MANAGEMENT OF HOSPITAL-ACQUIRED FUNGAL INFECTIONS

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Numbers of Cases of Sepsis in the United States, According to the Causative Organism, 1979-2000

Pathogens Causing Nosocomial Fungal Infections
NNIS Hospitals 1980-1990

Aspergillus
Candida spp.
C. glabrata
All other spp.

Steve-Soper, C. Laros, WR. Jour Inf Dis 1993; Vol 167: p. 1247-51
CANDIDA

- Most common fungal infection
- >100 species described
- Yeast-like organism that forms hyphae and pseudo-hyphae
- Wide range of clinical syndromes

CANDIDEMIA

<table>
<thead>
<tr>
<th>Species</th>
<th>St. Louis 1988-89</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>63%</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>13%</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>17%</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>7%</td>
</tr>
<tr>
<td>Other</td>
<td>1%</td>
</tr>
</tbody>
</table>
## Candidemia

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>63%</td>
<td>52%</td>
<td>48%</td>
<td>45%</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>13%</td>
<td>12%</td>
<td>24%</td>
<td>24%</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>17%</td>
<td>10%</td>
<td>19%</td>
<td>12%</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>7%</td>
<td>21%</td>
<td>7%</td>
<td>13%</td>
</tr>
<tr>
<td>Other</td>
<td>1%</td>
<td>7%</td>
<td>2%</td>
<td>6%</td>
</tr>
</tbody>
</table>

## Candidemia

<table>
<thead>
<tr>
<th>Species</th>
<th>Frequency (%)</th>
<th>Fluconazole MIC</th>
<th>Resistance (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>C. albicans</td>
<td>54</td>
<td>0.5</td>
<td>1-2</td>
</tr>
<tr>
<td>C. parapsilosis</td>
<td>15</td>
<td>2-4</td>
<td>0</td>
</tr>
<tr>
<td>C. tropicalis</td>
<td>10</td>
<td>1-2</td>
<td>0-4</td>
</tr>
<tr>
<td>C. glabrata</td>
<td>16</td>
<td>16-32</td>
<td>23-37</td>
</tr>
<tr>
<td>C. krusei</td>
<td>2</td>
<td>64</td>
<td>80-91</td>
</tr>
</tbody>
</table>

SENTRY Study, 1997-2000
2,047 bloodstream isolates

## Crude Mortality by Species of Candida BSI

1890 Cases of Candida BSI (US; 1995-2002)

Crude mortality (%)
CANDIDEMIA: ATTRIBUTABLE MORTALITY

- Retrospective case-control study
  - 1997-2001
  - 108 matched pairs
- Crude mortality:
  - 61% of cases
  - 12% of controls
- Attributable mortality:
  - 49% (38-60% CI)

Gudlaugsson O. et al. CID 37(9):1172-7, 2003

IDSA GUIDELINES FOR TREATMENT OF CANDIDIASIS

- Remove all existing central catheters
- Medical therapy:
  - Echinocandin: Caspofungin
  - Azole: Fluconazole
  - Amphotericin B preparation, or
  - Combination therapy
    - fluconazole plus amphotericin B

CID 2004;38:161-89
CONTROLLED CANDIDEMIA STUDIES: AZOLES

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Design</th>
<th>Endpoint</th>
<th>Success Rate</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rex, 1994</td>
<td>Flu v AmB</td>
<td>Up to 12 week</td>
<td>70% v 79%</td>
<td>33% v 40%</td>
</tr>
<tr>
<td>Rex, 2003</td>
<td>Flu v AmB_ Flu</td>
<td>Up to 12 week</td>
<td>56% v 69%</td>
<td>39% v 40%</td>
</tr>
<tr>
<td>Tull, 2003</td>
<td>Flu v Itra</td>
<td>12 week FU</td>
<td>41% v 35%</td>
<td>40%</td>
</tr>
<tr>
<td>Vori, 2004</td>
<td>Vori v AmB_Flu</td>
<td>Up to 12 week</td>
<td>41% v 41%</td>
<td>36% v 42%</td>
</tr>
</tbody>
</table>

CONTROLLED CANDIDEMIA STUDIES: ECHINOCANDINS

<table>
<thead>
<tr>
<th>STUDY</th>
<th>Design</th>
<th>Endpoint</th>
<th>Success Rate</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mora-Duarte, 2002</td>
<td>Caspo v AmB</td>
<td>End of IV Rx</td>
<td>73% v 62%</td>
<td>30% v 34%</td>
</tr>
<tr>
<td>2006</td>
<td>Anidulofungin v Flu</td>
<td>End of Rx</td>
<td>76% v 30%</td>
<td>23% v 33%</td>
</tr>
<tr>
<td>Pappas, 2007</td>
<td>Mica v Caspo</td>
<td>End of IV Rx</td>
<td>71% v 63%</td>
<td>31% v 26%</td>
</tr>
</tbody>
</table>

IDSA GUIDELINES FOR TREATMENT OF CANDIDIASIS

- Choice depends on:
  - Clinical status
  - Species and susceptibility
  - Relative drug toxicity
  - Prior exposure to antifungals
IDSA GUIDELINES FOR TREATMENT OF CANDIDIASIS

