ADVANCES AND CHALLENGES IN HEMATOLOGY

“Invasive fungal disease management in febrile neutropenia”

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Conflicts of interest

- Received research grants, speaker’s fee, ad board honoraria and/or travel support from:
  - Gilead Sciences
  - Pfizer Inc.
  - MSD
  - Basilea Pharmaceuticals
  - Astellas Pharma
  - Bio-Rad laboratories
  - F2G
  - Scynexis
  - Amplyx
  - Cidara
  - Vical

"Yes, I am employee of the month again. And yes, I'm the one who chooses the employee of the month. And no, I don't see a conflict of interest."
Management of Invasive Fungal Disease

**basic principles**

- **HOST IMMUNE STATE**
- **DRUG SUSCEPTIBILITY PATHOGEN**
- **LOCATION OF INFECTION/MANAGEMENT OF INFECTION SOURCE**
- **Successful outcome**
- **APPROPRIATE ANTIFUNGAL THERAPY**
- **TIMING**
- **APPROPRIATE DOSE**
- **SELECTION OF MOST POTENT AND SAFEST DRUG**

**PHARMACOKINETICS AND PHARMACODYNAMICS**

Andes et al., AAC 2009
The importance of early adequate therapy

- High white blood cell count at diagnosis of leukemia
- Disease stage in lymphoproliferative disorders
- High tumor burden in multiple myeloma
- High baseline serum galactomannan in aspergillosis

The importance of neutrophil recovery: a *post hoc* analysis of the SECURE trial

Empiric treatment

- First studied in 1982
- Trigger is a fever of unknown origin, particularly in severely neutropenic patients receiving broad-spectrum antibiotics, in the absence of clear clinical symptoms and conventional laboratory/radiologic findings
- Does not require any microbiologic or radiologic documentation

Treatment strategies for invasive fungal infection in febrile neutropenia are evolving

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- Does not require any microbiologic or radiologic documentation

Prophylaxis

- Introduced in the 1990s
- Antifungals are given to patients at high risk of invasive fungal infection who lack evidence of active infection

Treatment strategies for invasive fungal infection in febrile neutropenia are evolving

Empiric treatment
- First studied in 1982
- Trigger is a fever of unknown origin, particularly in severely neutropenic patients receiving broad spectrum antibiotics, in the absence of clear clinical symptoms and conventional laboratory/radiologic findings
- Does not require any microbiologic or radiologic documentation

Prophylaxis
- Introduced in the 1990s
- Antifungals are given to patients at high risk of invasive fungal infection who lack evidence of active infection

Diagnostic-based (pre-emptive)
- First studied in 2005 as an alternative to empiric therapy
- Trigger is a combination of risk assessment and biomarkers (galactomannan, β-D-glucan, PCR, microscopy, imaging findings (HRCT) and culture
- Does not require any symptoms or pathogen indication

A continuum of antifungal strategies

Prophylaxis

Diagnostic-driven

Empirical

Diagnostic-driven

Directed or targeted

New signs and/or symptoms? Is it a fungal infection?

- Yes: Specific antifungal therapy
- No: No antifungal therapy
- Maybe?: Need for TDM?

Which antifungal? Duration? Cost/toxicity? Interactions?

Empiric therapy

Withhold therapy

Diagnostic tests

Lab-based

Imaging

- Negative
- Positive

Is it a fungal infection?

- Yes: Etiology known? Stop empiric?
- No
- Maybe?:

Other considerations
- Local epidemiology?
- Local antifungal policies?
- Local mycology expertise?

AF, antifungal drug
TDM, therapeutic drug monitoring
TAT, turnaround time

Presenter’s opinion
Antifungal management in 2018: Interdisciplinary and stewardship

AFS Programme
Improved management of IFD
Liaising with AFS champions

ID specialist
Assessing clinical signs & symptoms, diagnostic advice, antifungal drug selection, duration of treatment

Radiologist
Interventional chest physician

Medical Microbiologist
Diagnostic test delivery & interpretation, antifungal susceptibility testing, antifungal drug selection

Hospital pharmacist
Antifungal drug dosages, PK issues in specific patient populations, drug-drug interactions, TDM & interpretation

Pediatric ID specialist
Assessing clinical signs & symptoms, diagnostic advice, antifungal drug selection, duration of treatment

Hematologist
Risk stratification, assessing clinical signs & symptoms, antifungal drug prescribing

Antifungal prophylaxis.... or not?

