OPTIONS AND LIMITATIONS OF ANTIFUNGAL DRUGS FOR VARIOUS FUNGAL INFECTIONS IN TRANSPLANT RECIPIENTS
A GOOD MATCH?
PACE OF DEVELOPMENT OF IMMUNOSUPPRESSIVE AGENTS

1950
1960
1970
1980
1990
2000

mycophenolate
rituximab
tacrolimus
sirolimus
leflunomide
bentamab
dacluzimab
alemtuzumab
basiliximab
methotrexate
cyclophosphamide
azathioprine
prednison
cyclosporin
ATG / OKT3
TRENDS INCIDENCE
INVASIVE FUNGAL INFECTIONS
Pagano et al. Haematologica 2006; 91:1068-1075

![Graph showing trends in incidence of Aspergillus and Candida fungal infections over years from 1999 to 2003.](image-url)
WELCOME TO MYCOLOGY

MOULDS
- Aspergillus
- Fusarium
- Zygo/mucormycetes

YEASTS
- Candida

cell membrane
- ergosterol

cell wall
- chitin
- mannoproteins
- β-glucan

eukaryotic
MODE OF ACTION OF ANTIFUNGALS

- acetyl-Co-A
- squalenes
- azoles
- lanosterol
- ergosterol
- amphotericin B
- β (1,3)-D-glucan synthesis
- nucleic acid synthesis
- 5-flucytosine
- candins
CLASSES OF ANTIFUNGALS

- 5-flucytosine
- azoles
- amphotericin B
- candins
PACE OF DEVELOPMENT OF NEW ANTIFUNGAL AGENTS

Adapted from Rex & Edwards, 1997

Amphotericin B
Nystatin
Griseofulvin

Flucytosine
Ketoconazole
Miconazole
Terbinafine
Fluconazole
Itraconazole
Posaconazole
Voriconazole
Isavuconazole
Caspofungin
Anidulafungin
Micafungin
AmBisome
Amphocil
Abelcet

<table>
<thead>
<tr>
<th>ASPERGILLUS</th>
<th>MUCOR</th>
<th>FUSARIUM</th>
<th>Scedosporia</th>
<th>Alternaria</th>
<th>Candida Resistant</th>
<th>Malassezia</th>
<th>Other Yeasts</th>
<th>Cryptococcus</th>
<th>Endemic Mycos</th>
<th>Penicillium</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>candins</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>polyenes</strong></td>
<td></td>
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<tr>
<td>(lipid forms)</td>
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<td><strong>new azoles</strong></td>
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<tr>
<td><strong>itraconazole</strong></td>
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</tr>
<tr>
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</tr>
</tbody>
</table>
SELECTION OF A DRUG

Criteria:

• Established efficacy in proven disease
• Safety and compatibility / interactions
• Intravenous and oral formulation
RATIONALE FOR A TREATMENT

NONE

CASE REPORT

COMPASSIONATE USE

PHASE II TRIAL

HISTORICAL CONTROLS

MATCHED CONTROLS

RANDOMIZED TRIAL

DOUBLE BLIND RANDOMIZED TRIAL

STRATIFIED DOUBLE BLIND RANDOMIZED TRIAL
CLINICAL RESEARCH – WHO PAYS??

F.D.A.

research funds

community

pharmaceutical companies

protocol
MAJOR CAUSE OF CONFUSION

Use of strategic trials
(empirical and prophylactic)
to assess
drug efficacy
DIFFICULTIES IN THE ASSESSMENT OF ANTIFUNGALS

- Appropriate use of diagnostics at start and at end of therapy
- Evolution of the underlying disease regression-progression
- Concurrent medication interaction, immunosuppression
SURVIVAL OF ASPERGILLOSIS IN RELATION TO PRESUMED RISK FACTORS

