Emerging Clinical Associations With Aspergillosis

COPD and Aspergillosis

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CONFLICTS OF INTEREST

Research grants (last three years): Basilea Pharmaceutica, bioMérieux, Astellas, Pfizer, Fundación Mutua Madrileña, Fondo de Investigación Sanitaria (FIS)

Conference fees (last three years): Astellas, Pfizer, Gilead, MSD
ISSUES TO HIGHLIGHT

1. The changing epidemiology of IA and its incidence in patients with COPD

2. Air–Patient relationship

3. Diagnosis of IA in non-neutropenic patients

4. Treatment and antifungal resistance
Changing epidemiology of invasive aspergillosis
Aspergillosis: epidemiology

ICUs 47%

ICUs 7%

Adult haem. 33%

Paed haem. 7%

ID 5%

Pneum. 7%

Thorac. surgery 1%
Aspergillosis: epidemiology

Patterson T. Med (Balt) 2000

Guinea J. ICAAC 2008 (M-717)

Cornillet. CID 2006
Aspergillosis and COPD

- Alterations in lung architecture
- Use of corticosteroids
- Frequent hospital admissions (antibiotics)
- Malnutrition
- Other comorbidity (diabetes, alcoholism)
Aspergillosis and COPD

Retrospective

2000–2007

Patients with COPD and *Aspergillus* in LRT

53 probable IPA cases (GOLD III and IV)

Classification of patients using Bulpa criteria
Aspergillosis and COPD

429 LRT samples

- BAL: 30 (7%)
- Other: 17 (4%)
- Sputum: 240 (56%)
- BAS: 142 (33%)
Aspergillosis and COPD: incidence

1,827 COPD admissions/year

Guinea J. CMI 2010
Aspergillosis and COPD: incidence

239 patients *Aspergillus* isolation

53 (22%) invasive aspergillosis

50% all cases of invasive aspergillosis
# Aspergillosis and COPD: incidence

<table>
<thead>
<tr>
<th>Study period</th>
<th>Number of patients</th>
<th>Predisposing conditions</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Postmortems performed</td>
<td>Cases of IA</td>
<td>Identified in postmortem</td>
</tr>
<tr>
<td>1980-1998</td>
<td>1043</td>
<td>107</td>
<td>75</td>
</tr>
<tr>
<td>1999</td>
<td>222</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>2003-2006</td>
<td>38</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>2004-2005</td>
<td>289</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>1984-2002</td>
<td>1630</td>
<td>83</td>
<td>73</td>
</tr>
<tr>
<td>2004-2005</td>
<td>67</td>
<td>42</td>
<td>16</td>
</tr>
<tr>
<td>1989-2008</td>
<td>No data</td>
<td>81</td>
<td>7</td>
</tr>
<tr>
<td>1982-2007</td>
<td>866</td>
<td>No data</td>
<td>8</td>
</tr>
</tbody>
</table>
Aspergillosis and COPD: incidence

<table>
<thead>
<tr>
<th>Incidence (cases/1,000 COPD hospital admissions)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3.1</td>
</tr>
<tr>
<td>3.6</td>
</tr>
</tbody>
</table>
Aspergillosis and COPD: risk factors

Aspergillus in LRT samples of patients with COPD

- IA 22%
- Non-significant 78%
## Aspergillosis and COPD: risk factors

Which variables can predict IPA?

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ICU admission</td>
<td>2.4</td>
</tr>
<tr>
<td>Heart insufficiency</td>
<td>2.1</td>
</tr>
<tr>
<td>&gt;700 mg prednisone</td>
<td></td>
</tr>
<tr>
<td>3 months prior to admission</td>
<td>3</td>
</tr>
<tr>
<td>during the admission</td>
<td>4.6</td>
</tr>
<tr>
<td>Antibiotics in the 3 months prior to admission</td>
<td>2.6</td>
</tr>
</tbody>
</table>
Aspergillosis and COPD: risk factors

Which doses of corticosteroids?

