FDA - Inhaled Antifungal Virtual Workshop

Antifungal Prophylaxis and Treatment in Solid Organ Transplant: Potential End Points of Inhaled Antifungal Administration

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25 – September - 2020
Cumulative Incidence of Invasive Fungal Infection in Solid Organ Transplantation

Current Epidemiology

Data on Distribution of Invasive Fungal Infection in SOT

IFIs: Invasive Fungal Infections; SOT: Solid Organ Transplant

Aspergillus in Lung Transplants

- **A. fumigatus**
- **A. flavus**
- **A. niger**
- **A. terreus**
- **A. non-fumigatus**

Time to Onset of Mold Infections in Lung Transplant


Lay of the Land: Antifungal Prophylaxis in Lung Transplant

3. Dummer JS. J Heart Lung Transplant. 2004 Dec;23(12):1376-81
Colonization of *Aspergillus*

214 Lung Transplant Recipients

- **Non-Cystic Fibrosis**
  - 151
  - Post-Tx Colonization 33% (50/151)
  - IA 26% (13/50)

- **Cystic Fibrosis**
  - 63
  - Pre-Tx colonization 38% (24/63)
  - Tracheobronchitis 29% (4/24)
  - Post-Tx colonization 27% (17/63)
  - IA 6% (1/17)

**Tx:** Transplantation; **IA:** Invasive Aspergillosis

Results: Risk Factors in Multivariate Analysis of 855 Lung Transplant Recipients

<table>
<thead>
<tr>
<th>Factor</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Single Lung Transplant</td>
<td>1.84 (1.09-3.10)</td>
<td>0.022</td>
</tr>
<tr>
<td>Acute Rejection, number of episodes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 – 2</td>
<td>0.95 (0.57-1.57)</td>
<td>0.83</td>
</tr>
<tr>
<td>3 – 4</td>
<td>0.90 (0.42-1.93)</td>
<td>0.792</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>1.94 (0.90-4.20)</td>
<td>0.092</td>
</tr>
<tr>
<td>CMV Infection</td>
<td>1.65 (0.99-2.76)</td>
<td>0.055</td>
</tr>
<tr>
<td>Aspergillus sp. colonization at 1 year</td>
<td>2.11 (1.28-3.49)</td>
<td>0.003</td>
</tr>
<tr>
<td>Antifungal Prophylaxis</td>
<td>0.86 (0.54-1.39)</td>
<td>0.544</td>
</tr>
</tbody>
</table>

Cystic Fibrosis was not associated with higher risk of IA
Uni- and Multivariate Models for Associations Between Risk Factors and Development of IA

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Univariate Cox model</th>
<th>Multivariate Cox model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HR (95% CI)</td>
<td>p-value</td>
</tr>
<tr>
<td>Aspergillus culture positive only (yes vs no)</td>
<td>5.22 (2.94 to 9.29)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>GM positive only (yes vs no)</td>
<td>8.92 (4.16 to 19.12)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Underlying disease: cystic fibrosis vs COPD</td>
<td>1.41 (0.56 to 3.55)</td>
<td>0.47</td>
</tr>
<tr>
<td>Pre-emptive therapy (received vs not received)</td>
<td>1.04 (0.46 to 2.32)</td>
<td>0.93</td>
</tr>
<tr>
<td>Pre-transplant Aspergillus culture positive (yes vs no)</td>
<td>1.95 (0.97 to 3.92)</td>
<td>0.06</td>
</tr>
<tr>
<td>CMV mismatch (D^+ / R^- vs non-D^+ / R^-)</td>
<td>1.69 (0.91 to 3.12)</td>
<td>0.10</td>
</tr>
<tr>
<td>Biopsy-proven rejection (yes vs no)</td>
<td>2.00 (1.04 to 3.83)</td>
<td>0.04</td>
</tr>
<tr>
<td></td>
<td>11.46 (5.86 to 22.43)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>21.86 (9.32 to 51.27)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>0.93 (0.35 to 2.47)</td>
<td>0.88</td>
</tr>
<tr>
<td></td>
<td>0.23 (0.09 to 0.58)</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>2.21 (1.01 to 4.83)</td>
<td>0.05</td>
</tr>
</tbody>
</table>

Total number of patients = 519; total number of invasive aspergillosis (IA) cases = 47. CI, confidence interval; COPD, chronic obstructive pulmonary disease; D, donor; GM, galactomannan; HR, hazard ratio; IA, invasive aspergillosis; R, recipient.
Other Consequences of Colonization

