Antifungal prophylaxis: Whom, what and when

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Antifungal Prophylaxis: Whom, What and When

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Disclosure

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Contents

• To be or not to be
• Recent advances
• The flip side
• Whom
• What
• Guidelines
• Conclusion

To be, or not to be, that is the question.

William Shakespeare
Antifungal strategies

Prophylaxis
Empirical (symptom-driven)
Pre-emptive (diagnosis-driven) (early treatment)
Definitive (etiology specific)

Targeted prophylaxis

GM+ PCR+
GM+ PCR+
Culture+ Tissue+
Possible Probable

Disease status

Temperature

69% of patients with proven/probable invasive mold diseases had fever.
The Rationale for Prophylaxis

• The substantial morbidity and mortality associated with invasive fungal diseases (IFD)
• The difficulty in obtaining a timely diagnosis
• The suboptimal response of best available treatments
• The substantial additional resource use in patients with IFD
  – Diagnostic approaches and therapeutic monitoring
  – Slow resolution of infection => prolonged suppressive therapy
  – Risk of recurrence in the immunosuppressive period
• Delay in subsequent chemotherapy which compromises overall outcome
RECENT ADVANCES
Fluconazole Prophylaxis Prevents IFI and Improves Survival After HSCT

- Survival Probability over Years After Transplant
  - Related and Unrelated Donor Transplant
  - Placebo
  - $p = 0.002$

- Fluconazole Prophylaxis Prevents IFI and Improves Survival After HSCT

- n = 355 autopsies
  - Fluconazole
    - Invasive Fungus: 37%
    - Aspergillus/Mucor: 29%
    - Candida: 8%
    - Hepatosplenic: 3%
  - No Fluconazole
    - Invasive Fungus: 43%
    - Aspergillus/Mucor: 18%
    - Candida: 27%
    - Hepatosplenic: 16%

- Incidence of IA
  - 1987 – 6%
  - 1993 – 11%

- Slavin MA et al, J Infect Dis 1995;171:1545-52
- Van Burik JA et al. Medicine 1998;77:246-54
Fluconazole vs Itraconazole prophylaxis

Allo-HSCT

Cumulative incidence of proven/probable IFI while on-treatment

Discontinuation of itraconazole 36%

“...itraconazole appears to prevent IMI in the subset of patients who tolerate the drug”

Posaconazole Prophylaxis

In AML/MDS with 3+7 induction:
- Posa vs. Itra/Flu (n= 308 vs. 298)
- Incidences of IFI decreased
- Survival benefits demonstrated

In Severe GVHD after allo-HSCT:
- Posa vs Flu (n=301 vs. 299)
- Incidences of IFI decreased
- Survival benefits NOT demonstrated

Voriconazole Prophylaxis vs Placebo

- n = 25, first induction for AML
- Incidences of Lung Infiltrates
- Stopped because of ethical concern with placebo arm

VCZ, voriconazole; PLC, placebo control; AML, acute myelogenous leukemia

Voriconazole vs. itraconazole in alloHSCT

- IMPROVIT Study
- Prospective, phase 3, randomized, open-label trial
- 47 transplant centers across 12 countries
- Survival benefits NOT demonstrated

### Success of prophylaxis*

<table>
<thead>
<tr>
<th></th>
<th>Voriconazole N=234</th>
<th>Itraconazole N=255</th>
<th>Differences (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>at d180</td>
<td>48.7%</td>
<td>33.2%</td>
<td>16.4% (7.7-25.1)**</td>
</tr>
<tr>
<td>at d100</td>
<td>54.0%</td>
<td>39.8%</td>
<td>15.4% (6.6-24.2)**</td>
</tr>
</tbody>
</table>

*Composite endpoints
1. **Survival** at day 180
2. No probable/proven breakthrough IFI
3. **Not discontinuation** of study drug for >14d during 100d prophylactic period

**P<0.05

Br J Hematol 2011;155:318-327
Voriconazole vs. fluconazole in allo-HSCT patients

**BMT-CTN Study**
- Prospective, randomized, double-blind trial
- 35 transplant centers in the Blood and Marrow Transplant Clinical Trials Network
- Adult and pediatric patients