- Controls with Aspergillus
- Controls without Aspergillus
- IPA Cases

Muquim A. Can Respir J 2005
Aspergillosis and COPD: risk factors

- **Other** 8 (12%)
- **SOT** 9 (13%)
- **Cirrhosis** 3 (5%)
- **Systemic dis.** 14

- **COPD** 33 (49%)
- **Other** 26 (31%)
- **Haemat.** 28 (34%)
- **COPD** 29 (35%)

94% received corticosteroids

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Meersseman W. AJRCCM 2004

Vandewoude K. Crit Care 2006
# Aspergillosis and COPD: outcome

<table>
<thead>
<tr>
<th>Patients with COPD</th>
<th>Corticosteroids</th>
<th>Mortality</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>21</td>
<td>100%</td>
<td>ICU</td>
</tr>
<tr>
<td>16</td>
<td>16</td>
<td>100%</td>
<td>ICU</td>
</tr>
<tr>
<td>13</td>
<td>13</td>
<td>100%</td>
<td>Doses ↑ hospital admission</td>
</tr>
<tr>
<td>53</td>
<td>49</td>
<td>72.7%</td>
<td>Not all in ICU (55%)</td>
</tr>
<tr>
<td>56</td>
<td>49</td>
<td>95%</td>
<td>Not all in ICU</td>
</tr>
</tbody>
</table>

References:
- Rello J. CID 1998
- Ader F. CMI 2005
- Guinea J. CMI 2010
- Bulpa P. Intensive Care Med 2001
- Bulpa P. Eu Resp J 2007
Air–Patient Relationship
Air–Patient Relationship

Molecular Epidemiology of *Aspergillus fumigatus*: an In-Depth Genotypic Analysis of Isolates Involved in an Outbreak of Invasive Aspergillosis

Jesús Guinea,1,2,3,4# Darío García de Viedma,1,2,3 Teresa Peláez,1,2,3,4 Pilar Escribano,1,2,3 Patricia Muñoz,1,2,3,4 Jacques F. Meis,5 Corné H. W. Klaassen,5 and Emilio Bouza1,2,3,4

Outbreak of Invasive Aspergillosis After Major Heart Surgery Caused by Spores in the Air of the Intensive Care Unit

T. Peláez,1,2,3 P. Muñoz,1,2,3 J. Guinea,1,2,3 M. Valero,1,2 M. Giannella,1,2 C. H. W. Klaassen,5 and E. Bouza1,2,3

1Department of Clinical Microbiology and Infectious Diseases, Hospital General Universitario Gregorio Marañón; 2Department of Medicine, Faculty of Medicine, Universidad Complutense, Madrid; 3Centro de Investigación Biomédica en Red de Enfermedades Respiratorias (CIBERES CDI06/06/0059), Palma de Mallorca, Spain; and 4Department of Medical Microbiology and Infectious Diseases, Canisius Wilhelmina Hospital, Nijmegen, The Netherlands
Air–Patient Relationship

- 10 patients with proven IA (n=2), probable IA (n=4), and colonized (n=4) by *A. fumigatus*
- Not severely immunocompromised (two with COPD)
- Environmental control in the air of the unit
- *Clinical* (n=108) and environmental (n=59) isolates
- Molecular genotyping (STRAf)

Pelaez T. CID 2012
Guinea J. J Clin Microbiol 2011
# Air–Patient Relationship

<table>
<thead>
<tr>
<th>Date</th>
<th>Diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>December 06</td>
<td>Mediastinitis</td>
</tr>
<tr>
<td>May 07</td>
<td>IPA</td>
</tr>
<tr>
<td>September 07</td>
<td>IPA</td>
</tr>
<tr>
<td>October 07</td>
<td>IPA</td>
</tr>
<tr>
<td>February 08</td>
<td>IPA</td>
</tr>
<tr>
<td>March 08</td>
<td>IPA</td>
</tr>
<tr>
<td>April 08</td>
<td>Mediastinitis and IPA</td>
</tr>
</tbody>
</table>
Air–Patient Relationship

Air-clinical matches

Pelaez T. CID 2012
Guinea J. J Clin Microbiol 2011
Basis of microbiological diagnosis of invasive aspergillosis in non-neutropenic patients
Diagnosis of Invasive Aspergillosis

Limitations of the diagnosis

1. Low index of suspicion (delay)
2. Diagnostic tools with limitations

Diagnosis based on the combination of

- Compatible clinical signs
- Histopathology findings
- Radiological findings
- Microbiological findings
Diagnosis of IA: culture

Moderate sensitivity:
- 50-60% in patients with invasive aspergillosis
- Late stages of the infection

Slow

Moderate PPV:
- 55.5% in ICU
- 22% in COPD
- 12% in non-selected patients

Levi SJ. Sem Respir Infect 1992
Rickerts V. CID 2007

Perfect J. CID 2001
Garnacho J. Crit Care 2005
Bouza. J Clin Microbiol 2005
Guinea J. CMI 2010
Diagnosis of IA: culture

- Patient with severe COPD receiving steroids
- Patient with pneumonia not responding to antibiotics
- New pulmonary infiltrates
- Positive culture
- Efforts to diagnose and start antifungal treatment
Diagnosis of IA: other procedures

