Treatment and Prevention of Fungal Infections

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Section of Infectious Diseases
Ankara, Turkey
Epidemiology of Sepsis in the US 1979-2000

# Candida as a Nosocomial Pathogen

<table>
<thead>
<tr>
<th>Rank</th>
<th>Pathogen</th>
<th>BSI per 10,000 admissions</th>
<th>Total (n=20,978)</th>
<th>% BSI</th>
<th>ICU (n=10,515)</th>
<th>Non-ICU (n=10,515)</th>
<th>% Crude Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CoNS</td>
<td>15.8</td>
<td>31.3</td>
<td></td>
<td>35.9</td>
<td>26.6</td>
<td>20.7</td>
</tr>
<tr>
<td>2</td>
<td>S aureus</td>
<td>10.3</td>
<td>20.2</td>
<td></td>
<td>16.8</td>
<td>23.7</td>
<td>25.4</td>
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<tr>
<td>3</td>
<td>Enterococcus spp</td>
<td>4.8</td>
<td>9.4</td>
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<td>9.8</td>
<td>9.0</td>
<td>33.9</td>
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<tr>
<td>4</td>
<td>Candida spp</td>
<td>4.6</td>
<td>9.0</td>
<td></td>
<td>10.1</td>
<td>7.9</td>
<td>39.2</td>
</tr>
<tr>
<td>5</td>
<td>E coli</td>
<td>2.8</td>
<td>5.6</td>
<td></td>
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<td>22.4</td>
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<tr>
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<td>Klebsiella spp</td>
<td>2.4</td>
<td>4.8</td>
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<td>5.5</td>
<td>27.6</td>
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<tr>
<td>7</td>
<td>P aeruginosa</td>
<td>2.1</td>
<td>4.3</td>
<td></td>
<td>4.7</td>
<td>3.8</td>
<td>38.7</td>
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<tr>
<td>8</td>
<td>Enterobacter spp</td>
<td>1.9</td>
<td>3.9</td>
<td></td>
<td>4.7</td>
<td>3.1</td>
<td>26.7</td>
</tr>
<tr>
<td>9</td>
<td>Serratia spp</td>
<td>0.9</td>
<td>1.7</td>
<td></td>
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<td>1.3</td>
<td>27.4</td>
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<tr>
<td>10</td>
<td>A baumannii</td>
<td>0.6</td>
<td>1.3</td>
<td></td>
<td>1.6</td>
<td>0.9</td>
<td>34.0</td>
</tr>
</tbody>
</table>

Postmortem Epidemiology of Invasive Fungal Infections

Incidence of Nosocomial Candidemia in ICU (NNIS)

Candidemia Isolates 1992-2001

Centers Participating in the EORTC/IFICG Candidemia Survey-1996

- Brussels
- Antwerp
- Gent
- Yvoir
- Verviers
- Paris
- Grenoble
- Nice
- Strasbourg
- Lyon
- Nantes
- Rotterdam
- Nijmegen
- Luxembourg
- London
- Edinburgh
- Glasgow
- Rome
- Genova
- Turin
- Verona
- Milan
- Stockholm
- Lausanne
- Bratislava
- Zagreb
- Riyadh
- Jerusalem

Candidemia During Neutropenia
Impact of Underlying Disease

Candidemia During Neutropenia
Impact of Prophylaxis

Hacettepe 1999-2006
Etiologic Agents of Candidemia

Sancak B & Arikan S, 2006
Agents of Candidemia
Hacettepe 2005 - 2006

Sancak B & Arikan S, 2006
Candidaemia: the European Experience

Review

Candidaemia in Europe: epidemiology and resistance

Anna Maria Tortorano\textsuperscript{a,\textasteriskcentered}, Christopher Kibbler\textsuperscript{b}, Javier Peman\textsuperscript{c}, Hannelore Bernhardt\textsuperscript{d}, Lena Klingspor\textsuperscript{e}, Renee Grillot\textsuperscript{f}

