Breakthrough Invasive Fungal Infections in the Hematopoetic Cell Therapy (HCT) Patient

Frank Tverdek PharmD BCPS AQ-ID CMO
UT MD Anderson Cancer Center
@FTverdek

Disclosures
• Nothing to disclose
• This presentation will contain reference to off-label use of certain antifungals; reference to those instances will be verbalized

Objectives
• Define breakthrough invasive fungal infection
• Describe the pathogens breaking through current antifungal prophylactic regimens
• Identify an appropriate antifungal regimen for a breakthrough fungal infection
Defining Invasive Fungal Infection (IFI)

- Generally accepted IFI criteria for use in fungal literature:
  - European Organization for Research and Treatment of Cancer/Invasive Fungal Infections Cooperative Group and the National Institute of Allergy and Infectious Diseases Mycoses Study Group (EORTC/MSG) Consensus Group
  - Differentiates likelihood of IFI based on variety of objective parameters
- **Proven** IFI: demonstration of fungal elements in diseased tissue
- **Probable** IFI: presence of host factor putting patient at risk of IFI, clinical features of an IFI, presence of mycological evidence
- **Possible** IFI: presence of host factor putting patient at risk of IFI, clinical features of an IFI, absence of mycological evidence

**Probable Invasive Fungal Infection**

- Host Factors (Patient with HCT, prolonged neutropenia)
- Clinical evidence of potential IFI (Radiologic, skin manifestations)

**Probable Invasive Fungal Infection**

- Host Factors (Patient with HCT, prolonged neutropenia)
- Clinical evidence of potential IFI (Radiologic, skin manifestations)
- Mycological evidence of disease (Galactomannan, Beta-D-glucan)
Proven / Definite Invasive Fungal Infection

- Demonstration of pathogen in diseased tissue

Breakthrough Invasive Fungal Infection (b-IFI)

- **Breakthrough IFI** defined as:
  - An invasive fungal infection (IFI) occurring during the exposure to an antifungal drug
  - Includes fungal organisms outside of spectrum of activity

- In contrast to:
  - **Persistent IFI** – ongoing IFI that continues to require antifungal therapy
  - **Refractory IFI** – progression of IFI necessitating a change in antifungal therapy
  - **Relapsed IFI** – reoccurrence of same fungal pathogen at same site subsequent to completion of initial fungal therapy

Clinical Impact of Breakthrough Fungal Infection

**Multicenter Swiss HCT Cohort Study**

- Details
  - Total patients: 479
  - Invasive Candida infections:
    - 2.3% of patients
    - 20% 12-week mortality
  - Invasive Mold infections:
    - 8.9% of patients
    - 58% 12-week mortality

**Retrospective Review Mucormycosis in US - Premier Database**

- Details
  - Total Patients: 555 cases out of 47 million
  - Underlying HCT in 63 of 555

- Hospitalization:
  - Length of stay (median): 17 (1-259) days
  - Mortality (in-hospital): 23%
  - Readmission (1 month): 23%
  - Cost per hospital stay (SD): $112,419, (159,144)
Contributory Factors to b-IFI

- General risk factors
  - Neutropenia depth and duration
  - High fungal inoculum exposure
  - Central venous catheters (specifically for Candida spp. infections)

- HCT specific factors
  - Allogeneic transplants (alloHCT) at more risk than autologous transplants (aHCT)
  - Early IFI (pre-engraftment): mucositis and profound neutropenia conspire
  - Late IFI: GVHD, corticosteroid (> 0.3 mg/kg/day) and cumulative immunosuppressive use

- Mold active agents typically reduce overall incidence of b-IFI
- Risk factors hold similar for both adult and pediatric IFI

ARS Slide #1 -> Objective 1

The following scenario best describes a breakthrough fungal infection (b-IFI)

a) A patient was receiving caspofungin for a C. albicans fungemia, and was switched to oral fluconazole today to facilitate transition to home

b) A patient with invasive pulmonary Aspergillosis is receiving voriconazole, pulmonary function is worsening and amphotericin liposomal is added to their regimen

c) A patient is receiving isavuconazole for invasive pulmonary Aspergillosis, now multiple blood cultures show growth of C. glabrata

d) A patient completed caspofungin therapy 6 days ago for C. krusei fungemia, now showing multiple blood cultures positive from 1 day ago with growth of C. krusei