**Cumulative incidence rates of IFIs**

<table>
<thead>
<tr>
<th></th>
<th>d180</th>
<th>d365</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>11.2%</td>
<td>13.7%</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>7.3%</td>
<td>12.7%</td>
</tr>
</tbody>
</table>

**Fungal-free survival (FFS)**

<table>
<thead>
<tr>
<th></th>
<th>d180</th>
<th>d365</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluconazole</td>
<td>75%</td>
<td>65%</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>78%</td>
<td>64%</td>
</tr>
</tbody>
</table>

**Structured monitoring**
- GM twice-weekly until d60 then once-weekly until d100
- GM twice-weekly until d100 if GVHD under steroid therapy
- Radiological studies and invasive diagnostic procedure while IFI was suspected: Chest CT, Sinus CT, Bronchoalveolar lavage or biopsy
- **Empirical** L-AmB or caspofungin as short as possible and for up to 14 days

**AML (independent risk factor of IFI)**
- Fewer IFIs (8.5% vs. 21%; p=0.04)
- Improved FFS (78% vs. 61%; p=0.04)
- No difference in OS (81% vs. 72%; p=0.32)

**Wingard J et al, Blood 2010;116:5111-8**

*PRESENTED AT MMTN CONFERENCE, 1-3 DEC 2017*
Mould-active compared with fluconazole prophylaxis to prevent invasive fungal diseases in cancer patients receiving chemotherapy or HSCT

- A meta-analysis that included 20 randomized trials
- reduced the risk of invasive aspergillosis compared with fluconazole prophylaxis
- reduced the risk of invasive fungal infection–related mortality compared with fluconazole prophylaxis (RR 0.67, 95% CI 0.47-0.96).
- no difference in overall mortality
- associated with an increased risk of adverse events leading to antifungal discontinuation

HSCT, haematopoietic stem-cell transplantation
Systematic review and mixed treatment comparison meta-analysis of randomized clinical trials of primary oral antifungal prophylaxis in alloHSCT recipients

Five RCTs, 2147 patients alloHSCT, allogeneic haematopoietic stem-cell transplantation
Treatment effect of mould-active compared with fluconazole prophylaxis in allogeneic hematopoietic cell transplant recipients

Proven/probable invasive fungal infection

Proven/probable invasive aspergillosis

Five RCTs, 2147 patients

All-cause mortality was similar across all mould-active agents
Mixed treatment comparison of systemic antifungal prophylaxis in neutropenic patients receiving therapy for haematological malignancies

- A systematic review of 25 studies identified
- Antifungal prophylaxis was more effective than no prophylaxis in reducing IFI risk.
- The IFI risk after voriconazole or posaconazole was lower than after fluconazole or itraconazole tablets.
- Posaconazole was also found to be more effective than no prophylaxis in reducing all-cause mortality.

Resistance, Toxicity, Cost, Breakthrough infections

THE FLIP SIDE
Antifungals are associated with a number of potential drug interactions, please consult the pharmacist for advice

<table>
<thead>
<tr>
<th>Antifungal</th>
<th>Affected Drug(s)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Posaconazole</td>
<td>Ciclosporin, tacrolimus, sirolimus, statins, Rifampicin, Midazolam, Phenytoin (and other anticonvulsants), busulfan, thiotepa</td>
<td>Ciclosporin/tacrolimus dose adjustments may be required</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>Ciclosporin, tacrolimus, Phenytoin, rifabutin, rifampicin, efavirenz, busulfan, thiotepa</td>
<td>Ciclosporin/tacrolimus dose adjustments may be required.</td>
</tr>
<tr>
<td>Ambisome</td>
<td>Increased risk of nephrotoxicity when given with other nephrotoxic drugs i.e. ciclosporin, tacrolimus, aminoglycosides. Can increase cardiotoxicity of digoxin due to Ambisome-induced hypokalaemia. Increased risk of hypokalaemia when used with corticosteroids and/or diuretics</td>
<td>Monitor renal function and electrolytes including potassium and magnesium levels</td>
</tr>
<tr>
<td>Micafungin</td>
<td>May increase levels of sirolimus, nifedipine or itraconazole</td>
<td></td>
</tr>
<tr>
<td>Fluconazole</td>
<td>Warfarin, ciclosporin, tacrolimus, rifabutin, phenytoin, sulphonylureas, theophylline</td>
<td></td>
</tr>
</tbody>
</table>
Breakthrough Candidemia in alloHSCT recipients, Japan