\textsuperscript{a} Istituto di Igiene e Medicina Preventiva, Universit\`a degli Studi di Milano, Via Pascual 36, 20133 Milano, Italy
\textsuperscript{b} Department of Medical Microbiology, Royal Free Hospital, Pond Street, London NW3 2QG, UK
\textsuperscript{c} Servicio de Microbiologia, Hospital La Fe, Avda Campanar 21, 46009 Valencia, Spain
\textsuperscript{d} Clinic of Internal Medicine A and Loeffler Institute of Medical Microbiology, Ernst Moritz Arndt Universitaet Greifswald, Friedrich Loeffler Str. 23a, 17487 Greifswald, Germany
\textsuperscript{e} Department of Clinical Bacteriology, Karolinska Institutet, Huddinge University Hospital, 14186 Huddinge, Sweden
\textsuperscript{f} Service de Parastologie–Mycologie, Centre Hospitalier Universitaire, BP 217, 38043 Grenoble Cedex 9, France
Candidaemia in Europe

Table 2
Underlying pathology/medical care of patients with candidaemia (n = 2089; more than one may be present in each episode)

<table>
<thead>
<tr>
<th>Underlying Pathology/Medical Care</th>
<th>No.</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>1007</td>
<td>48.2</td>
</tr>
<tr>
<td>Intensive care</td>
<td>839</td>
<td>40.2</td>
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<tr>
<td>Solid tumour</td>
<td>471</td>
<td>22.5</td>
</tr>
<tr>
<td>Steroids</td>
<td>364</td>
<td>17.4</td>
</tr>
<tr>
<td>Haematological malignancy</td>
<td>257</td>
<td>12.3</td>
</tr>
<tr>
<td>Premature birth</td>
<td>125</td>
<td>6.0</td>
</tr>
<tr>
<td>HIV infection</td>
<td>63</td>
<td>3.0</td>
</tr>
<tr>
<td>Burns</td>
<td>29</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Tortorano et al., Int J Antimicrob Agents 2006; 27: 359-366
Candidaemia in Europe

Distribution of Candida species

Tortorano et al., Int J Antimicrob Agents 2006; 27: 359
Secondary Fungal Infections in Neutropenic Cancer Patients

• 836 febrile neutropenic patients who responded initial empirical regimen
  – 63% with antibacterial prophylaxis
  – 57% with antifungal prophylaxis

• 129 (15%) had secondary infection(s)

Isolated Fungal Pathogens as Secondary Infections

- 40 patients with microbiologically documented secondary inf.
  - 19 patients with fungal pathogens
- 50 isolated pathogens
  - 21 (42%) fungi

Fluconazol Resistance
6082 Isolates, 32 Countries, 1992-2001

Candida biofilms and catheters
Antifungal Susceptibility of *Candida* Biofilms: Unique Efficacy of Amphotericin B Lipid Formulations and Echinocandins

D. M. Kuhn,1,2 T. George,2 J. Chandra,2 P. K. Mukherjee,2 and M. A. Ghannoum2*

Division of Infectious Diseases, Department of Medicine,1 and Center for Medical Mycology, Department of Dermatology,2
University Hospitals of Cleveland and Case Western Reserve University, Cleveland, Ohio 44106

**TABLE 1. MICs of antifungal agents against planktonic and biofilm-associated *C. albicans* (M61 and GDH) and *C. parapsilosis* (P/A71 and P92) strains**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Planktonically grown cells for strain:</th>
<th>Biofilm at 48 h for strain:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>M61</td>
<td>GDH</td>
</tr>
<tr>
<td>AMB</td>
<td>0.5</td>
<td>0.25</td>
</tr>
<tr>
<td>NYT</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Chlor</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>TRB</td>
<td>32</td>
<td>32</td>
</tr>
<tr>
<td>FLC</td>
<td>1</td>
<td>0.25</td>
</tr>
<tr>
<td>VRC</td>
<td>0.5</td>
<td>8</td>
</tr>
<tr>
<td>Ravu</td>
<td>0.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Lip-AMB</td>
<td>0.5</td>
<td>0.06</td>
</tr>
<tr>
<td>Lip-NYT</td>
<td>0.5</td>
<td>0.06</td>
</tr>
<tr>
<td>ABLC</td>
<td>0.25</td>
<td>0.06</td>
</tr>
<tr>
<td>Casp</td>
<td>0.125</td>
<td>0.125</td>
</tr>
<tr>
<td>Mica</td>
<td>0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

