MANAGEMENT OF HOSPITAL-ACQUIRED FUNGAL INFECTIONS

Paul D. Holtom, MD
Associate Professor of Medicine and Orthopaedics
USC Keck School of Medicine

History of Systemic Fungal Infections
- First reported in 1953, invasive aspergillosis is the most common life-threatening invasive mould infection worldwide.
- In the 1980s, candidemia incidence rose 5-fold:
  - Candida spp remain the fourth leading cause of nosocomial bloodstream infections (BSIs), based on data collected through 2002.
- Systemic infections due to rare pathogens are becoming more frequently recognized:
  - Fusarium spp—since the 1970s, increasingly common in patients with hematologic malignancies and other immunocompromising disorders.
  - Scedosporium apiospermum—increasingly encountered as a cause of life-threatening invasive infections.

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

Aspergilus
Candida spp.
C. glabrata
All other spp.

78.3%
13.1%
7.3%
1.3%

Beck-Sague, C, Jarvis, WR. Jour Inf Dis 1993; Vol 167: p 1247-51

Systemic Fungal Infection: Who Is at Risk?

<table>
<thead>
<tr>
<th></th>
<th>Moulds</th>
<th>Yeasts</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematopoietic Stem Cell Transplant (HSCT)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Autologous</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonmyeloablative autologous</td>
<td>+</td>
<td>(not plotted is routine)</td>
</tr>
<tr>
<td>Malignancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute leukemia</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Other hematologic malignancy</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Solid neoplasms</td>
<td>+</td>
<td></td>
</tr>
<tr>
<td>Solid Organ Transplant (SOT)</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>(less risky than surgery transplantation)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Critical Care</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>Concomitant Lung Disease/Critical Care</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>General Surgery</td>
<td>-</td>
<td>+</td>
</tr>
</tbody>
</table>

HAIs: FUNGAL

- *Candida*
  - UTI
  - Fungemia
  - Disseminated infection
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></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
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

CID 2004;38:161-89
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

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>Tuil, 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>12 week FU</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 Caspofungin</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

CID 2004;38:161-89

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

HAIs: FUNGAL

• Candida
• Aspergillus

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
- Compromised host

**Sequela**

- No Sequela
- Preexisting lung cavity
- Allergy/Asthma
- Hypersensitivity Conditions

**Aspergilloma**

**Chronic Invasion**

- Acute Invasion
- Mild

**Preexisting lung cavity**

**Compromised host**

**Normal Host**

**Sequela**

- Aspergilloma

**Hypersensitivity Conditions**

- Allergy/Asthma

**Retrospective Review of 595 Patients With IA Invasive Aspergillosis Patient Profiles**

- Risk factors:
  - Solid organ transplant 9%
  - Hematologic disease 25%
  - Pulmonary disease 9%
  - AIDS 8%
  - Bone marrow transplant 33%
  - Other 11%
  - None 2%

**Invasive Aspergillosis: Site of Infection in 595 patients**

- Pulmonary 55%
- Skin 5%
- Tracheobronchitis 1%
- Multorgan dissemination 19%
- Paranasal sinuses 5%
- CNS 6%

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

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

Review of 1941 Patients from 50 Studies

![Graph showing case fatality rates for different groups](image)


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**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>Aloh 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>Site of Infection</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;79:350-80
Aspergillosis and Candidiasis in AML Patients

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

<table>
<thead>
<tr>
<th>Incidence in (%)</th>
<th>Aspergillosis</th>
<th>Candidiasis</th>
</tr>
</thead>
<tbody>
<tr>
<td>213 (7.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>124 (4.1)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Attributable mortality 37.5% (80/213)

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

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