RECOMMENDATIONS

RANDOMIZED TRIAL
CONSISTENT SERIES
EXPERT / CONSENSUS

SOLID CLINICAL EVIDENCE
REASONABLE CLINICAL EVIDENCE
TRIVIAL CLINICAL EVIDENCE
# RECOMMENDATIONS

<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
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</thead>
<tbody>
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<td>🟢</td>
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<tr>
<td>B</td>
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<tr>
<td>C</td>
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<tr>
<td></td>
<td>A1</td>
<td>A1 II</td>
<td>A1 III</td>
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<td>A1</td>
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<th>B1 III</th>
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<td>B2</td>
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<tr>
<td>B3</td>
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<table>
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<th></th>
<th>C1</th>
<th>C1 II</th>
<th>C1 III</th>
</tr>
</thead>
<tbody>
<tr>
<td>C1</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C2</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>C3</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
487 FUNGAL INFECTIONS IN TRANSPLANT RECIPIENTS

Pappas et al. ICAAC, Chicago 2003; abstr M-1010

- Candida
- Aspergillus and other moulds
- Pneumocystis
- Endemic
- Crypto
487 FUNGAL INFECTIONS IN TRANSPLANT RECIPIENTS
Pappas et al. ICAAC, Chicago 2003; abstr M-1010

Candida
ANTI-CANDIDA DRUGS

**Selection criteria:**

- Established efficacy in proven disease
- Safety and compatibility / interaction
Selection criteria:

• Established efficacy in proven disease

• Safety and compatibility / interaction
POPULATION WITH INVASIVE CANDIDIASIS

Invasive candidiasis eligible for clinical trial
COMPARISON OF RESULTS FROM CLINICAL TRIALS ON CANDIDEMIA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Response</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole 400 mg/day</td>
<td>72%</td>
<td>39%</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>79%</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>62%</td>
<td>40%</td>
</tr>
<tr>
<td></td>
<td>71%</td>
<td>34%</td>
</tr>
<tr>
<td>Micafungin</td>
<td>74%</td>
<td>30%</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>74%</td>
<td>23%</td>
</tr>
<tr>
<td>Anidulafungin</td>
<td>65%</td>
<td>36%</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>76%</td>
<td>30%</td>
</tr>
<tr>
<td></td>
<td>15%</td>
<td>23%</td>
</tr>
</tbody>
</table>
CASPOFUNGIN VERSUS AMPHOTERICIN B FOR CANDIDEMIA

CASPOFUNGIN
70/50 mg/d
n = 92    candidemia

AMPHOTERICIN B
0.6-1.0 mg/kg/d
n = 94

<table>
<thead>
<tr>
<th>Overall response</th>
<th>Non-albicans response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Caspofungin</td>
<td>80%</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>70%</td>
</tr>
</tbody>
</table>
CASPOFUNGIN VERSUS AMPHOTERICIN B
CLINICAL ACTIVITY AGAINST CANDIDA SPECIES
Sable et al. ECCMID, Milan 2002; Abstr

- albicans: 100%
- parapsilosis: 100%
- tropicalis: 81%
- krusei: 77%
- glabrata: 85%
- guillermondii: 64%

- response to AMPHOTERICIN B:
  - albicans: 58%
  - parapsilosis: 66%
  - tropicalis: 71%
  - krusei: 80%
  - glabrata: 65%
  - guillermondii: 58%
Double-blind comparison, n = 541

Rate of Favorable Response

- Micafungin 100 mg/d (n=264): 90%
- AmBisome 3 mg/day (n=267): 90%

(neutropenia)
MICAFUNGIN versus CASPOFUNGIN FOR CANDIDIASIS – OUTCOME PER SPECIES


<table>
<thead>
<tr>
<th>Species</th>
<th>Micafungin (%)</th>
<th>Caspofungin (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>albicans</td>
<td>77%</td>
<td>68%</td>
</tr>
<tr>
<td>glabrata</td>
<td>74%</td>
<td>68%</td>
</tr>
<tr>
<td>tropicalis</td>
<td>85%</td>
<td>67%</td>
</tr>
<tr>
<td>krusei</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>parapsilosis</td>
<td>75%</td>
<td>75%</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td>74%</td>
</tr>
</tbody>
</table>
COMPARISON OF RESULTS FROM CLINICAL TRIALS ON CANDIDEMIA

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<td>40%</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>74%</td>
<td>34%</td>
</tr>
</tbody>
</table>
Non-neutropenics double-blind n=245