Current State of IFI Prophylaxis

<table>
<thead>
<tr>
<th>ITT Indication</th>
<th>Adults</th>
<th>Pediatrics</th>
</tr>
</thead>
<tbody>
<tr>
<td>Autologous w/ mucositis</td>
<td>Fluconazole or Micafungin</td>
<td>None</td>
</tr>
<tr>
<td>Autologous w/o mucositis</td>
<td>None</td>
<td>None</td>
</tr>
<tr>
<td>Allogenic</td>
<td>Fluconazole or Micafungin</td>
<td>Voriconazole, posaconazole or amphotericin B</td>
</tr>
<tr>
<td>Significant GVHD</td>
<td>Fluconazole</td>
<td>Voriconazole, posaconazole or amphotericin B</td>
</tr>
</tbody>
</table>

* For patients with neutropenia anticipated for > 7 days

https://www.nccn.org/professionals/physician_gls/PDF/infections.pdf (last accessed 12/1/19)


Science M. Pediatr Blood Cancer 2014; 61:393–400
Fluconazole IFI Prophylaxis in HCT

- Prior to fluconazole, hepatosplenic candidiasis was a major cause of morbidity and mortality in the immunocompromised patient
- Fluconazole reduced morbidity and mortality in HCT patients by preventing IFI
- Fluconazole's limited spectrum of activity characterizes its b-IFI
  - Non-C. albicans: Candida spp. (i.e. C. glabrata, C. krusei)
  - Aspergillus spp.
  - Mucor spp.
- Development of multiple mold active agents

Voriconazole IFI Prophylaxis in HCT

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Details</th>
<th>Primary Outcomes</th>
<th>Secondary Outcomes</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multicenter, prospective, double-blinded study in the U.S.</td>
<td>Voriconazole 200mg PO BID (N=295) compared to fluconazole 400mg PO daily (N=305) for day 0-100 post standard high-risk HCT</td>
<td>Fewer b-IFI in voriconazole arm vs. fluconazole: 7.3% vs. 11.2%; p=0.12</td>
<td>Relatively low incidence of GvHD</td>
<td>Largely driven by positive galactomannan as evidence of IFI; &quot;Probable IFI&quot; trend towards less Aspergillus spp. breakthrough in voriconazole arm</td>
</tr>
<tr>
<td>Study period: 2003-2006</td>
<td>Fungal free survival at 180 days similar (75% vs 78%; p=0.49)</td>
<td>Overall mixture of Candida spp., Aspergillus spp. &amp; Mucor spp.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Voriconazole b-IFI in HCT Patients

- Other retrospective studies have combined assessment of b-IFI during both prophylaxis and treatment
  - Mucorales (zygomycetes) is the most common breakthrough pathogen
  - Typically occurring late post transplant, especially during GVHD treatment
  - Mucor spp. considered to be resistant, often with high MIC values to voriconazole
  - Often manifesting in sinus and pulmonary infection
  - Resistant Candida spp.
    - Most commonly C. glabrata and C. krusei
    - Documented high MICs to voriconazole, ~2mcg/ml
    - Often manifesting as fungemia


**Voriconazole IFI Prophylaxis in Pediatric HCT**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Details</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective review in the U.S. (UT Southwestern)</td>
<td>Pediatric HCT patients (n=84) receiving primary antifungal prophylaxis with voriconazole (n=64) or Liposomal amphotericin B (n=25) or Micafungin (n=16)</td>
<td>IFI per 1000 prophylaxis days:</td>
<td></td>
<td>Unclear which IFI was attributed to each agent</td>
</tr>
<tr>
<td></td>
<td>Study period: 2012-2016</td>
<td>Voriconazole: 1.17</td>
<td>Liposomal amphotericin: 2.67</td>
<td>Voriconazole b-IFI was possible in 8/9 cases</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Liposomal amphotericin: 2.67</td>
<td>Micafungin: 2.08</td>
<td>Median age 9 years old (range 0-21)</td>
</tr>
<tr>
<td></td>
<td>Total of 21 b-IFIs, most were possible IFI</td>
<td></td>
<td>9 of 11 IFIs</td>
<td></td>
</tr>
<tr>
<td></td>
<td>5 total with positive Beta-D-glucan testing</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 possible galactomannan</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Posaconazole Suspension IFI Prophylaxis in HCT**

