soil
- 2nd most common cause of invasive mycotic infections
- Can also superficial skin infections
- May be confused with *Aspergillus spp* in the lab

**Fusarium spp.**

- Diagnosis –
  - Easily recovered from blood cultures
  - 60-70% of patients with fusariosis will have (+) blood cultures
- Treatment –
  - Frequently resistant to amphotericin B, azoles, & fluconazole
  - DOC: Voriconazole (VFend®)
  - Alternate: Posaconazole (oral only)
Mucor spp.

- Included in the zygomycosis group of infections
- Environmental mold
- Transmission through inhalation or ingestion of spores
- Risk Factors:
  - DKA
  - Immunosuppression
  - Others

Treatment:
- Early diagnosis is key
- Surgical debridement or resection if possible
- Antifungal therapy: Voriconazole (VFend®)
- Reverse immunosuppression if possible

Risk Factors:
- DKA
- Immunosuppression
- Others

References:
- http://www.doctorfungus.org/thefungi/mucor.htm
- www.sci.muni.cz/mikrob/Miniatlas/muc.htm

Treatment Principles

- Special population considerations
- Source control
- Antifungal class review
  - Mechanism of action
  - Spectrum of activity
  - Dosing
  - Adverse reactions
- Antifungal resistance issues
- Duration of therapy

Special Populations

- Burns:
  - 1st line treatment: Surgical debridement
  - Adjuvant systemic antifungal therapy
- Critically Ill Patients –
  - Hypothermia/Hyperthermia
  - Isolation of yeast/mold from any culture with risk factors
- Solid Organ Transplant
  - Time since transplant
  - Type of transplant dictates risk

Treatment

- Surgical debridement
- Removal of invasive devices (if possible)
  - Central venous lines (new stick)
  - Drains, pumps, etc
- Antifungal therapy
  - Polyenes/Amphotericin B Products
  - Fluconazole
  - Azoles
  - Echinocandins

Sites of Action

- Antifungal therapy
  - Polyenes/Amphotericin B Products
  - Fluconazole
  - Azoles
  - Echinocandins

References:
**Amphotericin B (Polyenes)**

- **MOA:** Bind ergosterol in cell membrane causing disruption and cell death
- **Lipophilic antifungal**
- **Spectrum of Activity:**
  - Candida spp.
  - Aspergillus spp.
  - Cryptococcus spp.
  - Others

- **Dose:**
  - 0.7-1.5 mg/kg IV daily
  - 3-5 mg/kg IV daily
  - 3-7 mg/kg IV daily

- **Infusion-related reactions:++
- Nephrotoxicity:+++ **
- CSF Penetration:+++++**

- **Adverse Reactions:**
  - Infusion-related reactions
  - Nephrotoxicity
  - LFT abnormalities

- **Drug Interactions:**
  - Digoxin (**↑** levels)
  - Tacrolimus (**↑** toxicity)
  - Cyclosporine (**↑** toxicity)

**Flucytosine**

- **MOA:** converted to 5-fluorouracil in the fungal cell and then disrupts RNA & protein synthesis
- **Spectrum of Activity:**
  - Candida spp.
  - Cryptococcus spp.

- **Rapidly develops resistance**

- **Dose:** 100-150 mg/kg/day PO divided q6
- **Pharmacokinetics:**
  - 75-90% bioavailable
  - CSF levels = 60-100% of blood levels
  - 75-90% excreted unchanged in urine
- **Adverse reactions:**
  - Myelosuppression (22%)
  - Renal insufficiency
  - Nausea/Vomiting/Diarrhea

**Azole Anti-fungals**

- **MOA:** inhibition of CYP450-dependant inosterol 14-α-demethylase → inhibition of ergosterol synthesis
- **Specific Agents:**
  - Fluconazole (Diflucan®)
  - Itraconazole (Sporonox®) – oral only
  - Voriconazole (VFend®)
  - Posaconazole (Noxafil®) – oral only
**Fluconazole (Diflucan®)**

- **Spectrum of Activity:**
  - Candida spp (except C. krusei)
  - Cryptococcus neoformans
  - Histoplasma capsulatum
  - Blastomyces dermatitidis
  - Others
- **Good empiric anti-fungal choice**
- **Dose:**
  - 800mg IV on Day #1, then 400mg IV/PO q24
  - Adjust for renal dysfunction


**Fluconazole (Diflucan®)**

- >90% oral bioavailability
- **Drug Interactions:**
  - Amiodarone
  - Warfarin (↑ INR)
  - Phenytoin (↓ levels)
  - Glyburide/Glipizide (mask hypoglycemia)
- **Adverse reactions:**
  - Rash (~10%)
  - Increased LFTs (~10%)


**Voriconazole (Vfend®)**

- **Spectrum of Activity:**
  - Aspergillus spp.
  - Candida spp.
  - Fusarium spp.
  - Histoplasma capsulatum
  - Blastomyces dermatitidis
  - Others
- **DOC:** Aspergillus spp.
- **Dose:**
  - IV/PO: 6 mg/kg q12 x 2 doses, then 4mg/kg q12