Survival in days

0 10 20 30 40 50 60

Anidulafungin
Fluconazole
ANIDULAFUNGIN versus FLUCONAZOLE IN CANDIDEMIA AND INVASIVE CANDIDOSIS

anidulafungin

<table>
<thead>
<tr>
<th>Species</th>
<th>Anidulafungin</th>
<th>Fluconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td>albicans</td>
<td>87%</td>
<td>81%</td>
</tr>
<tr>
<td>glabrata</td>
<td>69%</td>
<td>88%</td>
</tr>
<tr>
<td>tropicalis</td>
<td>76%</td>
<td>64%</td>
</tr>
<tr>
<td>parapsilosis</td>
<td>95%</td>
<td>60%</td>
</tr>
</tbody>
</table>
VORICONAZOLE VS AMPHO B FOLLOWED BY FLUCONAZOLE FOR CANDIDEMIA


VORICONAZOLE 6 → 3 mg/ kg

n = 422; 2:1 randomization

AMPHO B → FLUCONAZOLE

248

Favorable response EOT

65%

12 weeks

41%

36%

71%

41%

42%

COMPARISON OF RESULTS FROM CLINICAL TRIALS ON CANDIDEMIA

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<td>76%</td>
<td>23%</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>65%</td>
<td>36%</td>
</tr>
</tbody>
</table>
STRATEGIC TRIAL as a DRUG-EFFICACY TRIAL
OUTCOME OF CANDIDEMIA IN THE UK 1997-99

Day 30 mortality overall (n = 163) 26%

- No antifungal (n=31) 58%
- Fluconazole (n=76) 24%
- Amphotericin B (n=39) 18%
<table>
<thead>
<tr>
<th>Condition</th>
<th>AmBisome</th>
<th>Abelcet</th>
<th>Amphocil</th>
</tr>
</thead>
<tbody>
<tr>
<td>Candidiasis</td>
<td>80%</td>
<td>75%</td>
<td>59%</td>
</tr>
<tr>
<td>Aspergillosis</td>
<td>61%</td>
<td>46%</td>
<td>34%</td>
</tr>
<tr>
<td>Cryptococcosis</td>
<td></td>
<td>67%</td>
<td>45%</td>
</tr>
<tr>
<td>Fusariosis</td>
<td></td>
<td>83%</td>
<td>25%</td>
</tr>
<tr>
<td>Zygomycosis</td>
<td></td>
<td>72%</td>
<td>100%</td>
</tr>
</tbody>
</table>

*n = number of patients treated with each formulation.*
FEASIBILITY OF CASPOFUNGIN ALONE FOR CANDIDEMIA IN CANCER PATIENTS
Sipsas et al. ECCMID, Barcelona 2008; Abstract P-1019

65 candidemias

caspofungin 7 days

fungus related mortality

11%

success

80%
<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>ampho B’s candins voriconazole fluconazole</td>
<td></td>
<td>G(M)-CSF</td>
</tr>
<tr>
<td>B</td>
<td>fluconazole</td>
<td>ampho B followed by itraconazole</td>
<td>early start of antifungal treatment</td>
</tr>
<tr>
<td>C</td>
<td>posaconazole combinations</td>
<td>posaconazole combinations</td>
<td>posaconazole combinations</td>
</tr>
</tbody>
</table>

2007 EFFICACY ANTI-CANDIDA DRUGS
UNDERLYING DISEASE AND RESPONSE TO TREATMENT OF CANDIDEMIA

Selection criteria:

• Established efficacy in proven disease

• Safety and compatibility / interaction
Selection criteria:

• Established efficacy in proven disease

• Safety and compatibility / interaction
THERAPEUTIC WINDOW OF ANTIFUNGAL AGENTS

human

fungus

synthesis of

nucleic acid

protein

cholesterol

ergosterol

chitin

glucan

mannan
<table>
<thead>
<tr>
<th>NO NEPHROTOXIC AGENTS</th>
<th>19</th>
<th>0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYCLOSPORIN A</td>
<td>23</td>
<td>13%</td>
</tr>
<tr>
<td>OTHER DRUGS*</td>
<td>84</td>
<td>11%</td>
</tr>
<tr>
<td>CYCLOSPORIN N + OTHER</td>
<td>101</td>
<td>21%</td>
</tr>
</tbody>
</table>

* tacrolimus, foscarnet, cisplatinum, ifosfamide, aminoglycoside
VORICONAZOLE vs AMPHO B – FLUCONAZOLE
PATIENTS WITH CREATININE INCREASE

SAFETY OF LIPOSOMAL AMPHOTERICIN B IN THE ICU
Alvarez-Lerma et al. ECCMID, Barcelona 2008; Abstract P-1032

Retrospective!