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Details</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3, multicenter, randomized, double blinded</td>
<td>Posaconazole 200mg PO TID (n=301) compared to Fluconazole 400mg PO daily (n=299) for prophylaxis in HCT with GVHD</td>
<td>Decrease in b-IFI rate</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study period: 1999-2003</td>
<td></td>
<td>5.3% posaconazole vs. 9% fluconazole (p=0.07)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Invasive Aspergillus:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posaconazole 2% vs Fluconazole 7% (p=0.006)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mortality:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Posaconazole 1% vs Fluconazole 4% (p=0.40)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>b-IFI in posaconazole group:</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Three Aspergillus spp. by positive galactomannan test</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>One of each of the following pathogens</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Candida glabrata</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Pseudallescheria spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Trichosporin spp.</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Mold not specified</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Older posaconazole suspension</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Posaconazole IFI Prophylaxis – Newer Formulations**

- Retrospective review of 343 cases of posaconazole prophylaxis at MD Anderson Cancer Center in patients with hematologic malignancy
- HCT represented 20% of patients with 30% of HCT with GVHD
- Overall rate of b-IFI of 2%
### Retrospective review of posaconazole prophylaxis cases at OHSU

- **N= 547 patients; ~20 HCT, 18% with GVHD**
- **B-IFI rate: 1.6%**

#### Posaconazole Prophylaxis – Newer Formulations

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>HCT</th>
<th>Formulation</th>
<th>IFI Class</th>
<th>Site of infection</th>
<th>Identified fungal organism</th>
<th>Prophylaxis (Days)</th>
<th>trough Level (ng/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML</td>
<td>No</td>
<td>Suspension</td>
<td>Probable</td>
<td>Lung/trachea</td>
<td>Aspergillus fumigatus</td>
<td>15</td>
<td>None</td>
</tr>
<tr>
<td>CML</td>
<td>No</td>
<td>Suspension</td>
<td>Probable</td>
<td>Lung/trachea</td>
<td>Positive galactomannan</td>
<td>18</td>
<td>280</td>
</tr>
<tr>
<td>AML</td>
<td>No</td>
<td>Tablet</td>
<td>Proven</td>
<td>Skin</td>
<td>Fusarium proliferatum</td>
<td>17</td>
<td>1820</td>
</tr>
<tr>
<td>AML</td>
<td>No</td>
<td>Tablet</td>
<td>Probable</td>
<td>Lung</td>
<td>Positive galactomannan</td>
<td>25</td>
<td>None</td>
</tr>
<tr>
<td>GVHD</td>
<td>Allogeneic</td>
<td>Suspension</td>
<td>Proven</td>
<td>Blood</td>
<td>Candida glabrata</td>
<td>12</td>
<td>1200</td>
</tr>
<tr>
<td>AML</td>
<td>No</td>
<td>Tablet</td>
<td>Probable</td>
<td>Sinuses</td>
<td>Mucor species</td>
<td>66</td>
<td>None</td>
</tr>
<tr>
<td>AML</td>
<td>No</td>
<td>Tablet</td>
<td>Proven</td>
<td>Sinuses</td>
<td>Zygomyces species</td>
<td>13</td>
<td>None</td>
</tr>
<tr>
<td>AML</td>
<td>No</td>
<td>Tablet</td>
<td>Probable</td>
<td>Lung</td>
<td>Aspergillus niger</td>
<td>5</td>
<td>None</td>
</tr>
<tr>
<td>AML</td>
<td>No</td>
<td>Tablet</td>
<td>Probable</td>
<td>Lung</td>
<td>Positive galactomannan</td>
<td>7</td>
<td>None</td>
</tr>
<tr>
<td>AML</td>
<td>No</td>
<td>Tablet</td>
<td>Proven</td>
<td>Blood</td>
<td>Candida tropicalis</td>
<td>13</td>
<td>1600</td>
</tr>
<tr>
<td>AML</td>
<td>No</td>
<td>Tablet</td>
<td>Proven</td>
<td>Blood</td>
<td>Candida glabrata</td>
<td>78</td>
<td>1200</td>
</tr>
<tr>
<td>AML</td>
<td>Allogeneic</td>
<td>Tablet</td>
<td>Proven</td>
<td>Sinuses</td>
<td>No culture growth</td>
<td>39</td>
<td>None</td>
</tr>
<tr>
<td>AML</td>
<td>No</td>
<td>Tablet</td>
<td>Proven</td>
<td>Blood</td>
<td>Candida glabrata</td>
<td>58</td>
<td>1200</td>
</tr>
<tr>
<td>AML</td>
<td>No</td>
<td>Tablet</td>
<td>Probable</td>
<td>Lung</td>
<td>Positive galactomannan</td>
<td>7</td>
<td>None</td>
</tr>
<tr>
<td>AML</td>
<td>No</td>
<td>Tablet</td>
<td>Probable</td>
<td>Lung</td>
<td>Positive galactomannan</td>
<td>7</td>
<td>None</td>
</tr>
<tr>
<td>AML</td>
<td>No</td>
<td>Tablet</td>
<td>Probable</td>
<td>Blood</td>
<td>Candida glabrata</td>
<td>78</td>
<td>1200</td>
</tr>
</tbody>
</table>

