ASPERGILLOSIS
IN THE NON-NEUTROPENIC HOST

Dr J Garbino

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ASPERGILLOSIS
IN THE NON-NEUTROPENIC HOST

• INTRODUCTION

• SWISS ASPERGILLOSIS SURVEY IN THE NON-NEUTROPENIC HOST
Aspergillus Infection

• Introduction

- Aspergillus species are widespread in the environment and are the most common cause of invasive mould infection in immunocompromised individuals

  Warnock DW et al Curr Infect Dis Rep 2001

- First aspergillosis human case was described in patient with pulmonary tuberculosis cavities aspergilloma and it was microscopically observed in the sputum

  Bennet JH Transactions Royal Society of Edinburgh 1842
Aspergillus Infection

- Invasive aspergillosis remains an important cause of morbidity and mortality despite therapeutic interventions

  Kontoyianis et al Microbiol Infec Dis 2002

- Survival of patients with IA is generally poor at least partly due to the poor response to treatment options

  Orewn et al Curr Opin Pulm Med 2005
Aspergillus Infection

In addition to other factors predisposing FI (PN – Atb –Hosp)

Patients at risk for IA are patients with:
- Prolonged neutropenia
- Transplantation - Solid Org - BMT- HSCT- (CMV and GvHD)
- Treatments -Immunosuppressive therapy
  -Chemotherapy
  -Corticosteroid therapy
- Hematological malignancy

Paterson et al Medicine 2000;79:250
Soubani et al Chest 2002;37:289
Denning et al NEJM 1991;324:654
Saugier et al Bone M Transpl 1993;12:121
Guiot et al Clin Inf Dis 1994;18:525

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Invasive Aspergillosis - Incidence

• Aspergillosis is the second most frequent fungal infection

• The incidence of IA:
  – varies between institutions
  – is increasing in the last decades
  – varies according to underlying disease:
    Bone marrow transplant 3 - 7%
    Liver transplant 1.5 - 4%
    Lung / Cardiac transplant 10 - 15%
    Hematology malignancy 10 - 14%

Winston - Medicine 1979; 58:1
Wingard - Bone Marrow Transpl 1987;2:175
Bodey - Eur J Clin Micr Inf Dis 1993; 8:412
Aisner - Ann Intern Med 1979; 90 :4
McWhinney - Clin Inf Dis 1990; 12:1147
Iwen - Infect Control Hosp Epi 1993;14:131
Hofflin - Ann Intern Med 1987;106 : 209
Aspergillus Infection

IA is rarely reported in

- apparently immunucompetent patients or in
- patients who are “mildly” immunucompromised
  - alcoholism
  - chronic liver disease
  - diabetes
  - COPD

Karam et al. Infect. Dis. 1986;8
Clancy et al. Chest 1998;114
Some reports have described IA in a few immunocompetent adults and children, including patients who had IPA or Sinus Asp

- 2 nonimmunocompromised patients with IPA
  
  Karam et al. Infect. Dis. 1986;8

- 3 Inv sinus Aspergillosis in immunocompetent hosts
  
  Clancy et al Chest 1998;114

- 1 previously healthy adolescent IPA
  
  Hauger et al Clin Pediatr 1992;31

- 1 pulmonary aspergillosis in a healthy subject
  
  Batard et al Eur J Clin Microb Inf Dis 2003;22

- immunologically normal hosts (9 Inv sinus Asp - 2 brain abscesses- 3 IPA- 2 Lymph node IA- 1 osteomyelitis
  (Pakistan - 1 y)
  
  Karim et al Clin Inf Dis 1997;24
Aspergillus in ICU

• 127 of 1850 (6.9%) MICU admissions had IA or colonization (evidenced by microbiology or histology)

• 89 / 127 (70%) *did not* have hematological malignancy
  67 / 89 had proven or probable IA

  33 / 67 (50%) were COPD patients  Mortality 91%

*Meersseman et al Am J Resp Med Crit Care 2004 ;170*
Aspergillus in ICU

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Mycosis infections of the paranasal sinuses

