New Directions in Invasive Fungal Disease: Therapeutic Considerations

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Disclosure Statement for Coleman Rotstein MD

Financial Conflicts of Interest

- **Grant/Research Support:**
  - Astellas, Chimerix, Merck, Pfizer

- **Consultant (Honoraria paid):**
  - Astellas, Merck, Pfizer

- **Speakers Bureau (honoraria paid):**
  - Astellas, Merck, Pfizer, Sunovion
Objectives

- Review therapeutic strategies for invasive fungal infections (IFIs) in hematological malignancies.

- Discuss the benefits of empiric vs. preemptive therapy.

- Describe therapeutic options for *Candida*, *Aspergillus* and *Mucorales* IFIs.
Therapeutic Strategies for IFIs
Treatment Strategies

Prophylaxis

Empiric

Risk Factors and Febrile

Positive Markers but Afebrile

Preemptive

Documented Infection

Microbiologically/Clinically Documented with/without Symptoms

Targeted Therapy

Evidence of Disease

No Infection

Possible

Probable

Proven

Positive Markers but No Symptoms

Risk Factors but No Symptoms

Prophylaxis
Strategies for the Treatment of Invasive Fungal Infections in Cancer Patients

<table>
<thead>
<tr>
<th>Clinical signs and symptoms</th>
<th>No symptoms</th>
<th>No symptoms</th>
<th>Persistent febrile neutropenia</th>
<th>Clinical or radiological signs consistent with fungal infection</th>
<th>Clinical or radiological signs consistent with fungal infection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mycological results</td>
<td>Negative</td>
<td>Positive biomarkers</td>
<td>Negative</td>
<td>Negative</td>
<td>Positive biomarkers or positive microscopy/culture/histopathology</td>
</tr>
<tr>
<td>Type of treatment</td>
<td>Prophylaxis</td>
<td>Preemptive</td>
<td>Empiric</td>
<td>Preemptive</td>
<td>Directed</td>
</tr>
<tr>
<td>Proof of efficacy</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>

Herbrecht R, Berceanu A. CID 2008;46:886-889
Burden of Illness of IFIs in Hematological Malignancies
PATH Alliance Registry: Invasive Fungal Infections 2004-2008 [7526 IFIs in 6845 Patients (IA=13.3%)]

Azie N et al. Diagn Microbiol Infect Dis 2012;73:293-300
**IMI Trends in Patients with Haematological Malignancies – MD Anderson**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aspergillosis</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture negative</td>
<td>54 (68)</td>
<td>40 (62)</td>
<td>30 (48)</td>
<td>13 (46)</td>
<td>0.01</td>
</tr>
<tr>
<td><em>A. fumigatus</em></td>
<td>4 (5)</td>
<td>5 (8)</td>
<td>8 (13)</td>
<td>6 (21)</td>
<td>0.01</td>
</tr>
<tr>
<td><em>A. terreus</em></td>
<td>4 (5)</td>
<td>5 (8)</td>
<td>7 (11)</td>
<td>0 (0)</td>
<td>0.99</td>
</tr>
<tr>
<td><em>A. flavus</em></td>
<td>8 (10)</td>
<td>3 (5)</td>
<td>5 (8)</td>
<td>1 (4)</td>
<td>0.35</td>
</tr>
<tr>
<td>Other</td>
<td>1 (1)</td>
<td>0 (0)</td>
<td>1 (2)</td>
<td>1 (4)</td>
<td>0.40</td>
</tr>
<tr>
<td><strong>Fusarium</strong></td>
<td>4 (5)</td>
<td>2 (3)</td>
<td>4 (6)</td>
<td>1 (4)</td>
<td>0.96</td>
</tr>
<tr>
<td><strong>Mucorales</strong></td>
<td>4 (5)</td>
<td>10 (15)</td>
<td>7 (11)</td>
<td>6 (21)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

- Drop in autopsy rate - 0.63 autopsies/100 deaths 1989-93 vs. 0.06 in 2004-08 ($p<0.001$)
- *Aspergillus* dropped from 0.12-0.14 to 0.07/100 autopsies 2004-08 ($p=0.04$)
- *Mucorales* increased 0.06 to 0.2/100 autopsies 2004-2008 ($p=0.02$)