• Out of 768 allo-HSCT cases, 26 developed BC.
• Etiologies identified: *C. parapsilosis* (9 strains), *C. glabrata* (4 strains), *C. guilliermondii* (3 strains), and the other *Candida* species (6 strains).
• Agents used: micafungin (17 cases), liposomal AmB (5), itraconazole (2), and voriconazole (2).
• 85% of the causative *Candida* species of micafungin breakthrough were susceptible to micafungin. 75% of the strains were wild type for the administered agents.
• Systemic steroid administration and longer (≥ 5 days) severe neutropenic phase were independent risk factors of the breakthrough candidemia.

Plotted cost-effective plane for using posaconazole as antifungal prophylaxis in different countries

AML/MDS in induction, POSA vs. ITRA/FLU

Prophylaxis does NOT always cost more.
Prophylaxis for higher-risk populations does NOT always do better.
Disease- and country-specific cost-effectiveness is required.

2016 Taiwan guidelines. Data from Pharmacoecnomics 2011;29:251-68
Costs and health outcomes

- Network meta-analysis of 21 randomized controlled trials
- Resource use and costs obtained from the Singapore health care institution.
- All triazoles except itraconazole capsule were effective in reducing invasive fungal infections (IFIs).
- Posaconazole was more efficacious in reducing IFIs and all-cause deaths than were fluconazole and itraconazole.

### AML

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total cost (SGD)</th>
<th>Effectiveness</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of IFIs</td>
<td>No. of IFIs avoided</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>4,186.91</td>
<td>0.100</td>
<td></td>
</tr>
<tr>
<td>Itraconazole capsule</td>
<td>5,748.09</td>
<td>0.135</td>
<td>0.035</td>
</tr>
<tr>
<td>Itraconazole solution</td>
<td>4,172.47</td>
<td>0.066</td>
<td>0.034</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>4,909.45</td>
<td>0.037</td>
<td>0.063</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>14,095.61</td>
<td>0.049</td>
<td>0.051</td>
</tr>
</tbody>
</table>

### HSCT

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Total cost (SGD)</th>
<th>Effectiveness</th>
<th>ICER</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>No. of IFIs</td>
<td>No. of IFIs avoided</td>
</tr>
<tr>
<td>Fluconazole</td>
<td>4,271.27</td>
<td>0.100</td>
<td></td>
</tr>
<tr>
<td>Itraconazole capsule</td>
<td>5,893.90</td>
<td>0.135</td>
<td>-0.035</td>
</tr>
<tr>
<td>Itraconazole solution</td>
<td>4,697.85</td>
<td>0.066</td>
<td>0.034</td>
</tr>
<tr>
<td>Posaconazole</td>
<td>5,960.76</td>
<td>0.037</td>
<td>0.063</td>
</tr>
<tr>
<td>Voriconazole</td>
<td>17,442.68</td>
<td>0.049</td>
<td>0.051</td>
</tr>
</tbody>
</table>

*IFI, invasive fungal infection; LY, life-years; ICER, incremental cost-effectiveness ratio.*

Zhao et al. Antimicrob Agents Chemother 2015;60:376
Economic evaluation of azoles as primary prophylaxis in Spanish patients undergoing alloHSCT

Cost-effectiveness analysis decision-analytic model structure from the perspective of the Spanish National Health System

Economic evaluation of azoles as primary prophylaxis in Spanish patients undergoing alloHSCT (cont.)

