MEDIZINISCHE UNIVERSITÄT INNSBRUCK

INVASIVE PULMONARY MYCOSES IN LUNG TRANSPLANT RECIPIENTS

TRENDS IN MEDICAL MYCOLOGY, BEOGRAD, 06.12.2017

KLINIKEN SÜDOSTBAYERN

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Medical Mycology Supplement 1 2005, 43, S49 - S58

Taylor & Francis

Incidence of invasive aspergillosis following hematopoietic stem cell and solid organ transplantation: interim results of a prospective multicenter surveillance program

J. MORGAN*, K. A. WANNEMUEHLER†, K. A. MARR†, S. HADLEY‡, D. P. KONTOYIANNIS§, T. J. WALSH¶, S. K. FRIDKIN*, P. G. PAPPAS# & D. W. WARNOCK*

INCIDENCE

	N	cases/ 6 mo	cases/12 mo	CI/6 mo	CI/12mo
Autologous HSCT	2588	11	13	0.4	0.5
Allogeneic HSCT	2033	43	59	2,1	2,3
Lung	290	7	10	1,5	3,5
Liver	1058	3	3	0.3	0.3
Heart	349	3	3	0.8	0.8
Kidney	2147	3	3	0.1	0.1
Other SOT	266	1	1	0.4	0.4

MORTALITY

	N 0-1 mo	%	N 2 - 6 mo	%	N 7 - 12 mo	%	death N	death %
Autologous HSCT	7	53.8	4	30.8	2	15.4	7	53.8
Allogeneic HSCT	16	27.1	27	45.8	16	27.1	45	76.3
Lung	2	20.0	5	50.0	3	30.0	2	20.0
Liver	2	66.7	1	33.3	0		1	33.3
Heart	1	33.3	2	66.7	0		2	66.7
Kidney	3	100	0	0	0		2	66.7
Other SOT	1	100	0	0	0		0	

Morgan, Medical Mycology, 2005

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Morgan, Medical Mycology, 2005

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journal homepage: http://www.elsevier.com/locate/ijantimicag

The Nationwide Austrian *Aspergillus* Registry: a prospective data collection on epidemiology, therapy and outcome of invasive mould infections in immunocompromised and/or immunosuppressed patients

S. Perkhofer[a], C. Lass-Flörl[a,*], M. Hell[b], G. Russ[c], R. Krause[d], M. Hönigl[d], C. Geltner[e], J. Auberger[f], G. Gastl[f], M. Mitterbauer[g], B. Willinger[h], P. Knöbl[g], G. Resch[i], R. Waldner[j], A. Makrai[j], G. Hartmann[k], M. Girschikofsky[l], R. Greil[c]

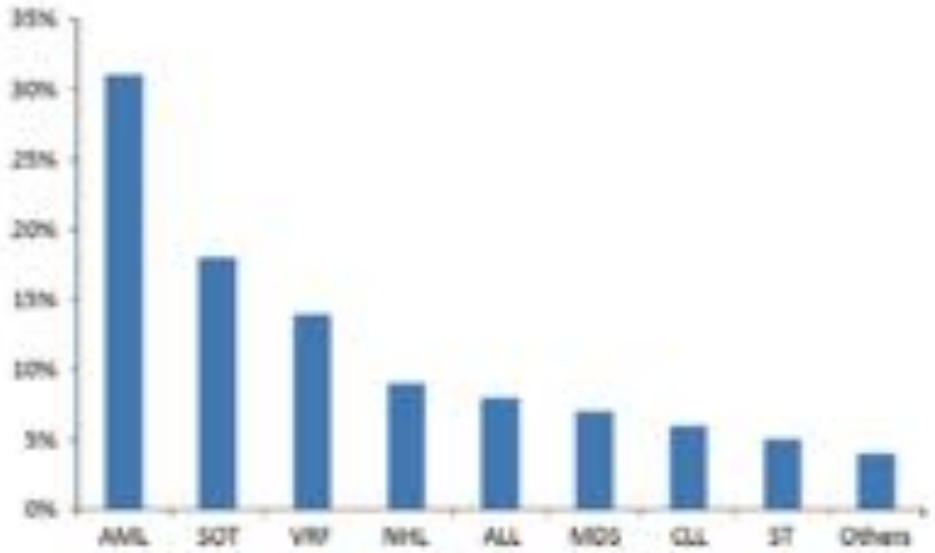


Fig. 1. Overview of underlying diseases in 186 patients with invasive mould infections. AML, acute myelogenous leukaemia; SOT, single-organ transplantation; VRF, various risk factors (mainly Intensive Care Unit patients without underlying haematological malignancies); NHL, non-Hodgkin's lymphoma; ALL, acute lymphatic leukaemia; MDS, myelodysplastic syndrome; CLL, chronic lymphatic leukaemia; ST, solid tumour.