• Surgical treatment of isolated sphenoid lesions
  in 1050 / 41 (18%) cases Aspergillus

  Castelnuovo et al  Acta Otorhinolaryngol 2000;20
Aspergillus in ICU
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Mycosis infections of the paranasal sinuses

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  Castelnuovo et al A Otorhinolaryngol 2000;20

Sinonasal with Craniocerebral Asp (25p) 12 years Pakistan (28%)

Siddiqui et al Neurosurgery 2004;55

IPA without underlying risk factors

underlying RF were not identified in 2% of 545 p with IPA

Patterson et al Medicine 2000;79

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SURVEY OF ASPERGILLOSIS
SURVEY OF ASPERGILLOSIS IN THE NON-NEUTROPENIC HOST IN THE SWISS UNIVERSITY HOSPITALS

« Aspergillosis Group »

Dr J Garbino - Dr J Bille - Dr S Zimmerli
Dr U Flückiger - Dr A Imhof

FUNGAL INFECTION NETWORK OF SWITZERLAND
• Aim of the study

To collect retrospectively cases of aspergillosis in the non-neutropenic host in the Swiss hospitals collaborating in the

FUNGAL INFECTION NETWORK OF SWITZERLAND
• **Primary Objectives**

To establish the frequency of
- Invasive aspergillosis (in any organ/site)
- Sub-acute or chronic pulmonary aspergillosis
- Aspergilloma

*in the non-neutropenic patient population*
• Secondary Objectives

- To describe the different clinical presentations of the infection and their clinical course
- To identify the patients' comorbidities
- To evaluate the contribution of the diagnostic procedures and diagnostic tools
- To evaluate our search strategies to identify patients
- To describe the antifungal treatment and outcome
• Study Characteristics

• Retrospective observational study (study started 2006)
• Data collection was done for 2-years (2004-2005).
• Patients to be included must presented
  a) signs and symptoms of disease
  b) evidence for mold infection by
     histology, microscopy, culture or PCR from the
     affected site.

• A review committee evaluated the inclusion of all patients.
• Collection of imaging and Aspergillus strains if were available.
• The study was done in the 5 University hospitals
• **Study Characteristics (cont)**

  • Search strategies used for the identification of patients were:
    - Microbiology laboratory results
    - Direct exams
    - Cultures
    - PCR
    - Galactomannan
    - Pathology Department
      - Autopsy
      - Biopsy
    - Radiology Department
    - Infectious diseases consultants' records
    - Surgical reports
• Study Population

The non-neutropenic (< 0.5 G/L for more than 10 days) and/or non-BMT patient population with

a) signs and symptoms of disease

b) evidence for Aspergillus (like) infection by
   - histology
   - microscopy
   - culture from the discussed site
   - molecular (PCR) or
   - antigen (GM)
Study Population \textit{(cont)}

This will comprise the following groups of patients:

- Immunocompromised hosts (except neutropenic, BMT)
- Solid organ transplant recipients
- Surgical patients
- ICU patients
- Patients with chronic lung diseases or cavities
- Patients under systemic immunosuppressive drugs
- Patients lacking recognized risk factors
Patients to be included will have a diagnosis of proven or probable:

- Invasive aspergillosis (any organ or site)
- Sub-acute or chronic pulmonary aspergillosis
- Aspergilloma
- Aspergillus rhinosinusitis
- Disseminated aspergillosis

Definitions Ascioglu et al CID 2002 (EORTC-MSG)
• Exclusion Criteria

Patients with the following diagnosis will be excluded:

• Patients with Allergic Brochopulmonary Aspergillosis
• Patients with Cystic fibrosis and colonization
• Invasive Aspergillosis in neutropenic patients
• Invasive Aspergillosis in leukemic patients
• Invasive Aspergillosis in BMT patients
• Sample Size

  • The study intended to include a minimum of 35-45 patients per year study period.

