Invasive fungal infections: What to do if there’s a fungus among us
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Infectious Diseases Pharmacotherapy Fellow

Objectives (Pharmacists)
- List three important interactions and monitoring parameters for a given antifungal agent
- Identify two scenarios where empiric antifungal therapy is warranted
- Identify drug(s) of choice for at least one invasive fungal infection

Objectives (Technicians)
- Describe the importance of utilizing an antifungal stewardship program
- State the most commonly used antifungal agents in the hospital setting
- When given a specific pathogen, list the most common antifungal agent(s) used to treat the infection.

Commercially Available Azoles
- Fluconazole
- Voriconazole
- Itraconazole
- Posaconazole
- Isavuconazole

Azoles: Mechanism of action
- Inhibit the synthesis of ergosterol, a vital component of the fungal cell membrane

Fluconazole: Dosing and Administration
- Available as IV or PO tablets
- Dosing ranges from 400-800mg (or 6-12mg/kg) once daily depending on indication and immune status
  - Lower doses are used for candiduria or esophageal candidiasis
- Doses should be reduced by 50% in patients on hemodialysis, CRRT, or with CrCl ≤50
Fluconazole: Spectrum

- Fluconazole has reliable activity against most types of Candida spp.
  - *C. glabrata* has variable resistance to all azoles, may require aggressive dosing
  - *C. krusei* is intrinsically resistant to fluconazole
- Also has activity against Cryptococcus spp.

Fluconazole: Susceptible-Dose Dependent

- *Candida* spp. isolates with MICs of 16 or 32 are considered susceptible dose-dependent
  - Fluconazole doses of 400-800 mg/day should be used for these isolates
- Fluconazole AUC/MIC ratios of 25 mg·hr/L have been associated with efficacy
- In healthy 70 kg patients doses of 400 mg correlate with an AUC of ~400 mg·hr/L

Fluconazole: Interactions and ADEs

<table>
<thead>
<tr>
<th>Inhibits</th>
<th>CYP 2C9 (strong), 2C19 (strong), 3A4 (moderate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phenytoin</td>
<td>Phenytoin</td>
</tr>
<tr>
<td>Warfarin</td>
<td>Warfarin</td>
</tr>
<tr>
<td>Dofetilide</td>
<td>Dofetilide</td>
</tr>
<tr>
<td>Sirolimus</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>Citalopram</td>
<td>Citalopram</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Substrate</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rifampin</td>
<td>May decrease serum concentrations</td>
</tr>
</tbody>
</table>

| ADEs    | Headache | N/V/D | LFT abnormalities | Additive QTc prolongation (especially in patients receiving >400mg/day) |

Voriconazole: Spectrum of Activity

- Voriconazole has reliable activity against Aspergillus spp., Candida spp., as well as Fusarium spp.
  - Some studies report variable in vitro susceptibility of C. glabrata

Voriconazole: Dosing and Administration

- Available as IV and PO tablets
- IV dosing is weight based
  - 6mg/kg q12h for 2 doses, then 4mg/kg q12h
- PO dosing is standardized
  - 100mg q12h for patients <40 kg
  - 200mg q12h for patients ≥40 kg
- Dosing should be reduced by 50% in patients with mild to moderate liver dysfunction (Childs-Pugh class A or B)
  - In severe liver dysfunction this should only be used if the benefits outweigh the risk

Voriconazole and Renal Dysfunction

- Voriconazole is not renally cleared
  - No dosage adjustment for renal dysfunction
- Per package insert:
  - Avoid IV administration in patients with a creatinine clearance < 50 mL/min
- Why is this?
Cyclodextrin toxicity

- Cyclodextrin is a solvent agent used in the formulation of IV voriconazole
- Pharmacokinetic data have shown that its clearance is directly correlated with renal function
  - Accumulates even in patients on HD, CRRT and PD
- Data from animal studies suggest accumulation of cyclodextrin can lead to renal and hepatic dysfunction

