Clinical Risk Factors for Invasive Aspergillosis

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Risk Factors for IA

**Risk factor**: variable associated with an chance of developing something

**Types of risk factors for IA:**
- **Clinical**: host-related, co-morbidities, transplant variables
- **Biologic**: iron overload, hyperglycemia
- **Environmental**
- **Host/pathogen interaction**

**Identifying clinical risk factors for IA:**
- **Clinical Trials**
- Cohort (usually retrospective)
- Case-control studies
- Case series
## Risk of Invasive Aspergillosis*

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hematopoietic Stem Cell Transplants</td>
<td>5-10</td>
</tr>
<tr>
<td>Solid Organ Transplants</td>
<td>10-15</td>
</tr>
<tr>
<td>Hematologic malignancies</td>
<td>5-25</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>1-9</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>0-5</td>
</tr>
<tr>
<td>Other Causes (Trauma, ICU, steroids)</td>
<td>4-7</td>
</tr>
<tr>
<td>Other immunosuppression</td>
<td>0-??</td>
</tr>
</tbody>
</table>

* Risk defined as cumulative incidence per year

Adapted from Maschmeyer et al., Drugs 2007;67:1567-1601
HSCT Risk Factors

- Age
- Underlying disease
- Stem cell source
- T-cell depleted products
- Corticosteroids (dose, duration)
- Conditioning regimen
- GVHD presence and treatment
- Neutropenia (pre- and post-engraftment)
- Lymphopenia
- CMV disease
- Iron overload
- Elevated ferritin
- Previous IA
- Respiratory viruses
- Antifungal prophylaxis

Marr et al. Blood 2002;100:4358
Maschmeyer et al., Drugs 2007;67:1567-1601.
Garcia-Vidal et al., CID 2008;47:1041-50
Epidemiology of invasive mold infections in allogeneic stem cell transplant recipients: biological risk factors for infection according to time after transplantation.

Garcia-Vidal et al., Clin Infect Dis 2008:47:1041-50

- Objectives:
  1) Analyze risk factors for IMI after HSCT
  2) Differentiate risk factors for early vs. late IMI
  3) Evaluate biological risk factors

- 1248 HSCT patients evaluated (1998-2002)
- 163 IMI cases, 142 (87%) with IA

Garcia-Vidal et al., CID 2008;47:1041-50.
Garcia-Vidal et al.

Risk Factors (for IMI) per multivariable analysis:

- Older age
- CMV disease
- Respiratory virus infection (influenza, parainfluenza)
- Severe acute GVHD
- Cell-line cytopenias
- High frequency of blood transfusions
Figure 3. Timing of invasive mold infections (IMIs). Early IMI refers to infection diagnosed from day 0 through day 40; late IMI refers to infection diagnosed from day 41 through day 100; very late IMI refers to infection diagnosed after day 100.
Garcia-Vidal et al.

Early (1-39)
- Unrelated donor
- HLA mismatch
- ATG
- CMV disease
- Transfusion
- Corticosteroids
- Hyperglycemia
- Lymphopenia
- Ferritin level

Late (40-100)
- Sex (female)
- Age
- CMV disease
- Transfusion
- Acute GVHD
- Corticosteroids

Garcia-Vidal et al., CID 2008;47:1041-50.
WELCOME TO ROME!
Lower respiratory tract infections increase risk of aspergillosis after a reduced-intensity allogeneic hematopoietic SCT

Martino et al, Bone Marrow Transplantation 2009 44;749

- Analyzed 219 patients with reduced intensity conditioning (fludarabine + BU or melphalan) transplanted between 1997-2007.
- Prospectively monitored patients for IA, viral infections
- 4-year cumulative incidence of IA was 15%
- 27 patients developed IA
- **Risk factors** (multivariable analysis):
  - Steroid therapy for moderate-to-severe GVHD
  - CMV disease
  - **Viral lower respiratory tract infection**
    (HR 4.3, 95% CI 2-9.4)
- **Viruses:** influenza A/B, parainfluenza virus, RSV, metapneumovirus, adenovirus
Increased bone marrow iron stores is an independent risk factor for IA in patients with high-risk hematologic malignancies and recipients of allogeneic hematopoietic stem cell transplantation. Kontoyiannis et al., Cancer 2007; 110:1303-6.

