The changing epidemiology of invasive aspergillosis

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08 Nov 2012
Outline

• How frequent is aspergillosis in the general population?

• Which diseases are associated with aspergillosis? What are the relative risks for the different diseases?

• Are there new risk factors on the horizon?
Question 1: What is correct?

1 Invasive aspergillosis in the ICU is more frequent than aspergillosis in a neutropenic patient on hemato ward

2 The incidence of mucormycosis = half of the incidence of invasive aspergillosis.

3 Based on culture, the highest colonisation rate of aspergillosis is found in patients with COPD

4 In anti-TNF treated patients, the risk of contracting invasive aspergillosis is around 20%

5 In patients with chronic granulomatous disease, the life time risk of aspergillosis is 30%
Question 2: What is wrong?

1 - Aspergillosis in critically ill patients with H1N1 is related to the steroids that are given to treat the ARDS

2 - Patients with mucormycosis are frequently co-infected with Aspergillus

3 - There are roughly 500,000 cases of acute invasive aspergillosis worldwide annually

4 - Among solid organ transplant recipients, liver transplants contain the highest risk to develop aspergillosis
Incidence of fatal invasive mycoses in USA

McNeil et al. 2001 *Clin Infect Dis* 33;641
## Estimated number of cases of invasive fungal infection UK [2002]

<table>
<thead>
<tr>
<th>Patient group</th>
<th>Number of patients</th>
<th>Invasive candidosis/candidaemia risk estimates**</th>
<th>Expected number invasive candidosis/candidaemia</th>
<th>Invasive aspergillosis risk estimates@</th>
<th>Expected number invasive aspergillosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allo HSCTx</td>
<td>793</td>
<td>4%</td>
<td>32</td>
<td>10%</td>
<td>79</td>
</tr>
<tr>
<td>Solid organ Tx</td>
<td>2953</td>
<td>5%</td>
<td>148</td>
<td>1.9%</td>
<td>56</td>
</tr>
<tr>
<td>Leukaemia</td>
<td>16269</td>
<td>3%</td>
<td>488</td>
<td>6%</td>
<td>976</td>
</tr>
<tr>
<td>Solid tumour (neutropenic)</td>
<td>28955</td>
<td>3%</td>
<td>869</td>
<td>2%</td>
<td>579</td>
</tr>
<tr>
<td>Advanced cancer</td>
<td>131678</td>
<td>1%</td>
<td>1316</td>
<td>1.5%#</td>
<td>1975</td>
</tr>
<tr>
<td>ICU</td>
<td>210130</td>
<td>1%</td>
<td>2101</td>
<td>0.2%</td>
<td>420</td>
</tr>
<tr>
<td>Burns</td>
<td>378</td>
<td>5.6%</td>
<td>21</td>
<td>1.9%</td>
<td>7</td>
</tr>
<tr>
<td>Renal dialysis</td>
<td>24536</td>
<td>0.2%</td>
<td>1</td>
<td>4%</td>
<td>26</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>661</td>
<td>0.2%</td>
<td>1</td>
<td>4%</td>
<td>26</td>
</tr>
<tr>
<td><strong>Totals</strong></td>
<td><strong>5466</strong></td>
<td></td>
<td><strong>4120</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

** no estimate for surgical patients, but some are in ICU, or have advanced cancer
@ no inclusion of most chronic chest, steroid-treated patients, an increasing group
# the literature figure is 6%, but felt to be autopsy selection bias, so reduced by 75%.

http://www.hpa.org.uk/web/HPAwebFile/HPAweb_C/1196942156347

**Probably significant underestimates**
Prospective data on culture

4 Danish hospitals (3 months) (Jan March 2007)
1. 11,368 airway samples
2. 129 – 151 patients
3. Proven (n=3), probable (n=11), ABPA (n=4), colonised (n=133)
4. 55% cystic fibrosis, 13% COPD, 7% hematological, 18% ICU
5. ? Incidence 0.9-1.1 per 100,000 inhabitants

An example of a prospective database

- SAIF network 2005-2007
- 393 adults from 12 hospitals
- 0.271 per 1,000 admissions
  - 15% proven disease
  - 78% haematological conditions
  - 92% lung involvement
  - lymphoproliferative disorders new emerging group
  - 12-week mortality 44.8%

Lortholary O et al, Clin Microbiol Infect 2011, 17, 1882-1889
Examples of at-risk patients and pace of progression