IV Voriconazole in Renal Impairment

<table>
<thead>
<tr>
<th>Population (n=128)</th>
<th>Retrospective review of patients receiving fluconazole (n=54), caspofungin (n=55) or voriconazole (n=19) who had CrCl &lt;50 at the time of administration.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of AKI</td>
<td>Rates of AKI were higher in the fluconazole group than for the caspofungin group (p=0.01) however rates of AKI in the voriconazole group was not significantly different</td>
</tr>
<tr>
<td>Logistic Regression analysis of causes related to AKI</td>
<td>In a multivariate logistic regression identified only infecting organism as associated with development of AKI</td>
</tr>
<tr>
<td>Conclusions</td>
<td>In multivariate analysis of patients with invasive fungal infections and renal dysfunction at baseline, IV voriconazole was not associated with increased risk of AKI</td>
</tr>
</tbody>
</table>

Voriconazole: Interactions and ADEs

<table>
<thead>
<tr>
<th>Inhibits</th>
<th>CYP 3A4 (strong), 2C9 (strong), 2C19 (strong)</th>
</tr>
</thead>
</table>
|          | • Cyclosporine (Reduce dose by 50%)  
|          | • Statins (switch to non-CYP metabolized)  
|          | • Sirolimus (Reduce dose by 90%)  
|          | • Phenothiazin (Reduce dose by 50%, increase voriconazole dose to 40mg PO or 5mg/kg IV)  
|          | • Tacrolimus (Reduce dose by 66%)  
|          | • Warfarin (monitor, may require decrease in dose) |
| Substrate | CYP 3A4, 2C9, 2C19 |
| ADEs     | Visual disturbances  
|          | Increased LFTs  
|          | Increased SCR  
|          | QTc prolongation |

Voriconazole: Dosing

**CAUTION**

Non-Linear Pharmacokinetics

<table>
<thead>
<tr>
<th>Formulation</th>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral: Solution</td>
<td>200 mg Q8h until disease stabilization</td>
<td>400 mg BID</td>
</tr>
<tr>
<td>Oral: Delayed Release Tablets</td>
<td>300 mg BID x2 doses</td>
<td>300 mg daily</td>
</tr>
<tr>
<td>Intravenous</td>
<td>300 mg BID x2 doses</td>
<td>300 mg daily</td>
</tr>
</tbody>
</table>

Posaconazole: Dosing and Administration

- Now available as oral solution, tablet and IV formulation
- Dosing differs based on indication and formulation used
- Delayed release tablets and IV solution are currently only FDA approved for fungal prophylaxis
**Posaconazole: Oral Solution**
- Poor absorption and bioavailability
  - Must administer with high fat meal or low pH drink
  - Avoid with administration of antacids
    - Decreases AUC by 32-39%
  - Saturable absorption
    - Max dose 800 mg/day divided 2-4x
  - Absorption decreased in patients with diarrhea and mucositis

**Posaconazole: Delayed Release Tablet**
- Good absorption independent of administration with food
- Less affected by antacids
- 200 mg dose results in average concentrations of 1300 ng/mL
  - Healthy patients
  - Substantial accumulation by day 14
  - AUC increased 3x from day 1 to day 14

**Posaconazole: IV Formulation**
- Increased exposure relative to tablets on day 1
- Cyclodextrin used for solubility
  - Per package insert:
    - Should be avoided in patients with CrCl < 50 ml/min unless the benefit outweighs the risk

**Posaconazole: Spectrum of Activity**
- Posaconazole is active against all clinically relevant yeasts and molds
  - In vitro studies suggest variable resistance with *C. glabrata*

**Posaconazole: Interactions and ADEs**
- Inhibits CYP 3A4 (strong)
  - A number of drugs are contraindicated with posaconazole including:
    - Simvastatin
    - Sirolimus
    - 3A4 substrates that may prolong QTc

<table>
<thead>
<tr>
<th>Substrate</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADEs</td>
<td>N/V/D, Fever, Headache, Hypokalemia, Increased LFTs, QTc prolongation, Thrombophlebitis (IV only), Infusion reactions (IV only)</td>
</tr>
</tbody>
</table>
The new kid on the block: Isavuconazole