179 ICU patients with sepsis or shock

61% on nephrotoxic drugs

Liposomal ampho B 3.5 mg/kg/day

25% adverse events

2% serious drug change for toxicity

0.5%
MICAFUNGIN versus AMBISOME IN CANDIDEMIA AND INVASIVE CANDIDOSIS

Double-blind comparison, n = 541

Change Glomerular Filtration Rate

-60 -40 -20 0 20 40

micafungin 100 mg/d (n=264)
AmBisome 3 mg/day (n=267)
SAFETY OF CASPOFUNGIN IN COMBINATION WITH IMMUNOSUPPRESSANTS
Kartsonis et al. ICAAC, Washington 2005; Abstract M-956

66 cases from phase III trials

- 6 cyclosporin
- 58 tacrolimus
- 3 serolimus
- 22 mycophenolate

Caspofungin: 70 → 50 mg/day

Adverse events:
- Hypercalcemia on tacrolimus + mycophenolate
CANDIDA INFECTIONS

- amphotericin B
- fluconazole
- liposomal amphotericin B
- voriconazole
- candins
FUNGAL INFECTIONS IN TRANSPLANT RECIPIENTS

Pappas et al. ICAAC, Chicago 2003; abstr M-1010

Aspergillus species
Invasive fungus

DIAGNOSIS OF A FUNGUS

4% in trials!!

REPRESENTATIVE!?
Selection criteria:

• Established efficacy in proven disease
• Safety and compatibility / interaction
• Miscellaneous
Selection criteria:

• Established efficacy in proven disease
• Safety and compatibility / interaction
• Miscellaneous
RESPONSE TO TREATMENT FOR ASPERGILLOSIS IN NORMAL PRACTICE


595 patients

% response

Ampho B

32%
RESULTS FIRST LINE TREATMENT OF INVASIVE ASPERGILLOSIS


% response

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% Response</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampho B</td>
<td>42/133 (32%)</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>76/144 (53%)</td>
</tr>
</tbody>
</table>
VORICONAZOLE versus AMPHOTERICIN B:
RESPONSE TO FIRST MODIFICATION
Patterson et al. Clin Infect Dis 2005; 41:1448-1452

- Voriconazole alone: 53% (n=92)
- Amphotericin B + lipid preparation: 32% + 4% (n=73)
VORICONAZOLE VERSUS AMFOTERICIN B IN INVASIVE ASPERGILLOSIS: SURVIVAL
VORICONAZOLE VERSUS AMPHOTERICIN B: RESPONSE OF SUBGROUPS


AMPHOTERICIN B FAVORS VORICONAZOLE

<table>
<thead>
<tr>
<th>Category</th>
<th>Success Rates (%, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>133 (-20, 0, 20, 40, 60)</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>112 (-20, 0, 20, 40, 60)</td>
</tr>
<tr>
<td>Extra Pulmonary</td>
<td>21 (-20, 0, 20, 40, 60)</td>
</tr>
<tr>
<td>Allogenic BMT</td>
<td>30 (-20, 0, 20, 40, 60)</td>
</tr>
<tr>
<td>Other hematol diseases</td>
<td>84 (-20, 0, 20, 40, 60)</td>
</tr>
<tr>
<td>Other immunosuppr</td>
<td>19 (-20, 0, 20, 40, 60)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>60 (-20, 0, 20, 40, 60)</td>
</tr>
<tr>
<td>Non-neutropenia</td>
<td>73 (-20, 0, 20, 40, 60)</td>
</tr>
<tr>
<td>Other hematol diseases</td>
<td>84 (-20, 0, 20, 40, 60)</td>
</tr>
<tr>
<td>Other immunosuppr</td>
<td>26 (-20, 0, 20, 40, 60)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>63 (-20, 0, 20, 40, 60)</td>
</tr>
<tr>
<td>Non-neutropenia</td>
<td>81 (-20, 0, 20, 40, 60)</td>
</tr>
<tr>
<td></td>
<td>Voriconazole</td>
</tr>
<tr>
<td>---------------------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Central Nervous System</td>
<td>35% (n=81)</td>
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</tr>
</tbody>
</table>