- Normal immunity, high inoculum
- Acute respiratory infection, i.e. influenza
- Chronic leukaemia
- HIV infection
- Short course glucocorticoids
- Temporary neutropenia
- Long term glucocorticoids etc
- AIDS
- Medical ICU, COPD + sepsis
- Solid organ transplant + rejection + CMV
- Leukemia and profound neutropenia
- Allogeneic stem cell transplant + GVHD
- Relapsed/uncontrolled leukemia

Risk of acquisition (and pace of progression)

Degree of immunocompromise
Acute pulmonary aspergillosis in immunocompetent subjects after exposure to bark chippings

MAIKEN CAVLING AREND Rutup ¹, B. RONAN O’DRISCOLL², ESKILD PETERSEN³ & DAVID W. DENNING⁴

From the ¹Unit of Mycology and Parasitology, Statens Serum Institute, Copenhagen, Denmark, ²Hope Hospital, Salford, University of Manchester, UK, ³Department of Infectious Diseases, Aarhus University Hospital-Skejby, Aarhus, Denmark, and ⁴The University of Manchester and Wythenshawe Hospital, Southmoor Road, Manchester, UK
## Clinical epidemiology (US data)

<table>
<thead>
<tr>
<th>Underlying Disease</th>
<th>Count</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological malignancy</td>
<td>464</td>
<td>48.3%</td>
</tr>
<tr>
<td>Solid organ transplant</td>
<td>280</td>
<td>29.2%</td>
</tr>
<tr>
<td>Stem cell transplant</td>
<td>268</td>
<td>27.9%</td>
</tr>
<tr>
<td>HIV/AIDS</td>
<td>14</td>
<td>1.5%</td>
</tr>
<tr>
<td>Immunodeficiency</td>
<td>4</td>
<td>0.4%</td>
</tr>
<tr>
<td>Other</td>
<td>22</td>
<td>2.3%</td>
</tr>
</tbody>
</table>

Adult HSCT recipients

D. Kontoyiannis et al., CID 2010, 50: 1091-1100

TRANSNET, 983 IFI
23 US transplant centers
2001-2006
Increased time to onset of IA in SOT

Time to Onset to IA in SOT

PATH Alliance

Days from Transplant

excludes outside values

MultiVis
Heart
Lung
Liver
Kidney

247
125
483
108
271

6
10
84
11
11
Invasive fungal infections in SOT recipients

Kubak Bm. Transpl Infect Dis 2002; 4: 24-31
Anti-TNF → granuloma suppression
Histoplasmosis in anti-TNF-treated patients
Anti TNF & *Histoplasma capsulatum*

10 cases; 9 infliximab
1 wk-6 mo after initiation
9 in ICU, 1 death
Lee, Arthritis Rheum 2002

Increased number of cases in USA (240 cases reported to FDA)
3 x more frequent than TB in anti-TNF-α living in endemic areas
Most frequent IFI; mortality = 20%
Infliximab (x7) > Etanercept
Pneumonia/dissemination (70-80%)
IRIS = 42% cases in Indianapolis
Screening not useful (Ag/Ab)
Anti-TNF may be restarted if ATF ≥ 1 year without relapse

Hage et al. CID 2010
## Incidence of IA in immunocompromised children

<table>
<thead>
<tr>
<th>Underlying disease</th>
<th>N</th>
<th>Incidence IA (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Malignancy</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>solid tumour</td>
<td>99 177</td>
<td>0.5 0.1 1 0.6 3.7</td>
</tr>
<tr>
<td>leukaemia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALL and AML</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hematologic disorder (AA)</strong></td>
<td>12 829</td>
<td>1.4</td>
</tr>
<tr>
<td><strong>Immunodeficiency</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>WAS</td>
<td>3733</td>
<td>3.2 30 6.5 3.3</td>
</tr>
<tr>
<td>CGD</td>
<td>267</td>
<td>30</td>
</tr>
<tr>
<td>CID</td>
<td>322</td>
<td>6.5</td>
</tr>
<tr>
<td>cong. hypogammaglobulinaemia</td>
<td>411</td>
<td>1.7</td>
</tr>
<tr>
<td></td>
<td>119</td>
<td>3.3</td>
</tr>
<tr>
<td><strong>BMT</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>allogeneic</td>
<td>3013</td>
<td>3.4</td>
</tr>
<tr>
<td>autologous</td>
<td>2219</td>
<td>4.5</td>
</tr>
<tr>
<td></td>
<td>822</td>
<td>0.3</td>
</tr>
<tr>
<td><strong>Solid-organ transplant</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>lung</td>
<td>1593</td>
<td>0.3 5 0.3 0.5</td>
</tr>
<tr>
<td>heart</td>
<td>39</td>
<td>5</td>
</tr>
<tr>
<td>liver</td>
<td>278</td>
<td>0.3</td>
</tr>
<tr>
<td></td>
<td>569</td>
<td>0.5</td>
</tr>
</tbody>
</table>

Zaoutis et al. Pediatrics 2006; 117: e711-e716
Where in the hospital does *invasive aspergillosis* occur?