#### Isavuconazole IFI Prophylaxis In High-Risk Patients

| Patient | Age/Sex | Malignancy | HCT | Neutropenia | Pathogen | IFI Class | Neutropenia | Primary Outcomes | Secondary Outcomes | Commentary |
|---------|---------|------------|-----|-------------|----------|-----------|-------------|--------------|-------------------|-------------------|------------|
| 1       | 74/F    | AML        | N   | Aspergillus spp | Probable | 26        | 10          | 6.3          | ND                | Isavuconazole Death |
| 2       | 71/M    | AML        | N   | Aspergillus spp | Probable | 18        | 15          | ND          | ND                | Isavuconazole Alive |
| 3       | 30/M    | R/R AML   | N   | Aspergillus spp | Probable | 180       | 125         | 3.3          | ND                | Ambisome Alive      |
| 4       | 57/M    | R/R AML   | N   | Fusarium dimerum | Probable | 25        | 8           | ND          | ND                | Isavuconazole Death |
| 5       | 45/F    | R/R AML   | Y   | Fusarium spp   | Proven   | 9          | 9           | ND          | ND                | Ambisome Alive      |
| 6       | 64/F    | R/R AML   | N   | A. fumigatus   | Probable | 38        | 13          | 4.3          | ND                | Voriconazole Alive  |
| 7       | 65/M    | R/R AML   | N   | A. fumigatus   | Probable | 38        | 40          | 4.3          | ND                | Voriconazole Death  |
| 8       | 60/M    | R/R AML   | N   | Rhizopus microsporus | Proven | 11        | 14          | ND          | ND                | Ambisome, posaconazole Alive |
| 9       | 64/F    | MF         | Y   | A. fumigatus   | Probable | 16        | 12          | 0.5          | ND                | Micafungin Death    |
| 10      | 67/M    | R/R ALL   | Y   | Syncephalastrum | Probable | 27        | 22          | 2           | ND                | Posaconazole Death  |

**Study Design:**
- Retrospective review in the U.S. (Oregon Health & Science University Hospital)

**Details:**
- Review of isavuconazole prophylaxis for high-risk immunocompromised patients (N=98)

**Primary Outcomes:**
- B-IFI rate: 8.2% per patient
- 5.8% per course

**Secondary Outcomes:**
- Mortality in 58% of patients within range of 7-34 days post diagnosis

**HCT details:**
- History of HCT in 36% patients
- GVHD in 26% of total HCT

**Considerable increase in b-IFI as compared to previous institutional posaconazole b-IFI rates of 1.6% in similar patients**