• Generic itraconazole was the least costly AFP (€162) relative to fluconazole (€500), posaconazole oral suspension (€8628) or voriconazole (€6850).
• Compared with posaconazole, voriconazole was associated with the lowest number of breakthrough IFIs (36 vs 60); thus, the model predicted fewer deaths from breakthrough IFI for voriconazole (24) than posaconazole (33), and the lowest predicted costs associated with other licensed antifungal treatment and IFI treatment in a cohort of 1000.
• Voriconazole resulted in cost savings of €4707 per patient compared with posaconazole. Itraconazole demonstrated a high probability of being cost-effective.
• As primary AFP in alloHSCT patients 180 days posttransplant, voriconazole was more likely to be cost-effective than posaconazole regarding cost per additional IFI and additional death avoided.

Limited targets/options of current antifungal agents

Antifungal strategy
- Prophylaxis (symptom-driven)
- Empirical (symptom-driven)
- Pre-emptive (early treatment)
- Definitive

Targeted prophylaxis

Temperature

Disease status
- Possible
- Probable
- Proven

Antifungal approved
- Fluconazole
- Itraconazole (AML, GVHD)
- Posaconazole (AML, GVHD)
- Micafungin (HSCT)
- Voriconazole (HSCT, GVHD)
- AmB
- Caspofungin (neutropenia)
- Micafungin (neutropenia)

Molds: Vori, AmB, etc.
- Candida: echinocandin, azoles, etc.

Presented at MMTN Conference, 1-3 Dec 2017
Copyright of speaker
Risk stratification is used to help target antifungal prophylaxis to those who would most benefit from it.

**WHOM**
High-risk disease population for IFI

- Chronic granulomatous disease
- Allogous HSCT with graft versus host disease
- Myelodysplastic syndrome treated with remission induction therapy
- Acute myeloblastic leukemia treated with remission induction therapy
- Lung or heart-lung transplantation
- Small bowel transplantation
- Liver transplantation
- Allogeneic HSCT without graft versus host disease
- Acute myeloblastic leukemia during consolidation therapy
- Acute lymphoblastic leukemia
- Heart transplantation
- Chronic lymphocytic leukemia
- Myelodysplastic syndrome
- Multiple myeloma
- Chronic obstructive pulmonary disease with acute exacerbation
- AIDS
- Non-Hodgkin’s lymphoma
- Autologous hematopoietic stem cell transplantation
- Kidney transplantation
- Solid tumors
- Auto-immune disorders
Mold and Yeast Infections in Patients with Hematological Malignancies

Incidence of IFI varied by primary diseases

<table>
<thead>
<tr>
<th>HM</th>
<th>No. of patients</th>
<th>No. of IFI (incidence)</th>
<th>Molds</th>
<th>Yeasts</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>No. cases</td>
<td>Incidence %</td>
</tr>
<tr>
<td>AML</td>
<td>3012</td>
<td>373 (12%)</td>
<td>239</td>
<td>7.9</td>
</tr>
<tr>
<td>ALL</td>
<td>1173</td>
<td>77 (6.5%)</td>
<td>51</td>
<td>4.3</td>
</tr>
<tr>
<td>CML</td>
<td>596</td>
<td>15 (2.5%)</td>
<td>14</td>
<td>2.3</td>
</tr>
<tr>
<td>CLL</td>
<td>1104</td>
<td>6 (0.5%)</td>
<td>5</td>
<td>0.4</td>
</tr>
<tr>
<td>NHL</td>
<td>3457</td>
<td>54 (1.6%)</td>
<td>30</td>
<td>0.9</td>
</tr>
<tr>
<td>HD</td>
<td>844</td>
<td>6 (0.7%)</td>
<td>3</td>
<td>0.35</td>
</tr>
<tr>
<td>MM</td>
<td>1616</td>
<td>7 (0.5%)</td>
<td>4</td>
<td>0.3</td>
</tr>
<tr>
<td>Total</td>
<td>11802</td>
<td>538 (4.6%)</td>
<td>346</td>
<td>2.9</td>
</tr>
</tbody>
</table>

- n = 3228 (1249 allo, 1979 auto) pts from 11 Italian HSCT centers
- Incidence of proven/probable IA: 7.8% in alloHSCT
- Attributable mortality in alloHSCT patients: 77.2%

Pagano L et al (Italian Multicenter Study), Haematologica 2006;91:1068-75; Clin Infect Dis 2007;45:1161-70
Neutropenia remains the most important risk factor

- Periodic in nature
- 2\textsuperscript{nd}-wave of infection
  - Neutropenia > 7 days..
  (difference in induction?)