- Isavuconazole is a newly approved azole antifungal with broad activity against fungi and molds
- Administered as the prodrug isavuconazonium sulfa
  - Rapidly cleaved to active drug via plasma esterases
- FDA approved for the treatment of Aspergillosis and Mucormycosis

Isavuconazole: Dosing and Administration

- Available as IV solution and oral capsules
  - Highly bioavailable
- No dose adjustments for renal dysfunction or Childs-Pugh class A or B liver dysfunction

<table>
<thead>
<tr>
<th>Indication</th>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of Aspergillosis</td>
<td>372 mg isavuconazone sulfate every 8 hours x 6 doses</td>
<td>372 mg isavuconazone sulfate daily (12-24h post maintenance doses)</td>
</tr>
<tr>
<td>Mucormycosis</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Isavuconazole: Spectrum of Activity

- MIC breakpoints for isavuconazole have not yet been established
- Based on in vitro data, isavuconazole appears to have activity against most clinically relevant yeasts and molds
  - Active against Mucorales, variable based on species
  - Limited activity against Fusarium spp.

Isavuconazole: Interactions and ADEs

- Inhibits CYP 3A4 (moderate)
- Induces CYP 2B6
  - Sirolimus
  - Midazolam
  - Tacrolimus
  - 2B6 Substrates
  - Bupropion
  - Contraindicated with strong inhibitors or inducers

ADEs
- N/V/D
- Headaches
- Hypokalemia
- Abdominal pain
- Increased LFTs

Echinocandins: Mechanism of Action

- Inhibit the formation of β-(1,3)-glucan, an important part of the fungal cell wall

Echinocandins: Spectrum of Activity

- All echinocandins have similar spectrums of activity
  - Active against Candida spp., including C. glabrata and C. krusei
    - Echinocandins have variable in vitro activity against C. parapsilosis
  - Limited activity against Aspergillus spp.
    - Fungistatic
    - May be appropriate in salvage therapy
**Echinocandins: Dosing and Administration**

- All commercially available echinocandins are IV only

<table>
<thead>
<tr>
<th>Drug</th>
<th>Loading Dose</th>
<th>Maintenance Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspofungin</td>
<td>70mg x 1</td>
<td>50mg daily</td>
</tr>
<tr>
<td>Micafungin</td>
<td>None</td>
<td>100mg daily</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>200mg x1</td>
<td>100mg daily</td>
</tr>
</tbody>
</table>

**Echinocandins: Interactions and ADEs**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate</td>
<td>Micafungin: CYP 3A4 (minor)</td>
<td>Micafungin may increase levels of sirolimus, usually is not clinically relevant, however monitoring is warranted</td>
</tr>
<tr>
<td>ADEs</td>
<td>LFT elevations</td>
<td>Fever</td>
</tr>
</tbody>
</table>

**Amphotericin: Mechanism of Action**

- Amphotericin has activity against most clinically relevant yeasts and molds
  - Variable activity against:
    - *Fusarium spp.*
    - *Zygomycetes*
  - Important gaps in coverage include:
    - *Aspergillus terreus*
    - *Candida lusitaniae*

**Amphotericin: Spectrum of Activity**

- Amphotericin B is only commercially available as IV formulation
- Dosing depends on formulations
  - Amphotericin B deoxycholate: 0.6-1.5mg/kg
  - Lipid formulations: generally 3-5 mg/kg
  - Liposomal amphotericin B has been studied in doses up to 12 mg/kg

**Amphotericin: Interaction and ADEs**

<table>
<thead>
<tr>
<th>Inhibits</th>
<th>N/A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Substrate</td>
<td>N/A</td>
</tr>
<tr>
<td>Avoid with concurrent use of</td>
<td>Other nephrotoxic agents</td>
</tr>
<tr>
<td>ADEs</td>
<td>Renal dysfunction</td>
</tr>
</tbody>
</table>

- Lipid formulations have been shown to be equally efficacious for most indications
- Lower rates of side effects- especially nephrotoxicity
  - Rates of infusion reactions similar!
Antifungal Stewardship