- Hematology adult: 1
- Intensive Care Unit: 7
- Thoracic Surgery: 5
- Pneumology: 7
- Infectious Disease: 47
- Hematology pediatric: 33

Cornillet et al, Clin Infect Dis 2006;43:577
<table>
<thead>
<tr>
<th>Parameter</th>
<th>All (n=127)</th>
<th>Proven (n=56)</th>
<th>Probable (n=49)</th>
<th>Possible (n=2)</th>
<th>Colonization (n=20)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs, mean</td>
<td>61</td>
<td>59</td>
<td>63</td>
<td>61</td>
<td>64</td>
</tr>
<tr>
<td>Sex, male, n</td>
<td>84</td>
<td>39</td>
<td>35</td>
<td>2</td>
<td>8</td>
</tr>
<tr>
<td>Haematological patients, n</td>
<td>38</td>
<td>26</td>
<td>12</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nonhematological patients, n</td>
<td>89</td>
<td>30</td>
<td>37</td>
<td>2</td>
<td>20</td>
</tr>
<tr>
<td>• COPD, n</td>
<td>35</td>
<td>12</td>
<td>21</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>• Solid organ transplants, n</td>
<td>9</td>
<td>4</td>
<td>5</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>• Systemic disease, n</td>
<td>17</td>
<td>6</td>
<td>8</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>• Cirrhosis, n</td>
<td>6</td>
<td>3</td>
<td>0</td>
<td>0</td>
<td>3</td>
</tr>
<tr>
<td>• Other, n</td>
<td>22</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>SAPS II, mean</td>
<td>54</td>
<td>57</td>
<td>52</td>
<td></td>
<td>54</td>
</tr>
<tr>
<td>Predicted mortality, %</td>
<td>53%</td>
<td>58%</td>
<td>49%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Observed mortality, %</td>
<td>86%</td>
<td>98%</td>
<td>90%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ICU length of stay, days</td>
<td>20</td>
<td>14</td>
<td>23</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemodialysis in ICU, n</td>
<td>54</td>
<td>27</td>
<td>20</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mechanical ventilation, n</td>
<td>123</td>
<td>56</td>
<td>47</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Neutropenia (&lt;500/mm$^3$), n</td>
<td>19</td>
<td>12</td>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Autopsy, n</td>
<td>76</td>
<td>52</td>
<td>19</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Meersseman W. Invasive aspergillosis in critically ill patients without malignancy *Am J Respir Crit Care Med* 2004
1109 admissions
Medical ICU
18 months
(06/05-12/06)
Modified EORTC criteria

10% of all admissions at risk
Prospective study
2.3% proven aspergillosis
Microscopic analysis on sterile material: histopathologic, cytopathologic, or direct microscopic examination of a specimen obtained by needle aspiration or sterile biopsy in which hyphae are seen accompanied by evidence of associated tissue damage. Culture on sterile material: recovery of Aspergillus by culture of a specimen obtained by lung biopsy

Probable invasive pulmonary aspergillosis (all three criteria must be met)

1. Host factors (one of the following)
   - Recent history of neutropenia (<500 neutrophils/mm³) for 110 d
   - Receipt of an allogeneic stem cell transplant
   - Prolonged use of corticosteroids at a mean minimum dose of 0.3 mg/kg/d of prednisone equivalent for 13 wk
   - Treatment with other recognized T-cell immunosuppressants
   - Inherited severe immunodeficiency

2. Clinical features (one of the following three signs on CT)
   - Dense, well-circumscribed lesion(s) with or without a halo sign
   - Air-crescent sign
   - Cavity

3. Mycological criteria (one of the following)
   - Direct test (cytology, direct microscopy, or culture) on sputum, BAL fluid, bronchial brush indicating presence of fungal elements or culture recovery of Aspergillus spp.
   - Indirect tests (detection of antigen or cell-wall constituents): galactomannan antigen detected in plasma, serum, or BAL fluid