  • The participating centers were the 5 University Hospitals of: Bale, Berne, Geneva, Lausanne and Zurich.
SURVEY OF ASPERGILLOSIS IN THE NON-NEUTROPENIC HOST IN THE SWISS UNIVERSITY HOSPITALS

Case Report Form
RETROSPECTIVE SURVEY OF ASPERGILLOSIS IN THE NON-NEUTROPENIC HOST IN THE SWISS UNIVERSITY HOSPITALS

RESULTS
Retrospective Survey of Aspergillosis in the non neutropenic host

Preliminary Results

All cases were reviewed by a DRC

Total number of patients included 143

Not included for analysis 9

Total number of patients analyzed 134

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Retrospective Survey of Aspergillosis in the non neutropenic host

Preliminary Results

Search Strategies used by the investigators for the identification of patients

The most frequent

Pathology registry 93 (54%)*
Microbiology registry 56 (32%)

* n of strategies / alone or in combination

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Patients Demographics

Total number of patients included = 134    Mean age - 58.7 y. (29-84)

Total male –82, Female 52

Mean age - 58.7 y. (29-84)

Total male –61%, Female 39%

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Retrospective Survey of Aspergillosis in the non neutropenic host

Type of Aspergillus infection

- Localized: 126 (94%)
- Disseminated: 8 (6%)

Sub-acute pulmonary (2.5%)
- 3 cases

Rhinosinusitis (4.5%)
- 6 cases

Colonisation (treated) 4.5%
- 6 cases

Chronic Pulmonary (4.5%)
- 6 cases

Invasive Aspergillosis (38%)
- 52 cases

Aspergilloma (46%)
- 61 cases

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### Preliminary Results

<table>
<thead>
<tr>
<th>Body sites</th>
<th>n*</th>
</tr>
</thead>
<tbody>
<tr>
<td>- Lung</td>
<td>77 (52%)</td>
</tr>
<tr>
<td>- Sinus</td>
<td>50 (33%)</td>
</tr>
<tr>
<td>- CNS</td>
<td>6 (3.9%)</td>
</tr>
<tr>
<td>- Bone</td>
<td>4 (2.6%)</td>
</tr>
<tr>
<td>- Cutaneous</td>
<td>3 (1.9%)</td>
</tr>
<tr>
<td>- Other +</td>
<td>10 (6.6%)</td>
</tr>
</tbody>
</table>

+ Eye, heart, knee, kidney, peritoneal fluid
* More than one site per patient possible

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### Retrospective Survey of Aspergillosis in the non neutropenic host

#### Diagnostic method

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>Microbiology (+)</td>
<td>97</td>
</tr>
<tr>
<td>Biopsy</td>
<td>34</td>
</tr>
<tr>
<td>Autopsy</td>
<td>19</td>
</tr>
<tr>
<td>Galactomannan (+)</td>
<td>15</td>
</tr>
<tr>
<td>PCR</td>
<td>10</td>
</tr>
</tbody>
</table>

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**Aspergillus** species distribution

- *A. fumigatus* 91 (81%)
- *A. flavus* 4 (4%)
- *A. niger* 2 (2%)
- *Aspergillus* sp 1 (1%)
- *Compatible diagnosis* 13 (12%)

* Histopathology findings compatible with Aspergillosis

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Retrospective Survey of Aspergillosis in the non neutropenic host

Underlying diseases/conditions

<table>
<thead>
<tr>
<th></th>
<th>Invasive Aspergillosis n=52</th>
<th>Aspergilloma n=61</th>
<th>Others n=21</th>
</tr>
</thead>
<tbody>
<tr>
<td>Steroids</td>
<td>29 (56%)</td>
<td>6 (10%)</td>
<td>6 (29%)</td>
</tr>
<tr>
<td>Surgery</td>
<td>13 (25%)</td>
<td>10 (16%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>Solid org transplant</td>
<td>14 (27%)</td>
<td>3 (5%)</td>
<td>4 (19%)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td>3 (6%)</td>
<td>0 (0%)</td>
<td>2 (10%)</td>
</tr>
<tr>
<td>ICU stay</td>
<td>22 (42%)</td>
<td>2 (3%)</td>
<td>3 (14%)</td>
</tr>
<tr>
<td>ICU + M. ventilation</td>
<td>17 (33%)</td>
<td>2 (3%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