- Unnecessary antifungal therapy can lead to increased costs, ADEs and increased resistance
- Antifungal stewardship has been shown to decrease the number of days of inappropriate and unnecessary antifungals
  - Single center in England showed savings of > $280,000 (~£180,000) in first year

Patient Case #1

- IC is a 44 y/o male, transferred from OSH for abdominal pain and found to have necrotic bowel 2/2 ingestion of cocaine
  - Partial colectomy performed on admit
  - SCr on admit is 11, requiring CRRT
- VS (ICU day 6):
  - HR 115
  - RR 24
  - Tmax 101.5°F
- Current antimicrobials:
  - Ceftazidime
  - Metronidazole
  - Vancomycin

Empiric Antifungal Therapy

- Low hanging fruit
  - Febrile neutropenic patients with persistent fever after 72-96 hours of broad spectrum antibiotics
- What about non-neutropenic patients?

Candida Risk Score

<table>
<thead>
<tr>
<th>Population (n=1,669)</th>
<th>Multicenter prospective observational cohort study of adult patients admitted to the ICU for at least 7 days.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intervention Data</td>
<td>Weekly samples were taken to determine colonization of the gastrointestinal, genitourinary or respiratory tracts</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient (d)</th>
<th>Standard Error</th>
<th>Wald χ²</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multifocal Candida species colonization</td>
<td>1.522</td>
<td>0.379</td>
<td>9.383</td>
<td>.002</td>
</tr>
<tr>
<td>Severity on ICU admission</td>
<td>-0.277</td>
<td>0.408</td>
<td>0.140</td>
<td>.699</td>
</tr>
<tr>
<td>Severity acute</td>
<td>0.876</td>
<td>0.599</td>
<td>2.244</td>
<td>.136</td>
</tr>
<tr>
<td>Total predicted mortality</td>
<td>-0.009</td>
<td>0.008</td>
<td>0.000</td>
<td>.999</td>
</tr>
<tr>
<td>Candida</td>
<td>-0.156</td>
<td>0.045</td>
<td>14.542</td>
<td>.000</td>
</tr>
</tbody>
</table>

Note: Intensive care unit.
Candida score = 2.03 x (total predicted mortality) + 2.03 x (sepsis) + 5.12 (multifocal Candida species colonization) + 2.51 (sepsis score) Candida case rounds = 5 x (total predicted mortality) + 5 x (sepsis score) + (multifocal Candida species colonization) + 3 x (sepsis score). All variables coded as follows: 0: present, 1.
Candida Risk Score

- Determined that a score >2.5 can help to select for patients who may benefit from early antifungal therapy

Validation of the Candida Risk Score

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients admitted to ICU and exhibited signs of hospital-acquired severe sepsis or septic shock (n=94)</th>
<th>Admitted to ICU for sepsis (n=95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rate of candidiasis</td>
<td>5.3%</td>
<td>16.8%</td>
</tr>
<tr>
<td>Cutoff used</td>
<td>&gt;3</td>
<td>&gt;3</td>
</tr>
<tr>
<td>PPV</td>
<td>23.8%</td>
<td>27.3%</td>
</tr>
<tr>
<td>NPV</td>
<td>100%</td>
<td>98.7%</td>
</tr>
</tbody>
</table>

- Very good negative predictor
- Candida risk score can help to identify patients at risk for invasive candidiasis but should be considered in the clinical context of the patient

Patient Case

- What is IC’s Candida Score?
  A. 1
  B. 2
  C. 3
  D. 4

Patient Case #1

- IC is a 44 y/o male, transferred from OSH for abdominal pain and found to have necrotic bowel 2/2 ingestion of cocaine
  - Partial colectomy performed on admission to BIDMC
  - SCr on admission is 11, requiring CRRT
  - VS (ICU day 6):
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- Patient has had low blood pressures since admission, currently being maintained on norepinephrine drip
- Current antimicrobials:
  - Ceftazidime
  - Metronidazole
  - Vancomycin

Patient Case #1

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  - Metronidazole
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(1,3)-β-D-glucan