Gerson M, Ann Intern Med 1984;100:345
GVHD is a major risk factor

Graft-versus-host disease

35% Methyl prednisolone ≥1 mg/kg/day

Jantunen E, Bone Marrow Transplant 1997;19:801
Grow W, Bone Marrow Transplant 2002;29:15
Prior IA is a risk factor

- **Recurrence risks**
  1. Longer neutropenia
  2. Advanced underlying disease
  3. Short interval from IA to transplant (<6 wks)
  4. Ablative conditioning regimen
  5. CMV disease
  6. Marrow or cord blood as graft
  7. Acute GVHD

  Martino R, Blood 2006; 108: 2928

- **Voriconazole reduce the risk for recurrence, the VOSIFI study**
  - 45 pts with prior IFI (31 IA, 5 *Candida*, 6 other)
  - 2 relapses (1 *Candida*, 1 *Scedosporium*) & 1 new mucormycosis

  Cordonnier C, Haematologica 2010;95:1762
## Changes in population at risk of IFI in hematology

<table>
<thead>
<tr>
<th>Change in patient population</th>
<th>Reasons/Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prolonged survival in immunocompromised condition (elder, relapsed/refractory...)</td>
<td>Better supportive care</td>
</tr>
<tr>
<td>Higher risk in transplantation</td>
<td>Haploidentical HSCT; Cord blood transplantation; CD34-selected or T-cell depleted graft</td>
</tr>
<tr>
<td>T-cell immunosuppression</td>
<td>New immunosuppressants (FK-506, etc); Chemotherapy agents (fludarabine, alemtuzumab, etc)</td>
</tr>
</tbody>
</table>
Risks can vary even with the same disease

<table>
<thead>
<tr>
<th>Regions</th>
<th>Austria</th>
<th>German</th>
<th>Italy</th>
<th>US</th>
<th>US</th>
<th>Japan (Hokkaido)</th>
<th>Taiwan</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study design</td>
<td>Prospective Single-center</td>
<td>Retrospective Single-center</td>
<td>Prospective Multi-center</td>
<td>Retrospective Single-center</td>
<td>Prospective Single-center</td>
<td>Retrospective Multi-center</td>
<td>Prospective Single-center</td>
</tr>
<tr>
<td>Disease</td>
<td>All HMs</td>
<td>All HMs</td>
<td>Fresh AML</td>
<td>Fresh AL</td>
<td>Fresh AML</td>
<td>All HMs (597 SCT)</td>
<td>Fresh and relapsed AL</td>
</tr>
<tr>
<td>Patient number</td>
<td>1095</td>
<td>592 (1693 C/T)</td>
<td>224</td>
<td>231</td>
<td>254</td>
<td>2821</td>
<td>401 (507 C/T)</td>
</tr>
<tr>
<td>Systemic antifungal prophylaxis</td>
<td>Fluconazole Itraconazole Lip-AmB</td>
<td>Oral AmB Itraconazole</td>
<td>Not remarked</td>
<td>No</td>
<td>No</td>
<td>Various</td>
<td>No</td>
</tr>
<tr>
<td>Chemotherapy regimens</td>
<td>C/T* Auto-SCT, Allo-SCT</td>
<td>C/T* Auto-SCT</td>
<td>Fludarabine-based induction</td>
<td>Standard induction</td>
<td>Standard induction</td>
<td>C/T* SCT</td>
<td>Induction</td>
</tr>
<tr>
<td>IFI Incidence</td>
<td>All fungi</td>
<td>15.0%</td>
<td>8.8%</td>
<td>4%@ (induction)</td>
<td>2%@ (consolidation)</td>
<td>5.9% (30 days)</td>
<td>11.1% (100 days)</td>
</tr>
<tr>
<td>Candida</td>
<td>5.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mold</td>
<td>42.5%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality%</td>
<td>All-cause</td>
<td>72.0%</td>
<td>42%</td>
<td>23.7% (6 months)</td>
<td>28.2%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IFI-attributed</td>
<td>25.1%</td>
<td>40.9%</td>
<td>60% (induction)</td>
<td>80% (consolidation)</td>
<td>22.2% (for C/T)</td>
<td>50% for SCT</td>
<td>25.8%</td>
</tr>
</tbody>
</table>
# Pretreatment risks assessment for IFDs