**Isavuconazole IFI Prophylaxis in High Risk Patients**

---

**Notes:**
Isavuconazole b-IFI in Retrospective “Real-World” use

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Disease and Transplant</th>
<th>Neutropenia</th>
<th>Indication</th>
<th>ISA Level (mcg/mL)</th>
<th>Breakthrough Infections</th>
<th>Treatment b-IFI</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>44F</td>
<td>F</td>
<td>ALL s/p alloHCT 5 months</td>
<td>Prophylaxis 2 months</td>
<td>2.8</td>
<td>Pneumonia</td>
<td>NA</td>
<td>Ambisome, voriconazole</td>
<td>Improvement</td>
</tr>
<tr>
<td>2</td>
<td>63F</td>
<td>F</td>
<td>Multiple Myeloma 8 days</td>
<td>Pneumonia</td>
<td>NA</td>
<td>Pneumonia</td>
<td>NA</td>
<td>Ambisome, voriconazole, posaconazole</td>
<td>Death</td>
</tr>
<tr>
<td>3</td>
<td>68M</td>
<td>M</td>
<td>Heart/Renal transplant N/A</td>
<td>Prophylaxis 1 month</td>
<td>2.2</td>
<td>Pneumonia</td>
<td>0.5</td>
<td>Ambisome, caspofungin, lobectomy</td>
<td>Death</td>
</tr>
<tr>
<td>4</td>
<td>65M</td>
<td>M</td>
<td>Aplastic anemia s/p alloHCT 1 month</td>
<td>Prophylaxis 13 days</td>
<td>NA</td>
<td>Pneumonia, fungemia</td>
<td>4</td>
<td>Ambisome, caspofungin, voriconazole</td>
<td>Death</td>
</tr>
<tr>
<td>5</td>
<td>37M</td>
<td>M</td>
<td>AML 4 months</td>
<td>Prophylaxis 5 weeks</td>
<td>NA</td>
<td>Pneumonia</td>
<td>0.5</td>
<td>Ambisome, caspofungin, voriconazole</td>
<td>Death</td>
</tr>
</tbody>
</table>
### Micafungin IFI Prophylaxis in HCT

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Details</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 3, multicenter, randomized, double-blinded</td>
<td>Micafungin (MICA) 50mg IV daily (N=425) compared to fluconazole (FLUC) 400mg IV daily (N=407) for IFI prophylaxis in HCT during pre-engraftment period</td>
<td>Efficacy: 80% micafungin vs. 73.3% fluconazole, p=0.03</td>
<td>b-IFI (MICA vs. FLUC): 1.6% vs. 2.4%, p=0.481; Micafungin b-IFI: Candida spp. (4), Probable Aspergillus spp. (7); Fluconazole b-IFI: Candida spp. (3), Aspergillus spp. (2), Probable (3), Proven (4); Mortality (MICA vs. FLUC): 4.4% vs 5.7%, p=0.322</td>
<td>Micafungin non-inferior to fluconazole during the pre-engraftment period Overall low rate b-IFI Micafungin with potentially less b-IFI due to Aspergillus spp.</td>
</tr>
</tbody>
</table>

### Caspofungin IFI Prophylaxis in HCT

<table>
<thead>
<tr>
<th>Study Design</th>
<th>Details</th>
<th>Primary Outcome</th>
<th>Secondary Outcomes</th>
<th>Commentary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retrospective cohort study in U.S. (MD Anderson Cancer Center)</td>
<td>Review of caspofungin IFI prophylaxis in patients with HCT (N=123)</td>
<td>B-IFI rate: 7.3% of patients</td>
<td>Infection with: Mixed Aspergillus spp. infection (2) Aspergillus terreus (1) Candida tenuis (1) Candida haemulon (1) Phanerochaete spp. (2) Exserohilum spp. (1) Cryptococcus spp. (1) Unspeciated mold (1)</td>
<td>B-IFI rate: 4.1% by day 100 4 of 5 with b-IFI B-IFI details: GVHD in 44.7% of patients Dosing: 85% 50mg IV daily 15% 35mg IV daily</td>
</tr>
</tbody>
</table>

### Echinocandin Prophylaxis Efficacy

- Since the early studies, multiple smaller retrospective studies performed and meta-analyses in HCT and hematologic malignancy
  - In pre-engraftment phase similar efficacy to fluconazole
  - During GVHD treatment, anti-mold azoles likely superior as higher rates of b-IFI
- Further characterization of breakthrough Candida spp., such as C. tropicalis demonstrate mutations leading to potential tolerance to echinocandins
ARS Slide #2 - Objective 2