- Multiple studies have shown widely variable data on the usefulness of this clinical test
- Detects part of fungal cell wall in Candida spp. and Aspergillus spp.
- Large multicenter trial with 163 patients with proven or probable IFI showed the following:
(1,3)-β-D-glucan - False positives

- Many factors have been proposed to cause false positive (1,3)-β-D-glucan tests
  - *Pneumocystis jiroveci* pneumonia (PJP)
  - Bacteremia
  - IVIg
  - Certain antibiotics
  - Hemodialysis with cellulose membranes
  - Certain wound care items

Candidemia: Risk Factors

- Central venous catheters
- Prolonged length of stay
- Renal failure
- Hemodialysis
- Parenteral nutrition
- Transplantation
- Immunosuppression
- Surgery
  - Especially abdominal surgery
- Broad spectrum antibiotics

Patient Case #1

- IC has a Candida Risk Score of 3 and multiple risk factors that have been associated with Candida infection in ICU patients
- Beta-D-Glucan is still pending
- Would you start antifungal therapy?
- What agent would you choose?

Diagnosis

- Yeast is a very uncommon cause of respiratory infection
- Yeast is a common urinary colonizer
  - First line treatment- take out urinary catheter
- No matter the quantity, yeast from blood is not a contaminant

Candidemia: Treatment

<table>
<thead>
<tr>
<th>Host/disease factors</th>
<th>Recommended therapy</th>
</tr>
</thead>
</table>
| Immune competent AND  
  azole naïve within 30 days AND  
  hemodynamically stable AND  
  no recent history of *C. krusei* OR *C. glabrata* | Fluconazole 800 mg x 1, then 400 mg IV daily |
| Immunocompromised OR  
  azole experienced within 30 days OR  
  hemodynamically unstable OR  
  recent history of *C. krusei* OR *C. glabrata* | Micafungin 100 mg IV Daily OR  
  Liposomal Amphotericin B 3mg/kg daily OR  
  Voriconazole 6mg/kg q12h, then 3mg/kg q12h |

Patient Case

- What agent would be the most appropriate to start in IC?
  A. No therapy at this time
  B. Fluconazole 800mg x1 then 400mg daily
  C. Caspofungin 70mg x1 then 50mg daily
  D. Liposomal amphotericin B 3mg/kg daily
Patient case #1

- IC was started on fluconazole 400mg daily (with an 800mg load)
- On day 14 yeast from blood culture is speciated to C. glabrata
- Still no susceptibilities
- How would this change your current management of this patient?

Candidemia: Other Considerations

- Endocarditis should be a concern in all patients with candidemia
  - TTE or TEE should be obtained in patients with clinical suspicion for endocarditis
- Central lines should be removed, if possible, as Candida spp. may form biofilms
- All patients should receive an ophthalmology exam at least once

Fluconazole vs. Anidulafungin for Invasive Candidemia

<table>
<thead>
<tr>
<th>Population</th>
<th>Patients &gt;15 y/o with Candida spp recovered from a normally sterile site within 96 hours of enrollment and had signs/symptoms of infection or radiological evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion</td>
<td>• C. krusei infection • Refractory Candida infection • &gt;1 week of antibiotics in last 30 days • &gt;48h of antifungal therapy • Osteomyelitis, endocarditis or meningitis</td>
</tr>
<tr>
<td>Intervention</td>
<td>Patients were randomly assigned to receive either fluconazole or anidulafungin and were stratified based on APACHE II score and neutrophil count</td>
</tr>
<tr>
<td>Treatment response</td>
<td>Anidulafungin had higher rates of response at the end of IV therapy if therapy was found to be non-inferior No difference in 28-day mortality</td>
</tr>
<tr>
<td>Conclusions</td>
<td>Echinocandins and fluconazole appear to be equally effective in this population (non-neutropenic patients with APACHE II&lt;20)</td>
</tr>
</tbody>
</table>