**VORICONAZOLE AGAINST CENTRAL NERVOUS SYSTEM ASPERGILLOSIS**

Schwartz et al Blood 2005; 106:2641-2645
RESULTS FIRST LINE TREATMENT OF INVASIVE ASPERGILLOSIS


<table>
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<tr>
<td>Voriconazole</td>
<td>76/144 (53%)</td>
</tr>
<tr>
<td>Lipo-AmB</td>
<td>53/107 (50%)</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>18/32 (56%)</td>
</tr>
</tbody>
</table>
CASPOFUNGIN AS FIRST-LINE THERAPY AGAINST ASPERGILLOSIS IN NEUTROPENIC PATIENTS

Viscoli et al. J Chemother 2007; 19, suppl 5:36

61 proven/prob aspergillosis

Chemotherapy acute leukemia and autologous stem cell recipients

51 MITT

- favorable
- stable
- progression

51%

34%

15%

54% 12 weeks survival
THE LIPID FORMULATIONS
HIGH VERSUS STANDARD DOSE LIPO AMPHO-B FOR INVASIVE MOULD INFECTIONS

lipos ampho B 10 mg/ kg x 14 followed by 3 mg/ kg/ day

201 proven & probable Invasive mould infections

End of treatment Favorable response

nephrotoxicity

hypokalaemia

Survivors 12 weeks

94 46%

31%

30%

59%

107 50%

14%

16%

72%
POSACONAZOLE - ABELCET
TRIALS FIRST LINE TREATMENT ASPERGILLOSIS
POSACONAZOLE FACTS

- **oral formulation only!**

- selection of less sick patients

- no data on first line therapy aspergillosis

DATA FROM RESCUE / SALVAGE THERAPY
PANDORRA’S BOX OF SALVAGE CASES

creatinine increase
renal failure
toxicity
3 days stable
life-threatening progression
treatment refractory
hyperpyrexia
a single shiver
intolerance

!subjective criteria!
PANDORRA’S BOX OF SALVAGE CASES

- toxicity treated with what? how much??
- intolerance
- treatment refractory
- co-medication?
- evolvement underlying disease??

What is treated? How much?
SALVAGE FOR INVASIVE ASPERGILLOSIS

Refractory / intolerant amphotericin B

- Posaconazole: n=107, response 40%
- Amphotericin B lipid complex: n=146, response 40%
- Caspofungin: n=146, response 40%
- ‘toto clifun’: n=xxx, response 40%
EVOLUTION OF ELEMENTS
DETERMINING SUCCESS OR FAILURE
POSACONAZOLE FACTS

itraconazole

posaconazole

voriconazole
## ITRACONAZOLE FOR ASPERGILLOSIS


<table>
<thead>
<tr>
<th>Condition</th>
<th>Number</th>
<th>Success at end of treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALL PATIENTS</strong></td>
<td>76</td>
<td>44%</td>
</tr>
<tr>
<td>Granulocytopenia / Cancer</td>
<td>13</td>
<td>62%</td>
</tr>
<tr>
<td>Bone marrow transplant</td>
<td>8</td>
<td>50%</td>
</tr>
<tr>
<td>AIDS</td>
<td>16</td>
<td>0%</td>
</tr>
</tbody>
</table>
EFFICACY OF ANTIFUNGALS IN NEUTROPENIC PATIENTS

- Voriconazole
- AmBisome
- Amphocil
- Caspofungin
- Ampho B

[Bar chart showing the efficacy of antifungals for neutropenic patients]
<table>
<thead>
<tr>
<th></th>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>voriconazole</td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2008 EFFICACY ANTI-ASPERGILLUS DRUGS
### 2008 Efficacy Anti-Aspergillus Drugs