Perkhofer, Int J Antimicrob Agents, 2010

Austrian registry

Patient characteristic	n (%)
Age (years) (mean ± S.E.)	52.9 ± 0.6
Age group (years)	
<18	7 (4)
19–39	26 (14)
40–60	82 (44)
>60	71 (38)
Male gender	108 (58)
Underlying disease[b]	
Acute myelogenous leukaemia	63 (34)
Acute lymphatic leukaemia	[illegible]
Chronic lymphatic leukaemia	10 (5)
Non-Hodgkin's lymphoma	19 (10)
Hodgkin's lymphoma	2 (1)
Multiple myeloma	1 (0.5)
Myelodysplastic syndrome	15 (8)
Solid tumour	[illegible]
Lung transplant recipients	31 (17)
Other	[illegible]
Allogeneic stem cell transplantation	37 (20)
Immunological risk factors[b]	
Neutrophil count <500 cells/mm³	80 (43)
Receipt of corticosteroid therapy	[illegible]
Receipt of immunosuppressive therapy	82 (44)
Inherited severe immunodeficiency	[illegible]
Environmental conditions	
HEPA rooms	56 (30)
Exposure to construction (builder's dust)	22 (12)
Standard rooms	[illegible]
Antifungal prophylaxis	80 (43)

Clinical characteristics of 186 immunosuppressed patients with invasive mould infections.

Characteristic	n (%)
Diagnosis	
Proven	63 (34)
Probable	56 (30)
Possible	[illegible]
Lung involvement	186 (100)
Treatment outcome	
Improvement	93 (50)
Stable	54 (29)
Deterioration	39 (21)
Prophylactic antifungal use[a]	80 (43)
Breakthrough infection during prophylaxis	24 (30)
Survival at 12 weeks	[illegible]
Diagnostic screening assays	
Any PCR	30 (16)
Serum/BAL galactomannan assay	48 (26)
β-D-glucan assay	6 (3)

PCR, polymerase chain reaction; BAL, bronchoalveolar lavage fluid.

[a] Administration of an antifungal drug for at least 1 week before clinical signs and symptoms of fungal infection.

Perkhofer, Int J Antimicrob Agents, 2010

Aspergillosis after LungTX

- Singh, Transplant Infection 2003
  Lung tranplants 6,2%
  - 54% bronchial anastomosis
  - 34% invasive
  - 22% disseminated
  overall mortality 52%
- Mattner, ISHLT 2007, ISHLT 2009
  Hannover Lung transplant program (Germany)
  IA 5,6%, Aspergillosis 28% (n=157 LuTX), early (17 days +/- 10)
  systemic prophylaxys ITRA 8%, VORI 2,3%
- Husain, Am J Transplant 2006
  Colonization in lungs; 28% pre-emtive strategy vs 2,5% prophylaxis
- Weigt S. S., Am J Transplantation 2009
  Aspergillus colonization is independent risk factor of BOS
  (bronchiolitis obliterans) preceeds diagnosis of BOS 261 days

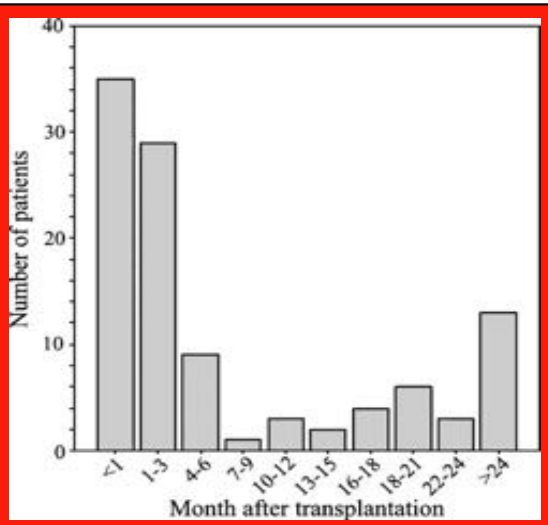
Eur J Clin Microbiol Infect Dis (2007) 26:879–886
DOI 10.1007/s10096-007-0376-3

ARTICLE

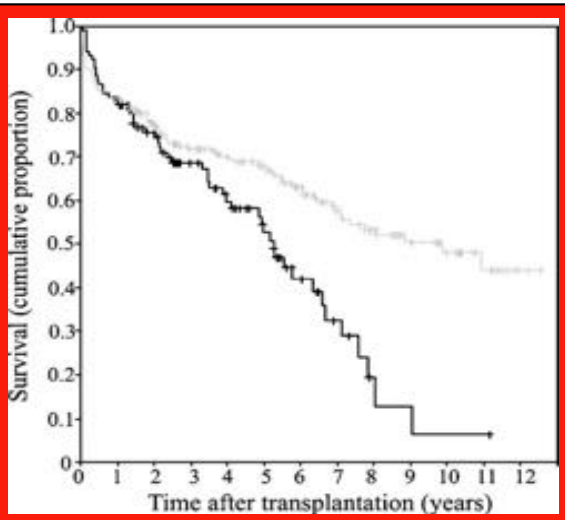
Aspergillus infection in lung transplant patients: incidence and prognosis