Fluconazole vs. echinocandins for C. glabrata fungemia

<table>
<thead>
<tr>
<th>Population</th>
<th>Retrospective multicenter study of patients receiving fluconazole or an echinocandin for the treatment of C. glabrata candidemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion</td>
<td>• Concomitant bacteremia • &gt;48h of antifungal therapy before first positive result</td>
</tr>
<tr>
<td>Complete response at day 14</td>
<td>No significant difference in response at day 14 (p=0.383) There was a trend towards decreased response when comparing patients treated with fluconazole with more severe illness</td>
</tr>
<tr>
<td>Survival</td>
<td>No difference in mortality at any point (28 day; p=0.544)</td>
</tr>
<tr>
<td>Conclusions</td>
<td>Echinocandins appear to be equally effective in this population (non-neutropenic patients with APACHE II&lt;20)</td>
</tr>
</tbody>
</table>

Patient Case

- IC is clinically improving on fluconazole and is now out of the ICU, however cultures are growing C. glabrata.
- What is the best course of action?
  A. Continue fluconazole 400mg daily
  B. Increase fluconazole to 800mg daily
  C. Switch to micafungin 100mg daily
  D. Switch to liposomal amphotericin 3 mg/kg

Candidal Endocarditis

- Few studies looking at treatment of patients with candidal endocarditis
- Treatment of choice is amphotericin B +/- flucytosine
- However, a small study suggests that echinocandins may have a role
  - All-cause mortality of patients treated with caspofungin similar to those treated with amphotericin B in a chart review
- In vitro data suggests that amphotericin B and echinocandins have better penetration into biofilms
INVASIVE ASPERGILLOSIS

Patient Case

- AG is a 65 year old male admitted for CSF relapse of AML, currently being treated with IT cytarabine
  - Multiple cycles
- On hospital day 30 he develops a fever to 102.3°F
- Currently has WBC count of 1.2, neutrophils are 35%
- Started on cefepime

Patient Case

- On day 3 of treatment with cefepime, patient continues to be febrile
- CT notes nodules in the lungs surrounded by ground glass opacities
- What diagnostic tests could help you determine the best treatment?

Aspergillus spp.

- Aspergillus spp. are molds that are ubiquitous worldwide
- Important cause of morbidity and mortality in immunocompromised patients
- Invasive infections most commonly occur in the lungs
- Most common species is Aspergillus fumigatus
  - May change based on location

Pulmonary Aspergillosis: Risk Factors

- Prolonged neutropenia
- Advanced HIV
- Inherited immunodeficiency syndrome
- Hematopoietic stem cell transplantation
- Lung transplantation

At this point, based on consensus definitions what level of certainty do we have that AG has Aspergillosis?

A. Possible
B. Probable
C. Proven
**Pulmonary Aspergillosis: Signs and symptoms**

- Nodules with halo sign on CT
- Positive fungal markers
  - Galactomannan
  - β-D-Glucan
- Cultures obtained via BAL, needle aspiration or thorascopic biopsy

**Galactomannan Assay**

- Galactomannan is a cell wall component of *Aspergillus* spp.
  - Released during invasive infection
- Large meta-analysis showed sensitivity of 71% and specificity of 89%
  - Better negative predictor than positive predictor
- False positives have been reported in patients receiving concurrent piperacillin-tazobactam therapy

**Pulmonary Aspergillosis: Diagnosis**

<table>
<thead>
<tr>
<th>Consensus Definition for Invasive Fungal Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prolifer</strong></td>
</tr>
<tr>
<td><strong>Possible</strong></td>
</tr>
<tr>
<td><strong>Probable</strong></td>
</tr>
<tr>
<td>1) Host is immunosuppressed</td>
</tr>
<tr>
<td>2) Pulmonary infection: CT with dense lesions, air crescent signs or cavitary lesions</td>
</tr>
<tr>
<td>3) Positive galactomannan or recovery of <em>Aspergillus</em> spp. from respiratory cultures</td>
</tr>
</tbody>
</table>

**Patient Case**

- What test would move our certainty of *Aspergillus* spp. infection from possible to probable?
  A. β-(1,3)-D-glucan assay
  B. Galactomannan assay
  C. Sputum culture with yeast
  D. Repeat CT to confirm halo