*a Results are representative of at least two separate experiments. Lip-AMB and Lip-NYT are the lipid complex formulations of AMB and NYT. For details of methods used, see text. *, unable to determine MIC.*
Rabbit Model of *Candida albicans* Biofilm Infection: Liposomal Amphotericin B Antifungal Lock Therapy

Matthew K. Schinabeck,¹,² Lisa A. Long,¹ Mohammad A. Hossain,³ Jyotsna Chandra,³ Pranab K. Mukherjee,³ Sotohy Mohamed,¹ and Mahmoud A. Ghannoum¹,*

Center for Medical Mycology and Mycology Reference Laboratory, Department of Dermatology,¹ and Division of Infectious Diseases, Department of Medicine,² University Hospitals of Cleveland and Case Western Reserve University, Cleveland, Ohio 44106

Intraluminal surface following 7 days therapy with:

Panel A: Saline

Panel B: L-AmpB

Panel C: Fluconazole
Invasive candidiasis in the intensive care unit

Luis Ostrosky-Zeichner, MD, FACP; Peter G. Pappas, MD, FACP

Objective: To review epidemiologic trends, advances in diagnosis and susceptibility testing, therapeutic options and guidelines, and management strategies for invasive candidiasis as relevant to the intensive care unit physician.

Data Sources, Study Selection, Data Extraction, Data Synthesis: Nonstructured review of peer-reviewed original articles, review articles, abstracts, guidelines, and consensus statements appearing in Medline, major scientific journals, and conference proceedings.

Conclusions: Invasive candidiasis is a problem associated with substantial morbidity and mortality that is highly prevalent in the intensive care unit setting. Recent epidemiologic studies have shown a trend toward increasing numbers of infections and a shift toward infections caused by non-albicans Candida species. Guidelines for the management of these diseases have been published and recommend amphotericin B, fluconazole, or caspofungin as the primary therapeutic option. The choice of agent should depend on local epidemiology and patient factors. The role of newer antifungal agents for this population, such as the new azoles and echinocandins, remains to be determined. Priority areas of research include diagnostics, risk identification, and management strategy assessment such as prophylactic, preemptive, and empirical therapy. (Crit Care Med 2006; 34:857–863)

Key Words: invasive candidiasis; intensive care unit; review; therapy; prophylaxis; antifungals
## Invasive Candidiasis in the ICU

<table>
<thead>
<tr>
<th>DRUG</th>
<th>USUAL DOSE FOR INVASIVE CANDIDIASIS</th>
<th>COMMENTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional amphotericin B</td>
<td>0.6-1.0 mg/kg IV every 24hrs</td>
<td>Infusion related reactions common, as well as arrhythmias. Monitor for nephrotoxicity (~30%)</td>
</tr>
<tr>
<td>Liposomal AmpB</td>
<td>3-5mg/kg IV every 24hrs</td>
<td>Broad spectrum with few infusion related reactions (especially with slow infusion) and less than 10% nephrotoxicity.</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>400-800mg PO or IV every 24hrs</td>
<td>PO to IV bioequivalence &gt;90%, even in patients who have gone through GI surgery. Some resistance and drug interactions. Mild to moderate increases in transaminase levels.</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>400 PO or IV every 24hrs</td>
<td>Less active than fluconazole against Candida. Oral form is not well absorbed and must be careful with IV formulation in renal failure. Many drug interactions</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>IV: 6 mg/kg IV every 12 hrs loading followed by 3mg/kg IV every 12 hrs PO: 800 mg loading followed by 200mg every 12 hrs</td>
<td>Many drug interactions that require careful review of concomitant medications. Visual and hepatic side effects common. IV formulation cannot be used in renal failure.</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>70mg loading followed by 50mg every 24hrs</td>
<td>Increases in liver function tests common. Avoid in hepatic failure and Child-Pugh B or C. Interactions with rifampin require adjusting and interaction with cyclosporine not fully characterized.</td>
</tr>
<tr>
<td>Micafungin</td>
<td>100-150 mg IV every 24hrs</td>
<td>Not FDA-approved for this indication but open label data shows efficacy.</td>
</tr>
</tbody>
</table>