*Lewis RE et al. Mycoses 2013;56:638-645*
Incidence of IFIs in AML Patients
1/1/05 – 6/30/10 - Johns Hopkins (N=254)

- N=254 AML patient undergoing induction chemo
- Rate of IFIs = 48.4%
- IC was 5.5%
- IMI was 42.5%
- 6 m mortality with IFI 23.7% (20.6% without IFI)

Timing of Mold Infections in Allo-BMT (Seattle), 1998-2002

*early: 0-40 d; late: 41-100 d; very late >100 d

Garcia-Vidal C et al. CID 2008;47:1041-1050
Impact of Prophylaxis
Prophylaxis in AML/MDS Over 12-Year Period, 1998-2010 (n=216)

**Empiric Antifungal Therapy**

- Fluconazole (31/93) 33.3%
- Itraconazole (33/115) 28.7%
- Voriconazole (19/202) 9.4%
- Posaconazole (11/149) 7.4%

*P* = <0.001

**Breakthrough IFIs: Proven, Probable or Possible**

- Fluconazole (15/36) 41.7%
- Itraconazole (12/49) 24.5%
- Voriconazole (9/58) 15.5%
- Posaconazole (2/67) 3.0%

# Azole Prophylaxis 1\textsuperscript{st} vs. 2\textsuperscript{nd} Generation Azoles - Meta-analysis: Proven & Probable IFIs

## Odds ratio

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Second-generation</th>
<th>First-generation</th>
<th>Odds ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Marks 2011</td>
<td>3</td>
<td>224</td>
<td>5</td>
</tr>
<tr>
<td>Wingard 2010</td>
<td>14</td>
<td>305</td>
<td>24</td>
</tr>
<tr>
<td>Cornely 2007</td>
<td>7</td>
<td>304</td>
<td>25</td>
</tr>
<tr>
<td>Ullmann 2007</td>
<td>16</td>
<td>301</td>
<td>27</td>
</tr>
</tbody>
</table>

Total (95\% CI) 1134 1133 100.0% 0.47 (0.32, 0.69)

Total events 40 81

Heterogeneity: Chi\textsuperscript{2}=2.59, df=3 (P=0.46); I\textsuperscript{2}=0%

Test for overall effect Z=3.84 (P=0.0001)

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# 1st vs. 2nd Generation Azoles: Meta-analysis: Cases of IA

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Second-generation</th>
<th>First-generation</th>
<th>Odds ratio M-H, Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Total</td>
<td>Events</td>
</tr>
<tr>
<td>Marks 2011</td>
<td>1</td>
<td>224</td>
<td>5</td>
</tr>
<tr>
<td>Wingard 2010</td>
<td>9</td>
<td>305</td>
<td>17</td>
</tr>
<tr>
<td>Cornely 2007</td>
<td>2</td>
<td>304</td>
<td>20</td>
</tr>
<tr>
<td>Ullmann 2007</td>
<td>7</td>
<td>301</td>
<td>21</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>1134</td>
<td>1133</td>
<td>100.0%</td>
</tr>
<tr>
<td>Total events</td>
<td>19</td>
<td>63</td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Chi²=4.18, df=3 (P=0.24); I²=28%
Test for overall effect Z=4.73 (P<0.00001)

Antifungal Prophylaxis: Neutropenia in AML

Probability of Death: Fluconazole > Posaconazole

Empiric vs. Preemptive Antifungal Therapeutic Strategies
Strategies for Treatment of IFIs

Risk factors
Early tests
Positive Culture

Prophylaxis
Empirical
Pre-emptive
Targeted

Relative Size of Treatment Target Population

Zaragosza R et al. Therapeutics and Clinical Risk Management 2008;4:1261-1280
Empiric Antifungal Therapy
**Comparison:** All Antifungals vs. Null Control – Including patients with suspected infection