## Immunogenetic status
- Toll-like receptors polymorphism
- C-type lectin receptor polymorphism
- Mannose binding lectin polymorphism
- Plasminogen polymorphism
- Others

## Underlying conditions
- Neutropenia
- Progressive cancer
- GvHD
- Anticancer chemotherapy
- Steroids
- T-cell suppressors

## Primary diseases
- Hematological malignancy
- Allo HSTCT, solid organ transplant
- Solid tumors, others

## Environmental factors
- Geo-climate
- Construction work
- Tobacco or cannabises use
- Contaminated food or spices
- Pets, potted plants, and gardening
- No HEPA filtered air during HSCT

## Other factors
- Diabetes
- Iron overload
- Trauma, burns
- Renal impairment
- Metabolic acidosis
- Prior respiratory disease

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A Risk Prediction Score for Invasive Mold Disease in Patients with Hematological Malignancies

<table>
<thead>
<tr>
<th>Variable</th>
<th>Frequency in patients with IMD (%)</th>
<th>β-coef</th>
<th>Wald x²</th>
<th>P value</th>
<th>Hazard Ratio (95% CI)</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of neutropenia</td>
<td>596 (41)</td>
<td>1.72</td>
<td>21.99</td>
<td>&lt; 0.001</td>
<td>5.60 (2.72-11.50)</td>
<td>4</td>
</tr>
<tr>
<td>Previous IMD</td>
<td>31 (9)</td>
<td>1.71</td>
<td>12.42</td>
<td>&lt; 0.001</td>
<td>5.55 (2.14-14.41)</td>
<td>4</td>
</tr>
<tr>
<td>Malignancy status</td>
<td>755 (50)</td>
<td>1.53</td>
<td>19.46</td>
<td>&lt; 0.001</td>
<td>4.64 (2.34-9.19)</td>
<td>3</td>
</tr>
<tr>
<td>Lymphopenia or lymphocyte dysfunction</td>
<td>415 (31)</td>
<td>0.90</td>
<td>9.57</td>
<td>&lt; 0.002</td>
<td>2.45 (1.39-4.34)</td>
<td>2</td>
</tr>
</tbody>
</table>

Impact of posaconazole prophylaxis on the incidence and mortality of invasive mold disease

WHAT
Science or art?
Systemic antifungal prophylaxis

AML/ MDS
Remission
Induction chemotherapy

HSCT
Pre- engraft
engraft

HSCT
Severe GVHD+
Immunosuppressive therapy

Fluconazole
Itraconazole

Fluconazole
Itraconazole
Micafungin IV

Fluconazole
Itraconazole
Voriconazole

Factors to be considered: efficacy, drug-drug interaction, toxicity, bioavailability, compliance, and cost
Systematically developed statements to assist practitioners and patients in making decisions about appropriate health care for specific clinical circumstances.