- Remove all existing central catheters
- Medical therapy
- Retinal examination
- Treatment duration:
  - 14 days after last positive blood culture and resolution of signs and symptoms

CID 2004;38:161-89

IMPACT OF IDSA GUIDELINES

- Prospective study
  - 119 pts at tertiary care hospital
- Initial antifungal therapy per guidelines
  - 76%

Patel et al. Diagnostic Microbiology & Infectious Disease. 52(1):29-34, 2005

IMPACT OF IDSA GUIDELINES

- Mortality with guidelines:
  - Follow guidelines: 24%
  - Not follow guidelines: 57% (p=0.003)
- Mortality with ID Consultation:
  - ID Consultation: 18%
  - No ID Consultation: 39% (p<0.01)

Patel et al. Diagnostic Microbiology & Infectious Disease. 52(1):29-34, 2005
ASPERGILLUS

- Common mold found in environment
- Infection due to inhalation of airborne organisms
- Risk factors:
  - Severe immunocompromise
  - Hematologic malignancy
  - Pulmonary disease
  - Environmental conditions (construction)

Consequences of Inhalation of Aspergillus Conidia

Conidial Entry → Normal Host → Colonization

- No Sequelae
- Preexisting lung cavity
- Aspergilloma
- Hypersensitivity Conditions

Compromised Host → Colonization → Allergy/Asthma

- Mild Invasion
- Severe Acute Invasion

Invasive Aspergillosis: Site of Infection in 595 patients

- Pulmonary: 55%
- Multiorgan dissemination: 19%
- Paranasal sinuses: 5%
- CNS: 6%
- Other: 9%
- Tracheobronchitis: 1%
- Skin: 5%

Patterson et al, Medicine, 2000;79:250-260
CHALLENGE OF INVASIVE ASPERGILLOSIS

- Invasive aspergillosis (IA) may lead to death within 10-14 days of first signs of infection
- Early therapy may decrease mortality
- Retrospective review: 595 pts with IA:
  - 19% had disseminated disease at time of diagnosis

**Invasive Aspergillosis Mortality Review of Literature after 1995**

Review of 1941 Patients from 50 Studies

**INVASIVE ASPERGILLOSIS: Disease Spectrum, and Outcome**

<table>
<thead>
<tr>
<th>Underlying Disease (n)</th>
<th>Complete/Partial Responses (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall (595)</td>
<td>37%</td>
</tr>
<tr>
<td>Severe Immunosuppression (363)</td>
<td>28</td>
</tr>
<tr>
<td>Allo BMT (151)</td>
<td>13</td>
</tr>
<tr>
<td>Hematological Malignancy (212)</td>
<td>39</td>
</tr>
<tr>
<td>Less Severe Immunosuppression (232)</td>
<td>51</td>
</tr>
<tr>
<td><strong>Site of Infection</strong></td>
<td></td>
</tr>
<tr>
<td>Pulmonary (330)</td>
<td>40%</td>
</tr>
<tr>
<td>Disseminated (without CNS) (114)</td>
<td>18</td>
</tr>
<tr>
<td>Central Nervous System (34)</td>
<td>9</td>
</tr>
</tbody>
</table>

Patterson TF, et al. Medicine, 2000;79:25-30
Aspergillosis and Candidiasis in AML Patients

Analysis of data from 3012 patients with AML from 18 centers in Italy from 1999 to 2003

- Attributable mortality 37.5% (80/213)
- 213 (7.1)
- 124 (4.1)
- Attributable mortality 35.5% (44/124)

**DIAGNOSTIC CHALLENGES IN ASPERGILLOSIS**

- Variable and non-specific clinical presentation
- No single, universally applicable test available to establish diagnosis
  - Gold standard: biopsy with evidence of tissue invasion
- Waiting for definitive diagnosis risks potentially fatal progression of disease

**Non-Culture Based Diagnosis of Invasive Aspergillosis**

- Culture
  - Biopsy, bronchial washings, sputum
  - Blood (limited utility)
- CT scan: halo or air crescent signs
- Product detected
  - Galactomannan EIA
  - Sensitivity lower in non-neutropenic pts
  - False positive results (pip/tazo)
- Metabolites/other antigens
  - 1,3-β-D-glucan/Factor G

Walsh et al. CID 2008;46:327-60
ASPERGILLOSIS: CURRENT THERAPIES

• Primary:
  – Voriconazole

• Alternate:
  – Liposomal AMB (3-5 mg/kg/d)
  – ABLC (5 mg/kg/d)
  – Caspofungin or micafungin
  – Posaconazole
  – Itraconazole

Walsh et al. CID 2008;46:327-60

Invasive Mycoses: Present and Future

• Epidemiology
  – Increasing number of patients at risk
  – Changing patterns of disease
  – Major cause of morbidity and mortality

• Improved prognosis
  – Prompt diagnosis
  – Host factors

• Antifungal therapy
  – Early, aggressive “induction” antifungal therapy
  – New approaches and new agents needed

THANK YOU