Antifungal Prophylaxis

>13,000 hits on PubMed

PROVEN EFFECTIVENESS
SAFETY PROFILE

Hematology
HCT recipients
Solid organ transplants
ICU patients
PID
AIDS

Diagnostic-driven approach (empiric approach)

Hematology
ICU patients

ICU, intensive-care unit; PID, primary immunodeficiency; HCT, hematopoietic cell transplantation
(Posacon) azole prophylaxis has become standard of care

### Efficacy in reducing invasive fungal disease

<table>
<thead>
<tr>
<th>Measure</th>
<th>ARR</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mortality attributed to IFD</td>
<td>3%</td>
<td>33</td>
</tr>
<tr>
<td>Invasive fungal disease</td>
<td>6%</td>
<td>17</td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>6%</td>
<td>17</td>
</tr>
<tr>
<td>Overall mortality after 100 days</td>
<td>7%</td>
<td>14</td>
</tr>
<tr>
<td>Empirical antifungals</td>
<td>12%</td>
<td>8</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>5%</td>
<td>20</td>
</tr>
</tbody>
</table>

IFD: invasive fungal disease; ARR: absolute risk reduction; NNT: number needed to treat; NNH: number needed to harm

## Antifungal prophylaxis meta-analysis of randomized controlled trials: mold-active vs. fluconazole

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RR (95% CI)</th>
<th>(p)-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevention of colonization</td>
<td>no data</td>
<td>-</td>
</tr>
<tr>
<td>Proven or probable invasive fungal disease (IFD)</td>
<td>0.71</td>
<td>0.03</td>
</tr>
<tr>
<td>Invasive aspergillosis</td>
<td>0.53</td>
<td>0.0004</td>
</tr>
<tr>
<td>Adverse events leading to discontinuation or modification</td>
<td>1.95</td>
<td>0.004</td>
</tr>
<tr>
<td>IFD-related mortality</td>
<td>0.67</td>
<td>0.03</td>
</tr>
<tr>
<td>Invasive aspergillosis related mortality</td>
<td>0.62</td>
<td>0.36</td>
</tr>
<tr>
<td>Overall mortality</td>
<td>1.00 (0.88-1.13)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Risk ratio (RR) <1 represents an advantage of mould-active coverage

Antifungal prophylaxis

Patient at “high” risk

- Local incidence of IFI (NNT)
- Local epidemiology
- Availability of diagnostics
- Impact of pre-admission factors

No prophylaxis

Fluconazole prophylaxis

Mold-active Prophylaxis: Azoles or aerosols

Impact on performance of biomarkers
Impact on drug of choice during subsequent approach
Long term toxicity issues
Resistance

Presenter’s opinion
The importance of an individualized approach acute myeloid leukemia as an example

<table>
<thead>
<tr>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Low Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Prior aspergillosis</td>
<td>• Not meeting criteria for high or low risk</td>
<td>• Newly diagnosed young patients (≤45 years) undergoing 1st remission-</td>
</tr>
<tr>
<td>• Salvage for refractory/relapsed leukemia</td>
<td></td>
<td>induction/consolidation therapy and without risk factors for IFDs</td>
</tr>
<tr>
<td>• Remission-induction for newly diagnosed acute leukemia:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– neutropenia at baseline</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– low CR probability</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– age ≥65 years</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– pulmonary dysfunction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>– high e-TRM score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mold-active azole prophylaxis</td>
<td>Fluconazole prophylaxis + serial biomarker monitoring</td>
<td>(Fluconazole prophylaxis)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>No serial biomarker monitoring</td>
</tr>
</tbody>
</table>

**Dynamic model: re-assessment based on post-treatment day-15 marrow blast count**

CR, complete remission
e-TRM, early treatment-related mortality

Nucci M and Anaissie E. Blood 2014; 124:3858–69
Antifungal management in febrile neutropenia: the next step

Population at risk

- No prophylaxis
  - Empirical

- Fluconazole prophylaxis
  - Empirical

- Mold-active prophylaxis
  - Empiric
## Empirical antifungal therapy
### updated ECIL recommendations: BII

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>Daily dose</th>
<th>Level of recommendation</th>
<th>CDC grading level of evidence for</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ampho B deoxy</td>
<td>0.5-1 mg/kg iv</td>
<td>B/D</td>
<td></td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Liposomal AmB</td>
<td>3 mg/kg iv</td>
<td>A</td>
<td></td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>ABLC</td>
<td>5 mg/kg iv</td>
<td>B</td>
<td></td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>ABCD</td>
<td>4 mg/kg iv</td>
<td>B</td>
<td></td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>400 mg</td>
<td>C</td>
<td></td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Itraconazole</td>
<td>200 mg iv</td>
<td>B</td>
<td></td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>2 x 3 mg/kg iv</td>
<td>B</td>
<td></td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>50 mg</td>
<td>A</td>
<td></td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Micafungin</td>
<td>100 mg</td>
<td>B</td>
<td></td>
<td>II</td>
<td>II</td>
</tr>
</tbody>
</table>