- Pre-BOS colonization with small conidia *Aspergillus* species, but not large, was a risk factor for BOS ($p = 0.002$, HR 1.44, 95% CI 1.14–1.82)

- Colonization with small conidia species also associated with risk of death ($p = 0.03$, HR 1.30, 95% CI 1.03–1.64)

- Not associated with CLAD$^2$
  - No differentiation between small and large conidia

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2. Peghin M Transplant IntlVolume 29, issue 1, January 2016 :51-62
Epithelial Lining Fluid Concentrations of Liposomal and Lipid Complex Amphotericin B

![Graph showing Log10 Total Amphotericin B Concentration vs Time Post-inhalation. The x-axis represents time post-inhaled dose in hours, ranging from 0 to 200. The y-axis represents Log10 total amphotericin B concentration in mcg/ml. The graph includes two markers: AmBisome ELF (mcg/L) and ABLC ELF (mcg/ml).]

Capitano B, FOCUS 2007. Poster#82
Husain S, Transplantation 2010 Dec 15;90(11):1215-9
# Reports of Prophylaxis with Inhaled Amphotericin in Lung Transplants

<table>
<thead>
<tr>
<th>Author</th>
<th>Year</th>
<th>No. of Pts</th>
<th>Type of AMB</th>
<th>Duration</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calvo V</td>
<td>1999</td>
<td>65</td>
<td>AMB d</td>
<td>120 days</td>
<td>100%</td>
</tr>
<tr>
<td>Reichenspurner H</td>
<td>1999</td>
<td>127 AMBd, 101 placebo</td>
<td>AMB d</td>
<td>During hospital stay</td>
<td>92% 90%</td>
</tr>
<tr>
<td>Monforte V</td>
<td>2001</td>
<td>72</td>
<td>AMB d</td>
<td>42 days</td>
<td>75%</td>
</tr>
<tr>
<td>Drew RH</td>
<td>2004</td>
<td>49 AMBd, 51 ABLC</td>
<td>AMB d, ABLC</td>
<td>7 weeks</td>
<td>86% 88%</td>
</tr>
<tr>
<td>Peghin M</td>
<td>2016</td>
<td>412</td>
<td>Liposomal AMB</td>
<td>Life long</td>
<td>94.7%</td>
</tr>
<tr>
<td>Baker AW * +/- Systemic antifungals</td>
<td>2020</td>
<td>815</td>
<td>ABLC</td>
<td>During Hospital stay</td>
<td>80.9% 11.4% candida</td>
</tr>
</tbody>
</table>

5. Baker AW Clinical Infectious Diseases® 2020;70(1):30–9
### Comparative Side Effect Profile of Inhaled Amphotericin Preparations

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Liposomal AMB (n=118)</th>
<th>Lipid Complex AMB (n=51)</th>
<th>Amphotericin B (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wheezing</td>
<td>5/118 (4%)</td>
<td>2/48 (4.2%)</td>
<td>3/47 (6.4%)</td>
</tr>
<tr>
<td>Cough</td>
<td>12 (10%)</td>
<td>1/47 (2.1%)</td>
<td>5/47 (10.6%)</td>
</tr>
<tr>
<td>Shortness of Breath</td>
<td>NR</td>
<td>1/47 (2.1%)</td>
<td>9/47 (19.9%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>8/118 (7%)</td>
<td>1/47 (2.1%)</td>
<td>4/47 (8.5%)</td>
</tr>
<tr>
<td>Decline in FEV1</td>
<td>None</td>
<td>5/45 (11.1%)</td>
<td>5/47 (10.6%)</td>
</tr>
<tr>
<td>Decline in FVC</td>
<td>None</td>
<td>5/45 (11.1%)</td>
<td>5/47 (10.6%)</td>
</tr>
<tr>
<td>More than one adverse event</td>
<td>NR</td>
<td>14/51 (27.5%)</td>
<td>21/49 (42.9%)</td>
</tr>
<tr>
<td>Discontinuation due to intolerance</td>
<td>3/118 (2.5%)</td>
<td>3/51 (5.9%)</td>
<td>6/49 (12.2%)</td>
</tr>
</tbody>
</table>

Roman A 2005, Drew RH Transpl 2004
Evolution of *Aspergillus* spp. Infection and Colonization