Which of the following fungal infections would be least likely to occur as b-IFI in a patient receiving posaconazole prophylaxis during treatment for acute GVHD:

A) Candida albicans fungemia
B) Aspergillus fumigatus pulmonary infection
C) Mucor spp. sinusitis
D) Galactomannan positive pulmonary infection

General Approach to b-IFI Assessment

- Evaluate the current antifungal regimen
  - Confirm patient was actually receiving prophylaxis
  - Oral azoles can be expensive for patients
  - Do they understand the dosing and frequency (i.e. 1 vs. 3 posaconazole tablets)
  - Evaluate likelihood of adequate absorption for oral agents
  - Severe mucositis?
  - Inability to swallow tablet/capsules?
  - Evaluate for presence of any drug-drug interactions
  - Review any TDM
    - Consider assessing antifungal serum level at diagnosis of b-IFI to evaluate potential for suboptimal exposure (i.e. itraconazole, posaconazole, voriconazole)

Therapeutic targets for Azole Therapy

- **Voriconazole**
  - Prophylaxis target >1.0 mcg/ml
  - Treatment target 2.0-5.5 mcg/ml
- **Posaconazole**
  - Substantial controversy exists as to optimal target
  - Possibly more than 600...700 ng/ml for prophylaxis?
- **Itraconazole**
  - Prophylaxis target > 1.0 mcg/ml
- **Unclear for Isavuconazole**
  - A practical approach is to determine how close your patient’s level is to the average level in the prophylaxis studies

General Approach to b-IFI Treatment

Consider goals of care
- Malignancy treatment status?
- Neutrophil recovery?
- What are the patient’s wishes?

Likely Pathogens
- Review prophylaxis drug spectrum of activity
- Recall the common culprits
- Review microbiology history

Evaluate for comorbid conditions
- Renal and hepatic status?
- Oral vs. IV routes?
- Concomitant bacterial infections?
- Interacting medications?
General Approach to b-IFI Treatment

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• What are the patient’s wishes?

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Likely Pathogens
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Review antifungal treatment history
• Check for any intolerances in the past
• Insurance coverage concerns?

Amphotericin B Therapy

• Amphotericin therapy remains the broadest spectrum antifungal
• It is considered the first line therapy in b-IFI when the pathogen is unknown
  —Mold infections breaking through any of the mold-active azoles
  —For Candida spp. infections in which resistance to echinocandins may suspected
• Delays in initiation of amphotericin associated with increased mortality
  • 70 patients with zygomycosis (Mucor spp. Infection) at MD Anderson Cancer Center
  • Regression tree analysis identified 6 days as threshold for worse outcomes
  • The 12 week mortality was 82.9% vs. 48.6% for 6 or more days and less than 6 days initiation, respectively

Choosing Additional Treatment Agents

• Amphotericin based therapy is often a shorter term solution as it is associated with nephrotoxicity
• Consideration of an additional agent or an altogether different agent than amphotericin b is debatable
• Some experts recommend changing the azole once b-IFI occurs
  —Voriconazole > posaconazole
  —Posaconazole > voriconazole or isavuconazole
  —Isavuconazole = voriconazole for suspected Aspergillosis, posaconazole for suspected Mucor spp.
• Addition of echinocandin to azole therapy as potential strategy
  —Based on a combination anidulafungin/voriconazole study for invasive Aspergillosis
  —Demonstrated combo therapy improved outcomes in patients who recovered neutrophils and had galactomannan-positive IFI
• Very sparse data on treating b-IFI and more studies needed
Objective 3

- What regimen is most appropriate for a HCT patient with b-IFI, manifesting as new pulmonary infection with two consecutive positive galactomannan values, while receiving posaconazole for prophylaxis during treatment of GVHD. Patient is otherwise stable from renal and hepatic standpoint. Plans are to remain hospitalized for the next 2-3 weeks.

A) Fluconazole monotherapy
B) Caspofungin monotherapy
C) Amphotericin liposomal plus voriconazole
D) Amphotericin liposomal plus fluconazole

Objective 3

- What agent is likely to have the broadest chance of targeting b-IFI in a patient receiving posaconazole prophylaxis?

A) Voriconazole
B) Caspofungin
C) Amphotericin liposomal
D) Isavuconazole

Questions?
Recommended References