ASPERGILLOSIS
IN THE NON-NEUTROPENIC HOST

Dr J Garbino

University Hospital Geneva

ASPERGILLOSIS
IN THE NON-NEUTROPENIC HOST

- INTRODUCTION
- SWISS ASPERGILLOSIS SURVEY IN THE NON-NEUTROPENIC HOST

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Aspergillus Infection

- **Introduction**

- Aspergillus species are wide spread 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

- **Aspergillosis**

- 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

Hibberd et al Clin Infect Dis 1994;19:33
Paterson et al Medicine 2000;79:250
Soubani et al Chest 2002;37:289
McWhinney et al Clin Inf Dis 1994;18:273
Denning et al NEJM 1991;324:654
Vogeser et al Eur J Clin Microb Inf Dis 1999;37:289
Saugier et al Bone M Transpl 1993;12:121
Guiot et al Clin Inf Dis 1994;18:525

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
Bodey - Eur J Clin Micr Inf Dis 1992; 11 :99
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
Levitz et al Adv. Intern. Med. 1984;30
Clancy et al Chest 1998;114
Ali et al J.Postgrad. Med.2003;49

Some reports have described IA in a few immuncompetent 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- 1osteomyelitis (Pakistan - 1 y)

  *Karim et al Clin Inf Dis 1997;**24***

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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

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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

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Castelnuovo et al A Otorhinolaryngol 2000;20

Sinonasal with Craniocerebral Asp (25p) 12years 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

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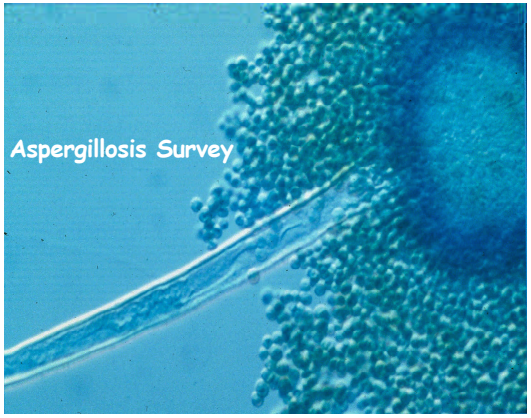
SURVEY OF ASPERGILLOSIS IN THE NON-NEUTROPENIC HOST IN THE SWISS UNIVERSITY HOSPITALS

« 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' comorbities

-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 *(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

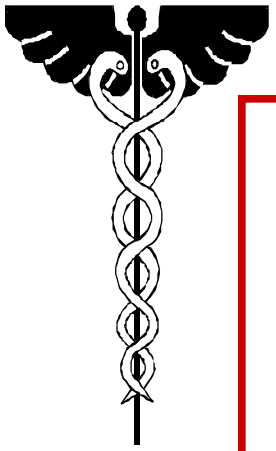
Patients with the following diagnosis will be excluded:

- 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

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

RESULTS

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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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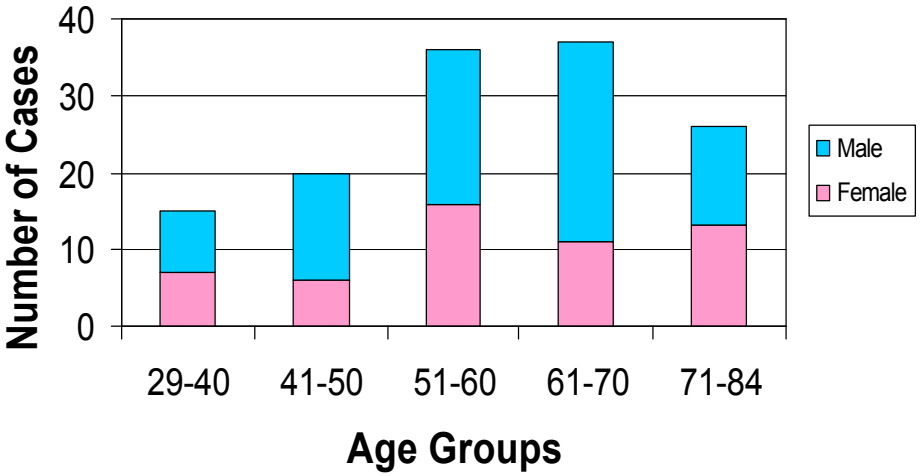
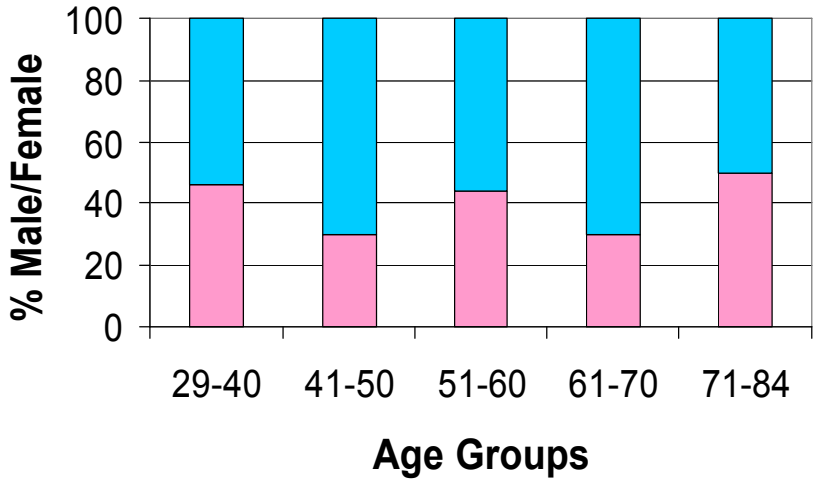
Retrospective Survey of Aspergillosis in the non neutropenic host