**Voriconazole (Vfend®)**

- **IV excipient accumulates in renal failure – use for loading dose only**
- **Drug Interactions:**
  - Amiodarone
  - Warfarin (↑ INR)
  - Digoxin (↑ levels)
  - Glyburide/Glipizide (mask hypoglycemia)
- **Adverse Reactions:**
  - Transient visual disturbances (24%)
  - Rash (6%)
  - Increased LFTs (4-20%)


**Itraconazole (Sporonox®)**

- **Spectrum of Activity:**
  - Candida spp.
  - Aspergillus spp.
  - Histoplasma capsulatum
  - Blastomyces dermatitidis
  - Others
- **Dosage:**
  - Serious infections: 200mg po q12
  - Oral Candida infections: 200mg po daily x 14 days


**Itraconazole (Sporonox®)**

- **Bioavailability:**
  - Capsules – increased with food
  - Solution – must take on empty stomach
- **Drug Interactions:**
  - Antacids (↓ absorption of itraconazole)
  - Digoxin (↑ levels)
- **Adverse Reactions:**
  - Nausea, vomiting, diarrhea
  - Hypertension, ↓ K, edema
**Posaconazole (Noxafil®)**

- **Spectrum of Activity:**
  - Candida spp.
  - Aspergillus spp.
  - Fusarium spp.
  - Cryptococcus neoformans
  - Others

- **Dose:**
  - 400mg po q12
  - Ophthalmic: 10mg/0.1mL to affected eye q1h (+ PO)


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**Echinocandins**

- **Synthetic, lipopeptide antifungals derived from Zalernon arboricola**
- **MOA:** non-competitive inhibition of the synthesis of the enzyme glucan synthase
- **Specific Agents:**
  - Caspofungin (Cancidas®)
  - Micafungin (Mycamine®)
  - Anidulafungin (Eraxis®)


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**Azole Antifungal Summary**

- Fluconazole – 1st line for *Candida albicans*
- Itraconazole – almost no place in therapy
- Voriconazole – DOC for *Aspergillus spp*
- Posaconazole – place in therapy to be determined


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**Echinocandins**

- **Advantages:**
  - No adjustment for renal dysfunction
  - Well tolerated
  - Effective against Candida biofilms


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**Azole Antifungal Summary**

- **Spectrum of Activity**:
  - *Candida albicans*
  - *C. glabrata*
  - *C. krusei*
  - *C. lusitaniae*
  - *C. tropicalis*
  - *C. guilliermondii*
  - *Aspergillus spp.*


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**Echinocandins**

- **Indications**:
  - Neutropenic fever
  - Candidemia
  - Intra-abdominal abscess
  - Candida peritonitis
  - Plural infections
  - Esophageal candidiasis
  - Refractory invasive Aspergillosis
  - Neutropenic fever


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**Echinocandins**

- **Dosage**:
  - Caspofungin: 70mg IV x 1, then 50mg IV q24
  - Micafungin: 100mg IV daily
  - Anidulafungin: 200mg IV daily, then 100mg IV daily

Fungal Infections – Kara Birrer, PharmD

**Caspofungin**
- Hepatic metabolism
- Fecal elimination

**Micafungin**
- Hepatic metabolism
- Fecal elimination
- Spontaneous degradation
- 30% Fecal elimination

**Anidulafungin**
- Hepatic metabolism
- Fecal elimination
- Spontaneous degradation
- 30% Fecal elimination

**ADRs**
- Phlebitis/thrombophlebitis
- T. LEs
- Possible histamine-mediated symptoms
- Infection-site reactions
- T. LEs
- Possible histamine-mediated symptoms
- Infusion-site reactions
- T. LEs
- Possible histamine-mediated symptoms
- Diarrhea
- Possible histamine-mediated symptoms

**Drug Interactions**
- Phenobarbital
- Tacrolimus
- Cyclosporine
- Nifedipine
- Sirolimus
- Cyclosporine

**Special Notes**
- Close- adjusting for hepatic failure
- Made w/ 20% alcohol – disulfiram-like reactions

**Anti-Fungal Resistance**
- Initially described in HIV population
- Mechanisms:
  - Clinical failure – the drug cannot eradicate the fungi
  - Cellular resistance (decreased response)
    - Intrinsic – fungi is always resistant
    - Acquired – fungi is initially susceptible & develops resistance
- Management:
  - Speciation of Candida isolates
  - Removal of invasive devices (biofilm source)
  - Aggressive dosing or alternative agents

**Duration of Therapy**
- **Candidemia**
  - Repeat blood cultures 3-5 days into therapy
  - Continue systemic anti-fungal agent for 14 days **AFTER** negative blood cultures
- **Candiduria**
  - Change catheter or remove if possible
  - If candiduria persists after catheter change - treat 7-14 days
- **Other fungal infections**
  - Duration based on clinical judgment or wound status
  - (Or ID consult recommendations)

**Brief Review**
- Fungi account for 25% of all healthcare-related infections
- Multiple risk factors – including ICU stay, broad-spectrum antibiotics, CVLs, steroids, & diabetes
- Most common organisms: *Candida spp.*
- Burn, critically ill, & transplant patients at highest risk
- Choose antifungal agent based on most likely organism