Ostrosky-Zeichner L & Pappas PG. Crit Care Med 2006; 34: 857
Delaying the Empirical Treatment of Candidemia

Hospital mortality

% Hospital mortality

n=157 patients with candidemia

<12 12-24 24-48 >48

Hours when antifungal therapy applied after blood cultures taken

Primary Diagnosis in Patients with Invasive Aspergillosis

595 patients

- BMT/Allo 25%
- Hematologic 28%
- Pulm 9%
- BMT/Auto 7%
- Other Immune 6%
- Solid Transplant 9%
- AIDS 8%
- Other 6%
- None 2%

Incidence of Aspergillosis After Allogeneic SCT, 1993-1998

Marr KA, et al. Blood 2002;100:4358
Invasive Aspergillosis Mortality

Between 1995-99
50 studies,
1941 patients

Changing Spectrum of Invasive Molds

Incidence per 1000 Patient Days

Incidence of Zygomycosis


n=929

Number of Cases

Time (Decade)

1940s 1950s 1960s 1970s 1980s 1990s

Diabetes
Injection Drug Users
No Underlying Condition
Deferoxamine Therapy
Solid Organ Transplantation
Bone Marrow Transplantation
Malignancy
1-year Survival Rate

Classical Risk Factors for Invasive Aspergillosis

• Hematological malignancies
  – Leukemia
  – MDS
  – SCT
  – GVHD
  – Prolonged neutropenia
  – Induction chemo

• Critically ill
  – COPD

• HIV/AIDS

• Transplant patients:
  – Lung, liver, heart, renal
  – Liver transplant
  – Acute/ chronic rejection
  – Steroids
  – Tacrolimus
  – Renal failure
  – CMV
Range of Activity for Selected Pathogens

<table>
<thead>
<tr>
<th>AMB</th>
<th>FCZ</th>
<th>ITZ</th>
<th>VZ</th>
<th>PCZ</th>
<th>RCZ</th>
<th>CF</th>
<th>MF</th>
<th>AF</th>
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<tbody>
<tr>
<td>Candida albicans</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td>Candida tropicalis</td>
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<td></td>
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<tr>
<td>Candida parapsilosis</td>
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<td></td>
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<td>Candida krusei</td>
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<tr>
<td>Candida glabrata</td>
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<tr>
<td>Cryptococcus neoformans</td>
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<tr>
<td>Aspergillus fumigatus</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Mucor spp</td>
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<tr>
<td>Rhizopus spp</td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Fusarium spp</td>
<td></td>
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Polyene: AMB = Amphotericin B
Azole: FCZ = Fluconazole; ITZ = Itraconazole; VZ = Voriconazole; PCZ = Posaconazole; RCZ = Ravuconazole
Echinocandin: CF = Caspofungin; MF = Micafungin; AF = Anidulafungin

Antifungal Strategies

Asymptomatic Fungal Infection

Specific Prophylaxis

Empirical

Pre-emptive

Prolonged febrile neutropenia

Radiology, cultures, serology

Non-specific Infiltrates, cultures

Prophylaxis

Asymptomatic

>15%

0%

Fungal Infection

Risk

Courtesy of E. Annaise
Diagnosis: CT SCAN

Halo sign

<table>
<thead>
<tr>
<th></th>
<th>D0</th>
<th>D3</th>
<th>D7</th>
<th>D14</th>
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<tbody>
<tr>
<td>%</td>
<td>96%</td>
<td>68%</td>
<td>22%</td>
<td>19%</td>
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Non-specific consolidation

