Yeast and Mould Infections in Neutropenic Patients and HSCT Recipients

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Issues
- Diseases
- Current epidemiology of infection
  - Incidence and Outcomes
- Diagnosis
- Therapies

Time line, and incidence of OI's changed with preventative therapy and type of BMT.
Diseases

- Candidemia
- Deep-tissue infection
  - Acute invasive candidiasis
  - Abcess formation in the presence of hematogenous spread
  - Multiple organs may be involved
    - Endocarditis
    - Abscesses
    - Chorioretinitis
  - 30-40% attributable mortality

Hepatosplenic Candidiasis

- Neutropenic - HSCT
- Typically does NOT present during neutropenia, although may develop
- Mucosal breakdown with invasion into portal vasculature
  - Clinical presentation largely secondary to inflammatory response to lesions
  - After engraftment: abdominal pain, increased LFTs (alk phosph), fever, leg / flank pain (?)
- Diagnosis may require invasive procedure
  - Differential: other fungi, bacteria, lymphoma
- Radiographic changes may get worse before better
- *C. albicans* most common (hyphal formation)

Distribution of *Candida* species: U.S. Hospitals

- *C. albicans* 53.8%
- *C. glabrata* 13.8%
- *C. parapsilosis* 11.4%
- *C. tropicalis* 11.4%
- *C. krusei* 2.4%
- Other 2.5%

N= 1890; 1995-2002
Mould Infections: Primary Pulmonary Disease

- Nodule +/- halo: typical presentation in neutropenic; evolves to cavitation
- More variability in non-neutropenic patients
  - Nodular disease
  - Bronchopneumonia
- Multiple microbial causes of disease
  - Aspergillus species
  - Zygomycetes
  - Other filamentous organisms

From: Marchetti and Calandra, Cohen and Powderly 2nd ed (in press)

Angioinvasion

- Multiple organisms disseminate to skin, brain, liver
- Differentiate syndromes caused by organisms that "sporulate" in vivo

From: Marchetti and Calandra, Cohen and Powderly 2nd ed (in press)

Diseases Caused by Aspergillus species

- Invasive pulmonary aspergillosis
- Genus Aspergillus > 250 different species
- A. fumigatus historically considered to be most common cause of disease

**Aspergillus fumigatus “group”**

- Isolates identified as *A. fumigatus* are heterogeneous—small phenotypic differences
- Different species suggested by polyphasic taxonomy definition
  - Multiple closely related and “new” species
    - *Aspergillus lentulus*
    - *Aspergillus fumisynnematus*
    - *Aspergillus udagawae*
    - *Neosartorya pseudofischeri*
  - Variable susceptibilities to antifungal drugs in vitro

**Other Sections**

- *Aspergillus ustus*
  - *A. ustus*
  - *A. pseudodeflectus*
  - *A. calidoustus*
  - High MICs to AmB, all azoles
- *Aspergillus terreus*
  - *A. terreus*
  - *A. alabamensis*
  - High MICs to AmB

**Epidemiology Update: Multicenter Surveillance Networks**

- **TRANSNET**
  - 23 US centers, 2001 - 2006
  - SOT, HCT, with denominator data
- **PATH Alliance**
  - Diagnosed in hospital
PATH Alliance: BMT
- IA most frequent (n=148, 59%) of 250 IFIs identified
  - Median 82 days after HCT (3-6542)
- IC (n=62, 25%)
  - Autologous 28 days (6-1559); allogeneic 108 days (0 – 2219)

Better outcomes of IA
- Variable identification by center
  - 2 centers reported 62.8% of IA

TRANSNET
- 23 US centers, 2001 - 2006
- 12-month CI / 100 transplant
  - 1.2 (autologous) – 8.1 (MM-URD allo)

References:
- Kontoyiannis et al. Clin Infect Dis, in press
TRANSNET BMT

Kontoyiannis et al. Clin Infect Dis, in press

25% survival after IA

Take-home points

- Variable incidence of IFI—especially IA, even within transplant types reported across centers
  - Diagnostic differences
  - Differences in follow up of transplant recipients
  - Variable case - mix
  - Type of transplants performed across centers
  - Type of patients, regimens within transplant types

Take-home points

- Variable incidence, even within transplant types reported across centers
- Better outcomes of IA compared to prior years
  - Historical death rates reported 60–80% 3 mo. - 1 year
Outcomes

- Cohort: >400 transplants in Seattle 1990 – 2004
- Outcomes improved
  - Type of transplant
  - Conditioning regimen, stem cell source
  - Underlying organ function
  - Changes in diagnosis and therapy


Diagnosis

- Culture improved, but still insensitive
- Numerous patients die with post-mortem diagnoses
- Movement in the field towards non-culture based platforms for both Candida and filamentous organisms