**Outcome:** Defervescence

<table>
<thead>
<tr>
<th>Study or sub-category</th>
<th>Antifungals n/N</th>
<th>Null Control n/N</th>
<th>OR (random) 95% CI</th>
<th>Weight %</th>
<th>OR (random) 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pizzo 1982</td>
<td>13/18</td>
<td>9/16</td>
<td>10.95 2.02 (0.48, 8.43)</td>
<td>10.95</td>
<td>2.02 (0.48, 8.43)</td>
</tr>
<tr>
<td>Lazarus 1984</td>
<td>7/8</td>
<td>0/6</td>
<td>2.12 65.00 (2.24, 1887.35)</td>
<td>65.00</td>
<td>65.00 (2.24, 1887.35)</td>
</tr>
<tr>
<td>EORTC 1989</td>
<td>47/68</td>
<td>34/64</td>
<td>34.95 1.97 (0.97, 4.02)</td>
<td>34.95</td>
<td>1.97 (0.97, 4.02)</td>
</tr>
<tr>
<td>Goldstone 1994</td>
<td>41/64</td>
<td>32/60</td>
<td>34.35 1.56 (0.76, 3.20)</td>
<td>34.35</td>
<td>1.56 (0.76, 3.20)</td>
</tr>
<tr>
<td>Fukuda 1994</td>
<td>27/37</td>
<td>16/25</td>
<td>17.63 1.52 (0.51, 4.53)</td>
<td>17.63</td>
<td>1.52 (0.51, 4.53)</td>
</tr>
<tr>
<td>Total</td>
<td>195</td>
<td>171</td>
<td>100.00 1.88 (1.14, 3.08)</td>
<td>100.00</td>
<td>1.88 (1.14, 3.08)</td>
</tr>
</tbody>
</table>

Total (95% CI)
Total events: 135 (Antifungals), 91 (Null Control)
Test for heterogeneity: Chi² = 4.72, df = 4 (P = 0.32), I² = 15.3%
Test for overall effect: Z = 2.50 (P = 0.01)
Caspofungin vs. L-AmB for Empiric Antifungal Therapy in Patients with Persistent Neutropenia

Walsh TJ et al. NEJM 2004;351:1391-1402
Voriconazole vs. L-AmB for Empiric Antifungal Therapy in FNE

P=0.02

<table>
<thead>
<tr>
<th></th>
<th>Voriconazole (n=415)</th>
<th>L-AmB (n=422)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall response</td>
<td>26.0</td>
<td>30.6</td>
</tr>
<tr>
<td>No breakthrough fungal infection</td>
<td>98.1</td>
<td>95.0</td>
</tr>
<tr>
<td>Survival</td>
<td>92.0</td>
<td>94.1</td>
</tr>
<tr>
<td>No discontinuation</td>
<td>90.1</td>
<td>93.4</td>
</tr>
<tr>
<td>Resolution of fever</td>
<td>32.5</td>
<td>36.5</td>
</tr>
<tr>
<td>Treatment of baseline fungal infection</td>
<td>46.2</td>
<td>66.7</td>
</tr>
</tbody>
</table>

Survival in Empiric Antifungal Therapy

- Odds ratio >1 indicates benefit to AmB for survival
- Caspofungin superior survival vs. AmB

Empiric Therapy Response

- Odds ratio <1 indicates benefit to AmB for response
- No clear benefit of any regimen vs. AmB

Preemptive Antifungal Therapy
Empiric vs. Preemptive Antifungal Therapy in Neutropenic Fever

- Empiric therapy employs fever as threshold to initiate AF therapy – fever non-specific
- Open label randomized non-inferiority trial
- Patients: hematological malignancy or autologous-HSCT with neutrophils <0.5X10^9/L for ≥10 days
- Compared:
  - Empiric therapy (AF therapy initiated for persistent fever @ 4 days or recurrent fever days 4 to 14)
  - Preemptive therapy (AF therapy started at any time after 4 days of fever with imaging of pneumonia, sinusitis, shock or other clinically documented site of infection or galactomannan assay ≥1.5 with accompanying CXR or CT scan)

Cordonnier C et al. CID 2009;48:1042-1051
Empiric vs. Pre-emptive Antifungal Therapy in Neutropenic Fever

- **AF therapy:**
  - AmB 1 mg/kg/d IV for pt with CrCl 40-59 ml/min if no concomitant nephrotoxins or ≥60 ml/min if concomitant nephrotoxic drugs
    
  or

  - L-AmB 3 mg/kg/d IV if CrCl 20-39 ml/min or 40-59 ml/mi if concomitant nephrotoxic drugs