Empirical antifungal therapy updated ECIL recommendations: BII

<table>
<thead>
<tr>
<th>Antifungal agent</th>
<th>Daily dose</th>
<th>Level of recommendation</th>
<th>CDC grading level of evidence for Efficacy</th>
<th>CDC grading level of evidence for Safety</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liposomal AmB</td>
<td>3 mg/kg iv</td>
<td>A</td>
<td>I</td>
<td>I</td>
</tr>
<tr>
<td>Caspofungin</td>
<td>50 mg iv</td>
<td>A</td>
<td>I</td>
<td>I</td>
</tr>
</tbody>
</table>

- Caspofungin (intravenous)
  - Excellent safety profile
  - Excellent *Candida* spp. activity, including biofilms
  - ‘Moderate’ activity against *Aspergillus* spp. and no activity against non-*Aspergillus* molds
- Liposomal amphotericin B (intravenous)
  - Broad-spectrum of activity, including *Aspergillus* spp. and non-*Aspergillus* molds
  - Excellent *Candida* spp. activity, including biofilms
  - [Nephro]toxicity manageable

‘Breakthrough IFI (bIFI)’ in high-risk patients receiving mold-active prophylaxis

<table>
<thead>
<tr>
<th>Breakthrough fungal infection</th>
<th>AML N=250</th>
<th>HSCT N=409</th>
</tr>
</thead>
<tbody>
<tr>
<td>Persistent febrile neutropenia (%)</td>
<td>67.2%</td>
<td>38.6%</td>
</tr>
<tr>
<td>Any lung infiltrate plus fever</td>
<td>20.4%</td>
<td>9.8%</td>
</tr>
<tr>
<td>bIFI</td>
<td>24%</td>
<td>12.5%</td>
</tr>
<tr>
<td>Possible bIFI</td>
<td>17.6%</td>
<td>9%</td>
</tr>
<tr>
<td>Probable bIFI</td>
<td>4.4%</td>
<td>2%</td>
</tr>
<tr>
<td>Proven</td>
<td>2%</td>
<td>1.5%</td>
</tr>
</tbody>
</table>

Changing fungal epidemiology in patients receiving mold-active azole prophylaxis

Posaconazole or voriconazole prophylaxis at Duke University (2009–2013)

24 episodes

P = 0.003

66 episodes

Lipid-based formulation AmB = first choice after mold-active prophylaxis

### Prospective study of amphotericin B formulations in immunocompromised patients

<table>
<thead>
<tr>
<th></th>
<th>L-AmB</th>
<th>ABLC</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Duration of therapy, days</strong></td>
<td>17.5</td>
<td>9.7</td>
</tr>
<tr>
<td><strong>Daily dose, by weight</strong></td>
<td>2,6 mg/kg</td>
<td>3,7 mg/kg</td>
</tr>
<tr>
<td><strong>Patients with normal kidney function at baseline</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>slight worsening (%)</td>
<td>21.1</td>
<td>20.9</td>
</tr>
<tr>
<td>moderate worsening (%)</td>
<td>5.9</td>
<td>23.3</td>
</tr>
<tr>
<td>severe worsening (%)</td>
<td>3.0</td>
<td>11.6</td>
</tr>
</tbody>
</table>

**Definitions**

- Slight: a serum creatinine level >1.5-2 times that noted at baseline
- Moderate: a serum creatinine level 2-3 times that noted at baseline
- Severe: a serum creatinine level > 3 times that noted at baseline

**Severe nephrotoxicity is a strong independent predictor of death for patients with normal renal function at baseline [OR 6.3 (2.74-14.46)]**

Severe nephrotoxicity vs. no nephrotoxicity: 53% vs. 18% mortality

Hematological toxicity of different formulations of amphotericin B

<table>
<thead>
<tr>
<th></th>
<th>Anemia OR</th>
<th>Leukopenia OR</th>
<th>Thrombocytopenia OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmB-deoxycholate</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
<td>1 (reference)</td>
</tr>
<tr>
<td>Liposomal AmB</td>
<td>0.61</td>
<td>0.8</td>
<td>0.67</td>
</tr>
<tr>
<td>ABLC</td>
<td>1.26</td>
<td>2.58</td>
<td>1.33</td>
</tr>
</tbody>
</table>

Use of ABLC is associated with severe leukopenia whereas use of liposomal amphotericin B is an independent protective factor

Falci DR et al. Leuk Lymph 2015; 56: 2889-94
Antifungal management in febrile neutropenia the next step

Population at risk

- No prophylaxis
  - Empirical
- Fluconazole prophylaxis
  - Empirical
- Mold-active prophylaxis
  - Empiric
Fungal diagnostics: what is available in 2018?