- Compared 33 patients with IA and 33 high-risk patients without IFI (9/2002-3/2003)
- Calculated and compared bone marrow iron stores and other characteristics
- Patients similar, except APACHE II greater in cases
- 23 (70%) cases, compared with 6 (18%) controls had elevated iron stores (p<0.001)
- Increased BMIS and APACHE II were independent predictors of IA (logistic regression)
Cancer Patients

- Neutropenia
- Type of cancer
- Corticosteroid use
- Chemotherapy

Maschmeyer et al., Drugs 2007;67:1567-1601
Rubio et al., J Pediatric Hematol Oncol 2009; 31:642-646.
Clinical characteristics of 45 patients with invasive aspergillosis. Restrospective analysis of 1711 lung cancer cases.

Yan et al., Cancer 2009;115:5018-25.

- All lung cancer patients with IPA seen during 2000-2007 were evaluated
- 45 (2.63%) cases of IPA in 1711 lung cancer patients
- **Risk Factors:**
  - Stage IV cancer
  - Chemotherapy (preceding month)
  - Corticosteroid therapy > 3 days
Solid Organ Transplants

- **Lung**: Single lung, rejection, reperfusion injury, *Aspergillus* colonization, anastamotic site ischemia, hypogammaglobulinemia, CMV, cystic fibrosis(?), antifungal prophylaxis(?)

- **Liver**: Poor allograft function, pre-transplant hepatic failure, Re-transplantation, renal insufficiency, dialysis, high transfusion requirement, iron overload, steroids, ICU stay

- **Heart**: ?

- **Kidney or Kidney/Pancreas**: ?

Silveira and Husain, Medical Mycology 2007;45:305-20.
IA in SOTs

Expressed as IA cases per 100 patients transplanted

TRANSNET, unpublished data
Permission from Tom Chiller and Pete Pappas
Risk factors for invasive aspergillosis in solid organ transplant recipients: a case-control study
Gavalda et al., Clinical Infectious Diseases 2005:41:52-9.

- Retrospective case-control study of 156 cases of proven/probable IA, matched to 312 controls
- 11 Spanish centers (REISTRA), total of 11,014 SOT patients
- Study period: transplant program start date to 2001

- **IA Cases:**
  - Liver 80 (51.3%)
  - Heart 47 (30.1%)
  - Lung 17 (10.9%)
  - Kidney 10 (6.4%)
  - Kidney/Pancreas 2 (1.3%)
<table>
<thead>
<tr>
<th>Early (&lt;3 months)</th>
<th>Late (&gt;3 months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV mismatch</td>
<td>Age &gt; 50 years</td>
</tr>
<tr>
<td>ICU stay</td>
<td>Renal failure</td>
</tr>
<tr>
<td>Renal failure</td>
<td>Immunosuppressive use</td>
</tr>
<tr>
<td>Hepatic failure</td>
<td>&gt; 1 bacterial infection</td>
</tr>
<tr>
<td>Hemodialysis</td>
<td>Chronic-graft rejection</td>
</tr>
<tr>
<td>&gt;1 bacterial infection</td>
<td>Immunosuppression-related neoplasm</td>
</tr>
<tr>
<td>CMV disease</td>
<td></td>
</tr>
</tbody>
</table>
IA in the ICU

- Potentially emerging problem (247,000 Google hits 1/15; 248,000 hits 2/1)
- Incidence of up to 6% in Medical ICUs
- Non-traditional groups at risk:
  - Corticosteroid use
  - COPD
  - Cirrhosis
  - HIV
  - Malnutrition
  - Prolonged antibiotic use

Meerssemen et al., CID 2007:45:205-16
IA in COPD Patients

• Increasing reports of the importance of COPD as a risk factor or an underlying co-morbidity in patients with IA
• It is estimated that up to 10% of cases of IA occur in patients with COPD and up to 5% of patients with COPD have IA.
• Mortality in COPD patients with IA ranges from 30-100%
• Problem: certainty of diagnosis of IA
• Risk factors- few data:
  - Corticosteroid treatment (daily oral doses of >20 mg of prednisone)
  - Previous antibiotic use
  - Late-stage COPD
  - Viral infection
  - Inhaled steroids

Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome.
Guinea et al. Clinical Microbiology and Infection 2009

- Retrospective study of COPD admissions who had isolation of *Aspergillus* from a pulmonary sample (2000-2007)
- 14,618 with COPD, 239 of whom had positive *Aspergillus* respiratory tract cultures
- 53 cases of probable IA identified (3.6 cases/1000 COPD admissions)
- IPA present in 22% of cases of COPD with positive *Aspergillus* cultures
IA in COPD Patients

Guinea et al, *Clin Microbiol Infect* 2009
## Risk Factors for IA in COPD

<table>
<thead>
<tr>
<th>Factor</th>
<th>OR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>2.4</td>
<td>1.09, 5.29</td>
</tr>
<tr>
<td>Steroids(^1)</td>
<td>2.98</td>
<td>1.26, 7.0</td>
</tr>
<tr>
<td>Steroids(^2)</td>
<td>4.67</td>
<td>2.02, 10.3</td>
</tr>
<tr>
<td>Antibiotic use</td>
<td>2.57</td>
<td>1.2, 5.4</td>
</tr>
<tr>
<td>Chronic HF</td>
<td>2.1</td>
<td>0.98, 4.5</td>
</tr>
</tbody>
</table>

\(^1\) accumulated dose prior to admission
\(^2\) accumulated dose during admission

Guinea et al, *Clin Microbiol Infect* 2009
**Study Design Schematic**

**Exclude** patients having conditions apart from COPD that might put them at increased risk of IA:
- Hematologic malignancy (200.xx – 208.xx)
- AIDS/HIV (042)
- Bone marrow transplants (41.00 - 41.09)
- Solid organ transplants (37.51, 55.6x, 50.5x, 46.97, 33.5x, 33.6)
- Allergic Aspergillosis (sinusitis) (518.6)
- Chronic mycotic otitis externa (380.15)
- Thoracic/lung surgeries (32.3, 32.4, 32.5)
- Aplastic anemia (284.x)
- Neutropenia (288.0x)
- Reticuloendothelial / immunity disorders (279.x; EXCEPT 279.4)
- Patients discharged alive with onset of antifungal during hospital stay < 1 week
- Patients discharged alive, with hospital stay >= 1 week, but anti-fungal therapy < 1 week
- Patients < 18 years of age
- Patients not having a complete hospital stay (admission and discharge date) during the time frame

**Extract COPD + Aspergillosis** patients using:
- ICD-9 = 117.3x (Aspergillosis) **AND**
- ICD-9 = 491, 492, 493.2x, 496 (COPD)

**Identify the “Invasive” Aspergillosis (CASES)** using the following proxies:
- Pneumonia in Aspergillosis (484.6) + COPD
- Pneumonia in Cytomegalovirus infection (484.1) + COPD + Aspergillosis
- Pneumonia in Influenza (487.0) + COPD + Aspergillosis
- Pneumonia in other systemic mycosis (484.7) + COPD + Aspergillosis

**Perform descriptive analysis on the CASES:**
- Socio-demographic characteristics
- Mortality
- Length of treatment and switching pattern
- Length of hospitalization
- Re-hospitalization
- Procedures (surgical, mechanical ventilation)
- Total cost and cost component

**Identify the matched COPD patients without aspergillosis (CONTROLS)** in a case-to-control ratio of 1:2, based on age, gender, race, payer, hospital characters, geographical area, comorbidity index, and severity of illness.

**Perform comparative analysis between the two cohorts** on resource utilization and mortality using univariate descriptive analyses. Statistical comparisons were made using Kruskal-Wallis (non-parametric tests and Chi-square tests.)