Diagnostic tests relying on identification of (1-3)-β-D-Glucan

- Activates Limulus amebocyte lysate
- Factor G initiates cascade. Output measured by
  - Turbidity after gel clot: WB003 (Wako Pure Chem. Indus.)
  - Chromogenic substrate: Fungitec G test (Seikagaku) and Fungitell, (Assoc. Cape Cod)

\[
\text{Endotoxin} \downarrow \text{Factor C} \rightarrow \text{Activated Fact. C} \rightarrow \text{Activated Fact. G} \rightarrow \text{Factor G} \rightarrow \text{Clotting Enzyme}
\]

\[
\text{Activates Limulus amebocyte lysate} \text{ \rightarrow (1-3)-β-D-glucan}
\]

\[
\text{Factor B} \rightarrow \text{Activated Fact. B} \rightarrow \text{Coagulin (gel)} \text{ \rightarrow Chromogenic method}
\]
(1-3)-β-D-Glucan Detection

- 279 patients with variable diagnoses
  - Case control design with variable control groups


Galactomannan

- Linear core of mannan with α1,2 and α1,6 linkages
- Antigenic side chain of β1,5 galactofuranosyl target of EbA2 Ab
  - Double sandwich ELISA

Mennen-Kersten et al Lancet Infect Dis 2004 4 349

Table 2: Five-year summary of published studies investigating performance of the galactomannan EIA used for diagnosis of aspergillosis

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sample size</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Marrero et al (2005)</td>
<td>Hematopoietic malignancies</td>
<td>100</td>
<td>99.9</td>
<td>99.9</td>
</tr>
</tbody>
</table>

NOTE: HCT hematopoietic cell transplantation, NA not available
* Denotes number of samples, not number of patients

Marr and Leisenring Clin Infect Dis 2005; 41:S381
BAL studies

- HCT: Case (n=50) control (n=50)
  - Galactomannan sensitivity in culture-positive BAL fluid: 89%
  - Sensitivity in culture-negative BAL fluid (proven disease): 59%
  - False positives in 6% of samples tested
- 99 hematology patients
  - AUC ROC = 0.93

Antifungals: Candidemia

Sites of Action of Systemic Antifungal Agents

Cell membrane
- Polymers: Amphotericin B, Lipid formulations of amphotericin B, Nystatin

DNA
- Antimetabolites: 5-fluorocytosine

Cell wall
- Echinocandins: Caspofungin, Micafungin, Anidulafungin
- Hydantoin
- Cytoplasm
- Azoles: Fluconazole, Ketoconazole, Itraconazole, Voriconazole, Posaconazole

Echinocandins

Fungal Cell Wall

GTP
UDP
Glucose
Catalytic subunit
Regulatory subunit (GTPase)
Continuous fibrils of Glucan
Surface-Layer Mannoprotein
β1-6 Tail
β1-6 Branched Glucan
Entrapped Mannoprotein
Chitin
Plasma Membrane
Glycosyl Phosphatidylinositol (GPI) Anchor (to mannoproteins)
β (1,3) Glucan Synthase Enzyme Complex
Non-competitive inhibition by: Lipopeptide Class of Antifungals (Echinocandins, Pneumocandins, Papulacandins)
Antifungals: Filamentous Fungal Infections

Cell wall
- Echinocandins: Caspofungin, Micafungin, Anidulafungin

Cytoplasm
- Azoles: Fluconazole, Ketoconazole, Itraconazole, Voriconazole, Posaconazole

DNA
- Antimetabolites: 5-Fluorocytosine

Cell membrane
- Polyenes: Amphotericin B, Lipid formulations of amphotericin B, Nystatin

Voriconazole
- Voriconazole vs. AmB-d
  - Global, randomized, double-blind trial: Primary therapy of IA
    - Voriconazole = better responses, better survival
  - Voriconazole issues: dosing, need for therapeutic level monitoring

Prophylaxis in allogeneic HSCT
- Voriconazole vs. fluconazole
  - No difference in fungal free survival
  - Fewer IFI

Efficacy of Liposomal AmB (L-AmB) in Invasive Mycoses: AmBiLoad Trial

- 14-day loading dose of L-AmB 3 or 10 mg/kg/d followed by L-AmB 3 mg/kg/d
- IPA: 96% vs. 97%; CT Halo: 58% vs. 60%; Allo-SCT: 16% vs. 19%
- Neutropenia: 71% vs. 76%
- Survival: 72% vs. 59%
- Toxicity: 30% vs. 32%

L-AmB = liposomal amphotericin B; CR+PR = complete and partial responses; EOT = End of Therapy; IPA = invasive pulmonary aspergillosis; Allo-SCT = allogeneic stem cell transplant

Wingard et al. Amer Society Hematology 2008
Conclusions

- Fungal infections—especially filamentous organisms account for large morbidity in patients with hematologic malignancies
- Reported incidence varies
- Outcomes of IA improved in many centers
- New diagnostics, new therapies
- Many controversies