Direct Tests:
- Culture
- Direct Microscopy
- Histopathology
- Galactomannan (GM)
  - Mannan/anti-mannan
  - C. albicans germ tube antibodies

Indirect Tests:
- Galactomannan (GM)
- T2 Candida and T2MR
- 1,3 β-D-glucan
- Polymerase chain reaction
- Lateral flow assays
- Electronic nose/EBC
- Mass Spectrometry (MALDI-TOF)

EBC: exhaled breath condensate; MALDI-TOF: Matrix Assisted Laser Desorption/Ionization-Time of Flight; MR: magnetic response

Diagnostics-driven approaches

Prolonged neutropenic patient
- GM screening implemented
- Results same/next day
- CT scan accessible
- Bronchoscopy + BAL available
- No mould-active prophylaxis

CT abnormal
Screen pos
Probable IFD

CT suggestive
Screen pos
IFD? Other causes?

CT non-specific
Screen neg
Any case possible

CT normal
Screen pos
False-positive test of extrapulmonary IFD

CT normal
Screen neg
Rules out IFD

CT abnormal
Screen neg
Further diagnosis

IFD?
Other causes?

Any case possible

False-positive test of extrapulmonary IFD

Bronchoscopy + BAL GM

 Imaging (CT sinus/abdomen)

No

BAL GM negative

Consider mucormycosis

Yes

Treatment for IPA

Response at Day 7-10

No

Duration therapy
‘Step down’
Out-patient follow up

Presenter’s opinion
Galactomannan and PCR-based screening for invasive aspergillosis: a diagnostic meta-analysis

<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity, % (95% CI)</th>
<th>Specificity, % (95% CI)</th>
<th>Positive LR (95% CI)</th>
<th>Negative LR (95% CI)</th>
<th>DOR (95% CI)</th>
<th>AUROC (95% CI)</th>
<th>PPV, % (95% CI)</th>
<th>NPV, % (95% CI)</th>
<th>PubBias</th>
</tr>
</thead>
<tbody>
<tr>
<td>PCR</td>
<td>84 (71–92)</td>
<td>76 (64–85)</td>
<td>3.5 (2.3–5.4)</td>
<td>0.21 (.11–.39)</td>
<td>17 (7–38)</td>
<td>0.87 (.84–.90)</td>
<td>38</td>
<td>96</td>
<td>4.50 (P = .55)</td>
</tr>
<tr>
<td>2 PCRs</td>
<td>57 (40–72)</td>
<td>93 (87–97)</td>
<td>8.4 (4.2–17.1)</td>
<td>0.46 (.32–.67)</td>
<td>18 (7–45)</td>
<td>0.87 (.84–.90)</td>
<td>59</td>
<td>92</td>
<td>3.7 (P = .76)</td>
</tr>
<tr>
<td>GM</td>
<td>92 (83–96)</td>
<td>90 (81–95)</td>
<td>9.3 (4.6–18.7)</td>
<td>0.09 (.04–.19)</td>
<td>104 (37–295)</td>
<td>0.96 (.94–.98)</td>
<td>61</td>
<td>98</td>
<td>5.5 (P = .53)</td>
</tr>
<tr>
<td>2 GMs</td>
<td>62 (48–74)</td>
<td>95 (91–97)</td>
<td>12.1 (6.3–23.3)</td>
<td>0.40 (.29–.57)</td>
<td>30 (13–70)</td>
<td>0.94 (.92–.96)</td>
<td>67</td>
<td>93</td>
<td>7.00 (P = .46)</td>
</tr>
<tr>
<td>GM or PCR</td>
<td>99 (96–100)</td>
<td>64 (49–77)</td>
<td>2.8 (1.9–4.1)</td>
<td>0.02 (.01–.06)</td>
<td>128 (37–442)</td>
<td>0.99 (.97–.99)</td>
<td>33</td>
<td>10</td>
<td>0.24 (P = .97)</td>
</tr>
<tr>
<td>GM and PCR</td>
<td>68 (54–80)</td>
<td>98 (94–100)</td>
<td>43.2 (12.6–149)</td>
<td>0.32 (.21–.49)</td>
<td>135 (38–475)</td>
<td>0.93 (.91–.95)</td>
<td>88</td>
<td>95</td>
<td>5.34 (P = .51)</td>
</tr>
</tbody>
</table>