Non-culture-based procedures

Galactomannan

β-1,3-d-glucan

PCR Aspergillus
Diagnosis of IA: galactomannan

- Polysaccharide component of the fungal wall
- Initiation of fungal growth
- Platelia *Aspergillus* ® (Bio-Rad)

- Basically assayed on serum samples
**Diagnosis of IA: galactomannan**

- Meta-analysis of 27 studies (↑ heterogeneity)
- Differences in cut-off chosen to define positivity

<table>
<thead>
<tr>
<th></th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proven</td>
<td>0.71</td>
<td>0.89</td>
</tr>
<tr>
<td>Proven and probable</td>
<td>0.61</td>
<td>0.93</td>
</tr>
<tr>
<td>SOT</td>
<td>41</td>
<td>85</td>
</tr>
</tbody>
</table>

Sensitivity varies with the underlying disease

*Pfeiffer. Clin Infect Dis 2006*
Diagnosis of IA: galactomannan

Serum determination

<table>
<thead>
<tr>
<th>Threshold</th>
<th>Sensitivity</th>
<th>Specificity</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥0.5</td>
<td>60%</td>
<td>92.3%</td>
</tr>
<tr>
<td>≥1</td>
<td>40%</td>
<td>100%</td>
</tr>
<tr>
<td>≥1</td>
<td>53%</td>
<td></td>
</tr>
<tr>
<td>≥0.5</td>
<td>58%</td>
<td>88%</td>
</tr>
<tr>
<td>≥0.5</td>
<td>46%</td>
<td>83.3%</td>
</tr>
</tbody>
</table>
Diagnosis of IA: galactomannnan
Diagnosis of IA: galactomannan

NEUTROPENIC  NON-NEUTROPENIC
Diagnosis of IA: galactomannan

1109 patients admitted → 110 patients included

- No IPA: 43 (39%)
- Colonization: 3 (3%)
- Proven: 26 (24%)
- Probable: 8 (7%)
- Possible: 27 (24%)

EORTC definitions

- Only 4/26 ante-mortem diagnosis
- Mortality 100%

33% haematological cancer
(22% neutropenia)

Meersseman W et al. AJRCCM 2008
Diagnosis of IA: galactomannan

- Mean: BAL day +6 admission to the ICU
- 156 BAL samples (GM + >0.5)
## Diagnosis of IA: galactomannan

<table>
<thead>
<tr>
<th></th>
<th>S (proven)</th>
<th>Sp</th>
</tr>
</thead>
<tbody>
<tr>
<td>Culture</td>
<td>58%</td>
<td>-</td>
</tr>
<tr>
<td>GM serum</td>
<td>42%</td>
<td>96%</td>
</tr>
<tr>
<td>GM BAL</td>
<td>88%</td>
<td>87%</td>
</tr>
</tbody>
</table>

9/26 no antifungal therapy

Meersseman W et al. AJRCCM 2008
Diagnosis of IA: $\beta$-1,3-d-glucan

- Panfungal biomarker
- Serum detection
- No data on COPD patients

<table>
<thead>
<tr>
<th>S</th>
<th>Sp</th>
<th>Method</th>
<th>Reference</th>
</tr>
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<tbody>
<tr>
<td>79%</td>
<td>87.7%</td>
<td>Meta-analysis</td>
<td>Karageorgopoulos CID 2011</td>
</tr>
<tr>
<td>76%</td>
<td>85%</td>
<td>Meta-analysis</td>
<td>Lu Y Internal Med 2011</td>
</tr>
<tr>
<td>80%</td>
<td>82%</td>
<td>IFI</td>
<td>Onishi A JCM 2012</td>
</tr>
<tr>
<td>77%</td>
<td></td>
<td>Invasive aspergillosis</td>
<td>Karageorgopoulos CID 2011</td>
</tr>
</tbody>
</table>
Antifungal of choice for treatment of invasive aspergillosis in patients with COPD
Aspergillosis and COPD: treatment

- Poor clinical response with amphotericin B
- Voriconazole for primary treatment (A-I)
- IV 6 mg/kg/12 h for 1 day, followed by 4 mg/kg/12 h
- Few COPD patients in the clinical trials
- PK/PD considerations (serum levels):
  - Poly-medications (ICU)
  - Difficult interpretation
  - Azole resistance (Netherlands and UK)

Herbretch. NEJM 2002
Verweij. NEJM 2007
Walsh T. CID 2008
Howard. EID 2009
• COPD is emerging as a cause of IA

• Incidence is unknown but it is probably underestimated

• Corticosteroids as a risk factor

• Difficulty obtaining a diagnosis of IA

• Optimal treatment should be defined

• Problems of azole resistance