<table>
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<th>D3</th>
<th>D7</th>
<th>D14</th>
</tr>
</thead>
<tbody>
<tr>
<td>%</td>
<td>0%</td>
<td>8%</td>
<td>28%</td>
<td>63%</td>
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Air crescent sign

<table>
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<th>D0</th>
<th>D3</th>
<th>D7</th>
<th>D14</th>
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<tbody>
<tr>
<td>%</td>
<td>0%</td>
<td>8%</td>
<td>28%</td>
<td>63%</td>
</tr>
</tbody>
</table>

Amphotericin B Deoxycholate

The good, the bad...and the ugly

If this is the cure, I’ll go for the disease...

Courtesy of Ben De Pauw
Echinocandins
Identical Triplets!!

- All given 50-150 mg/d (Higher doses possible)
- Primary use candidiasis (including fluconazole resistant strains)
- Salvage for invasive aspergillosis
- Combined with vori or AmpB
- No major toxicity
- Few drug interactions (not metabolized by cytochromes)
- No effect for cryptococcosis and trichosporonosis

From Graybill JR. ICAAC-2005
Voriconazole

**Good things**
- 90% oral absorption
- 60% CNS penetration
- Broad spectrum of activity
- Drug of choice for invasive aspergillosis

**Bad things**
- Complex clearance by cytochromes
  - Drug levels variable
  - Drug interactions
- Photopsia, liver toxicity, skin rash
- Iv vehicle nephrotoxic
- No effect against zygo and scedosporium
- No drug in urine

From Graybill JR. ICAAC-2005
**Posaconazole**

<table>
<thead>
<tr>
<th>Good things</th>
<th>Bad things</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Not metabolized by cytochromes</td>
<td>• Absorption less than vori</td>
</tr>
<tr>
<td>• Toxicity = Fluconazole</td>
<td>• Very few levels in urine</td>
</tr>
<tr>
<td>• Activity similar to vori + zygomycosis</td>
<td>• No iv drug available yet</td>
</tr>
</tbody>
</table>

From Graybill JR. ICAAC-2005
Initial Therapy for Invasive Aspergillosis

Voriconazole vs. AmB-d

Responses at week 12
- Amphotericin B-d: 32%
- Voriconazole: 53%

Survival at week 12
- Voriconazole: 71%

AmBiLoad

Responses at EOT
- L-AmB 10 mg/kg/day: 46%
- L-AmB 3 mg/kg/day: 50%

Survival at week 12
- L-AmB 3 mg/kg/day: 72%

A Fungal Achilles’ Heel

Cell growth

Erg
Calcineurin
Hsp90

Cell death

Drug resistance cannot develop

Cyclosporin A
FK506

Erg
Calcineurin
Hsp90

Drug resistance can develop

Fluconazole
Calcineurin
Hsp90

Geldanamycin

Heitman J. Science 2005;309:2175
Cowen LE, Lindquist S. Science 2005;309:2185
Efungumab (Mycograb®) plus L-AmpB vs L-AmpB in Invasive Candidiasis

• Prospective, randomized, double-blind trial
  – Human recombinant antibody to Hsp90 plus LAmPB vs LAmPB plus placebo
  – Patients with cultured confirmed candidiasis
  – 117 patients with MITT from 10 European and 2 US centers

Efungumab (Mycograb®) plus L-AmpB vs L-AmpB in Invasive Candidiasis

Overall Clinical Mycologic Mortality

Response at day 10

P<.001
P<.025

Primary Antifungal Prophylaxis
Unresolved Issues

• To whom?
• Effective?
  – Prevention of yeast and mould infections
  – Total and fungus-related mortality
  – Decrease in empirical antifungal therapy
• Increased toxicity?
• Selection of resistance?
• Serum level monitoring?
2nd European Conference on Infections in Leukemia

2007 update of the ECIL-1 guidelines for Antifungal prophylaxis in leukemia patients, including allogeneic HSCT recipients

Johan Maertens (B, chair), Pascale Frére (B), Cornelia Lass-Flörl (Au), Werner Heinz (D), Oliver Cornely (D, co-chair)