Patients Demographics

Total number of patients included = 134 **Mean age - 58,7 y. (29-84)**





Total male –82, Female 52

Total male –61%, Female 39%

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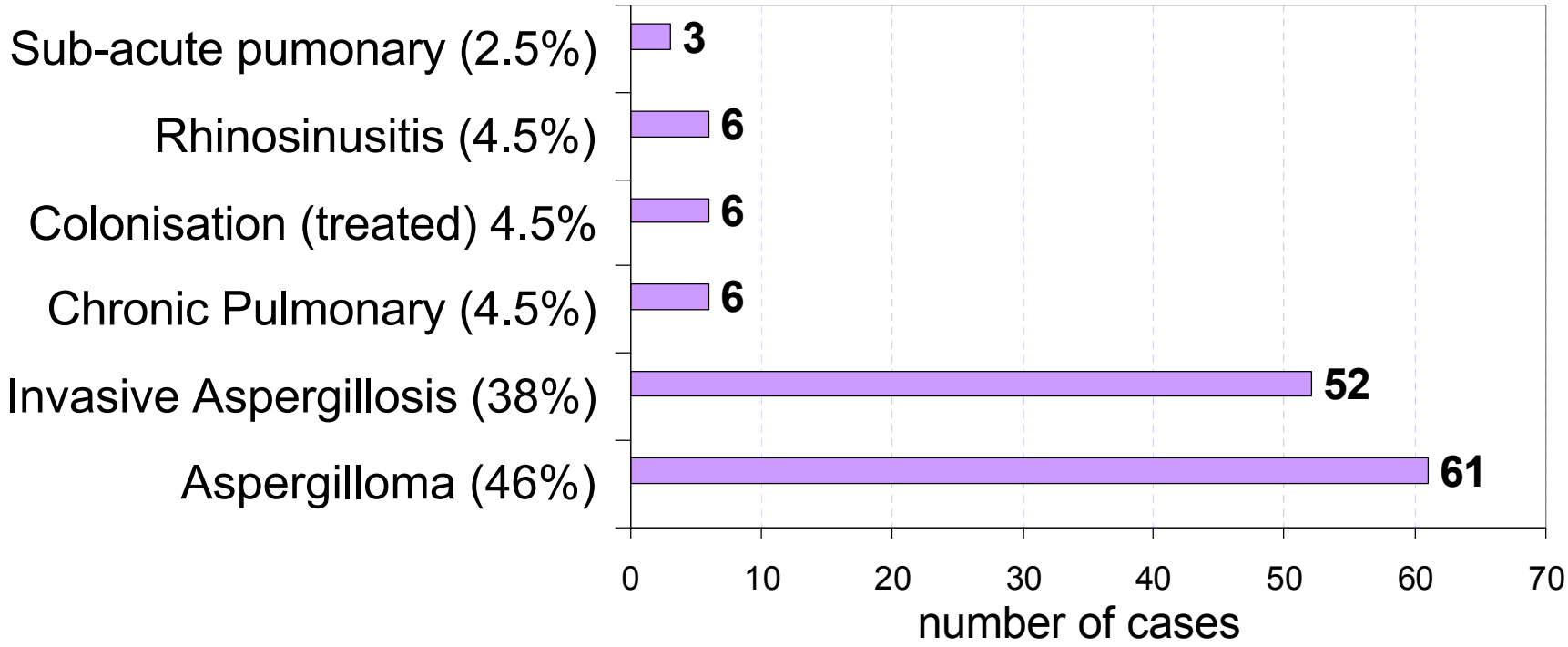
Type of Aspergillus infection

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



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Retrospective Survey of Aspergillosis in the non neutropenic host

Preliminary Results

Body sites	***n****
- Lung	77 (52%)
- Sinus	50 (33%)
- CNS	6 (3.9%)
- Bone	4 (2.6%)
- Cutaneous	3 (1.9%)
- Other +	10 (6.6%)