☆ $p< 0.001$

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Underlying diseases/conditions

<table>
<thead>
<tr>
<th></th>
<th>Invasive Aspergillosis n= 52</th>
<th>Aspergilloma n=61</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lung Diseases</td>
<td>19 (36%)</td>
<td>9 (15%)</td>
</tr>
<tr>
<td>Tbc</td>
<td>0 (0%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>COPD</td>
<td>11 (21%)</td>
<td>4 s</td>
</tr>
<tr>
<td>Others*</td>
<td>8 (15%)</td>
<td>4 (6%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>12 (23%)</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>4 (8%)</td>
<td>3 (5%)</td>
</tr>
<tr>
<td>HIV</td>
<td>1 (2%)</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>2 (4%)</td>
<td>3 (5%)</td>
</tr>
</tbody>
</table>

* Lung fibrosis, Sarcoidosis, Bronchiectasias, Resp. Burn, Emphysema
Retrospective Survey of Aspergillosis in the non neutropenic host

<table>
<thead>
<tr>
<th>Condition</th>
<th>Surgical (only)</th>
<th>Antifungal (only)</th>
<th>Surgical + Antifungal</th>
<th>No Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aspergilloma (n=61)</td>
<td>42</td>
<td>4</td>
<td>13</td>
<td>2</td>
</tr>
<tr>
<td>Invasive (n=52)</td>
<td>0</td>
<td>18</td>
<td>17</td>
<td>17</td>
</tr>
<tr>
<td>Rhinosinusitis (n=6)</td>
<td>5</td>
<td>0</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sub-acute pulmonary (n=3)</td>
<td>1</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Colonization (n=6)</td>
<td>0</td>
<td>6</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chronic pulmonary (n=6)</td>
<td>1</td>
<td>4</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>49</strong></td>
<td><strong>33</strong></td>
<td><strong>33</strong></td>
<td><strong>19</strong></td>
</tr>
</tbody>
</table>
## Treatment (n = 134)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Alive</th>
<th>Death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical treatment without antifungal</td>
<td>49 (36%)</td>
<td>44</td>
</tr>
<tr>
<td>Surgical treatment + antifungal</td>
<td>33 (25%)</td>
<td>30</td>
</tr>
<tr>
<td>Antifungal only</td>
<td>33 (25%)</td>
<td>26</td>
</tr>
<tr>
<td>No treatment *</td>
<td>19 (14%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*due to post-mortem diagnosis
## Retrospective Survey of Aspergillosis in the non neutropenic host

### Mortality

<table>
<thead>
<tr>
<th>Patients alive</th>
<th>100 (73.9%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients dead</td>
<td>34 (25.4%)*</td>
</tr>
</tbody>
</table>

- Invasive Aspergillosis 23/52 (44.2%)
- Aspergilloma 5/61 (8.2%)
- Sub-acute pulmonary 1/3 (33%)
- Chronic pulmonary 1/6 (16%)

*cause of death = Aspergillus infection = 14 / 34 (41%)

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Retrospective Survey of Aspergillosis in the non neutropenic host

Summary

The results of the survey showed

- Most of the cases were Aspergilloma (45%) and IA (39%)
- Lung was the most frequent body site infected (52%)
- Microbiology was the diagnostic tool more + results
- *A. fumigatus* was the most frequent species identified (81%)
- Overall mortality rate (25.4%)* 41% cause of death due to Asp Inf
- In IA: mortality 44%*
  - steroids increases risk to IA (OR 7.3) p<0.001
  - ICU stay (OR 11.2) p<0.001

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Retrospective Survey of Aspergillosis in the non neutropenic host

Conclusion

The high number of patients with IA / AO
The high mortality rate in patients with IA
The high number of IA cases diagnosed post-mortem

shows the importance of improving the diagnosis allowing to start an early treatment to improve outcome