**Impact of mold-active prophylaxis on GM performance**

<table>
<thead>
<tr>
<th>Serum galactomannan performance</th>
<th>Screening</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive predictive value</td>
<td>Duarte 2014 posaconazole</td>
<td>Vena A 2017 micafungin</td>
</tr>
<tr>
<td></td>
<td>11.8%</td>
<td>3.2%</td>
</tr>
<tr>
<td>Negative predictive value</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

# Invasive aspergillosis: first-line therapy recommendations

<table>
<thead>
<tr>
<th>Drugs</th>
<th>IDSA¹</th>
<th>ECIL²</th>
<th>ESCMID-ECMM-ERS³</th>
<th>Australia⁴</th>
</tr>
</thead>
<tbody>
<tr>
<td>AmB DC</td>
<td></td>
<td>A against</td>
<td>DI</td>
<td>Alternative</td>
</tr>
<tr>
<td>AmB-LS</td>
<td>Strong Moderate quality</td>
<td>BI</td>
<td>BII</td>
<td>Alternative</td>
</tr>
<tr>
<td>ABLC</td>
<td>Weak Low quality</td>
<td>BII</td>
<td>CIII</td>
<td></td>
</tr>
<tr>
<td>ABCD</td>
<td>Weak Low quality</td>
<td>CI</td>
<td>DI</td>
<td></td>
</tr>
<tr>
<td>Itraconazole</td>
<td></td>
<td></td>
<td>CIII</td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Voriconazole</strong></td>
<td></td>
<td>AI</td>
<td>AI</td>
<td>Recommended</td>
</tr>
<tr>
<td><strong>Isavuconazole</strong></td>
<td></td>
<td>AI</td>
<td>AI</td>
<td></td>
</tr>
<tr>
<td>Caspofungin</td>
<td>Not recommended</td>
<td>CII</td>
<td>CII</td>
<td></td>
</tr>
<tr>
<td>Micafungin</td>
<td>Weak recommendation; moderate quality evidence</td>
<td></td>
<td>CIII</td>
<td></td>
</tr>
<tr>
<td><strong>Combination</strong></td>
<td>Weak Moderate quality</td>
<td>Discouraged</td>
<td>CI</td>
<td>No supportive evidence</td>
</tr>
</tbody>
</table>

## European recommendations for first-line treatment of mucormycosis:

**antifungal therapy + surgery + control underlying conditions**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>ECIL-6¹</th>
<th>EFISG²</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amphotericin B deoxycholate</td>
<td>C II</td>
<td>D I</td>
</tr>
<tr>
<td>Liposomal amphotericin B</td>
<td>B II</td>
<td>A IIₜₜ</td>
</tr>
<tr>
<td>Amphotericin B lipid complex</td>
<td>B II</td>
<td>B IIₜₜ</td>
</tr>
<tr>
<td>Amphotericin B colloidal dispersion</td>
<td>C II</td>
<td></td>
</tr>
<tr>
<td>Posaconazole</td>
<td>C III</td>
<td>B IIₜₜ</td>
</tr>
<tr>
<td>Combination therapy</td>
<td>C III</td>
<td>C III</td>
</tr>
<tr>
<td>Deferasirox</td>
<td>A II against</td>
<td>D II</td>
</tr>
</tbody>
</table>

²Cornely O. et al. Clin Microbiol Infect 2014; Suppl 3: 5-26
Invasive candidiasis/candidemia in neutropenic patients

• Factors associated with better survival
  • TREATMENT WITH AN ECHINOCANDIN (OR 0.65, 95% CI 0.45-0.94, p=0.02)
  • REMOVAL OF CENTRAL VENOUS CATHETER (OR 0.50, 95% CI 0.35-0.72, p=0.0001)
• Same recommendation for all echinocandins
• After species identification, treatment should be guided by susceptibility testing
• In case catheter cannot be removed: echinocandin or liposomal amphotericin B
• Resistance is on the move (especially *Candida glabrata*)

1 Andes AR. et al. Clin Infect Dis 2012; 54: 1110-1122
Antifungal management in febrile neutropenia

Population at risk

- No prophylaxis
  - Empirical: Caspofungin L-AmB
  - Diagnostic driven: Depends on evidence found

- Fluconazole prophylaxis
  - Empirical: Caspofungin L-AmB
  - Diagnostic driven: Depends on evidence found

- Mold-active prophylaxis
  - Empiric: Liposomal AmB


Presenter's opinion