<table>
<thead>
<tr>
<th>I</th>
<th>II</th>
<th>III</th>
</tr>
</thead>
<tbody>
<tr>
<td>A voriconazole</td>
<td>amphotericin</td>
<td>G(M)-CSF combinations</td>
</tr>
<tr>
<td>B liposomal</td>
<td>caspofungin ampho lipid complex</td>
<td></td>
</tr>
<tr>
<td>amphotericin</td>
<td>itraconazole</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>posaconazole</td>
<td></td>
</tr>
</tbody>
</table>
## Invasive Pulmonary Aspergillosis

<table>
<thead>
<tr>
<th>Agent</th>
<th>Grade</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Voriconazole</td>
<td>A I</td>
<td>2x6 mg/ kg D1 then 2x4 mg/ kg (initiation with oral: C III)</td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>D I</td>
<td></td>
</tr>
<tr>
<td>Ambisome</td>
<td>B I</td>
<td>dose 3 - 5 mg/ kg</td>
</tr>
<tr>
<td>ABLC</td>
<td>B II</td>
<td>dose 5 mg/ kg</td>
</tr>
<tr>
<td>ABCD</td>
<td>D I</td>
<td></td>
</tr>
<tr>
<td>Caspofungin</td>
<td>C III</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td>C III</td>
<td>start with iv</td>
</tr>
<tr>
<td>Combination</td>
<td>D III</td>
<td></td>
</tr>
</tbody>
</table>

In the absence of data in 1st line, posaconazole has not been graded
Selection criteria:

• Established efficacy in proven disease
• Safety and compatibility / interaction
• Miscellaneous
# Anti-Aspergillus Drugs

## Selection Criteria:

- Established efficacy in proven disease
- Safety and compatibility / interaction
- Miscellaneous
LIMITS TO VORICONAZOLE: INTERACTIONS AND ADVERSE EVENTS

- Visual effects
- Hallucinations
- Liver toxicity
- Nausea
- Allergy
AZOLE SPECIAL CHARACTERISTICS

VORICONAZOLE metabolites

VORICONAZOLE CYP2C19
LIMITS TO VORICONAZOLE: INTERACTIONS AND ADVERSE EVENTS

- Visual effects
- Hallucinations
- Liver toxicity
- Nausea
- Allergy
LIMITS TO VORICONAZOLE: INTERACTIONS AND ADVERSE EVENTS

- warfarin
- cyclosporin
- tacrolimus
- sulphonureas
- statins
- benzodiazepines
- vinca alkaloids
- sirolimus
- rifabutin
- rifampicin
- terfenadine

Visual effects
Hallucinations
Liver toxicity
Nausea
Allergy
AMPHOTERICIN B NEPHROTOXICITY RELATION TO MORTALITY


Patients on Ampho B  N=108

Nephrotoxicity  23%

Mortality
- with nephrotoxicity  69%
- without  23%
AMPHO-B VERSUS AMBISOME® AS EMPIRICAL THERAPY IN HEMATOLOGICAL MALIGNANCIES


<table>
<thead>
<tr>
<th></th>
<th>AMPHO-B 1 mg/kg/24 day</th>
<th>AMBISOME 1 mg 3 mg/kg/day</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>102</td>
<td>118</td>
</tr>
<tr>
<td>DEATH DUE TO FUNGAL INFECTION</td>
<td>1%</td>
<td>1%</td>
</tr>
<tr>
<td>ADVERSE EVENTS</td>
<td>39%</td>
<td>6%</td>
</tr>
<tr>
<td>NEPHROTOXICITY</td>
<td>24%</td>
<td>10%</td>
</tr>
</tbody>
</table>
ANTI-ASPERGILLUS DRUGS

Selection criteria:

• Established efficacy in proven disease
• Safety and compatibility / interaction
• Miscellaneous
ANTI-ASPERGILLUS DRUGS

Selection criteria:

• Established efficacy in proven disease

• Safety and compatibility / interaction

• Miscellaneous
VORICONAZOLE LEVELS IN CASES TREATED FOR ASPERGILLOSIS
Pascual et al Clin Infect Dis 2008; 46:201-211

FAILURE level <1: 46%
>1: 12%
PROPHYLAXIS

EMPIRICAL THERAPY

THERAPY

POSA CONAZOLE

CASPO FUNGIN - LIPOSOMAL AMPHO B

VORICONAZOLE
INDICATION NOT RELEVANT!!!