September 28 - 29 2007, Juan-les-Pins - France
Do you Use Antifungal Prophylaxis? 
(N= 38)
# Do you Use Antifungal Prophylaxis?
(N= 38)

<table>
<thead>
<tr>
<th></th>
<th>Allo</th>
<th>Auto</th>
<th>Induction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluco</td>
<td>57.1</td>
<td>57.1</td>
<td>55</td>
</tr>
<tr>
<td>Itra caps</td>
<td>7.1</td>
<td>9.5</td>
<td>5</td>
</tr>
<tr>
<td>Itra sol</td>
<td>21.4</td>
<td>14.3</td>
<td>20</td>
</tr>
<tr>
<td>Itra iv</td>
<td>3.6</td>
<td>4.8</td>
<td>5</td>
</tr>
<tr>
<td>Vorico</td>
<td>3.6</td>
<td>4.8</td>
<td>5</td>
</tr>
<tr>
<td>Ambisome</td>
<td>3.6</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Nystatin</td>
<td>10.7</td>
<td>14.3</td>
<td>15</td>
</tr>
<tr>
<td>Non-abs amphoB</td>
<td>17.9</td>
<td>19.0</td>
<td>25</td>
</tr>
<tr>
<td>AmphoB aerosol</td>
<td>7.1</td>
<td>-</td>
<td>-</td>
</tr>
</tbody>
</table>
Oral Fluconazole Prophylaxis in Neutropenic Patients - A Metaanalysis

• 16 randomized controlled trial
• 3734 patients
  – 400 mg/gün, 1539 hasta (8 çalışma)
  – 50-200 mg/gün, 2195 hasta (8 çalışma)
• Karşılaştırmalı rejimleri
  – Plasebo
  – Tedavisiz grup
  – Oral poliyenler

Meta-analysis of Oral Fluconazole Prophylaxis Trials in Neutropenics

• 16 randomized controlled trials
• 3734 patients included
  – 400 mg/d, 1539 pts (8 trials)
  – 50-200 mg/d, 2195 pts (8 trials)
• Comparative regimens
  – Placebo
  – No treatment
  – Oral polyenes

Meta-analysis of Oral Fluconazole Prophylaxis Trials in Neutropenics

16 Trials

- Only BMT pts 2 trials
- BMT and others 8 trials
- No BMT pts 6 trials

1373 patients

Death & Invasive Fungal Infection

Fungus-related death

Invasive fungal infection

Superficial Fungal Infections

Favors control

Favors fluconazole

Dose of Fluconazole

Superficial fungal infection

Empiric Use of Amphotericin B

Systemic Fungal Infections

- Favors control
- Favors fluconazole

- Systemic Aspergillosis
- Systemic C. krusei or T. glabrata

Colonization by *C. krusei* or *T. glabrata*


Favors control

Favors fluconazole

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**C. krusei** colonization

**T. glabrata** colonization

Polyens

- Oral suspension has no effect
- Aerosol Amp B has no effect
  - Prospective randomised trial: *Blood 1999;93:3654*
- Iv Fungizone® has no effect
  - 0.1-0.2 mg/kg/d or 0.5 mg/kg 3 times weekly
    - Nephrotoxic
- Lipid formulations have no effect
  - High cost
  - No studies with statistical power
Echinocandins

• Micafungin is superior than fluconazole
  – 882 SCT patients
    • Randomized, double-blind trial
    • Adults and children
  – Efficacy 83% vs 73% (p=.03)
  – Colonization, breakthrough infection, mortality and toxicity equal in both arms

Itraconazole

- Oral capsule similar to placebo or fluconazole 100 mg/d
- 400 mg/d oral solution found effective in a metaanalysis with 3597 patients*
  - Significant decrease in
    - Invasive fungal infections and related mortality
    - Intravascular aspergillosis
- In SCT patients 200 mg iv followed by 200 mg bid oral long term use is superior than fluconazole
  - Toxicity
  - Intolerance