![Graph showing the evolution of Aspergillus spp. infection and colonization before and after 2009.](image)

- **Before 2009**
  - Person-time incidence rate: 0.18
  - 38.1% *Aspergillus* spp. with reduced susceptibility or resistance to AB
  - 61.9% *Aspergillus* spp. sensitive to AB

- **After 2009**
  - Person-time incidence rate: 0.12
  - 58.8% *Aspergillus* spp. sensitive to AB

*P* = 0.04
Emergence of Resistance: non-Aspergillus Molds

- Pre-transplantation non-aspergillus molds isolated in 55 different respiratory samples from 49 lung transplant recipients
- Post-transplantation non-aspergillus species molds isolated in 117 different respiratory samples from 70 lung transplant recipients

Some Definitions Regarding Colonization

• **Eradication of fungal colonization**
  - Was defined by negative fungal culture of respiratory specimens (e.g. a single negative culture from BAL or 2 negative sputum cultures) at the end-points.

• **Recurrent colonization**
  - Was defined as the isolation of the same fungal species repeatedly during the follow-up period, with the recurrent isolation occurring at least 1 month after completion of the first course of prophylaxis.

• **New colonization**
  - Was defined as colonization by a different fungal species from the baseline colonization during the follow-up period, occurring at least 1 month after completion of the first course of prophylaxis.

• **Persistent colonization**
  - Was defined as ongoing isolation of the same fungal species as that identified at baseline despite prophylaxis.
What is Different for Mold Infection in SOT

• **Risk period is longer**
  - Until a year in lung transplantation
  - 3 months in heart transplantation

• **Unique clinical presentation**
  - Mold colonization, tracheobronchitis, bronchial anastomotic infections (BAI)

• **Clinical risk factors for mold are not well defined**
  - Lack of robust data in Heart Transplant

• **Differential characteristics of biomarkers**
  - Lack of sensitivity of serum Galactomannan, higher false positivity with BAL

• **Long term safety of inhaled drugs are not known. Concerns related to graft**
  - Lung transplantation
Universal Prophylaxis in Lung Transplantation

• **Recommended duration first 4-6 months post transplantation**

• **Primary End Points**
  - Proportion of patients with probable or proven fungal infection (Tracheobronchitis, bronchial anastomosis infection, Pulmonary or systemic fungal infection) at 6 months post transplant
  - Proportion of patients with mold colonization at 6 months post transplant

• **Secondary End Points (Safety)**
  - Rate of prevalence of side effects during therapy or within 30 days of cessation:
    - Headache
    - Dizziness and fatigue
    - Fever
    - Nausea
    - Vomiting
    - Wheezing
    - Cough
    - Shortness of Breath
    - Taste preservation
    - Decline in FEV1
    - Decline in FVC
    - Elevation of serum creatinine > 50% of baseline elevation of liver enzymes (≥ 3 times)
    - Neutropenia (absolute neutrophil count ≤ 1000) during the treatment

  - Pulmonary Function Test at baseline (2 weeks), 3, 6, 9, 12 months
  - Tolerance – need to discontinue for side-effects
Universal Prophylaxis in Lung Transplantation (Cont’d)

- **Secondary End Points (Efficacy)**
  - Proportion of patients with probable or proven fungal infection (Tracheobronchitis, bronchial anastomosis infection, Pulmonary or systemic fungal infection) at 1 year post transplant
  - Proportion of patients with mold colonization at 1 year post transplant.
  - Rate of breakthrough fungal infection during prophylaxis (at least one week into treatment or in a week post cessation of therapy)
  - Quality of Life at the baseline 3, 6, 9, 12 months post transplant
  - Time to development of mold colonization, tracheobronchitis/bronchial anastomotic infection, or invasive pulmonary infection at 1 year post transplant.
  - Mortality – all-cause and fungal infection-related mortality (all types) at 1 year post transplant
  - Use of empiric antifungals at 1 year post transplant
  - Time to diagnosis of CLAD
  - *Aspergillus* resistance rates and rates of resistant organisms – e.g. *L. prolificans*
Pre-emptive Therapy in Lung Transplantation

- Directed by positive BAL GM (>1.0) or *Aspergillus* culture/PCR in BAL without radiological or bronchoscopic evidence of disease during first year of transplantation
- Recommended duration 3-4 months