**Entire COPD cohort**

**Remaining COPD Patients without aspergillosis**

*Perspective database (>400 hospitals)*

Thanks to Miriam Tarallo
Non-antibody Immunosuppressants

Antimetabolites
- Purine Synthesis Inhibitors:
  - Azathioprine
  - Mycophenylate (MMF)
  - Pentostatin
- Pyrimidine Synthesis Inhibitors:
  - Leflunomide
  - Teriflunomide
- Antifolate:
  - Methotrexate

Calcineurin Inhibitors
- Tacrolimus
- Cyclosporin
- Pimecrolimus

mTOR
- Sirolimus
- Everolimus
- Deforolimus
- Temsirolimus
- Zotarolimus

TNF-α Inhibitors
- Thalidomide
- Lenalidomide

IL-1 Receptor Antagonists
- Anakinra

Steroids

Adapted from Wikipedia
Antibody Immunosuppressants

- **Non-cellular Target**
  - Complement: Eculizimab
  - TNFs: Infliximab, Adalimumab, Certolizumab, afelimomab
  - IgE: Omalizumab
  - IL-5: Mepolizumab
  - Interferon: Faralimomab
  - IL-6: Elsilimomab
  - IL-12/13: Ustekinumab

- **Cellular Target**
  - CD3: Muronomab-CD3, Otelixizumab, Teplizumab, Vizilumab
  - CD4: Clenoxilimab, Kelixinab, Zanolibumab
  - CD20: Rituximab
  - CD40: Teneliximab
  - CD-52: Alemtuzumab
  - Integrin: Natalizumab
  - IL-6 Receptor: Tocilizumab
  - IL-2 Receptor: Basiliximab, Daclizumab

- **Others**
  - Polyclonal: Anti-thymocyte globulin
  - Fusion Proteins: Etanercept
  - CTLA-4: Abatacept, Belatacept

Adapted from Wikipedia
Background: Anti-TNF Therapy

- **Tumor Necrosis Factor**: expressed in many cells of the immune system and induces responses in both innate and adaptive immunity
- Transmembrane and soluble forms that differentially bind to two TNF receptors
- **Roles:**
  1) Recruitment of inflammatory cells
  2) Activates macrophages
  3) Regulates inflammation (induces apoptosis)
- TNF-RI (p55)- role in inflammation and granuloma formation
- TNF-RII (p75)- affects survival of macrophages

Ehlers, CID 2005
### Table 2. Fungal Infections Associated With Anti-Tumor Necrosis Factor α Therapy

<table>
<thead>
<tr>
<th>Infectious agents</th>
<th>Infliximab</th>
<th>Etanercept</th>
<th>Adalimumab</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Aspergillus</em> species (n=64)</td>
<td>48</td>
<td>14</td>
<td>2</td>
</tr>
<tr>
<td>Zygomycetes (n=4)</td>
<td>3</td>
<td>NC</td>
<td>1</td>
</tr>
<tr>
<td><em>Candida</em> species (n=64)</td>
<td>54</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td><em>Cryptococcus</em> species (n=28)</td>
<td>17</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td><em>Blastomyces</em> species (n=2)</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
</tr>
<tr>
<td><em>Coccidioides</em> species (n=29)</td>
<td>27</td>
<td>2</td>
<td>NC</td>
</tr>
<tr>
<td><em>Histoplasma</em> species (n=84)</td>
<td>72</td>
<td>8</td>
<td>4</td>
</tr>
<tr>
<td><em>Sporothrix</em> species (n=1)</td>
<td>1</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td><em>Prototheca</em> species (n=1)</td>
<td>1</td>
<td>NC</td>
<td>NC</td>
</tr>
<tr>
<td>Tinea or pityriasis</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>versicolor (n=6)</td>
<td>3</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>226</td>
<td>44</td>
<td>11</td>
</tr>
</tbody>
</table>

*a* ND = no data available; NC = no cases identified.