- **End point:** survival 14 days after recovery from neutropenia

- **More IFIs in pt receiving induction chemo vs. consolidation or a-BMT 15 (16.4%) vs. 2 (3.9%), p<.01**

*Cordonnier C et al. CID 2009;48:1042-1051*
## Empiric vs. Pre-emptive Antifungal Therapy in Neutropenic Fever

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Empiric N=150</th>
<th>Pre-emptive N=143</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treated with AF therapy</td>
<td>92/150 (61.3%)</td>
<td>56/143 (39.2%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Duration of fever before AF therapy median days</td>
<td>7</td>
<td>13</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Duration of AF therapy mean days</td>
<td>7.0 +/-8.5</td>
<td>4.5 +/-7.3</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Proven &amp; probable IFIs</td>
<td>2.7% (4/150)</td>
<td>9.1% (13/143)</td>
<td>&lt;.02</td>
</tr>
<tr>
<td>Cost of AF therapy €</td>
<td>2252 +/-4050</td>
<td>1478 +/-3329</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>LOS mean days</td>
<td>30.3 +/-10.5</td>
<td>30.3 +/-10.2</td>
<td>NS</td>
</tr>
<tr>
<td>Aspergillus infections</td>
<td>4</td>
<td>8</td>
<td>NS (108)</td>
</tr>
<tr>
<td>Survival</td>
<td>97.3%</td>
<td>95.1%</td>
<td>NS</td>
</tr>
</tbody>
</table>

Cordonnier C et al. CID 2009;48:1042-1051
Pre-emptive vs. Empiric for Invasive Mold Disease

- Odds ratio <1 indicates benefit of preemptive therapy for survival

Treatment of IC & IA
## Canadian C/IC Guidelines

### Therapeutic strategy

<table>
<thead>
<tr>
<th>Empiric therapy:</th>
<th>Antifungal therapeutic options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenic</td>
<td>Preferred</td>
</tr>
<tr>
<td></td>
<td>IV LFAmB 3 mg/kg/day (A-I); or caspofungin 70 mg on day 1, then IV 50 mg daily (A-I); or IV AmB-d 0.6 mg/kg/day to 1.0 mg/kg/day (B-II in the absence of risk factors for nephrotoxicity)</td>
</tr>
</tbody>
</table>

Bow EJ et al. CJIDMM 2010;21:e122-e150
## Canadian C/IC Guidelines

### Antifungal therapeutic options

<table>
<thead>
<tr>
<th>Therapeutic strategy</th>
<th>Preferred</th>
<th>Second line</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenic therapy for microbiologically or histologically documented C/IC</td>
<td>IV AmB-d 0.6 mg/kg/day to 1.0 mg/kg/day (A-I); or IV LFAmB 3 mg/kg/day (A-I); or IV ECH (IV anidulafungin 200 mg → 100 mg daily [B-III]; or IV caspofungin 70 mg → 50 mg daily [A-I]; or IV micafungin 100 mg daily [B-III])</td>
<td>Fluconazole 800 mg or IV/oral 400 mg/day daily (for less severely ill patients [A-III]); or IV voriconazole 6 mg/kg every 12 h for 24 h then 4 mg/kg every 12 h or oral doses of 200 mg twice daily (if risk of mould infection is present) (B-I)</td>
</tr>
</tbody>
</table>

Bow EJ et al. CJ IDMM 2010;21:e122-e150
New Formulations

- Posaconazole po tablets – prophylaxis or treatment 300 mg daily (3 x 100 mg)
- Administered fasting or irrespective of food
- Posaconazole IV formulation 300 mg q day
Antifungal Therapy for IA – IDSA Guidelines

- IA involving lung, sinus, tracheobronchial tree and CNS:
  - Primary therapy – Voriconazole 6 mg/kg q12h X 1 d then 4 mg/kg q12h IV → 200 mg bid po [A-I]
  - Alternative – L-AmB 3-5 mg/kg/d (A-I), caspofungin 70 mg → 50 mg/d IV, Micafungin 100-150 mg/d IV, Posaconazole 200 mg qid po initially then 400 mg bid po after stabilization or Itraconazole (dose depends on formulation) [All B-II]