Posaconazole

- **Allo-GVHD**
  - Double-blind, randomized
  - Acute or chronic GVHD in SCT patients
  - Posaconazole 200 mg tid, po or 400 mg od, po fluconazole
  - Given up to 112 d
  - 2 m follow up after completion of treatment

- **AML-MDS**
  - Prospective, randomized, investigator blind
  - >7 d neutropenic patients with newly diagnosed or first relapse AML or MDS
  - Posaconazole 200 mg tid or 400 mg od, po susp flu or 200 mg bid, itra po susp
  - Given at each chemo up to 84 d
  - Follow up to 100 d after randomization

Incidence of Proven/Probable IFIs While on Treatment*

**HSCT + GVHD**

- **All IFIs**
  - **POS**: 7/291 (2%)
  - **Comparator**: 22/288 (8%)
  - *P* = .0038

- **Invasive aspergillosis**
  - **POS**: 3/291 (1%)
  - **Comparator**: 17/288 (6%)
  - *P* = .0013

**AML/MDS**

- **All IFIs**
  - **POS**: 7/304 (2%)
  - **Comparator**: 25/298 (8%)
  - *P* = .0009

- **Invasive aspergillosis**
  - **POS**: 2/304 (1%)
  - **Comparator**: 20/298 (7%)
  - *P* = .0001

*Populations are all-treated (ITT subset who received ≥1 dose of study drug) in HSCT + GVHD study and ITT population in AML/MDS study.
†Primary end point.
Incidence of Proven/Probable IFIs During Fixed Time Period*

**HSCT + GVHD**
- **All IFIs**: 5% (16/301) vs. 9% (27/299), $P = .0740$
- **Invasive aspergillosis**: 2% (7/301) vs. 7% (21/299), $P = .0059$

**AML/MDS**
- **All IFIs**: 5% (14/304) vs. 11% (33/298), $P = .0031$
- **Invasive aspergillosis**: 1% (4/304) vs. 9% (26/298), $P < .0001$

*Within 112 days and 100 days postrandomisation for the HSCT + GVHD and AML/MDS studies, respectively.

†Primary end point.
Antifungal Prophylaxis
ECIL 2 2007

• Allogeneic transplantation
  – Fluconazole 400 mg/d iv/po (Al)
  – Itraconazole 200 mg iv followed by 200 mg bid, Os (BI)
  – Posaconazole 200 mg tid, Os (AI)
  – Micafungin 50 mg/d iv (Cl)
  – Polyene i.v. (Cl)

• Nonablative chemotherapy
  – Fluconazole 50-400 mg/d i.v./po (Cl)
  – Itraconazole 2.5 mg/kg bid, Os (Cl)
  – Posaconazole 200 mg tid Os (AI)
  – No data with candins
  – Polyene iv (Cl)
Recommendations for Prevention of Nosocomial Aspergillosis

- Air filtration
- Avoidance of dust generating activities
- Isolation of hospital construction sites
- Protection when entering areas with unfiltered air
- No unprocessed food
- No potted ornamental plants and dry flowers
## Air Filtration And Aspergillosis

<table>
<thead>
<tr>
<th>Type of filtration</th>
<th>Spores (cfu/m³)</th>
<th>Incidence of aspergillosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-HEPA</td>
<td>2.0</td>
<td>15 %</td>
</tr>
<tr>
<td>Post-HEPA (room)</td>
<td>0.8</td>
<td>8 %</td>
</tr>
<tr>
<td>Post-HEPA (corridor)</td>
<td>0.14</td>
<td>4 %</td>
</tr>
<tr>
<td>Post-HEPA (rooms with whole-wall LAF + HEPA)</td>
<td>0.009</td>
<td>-</td>
</tr>
</tbody>
</table>

Rhame 1984, Sherertz 1987
What Future Holds?

• Manage better diagnostic techniques
  – HRCT scan
  – Galactomannan, beta-glucan
  – PCR

• Better immunomodulation

• How to use combination therapy, if ever?
  – targeted?
  – preemptive?
  – primary?
  – salvage?
  – with non-antibiotic agents?