\+ Eye, heart, knee, kidney, peritoneal fluid

* More than one site per patient possible

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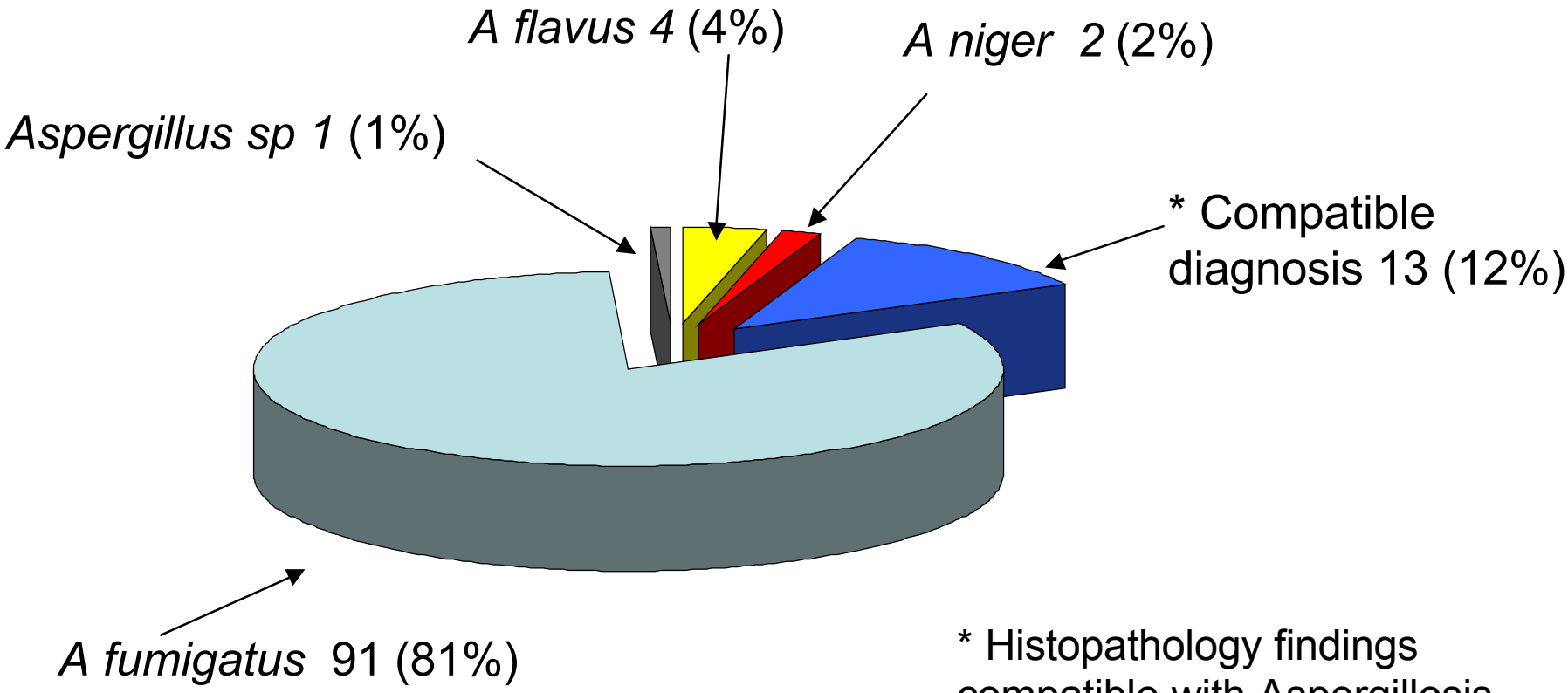
Diagnostic method

- Microbiology (+)	97
- Biopsy	34
- Autopsy	19
- Galactomannan (+)	15
- PCR	10

Retrospective Survey of Aspergillosis in the non neutropenic host

Aspergillus species distribution



* Histopathology findings compatible with Aspergillosis

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Retrospective Survey of Aspergillosis in the non neutropenic host

Underlying diseases/conditions

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

☆p< 0.001

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Retrospective Survey of Aspergillosis in the non neutropenic host

Underlying diseases/conditions

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

* Lung fibrosis, Sarcoidosis, Bronchioctasias, Resp. Burn, Emphysema

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Retrospective Survey of Aspergillosis in the non neutropenic host

Treatment

	Surgical (only)	Antifungal (only)	Surgical + Antifungal	No Treatment
Aspergilloma *(n=61)*	42	4	13	2
Invasive *(n=52)*	0	18	17	17
Rhinosinusitis (*n=6*)	5	0	1	0
Sub-acute pulmonary (*n=3*)	1	1	1	0
Colonization *(n=6)*	0	6	0	0
Chronic pulmonary *(n=6)*	1	4	1	0
Total	**49**	**33**	**33**	**19**

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Treatment

Treatment (n = 134)

		Alive	Death
- Surgical treatment without antifungal	49 (36%)	44	5 (10%)
- Surgical treatment + antifungal	33 (25%)	30	3 (9%)
- Antifungal only	33 (25%)	26	7 (22%)
- No treatment *	19 (14%)	0	19

**due to post-mortem diagnosis*

Retrospective Survey of Aspergillosis in the non neutropenic host

Mortality

• Patients alive	**100** (73.9%)
• Patients dead	**34** (25.4%)*
– 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

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