**Voriconazole vs. D-AMB for invasive aspergillosis**

<table>
<thead>
<tr>
<th>Population</th>
<th>Randomized open label study of patients with probable or definite invasive aspergillosis and were immunosuppressed. Mostly with lung involvement only and hematologic cancers.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exclusion</td>
<td>Repeated 96 hours of therapy with amphotericin B or itraconazole, received interacting medications had LFTs &gt;5x ULN, or were on mechanical ventilation.</td>
</tr>
<tr>
<td>Intervention</td>
<td>Randomized to receive amphotericin B deoxycholate 1.5mg/kg daily OR Voriconazole 6mg/kg q12h for two doses then 4mg/kg q24h</td>
</tr>
<tr>
<td>Response at week 12</td>
<td>Complete or partial response was 52.8% in voriconazole group and 31.6% in the amphotericin group (CI: 10.4-32.9)</td>
</tr>
<tr>
<td>Survival at week 52</td>
<td>Survival in voriconazole group was 70.8% and 57.9% in the amphotericin B group (CI: 0.4-0.88)</td>
</tr>
<tr>
<td>Conclusion</td>
<td>Voriconazole was found to have superior outcomes with respect to amphotericin B deoxycholate. Additionally voriconazole was better tolerated but had higher rates of visual disturbances.</td>
</tr>
</tbody>
</table>

**Pulmonary Aspergillosis: Treatment**

- Voriconazole is the treatment of choice
  - 6mg/kg q12 for 2 doses, then 4mg/kg
- Amphotericin B may also be effective
  - Amphotericin B deoxycholate dosed 1mg/kg daily
  - Lipid formulations better tolerated
    - Liposomal amphotericin B dosed 3-5 mg/kg/day
    - *A. terreus* is intrinsically resistant to amphotericin

**Lipid formulations** better tolerated
- Amphotericin B deoxycholate dosed 3-5 mg/kg/day
- Liposomal amphotericin B dosed 3-5 mg/kg/day
### Combination Therapy

**Population** (n=4G)
- Randomized double-blind placebo-controlled trial of combination therapy in proven or probable invasive aspergillosis. Patients had to be >16 years of age.

**Exclusion**
- Progressive hematologic malignancies not likely to response to treatment or life expectancy <30 days, mechanical ventilation >95 hours of antifungals before enrollment, pregnant or lactating, severe liver dysfunction.

**Intervention**
- Randomized to receive voriconazole 6 mg/kg q12 h x2 doses then 4 mg/kg BID for a total of 6 weeks of treatment (could switch to PO after 7 days)
- OR
- Caspofungin 70 mg once then 50 mg daily
- OR
- Voriconazole 6 mg/kg q12h for two doses then 4 mg/kg q12h plus anidulafungin 200 mg/day for 2-4 weeks.

**Mortality at week 6 (mITT)**
- Mortality in combination therapy was 19.3% vs 27.8% in the monotherapy group (Difference 8.3% CI -19 to 1.5, p=0.086)

**Conclusion**
- Combination of voriconazole with anidulafungin resulted in a decrease in mortality in the mITT group, however this was not statistically significant. Multivariate analyses identified initial galactomannan level as being predictive of mortality.

### Isavuconazole in Aspergillosis

- Studies have not yet been published
- Randomized double blind study of patients with possible, probable or proven infection (n=231)
- No differences noted in 6 week all cause mortality or overall response at end of treatment
- Less ADEs in patients on isavuconazole, no difference in serious ADEs or ADEs leading to d/c

### Salvage Therapy

- Other agents have been studied in salvage therapy
  - Posaconazole 200mg QID
  - Caspofungin 70 mg once then 50 mg daily
  - Micafungin 100 mg daily

### Patient Case

**Patient Case**
- The team would like to know which medication to start for the treatment of AG’s suspected Aspergillosis. What is the best option?
  - A. Caspofungin
  - B. Liposomal amphotericin B
  - C. Voriconazole
  - D. Posaconazole

### References