• Established efficacy in proven disease
COSTS OF ANTIFUNGAL DRUGS

- Initial drugs
- Supportive drugs
- Second line antifungals
- Hospital stay
- Diagnostic tests
VORICONAZOLE VERSUS AMPHOTERICIN B FOR
INVASIVE ASPERGILLOSIS: COSTS

- Costs per patient
  - Voriconazole: $30,664
  - Amphotericin B: $34,144
- Costs per success
  - Voriconazole: $58,100
  - Amphotericin B: $108,124
- Costs per survivor
  - Voriconazole: $43,310
  - Amphotericin B: $58,971

Initial drugs
Supportive drugs
Second line antifungals
Hospital stay
Diagnostic tests
ASPERGILLOSIS

- caspofungin
- voriconazole
- amphotericin B
- liposomal amphotericin B
INVASIVE ASPERGILLOSIS IN CHILDREN

Burgos et al. Pediatrics 2008; 121:e1286-e1294

139 patients, median 10 years (17 days - 18 years)

Mortality aspergillosis: 53%
COMBINATION ANTIFUNGAL THERAPY
SURVIVAL AFTER COMBINATION THERAPY FOR ASPERGILLOSIS


Overall Survival

Combination

Voriconazole

days after diagnosis
SURVIVAL AFTER COMBINATION THERAPY FOR ASPERGILLOSIS
VORICONAZOLE PLUS CASPOFUNGIN FOR ASPERGILLUS IN SOLID ORGAN TRANSPLANTS

Singh et al. Transplantation 2006; 81:320-325

Historical Controls

2003-2005 multicenter

VORICONAZOLE + CASPOFUNGIN

38 compare 34

50% mortality day 90 26%
**SINGLE AGENT OR COMBINATION TO TREAT INVASIVE ASPERGILLOSIS?**

*Kubin et al. ICAAC, San Francisco 2006; Abstract M-899*

**Retrospective 146 proven/probable primary cases**

<table>
<thead>
<tr>
<th></th>
<th>Monotherapy</th>
<th>Caspofungin + Voriconazole</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>n</strong></td>
<td>124</td>
<td>22</td>
</tr>
<tr>
<td><strong>47 AmBisome-33</strong></td>
<td>47</td>
<td>47</td>
</tr>
<tr>
<td><strong>Voriconazole</strong></td>
<td>77</td>
<td>15</td>
</tr>
</tbody>
</table>

| **Response**        | 24%          | 21%                        |
| **12 wk Mortality** | 55%          | 46%                        |
APPROACHES TO ASPERGILLUS INFECTIONS IN BMT AND LEUKEMIA

O’Connor et al. ICAAC, Chicago 2003; abstr M-997

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmBisome/ Abelcet</td>
<td>18</td>
<td>68%</td>
</tr>
<tr>
<td>AmBisome + Candin</td>
<td>14</td>
<td>85%</td>
</tr>
</tbody>
</table>

n=22
37 patients 30 days after hospital discharge
retrospective - all surgical debridement

**caspo + ABLC**

- 100% alive and well

**ABLC alone**

- 45%
MODE OF ACTION OF ANTIFUNGALS

- acetyl-Co-A
- squalenes
- azoles
- lanosterol
- amphotericin B
- ergosterol
- β (1,3)-D-glucan synthesis
- candins
487 FUNGAL INFECTIONS IN TRANSPLANT RECIPIENTS

Pappas et al. ICAAC, Chicago 2003; abstr M-1010
STRANGE DUCKS IN THE IMMUNOSUPPRESSED POND

- *Pseudallescheria boydii*
- *Scedosporium*
- *Saccharomyces cerevisiae*
- *Fusarium*
- *Mucor/Rhizopus*
- *Trichosporon*
- *Alternaria*
- *Malassezia furfur*
# Voriconazole for Scedosporiosis