- Empiric and preemptive antifungal therapy:
  - L-AmB 3 mg/kg d IV, Caspofungin 70 mg → 50 mg/d IV or Voriconazole 6 mg/kg q12h X 1 d then 3 mg/kg/d IV → Voriconazole 200 mg bid po

Clinical Success in the Treatment of Refractory Aspergillosis

1. Kuback. FOFI 2002
2. White. CID 1997:24;633
4. Perfect. CID 2003:36;1122
5. Walsh. CID 2007;44:2-12
7. Ratanatharathorn. ASH 2002
Combination Therapy for IA
Voriconazole & Anidulafungin Combination vs. Voriconazole Therapy for Treatment of IA (Hematologic Malignancy & HSCT)

6 Week Mortality

- Combination therapy: 19.3%
- Monotherapy: 27.5%

n=277 (Δ -8.2 [95%CI, -19.0 to 1.5]; p=0.087)

Voriconazole & Anidulafungin Combination vs. Voriconazole Therapy for Treatment of IA (Hematologic Malignancy & HSCT)

Radiographic findings & + GM
n=218 [Δ -11.5 (95% CI, -22.7 to -0.4); p=0.037]
Therapeutic Drug Monitoring (TDM) For Voriconazole

- RCT of voriconazole levels adjusted via TDM to target level (1.0-5.5 mg/L) vs. fixed standard dose (6 mg/kg BID → 4 mg/kg BID); most of pt. hematologic disease.
- Lower adverse events with TDM group 45 vs. 17% (p=.02).
- Complete or partial response in TDM group 81% vs. 57% in standard dose group (p=.04).

Kim WB et al. CID 2012;55:1080-1087

- Canadian TDM Guidance: For efficacy: voriconazole prophylaxis level >0.5 mg/L; treatment level 1.5 to 5.5 mg/L; toxicity associated with >5.5 mg/L.
- TDM for posaconazole not usually required (only when using PPIs): prophylaxis level >0.7 mg/L & therapy 1.0-1.5mg/L.

Laverdiere M et al. CJIDMM 2014;25:327-343
Treatment of Documented Infection

- (b) Odds ratio >1 indicates survival benefit to AmB.
- (c) Odds ratio <1 indicates response benefit for AmB.

### Treatment of Mucormycosis in Adult Patients (ESCMID)

<table>
<thead>
<tr>
<th>Population</th>
<th>Intention</th>
<th>Intervention</th>
<th>SoR</th>
<th>QoE</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First-line therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To cure and to increase survival rates</td>
<td>Surgical debridement in addition to antifungal treatment</td>
<td>A</td>
<td>I lu</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Immunocompromised</strong></td>
<td>To increase survival rates</td>
<td>Immediate treatment initiation</td>
<td>A</td>
<td>I lu</td>
</tr>
<tr>
<td></td>
<td>To cure and to increase survival rates</td>
<td>L-AmB ≥5 mg/kg</td>
<td>A</td>
<td>I lu</td>
</tr>
<tr>
<td><strong>CNS</strong></td>
<td>To cure</td>
<td>L-AmB 10 mg/ kg, initial 28 days</td>
<td>A</td>
<td>II</td>
</tr>
<tr>
<td><strong>Any</strong></td>
<td>To cure</td>
<td>Posaconazole 4 x 200 mg/ day or 2 x 400 mg/ day</td>
<td>B</td>
<td>I lu</td>
</tr>
<tr>
<td><strong>Salvage therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>To cure</td>
<td>Posaconazole + L-AmB</td>
<td>C</td>
<td>III</td>
</tr>
</tbody>
</table>

*Cornely OA et al. Clin Microbiol Infect 2014;20(S3):5-26*
Various therapeutic strategies can be used for the prevention and treatment of IFIs in patients with hematological malignancies.

Empiric antifungal therapy is more widely used than preemptive therapy and may produce better survival; the preemptive strategy permits more directed therapy.

New formulations of antifungal therapy and the use of combination therapy may be useful for certain types of IFIs.