**Primary End Points**
- Negative BAL for GM or Aspergillus culture/PCR at the end of therapy
- Proportion of patients with mold colonization, probable or proven fungal infection (Tracheobronchitis, bronchial anastomosis infection, pulmonary or systemic fungal infection) at 6 months post cessation of therapy

**Secondary End Points (Safety)**
- Rate of prevalence of side effects during therapy or within 30 days of cessation
  - Headache
  - Dizziness and fatigue
  - Fever
  - Nausea
  - Vomiting
  - Wheezing
  - Cough
  - Shortness of Breath
  - Taste preservation
  - Decline in FEV1
  - Decline in FVC
  - Elevation of serum creatinine>50% of baseline elevation of liver enzymes (≥ 3 times)
  - Neutropenia (absolute neutrophil count ≤ 1000) during the treatment.

- Pulmonary function Test at baseline, 3, 6, 9, 12 months
- Tolerance – need to discontinue for side-effects
Pre-emptive Therapy in Lung Transplantation

(Cont’d)

• Secondary End Points (Efficacy)
  - Proportion of patients with fungal infection (mold colonization, probable or proven
    Tracheobronchitis, bronchial anastomosis infection, pulmonary or systemic fungal infection at 1
    year post transplant *
  - Rate of breakthrough fungal infection during treatment (at least one week into treatment or in a
    week post cessation of therapy)
  - QOL at the baseline, 3, 6, 9, 12 months post transplant
  - Time to development of colonization (non candida), probable or proven
    tracheobronchitis/bronchial anastomotic infection, or invasive pulmonary infection at
  - Mortality – all-cause and fungal infection-related mortality (all types) at 1 year post transplant
  - Use of empiric antifungals at 1 year post transplant
  - Time to diagnosis of CLAD
  - Aspergillus resistance rates and rates of resistant organisms – e.g. L. prolificans

*In cases of comparison between two preemptive arms outcome should be 1 year post initiation of therapy
Heart Transplantation

- No need for routine prophylaxis
- May Consider prophylaxis
  - Episode of IA in the heart transplant program
  - Isolation of Aspergillus in the BAL of heart transplant
Heart Transplant Prophylaxis

• Prophylaxis in the setting of outbreak in the program
• Recommended duration 6 weeks - 3 months

• **Primary End Points**
  o Negative BAL GM or *Aspergillus* culture/ PCR four weeks post cessation of therapy
  o Proportion of patients with probable or proven fungal infection (Pulmonary or systemic fungal infection) at 3 months post cessation of therapy

• **Secondary End Points (Safety)**
  o Rate of prevalence of side effects during therapy or within 30 days of cessation
    ▪ Headache
    ▪ dizziness and fatigue
    ▪ Fever
    ▪ Wheezing
    ▪ Cough
    ▪ Shortness of Breath
    ▪ Taste preservation
    ▪ Nausea
    ▪ Vomiting
    ▪ Decline in FEV1
    ▪ Decline in FVC
    ▪ elevation of serum creatinine≥50%
    ▪ of baseline elevation of liver enzymes (≥ 3 times)
    ▪ neutropenia (absolute neutrophil count ≤ 1000) during the treatment
  o Pulmonary Function Test at baseline weeks 2, 4, 6 and 12 wks.
  o Tolerance – need to discontinue for side-effects
Secondary End Points (Efficacy)

- Proportion of patients with probable or proven fungal infection (Pulmonary or systemic fungal infection) at 6 months post cessation
- Rate of breakthrough fungal infection during treatment (at least one week into treatment or within 7 days post cessation)
- QOL at the baseline, 3, 12 months
- Time to development of probable or proven invasive pulmonary infection at 1 year post transplant
- Mortality – all-cause and fungal infection-related mortality (all types) at 1 year post transplant
- Use of empiric anti mold antifungals at 1 year post transplant
Treatment of IFI with Inhaled Antifungal

• Not recommended with nebulized drugs ALONE due to the lack of existing data and possible systemic fungal disease

• Potential clinical syndromes it can be used in include
  o Tracheobronchitis
  o Bronchial anastomotic infection

• Endpoints
  o Microbiological cure at the end of therapy {Aspergillus culture/PCR or GM negative}
  o Normal looking airways or a bronchial anastomosis during bronchoscopy at the end of therapy
  o Used inhaled antifungals in conjunction with systemic antifungals
THANK YOU!

Contact: shahid.husain@uhn.ca