Possible invasive pulmonary aspergillosis
Presence of host factors and clinical features (cf. probable invasive aspergillosis) but in the absence of or negative mycological findings.
Clinical relevance of *Aspergillus* isolation from ETA in critically ill patients

Putative IPA

1. LRT sample positive for *Aspergillus* (entry criterion)
2. Compatible signs and symptoms
3. Abnormal medical imaging of chest
4. Either: (a) Host risk factors:
   - neutropenia,
   - hemato-oncologic malignancy + cytostatics
   - steroid treatment >20 mg/day
   - immunodeficiency

(b) BAL: semi-quantitative positive culture +/++
   and
   - positive cytologic exam (branching hyphae)

Spectrum from colonisation to invasive disease

Colonisation → Possible → Putative → Proven
A Clinical Algorithm to Diagnose Invasive Pulmonary Aspergillosis in Critically Ill Patients

Stijn I. Blot, Fabio Silvio Taccone, Anne-Marie Van den Abeele, Pierre Bulpa, Wouter Meersseman, Nele Brusselaers, George Dimopoulos, José A. Paiva, Benoit Misset, Jordi Rello, Koenraad Vandewoude, Dirk Vogelaers, and the AspICU Study Investigators

1General Internal Medicine and Infectious Diseases, Ghent University, Ghent, Belgium; 2Department of Intensive Care, Hôpital Erasme, Université Libre de Bruxelles, Brussels, Belgium; 3Department of Microbiology, General Hospital St. Lucas, Ghent, Belgium; 4Department of Intensive Care, Mont-Godinne University Hospital, Université Catholique de Louvain, Yvoir, Belgium; 5Medical Intensive Care Unit, University Hospital Leuven, Leuven, Belgium; 6Department of Critical Care Medicine, Attikon University Hospital, University of Athens Medical School, Athens, Greece; 7Department of Emergency and Intensive Care, Centro Hospitalar S. Joao and University of Porto Medical School, Porto, Portugal; 8Department of Intensive Care, Fondation Hôpital Saint-Joseph, Université Paris-Descartes, Paris, France; and 9Hospital Universitari Vall d’Hebron, Vall D’Hebron Institute of Research, CIBERES, Universitat Autonoma de Barcelona, Barcelona, Spain
Invasive pulmonary aspergillosis is a frequent complication of critically ill H1N1 patients: a retrospective study
Pulmonary aspergillosis in patients with chronic obstructive pulmonary disease: incidence, risk factors, and outcome

J. Guinea¹,², M. Torres-Narbona¹, P. Gijón¹, P. Muñoz¹,², F. Pozo²,³, T. Peláez¹,², J. de Miguel⁴ and E. Bouza¹,²

¹) Clinical Microbiology and Infectious Diseases Department, Hospital General Universitario Gregorio Marañón, Universidad Complutense, 2) CIBER de Enfermedades Respiratorias (CIBERES CD06/06/0058), Palma de Mallorca, 3) Pneumology Department and Clinical Epidemiology Unit, Hospital Universitario Doce de Octubre and 4) Pneumology Department, Hospital General Universitario Gregorio Marañón, Universidad Complutense, Madrid, Spain

Clin Microbiol Infect 2010; 16: 870–877
Incidences of mucormycosis over 6 decades (1940–1999), by host population, 929 cases

Incidence of mucormycosis cases in a Belgian hospital from 2000 through 2009

- 31 patients: 21 proven, 10 probable
- M/F: 16/15
- Mean age: 54 years (12-79 years)
- 61% haematological patients
- 45% co-infections with Aspergillus (halo-sign!)
- Mortality rate = 65% (48%, directly related to infection)

V. Saegeman et al., Emerg Infect Dis 2010, 16: 1456-1458.
Distribution of mucorales in France

- Retrozygo», 101 mucormycosis cases 2005-2007

- Rhizopus oryzae 32%
- Lichtheimia spp. 29%
- Rhizopus microsporus 17%
- Rhizomucor pusillus 7%
- Cunninghamella spp. 7%
- Other 8%

Lanternier F, CID 2012
Azole resistance frequency in A. fumigatus 1997–2009

Emergence of azole resistance in *Aspergillus fumigatus* and spread of a single resistance mechanism

R mechanisms: TR/L98H in 30 of 32 (94%) isolates

Some conclusions…

• It is difficult to determine true incidence figures (roughly between 2-10%)
• New risk groups have arisen (mainly COPD, critically ill patients, steroid treated patients)
• Some genetic factors might be important, especially in immunocompromised patients
• Be aware of azole resistance
• Be aware of co-infections aspergillus - mucor