*b* In this case etanercept was used as well, but symptoms worsened while the patient received infliximab.
Differential Effects of TNF-α Inhibitors

<table>
<thead>
<tr>
<th>Pathogen, type of infection</th>
<th>Infliximab group (n = 233,000)</th>
<th>Etanercept group (n = 113,000)</th>
<th>Rate ratio</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Mycobacterium tuberculosis</em></td>
<td>335 (143.8)</td>
<td>39 (34.5)</td>
<td>4.17</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><em>Histoplasma capsulatum</em></td>
<td>39 (16.7)</td>
<td>3 (2.7)</td>
<td>6.30</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><em>Candida</em> species</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>38 (16.3)</td>
<td>8 (7.1)</td>
<td>2.30</td>
<td>.006</td>
</tr>
<tr>
<td>NS</td>
<td>26 (11.2)</td>
<td>7 (6.2)</td>
<td>1.80</td>
<td>.065</td>
</tr>
<tr>
<td>Systemic</td>
<td>10 (4.3)</td>
<td>1 (0.9)</td>
<td>4.85</td>
<td>.046</td>
</tr>
<tr>
<td><em>Listeria</em> species</td>
<td>36 (15.5)</td>
<td>2 (1.8)</td>
<td>8.73</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><em>Mycobacterium</em> species (NS)</td>
<td>30 (12.9)</td>
<td>7 (6.2)</td>
<td>2.08</td>
<td>.023</td>
</tr>
<tr>
<td><strong>Aspergillus species</strong></td>
<td>29 (12.4)</td>
<td>10 (8.8)</td>
<td>1.41</td>
<td>.17</td>
</tr>
<tr>
<td><em>Cryptococcus</em> species</td>
<td>11 (4.7)</td>
<td>8 (7.1)</td>
<td>0.67</td>
<td>.91</td>
</tr>
<tr>
<td><em>Nocardia</em> species</td>
<td>10 (4.3)</td>
<td>1 (0.9)</td>
<td>4.85</td>
<td>.046</td>
</tr>
<tr>
<td><em>Salmonella</em> species</td>
<td>7 (3.0)</td>
<td>4 (3.5)</td>
<td>0.85</td>
<td>.75</td>
</tr>
<tr>
<td><em>Toxoplasma</em> species</td>
<td>5 (2.1)</td>
<td>0 (0)</td>
<td>...</td>
<td>.088</td>
</tr>
<tr>
<td><em>Brucella</em> species</td>
<td>2 (0.9)</td>
<td>0 (0)</td>
<td>...</td>
<td>.38</td>
</tr>
<tr>
<td><em>Bartonella</em> species</td>
<td>1 (0.4)</td>
<td>0 (0)</td>
<td>...</td>
<td>.62</td>
</tr>
<tr>
<td><em>Leishmania</em> species</td>
<td>1 (0.4)</td>
<td>0 (0)</td>
<td>...</td>
<td>.62</td>
</tr>
<tr>
<td><em>Mycobacterium leprae</em></td>
<td>1 (0.4)</td>
<td>0 (0)</td>
<td>...</td>
<td>.62</td>
</tr>
<tr>
<td><strong>Overall</strong></td>
<td>556 (238.6)</td>
<td>83 (73.5)</td>
<td>3.25</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

NOTE: Data are no. of patients (no. per 100,000 patients who received the drug). NS, species was not specified.

* By χ² analysis.
* By Poisson analysis.
* Resulted in leprosy.
Anti-TNF and Aspergillosis

Multiple Studies/Registries In Progress:

1) Biologics Safety Project (SABER)
   - AHRQ/FDA-funded
   - Databases from CMS, TennCare, Kaiser Permanente

2) US Veteran’s Health Administration database
   - 330,000 unique RA/inflammatory arthritis patients

3) German biologics register (RABBITT) (2001-present)
AIDS and Aspergillosis
HIV and Aspergillosis

- Relatively uncommon infection, with an overall incidence of <1%. Is it increasing?
- 2003 NIS database of 10,400 aspergillosis cases, 3.7% in HIV-infected, incidence of 0.43%\(^1\)

Risk Factors:
- Advanced AIDS
- Neutropenia (zidovudine, sulfa)
- Steroids
- Antibiotics
- Marijuana or alcohol use
- Previous *Pneumocystis* infection
- Tuberculosis?

\(^1\) Tong et al, Int J Infect Dis 2009;13;24-36
Conclusions

• Increasing groups at risk for IA
• Data on clinical risk factors are lacking for certain groups (TNF, SOTs)
• Timing is everything
• Interest in biologic factors
• Tailoring prevention strategies to risk factors is the goal