GUIDELINES
Guidelines for the use of antifungal agents in patients with invasive fungal infections in Taiwan

Infectious Diseases Society of Taiwan; Medical Foundation in Memory of Dr. Deh-Lin Cheng; Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education; and CY Lee’s Research Foundation for Pediatric Infectious Diseases and Vaccine

Guideline

Guidelines for the Use of Antifungal Agents in Patients with Invasive Fungal Infections in Taiwan — Revised 2009

The Infectious Diseases Society of Taiwan; The Hematology Society of Taiwan; Taiwan Society of Pulmonary and Critical Care Medicine; Medical Foundation in Memory of Dr. Deh-Lin Cheng; Foundation of Professor Wei-Chuan Hsieh for Infectious Diseases Research and Education; and CY Lee’s Research Foundation for Pediatric Infectious Diseases and Vaccine.
From Evidences to Guidelines

• Grading the quality of evidence (very low, low, moderate, and high) and the strength of the recommendation (weak or strong).

• The strengths of recommendations are based on, but not limited to:
  1. quality of evidence.
  2. balance between benefits (e.g., treatment efficacy and benefit of early intervention) and harms (e.g., potential toxicity and drug-drug interaction and negative impact of delay in intervention);
  3. disease burdens,
  4. resources and cost.

A risk-adapted and dynamic antifungal strategy

Patients with hematological diseases and hematopoietic stem cell transplantation recipients who are at risk of invasive fungal diseases

Proactive approach before immunosuppressive therapy

Select antifungal prophylactic strategy and regimen

- No prophylaxis
- Anti-Candida prophylaxis
- Anti-Aspergillus prophylaxis

Reactive approach: when clinical evidences of infection develop, such as persistent or relapsing fever after 96 hours (3-5 days) of apparently adequate antibacterial therapy and no other etiology identified

Select antifungal therapeutic strategy and regimen

- Symptom-driven therapy
- Diagnosis-driven therapy

2016 Taiwan guidelines
## Selection of antifungal strategy

<table>
<thead>
<tr>
<th>Factor</th>
<th>Prophylaxis</th>
<th>Empirical (symptom-driven)</th>
<th>Pre-emptive (diagnosis-driven)</th>
<th>Target (definitive)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proactive assessment</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Epidemiology: local incidences and risk of IFD</td>
<td>High</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diagnostics tools in facility: availability, accessibility, performance, and turn-around time</td>
<td>Low</td>
<td>Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Accessibility to healthcare setting during high risk period</td>
<td>Poor</td>
<td>Good</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Therapeutics: compliance, bioavailability, direct toxicity and drug-drug interaction</td>
<td>Easy</td>
<td>Complex</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cost-effectiveness</td>
<td>High</td>
<td>Low</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
General recommendations

- Strategies to reduce risk of invasive fungal diseases through modifying risk factors such as control of underlying diseases or conditions, environmental control to reduce exposure to fungi, and patient education for personal hygiene and food safety are important before adapting prophylactic strategy.
- Prophylactic use of anti-mold agents reduces the yields of galactomannan antigen assay and molecular diagnostics.
- Prophylactic strategy may increase the uncertainty or difficulty of managing subsequent fungal infections.
- If the risk of invasive mold diseases is low, may use fluconazole as antifungal prophylaxis and combine with a mould-directed diagnostic approach.
- Duration of therapy is based on recovery from neutropenia or immunosuppression.
# Primary prophylaxis

<table>
<thead>
<tr>
<th>Diagnosis or status of the hosts</th>
<th>Primary</th>
<th>Alternative</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>AML and MDS patients receiving induction chemotherapy</td>
<td>Nystatin (S/L)*</td>
<td>Posaconazole (S/H) Itraconazole (W/H) Fluconazole 50-400 mg (W/H) AmB-d (W/H)</td>
<td>Clinical trials for fluconazole showed various results. continued until myeloid reconstitution has occurred.</td>
</tr>
<tr>
<td>Allogeneic HSCT, initial neutropenic phase</td>
<td>Nystatin (S/L) Fluconazole 400 mg iv or po (S/H) Micafungin 50 mg (W/H)</td>
<td>Voriconazole 200 mg (4 mg/kg) bid po (W/H) Itraconazole (W/H) AmB-d (W/H)</td>
<td></td>
</tr>
<tr>
<td>Allogeneic HSCT, GVHD phase</td>
<td>Nystatin (S/L) Posaconazole (S/H) Voriconazole (S/H)</td>
<td>Itraconazole (W/H) Fluconazole (W/H) AmB-d (W/H)</td>
<td>Prophylactic use of anti-mold agents is recommended in patients with severe GVHD under treatment with high dose steroid or equivalent immunosuppressants</td>
</tr>
</tbody>
</table>