*Troke et al. Antimicrob Ag Chemother 2008; 52:1743-1750*

<table>
<thead>
<tr>
<th></th>
<th>Number</th>
<th>Response</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total</strong></td>
<td>107</td>
<td>57%</td>
</tr>
<tr>
<td><strong>Primary</strong></td>
<td></td>
<td>61%</td>
</tr>
<tr>
<td><strong>Others</strong></td>
<td></td>
<td>56%</td>
</tr>
<tr>
<td><strong>Scedosporium apiospermum</strong></td>
<td>70</td>
<td>54%</td>
</tr>
<tr>
<td><em>(Pseudallescheria boydii)</em> in CNS</td>
<td>21</td>
<td>43%</td>
</tr>
<tr>
<td><strong>Scedosporium prolificans</strong></td>
<td>35</td>
<td>40%</td>
</tr>
<tr>
<td><strong>Mortality</strong></td>
<td>43</td>
<td>40%</td>
</tr>
<tr>
<td>Category</td>
<td>Count</td>
<td>Success Rate</td>
</tr>
<tr>
<td>--------------------------------</td>
<td>-------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Total cases</td>
<td>59 cases</td>
<td></td>
</tr>
<tr>
<td>Empirical antifungals</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>Amphotericin B</td>
<td>39</td>
<td>23%</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>12</td>
<td>44%</td>
</tr>
<tr>
<td>Surgery</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

8 switches

30 failures

9 successes = 23%

7 successes = 44%
POSACONAZOLE RESCUE FOR ZYGOMYCOSIS
Kontoyiannis et al. ICAAC, Washington 2005; Abstract M-974

91 patients

81 refractory

10 intolerant

<table>
<thead>
<tr>
<th>Organism</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhizopus</td>
<td>25</td>
<td>52%</td>
</tr>
<tr>
<td>Mucor</td>
<td>17</td>
<td>76%</td>
</tr>
<tr>
<td>Cunninghamamella</td>
<td>8</td>
<td>75%</td>
</tr>
<tr>
<td>Rhizomucor</td>
<td>7</td>
<td>28%</td>
</tr>
<tr>
<td>Absidia</td>
<td>2</td>
<td>100%</td>
</tr>
</tbody>
</table>
CONCLUSIONS

* virtually all data come from ‘company’ trials

* there is a choice of drugs rather than a drug of choice against **candidiasis**
  preference depends on situation

* data on **aspergillosis** are difficult to interpret but voriconazole, liposomal amphotericin B and, to a lesser extent, caspofungin have shown activity
THE RATIONALE OF EARLY THERAPY FOR INVASIVE FUNGAL INFECTIONS
STRATEGY FOR THE TREATMENT OF DISSEMINATED CANDIDIASIS

Spellberg et al. Clin Infect Dis 2006; 42:244-251

- Fluconazole
- Echinocandin
- Lipid ampho-B
- Voriconazole

1. If invasive candidiasis is proven/probable:
   - NO
   - C. glabrata C. krusei?
     - NO
       - Hemodynamically unstable?
         - NO
           - Fluconazole
         - YES
           - Echinocandin
             - YES
               - Voriconazole
               - YES
EVOLUTION MORTALITY OF POSITIVE CANDIDA BLOODCULTURE


<table>
<thead>
<tr>
<th>Year</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>1980-6</td>
<td>63%</td>
</tr>
<tr>
<td>1979-87</td>
<td>53%</td>
</tr>
<tr>
<td>1989</td>
<td>22%</td>
</tr>
<tr>
<td>1989-93</td>
<td>25%</td>
</tr>
</tbody>
</table>

- Goodrich: n = 1506
- Verfaille: 533
- O’Donnell: 331
- Jantunen: 142
invasive aspergillosis

YES

AmBisome

cyclosporin
P450 inducers
liver function abnormal

NO

voriconazole

caspofungin
G(M)CSF? interferon? combinations??
BASIS FOR A RATIONAL CHOICE

candin
ampho B
azole

efficacy established

Drug