*Grading of recommendation (strong, weak)/evidence (high-, low-quality) 2016 Taiwan Guideline
Secondary Antifungal Prophylaxis

- Second prophylaxis is strongly recommended in patients with previously defined IFD during a period of myelosuppression (eg, during induction chemotherapy in AML patients) (S/L).
- The choice of agent depends on etiology of prior infection, and in part upon the need to avoid drug interactions while chemotherapy is being given.
  - Voriconazole is the first-line agent for Aspergillus spp and has been best studied as secondary prophylaxis, but mold-active azoles are usually not given concomitantly with certain chemotherapy regimens with hepatically metabolized drugs.
Secondary Antifungal Prophylaxis

• Duration:
  – at least until myeloid reconstitution has occurred
  – follow-up imaging and fungal markers obtained 2~4 weeks after antifungal prophylaxis has been discontinued to ensure that reactivation has not occurred.
  – Patients undergoing repeated courses of myelosuppressive chemotherapy should generally continue secondary prophylaxis until completion of the course of chemotherapy.

Introduce concept of health economics and provides data translated from local disease burdens

<table>
<thead>
<tr>
<th>Patient population</th>
<th>Study design</th>
<th>Study period</th>
<th>Study number</th>
<th>IFD category</th>
<th>IFD incidence</th>
<th>NNT</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Proven</td>
<td>34.6%</td>
<td>3</td>
<td></td>
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<tr>
<td>Adult AML</td>
<td>Retrospective, Single center</td>
<td>2010-2014</td>
<td>39 patients</td>
<td>Proven/Probable</td>
<td>17.9%</td>
<td>6</td>
<td>Yang XY, et al</td>
</tr>
<tr>
<td>Pediatric AML</td>
<td>Prospective, Single center</td>
<td>2010-2012</td>
<td>28 courses</td>
<td>Proven/Probable</td>
<td>17.9%</td>
<td>6</td>
<td>Yeh TC, et al</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>76 courses</td>
<td></td>
<td>7.9%</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>56 courses</td>
<td></td>
<td>1.8%</td>
<td>56</td>
<td></td>
</tr>
<tr>
<td>Pediatric AML</td>
<td>Prospective, Single center</td>
<td>2010-2012</td>
<td>62 courses</td>
<td>Proven/Probable</td>
<td>14.5%</td>
<td>7</td>
<td>Yeh TC, et al</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>59 courses</td>
<td></td>
<td>0%</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>59 courses</td>
<td></td>
<td>1.7%</td>
<td>59</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: IFD, invasive fungal diseases; NNT, number needed to treat.

* NNT is calculated on the inverse of the absolute risk reduction with antifungal prophylaxis. and the incidence of IFDs with antifungal prophylaxis is based on the data from the study by Cornely, et al.


ALL: acute lymphoblastic leukemia; AML: acute myelogenous leukemia; IFD: invasive fungal disease; NNT: number needed to treat.
Conclusion
Summary

• Debates remain regarding the universal systemic primary prophylaxis due to concerns of resistance, toxicity, cost and breakthrough infections.

• Primary prophylaxis has been proven to be cost-effective in selected high-risk patients with hematologic malignancies.

• Selection of prophylactic strategy should be individualized based on risk-benefit assessment at each hospital, or, even for each patient, after considering factors such as: epidemiology, diagnostics, therapeutics and cost-effectiveness.

• Selection of a prophylactic agent should be based on knowledge of the host, the agents, and the strategies available. Consideration should be given to the efficacy, bioavailability, toxicity, drug drug interaction, compliance, and cost.
Thanks for your attention.