M. Iversen · C. M. Burton · S. Vand · L. Skovfoged · J. Carlsen · N. Milman · C. B. Andersen · M. Rasmussen · M. Tvede

- 31% CI (n=105), 25% colonization, 6% invasive
- risk factor: CF, older lungs, Daclizumab vs. ATG

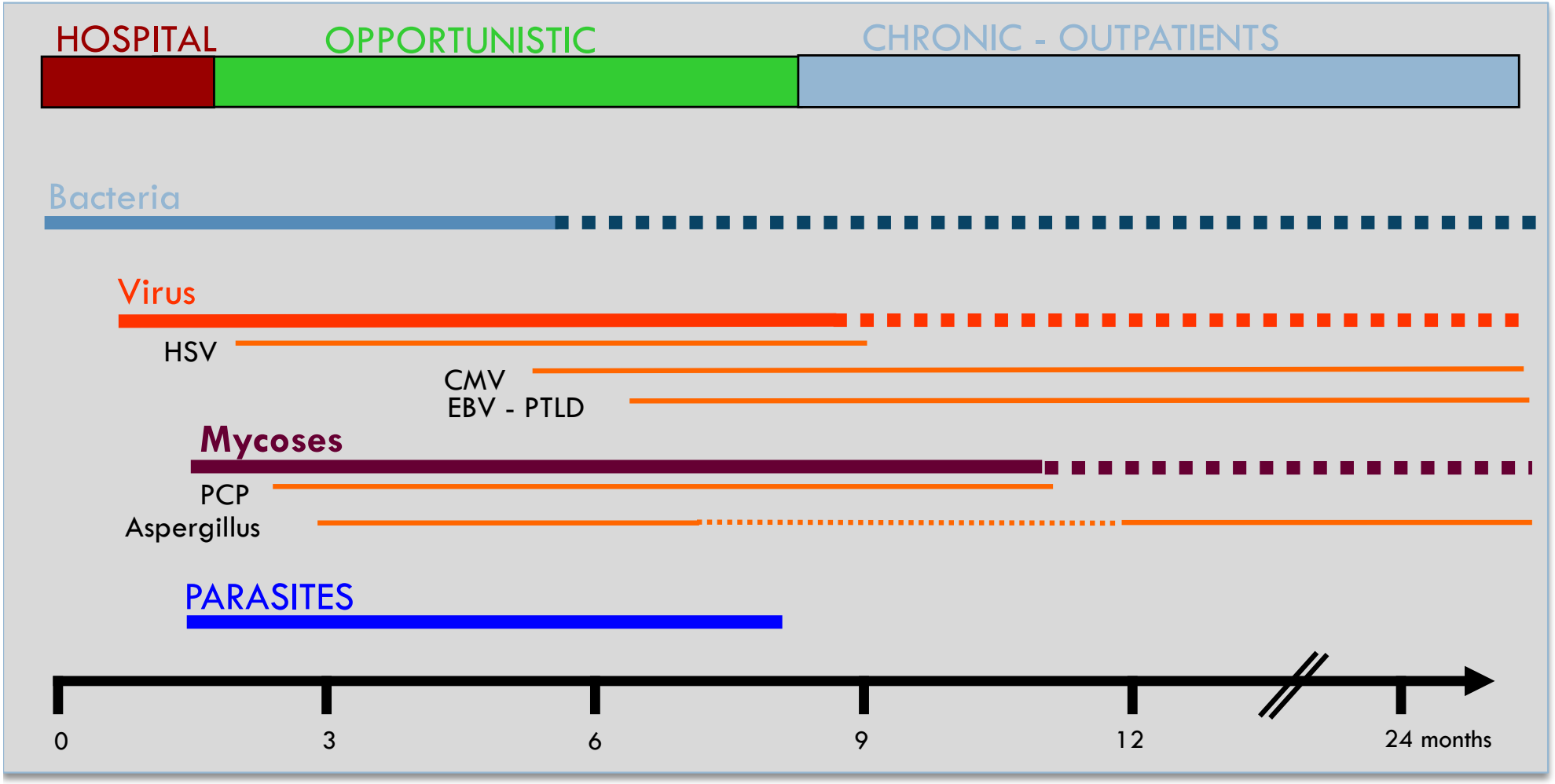


Histogram demonstrating the time at which lung transplant patients have evidence of pulmonary Aspergillus infection



Kaplan-Meier plot showing survival of infected (black line) versus non-infected (grey line) patients with pulmonary Aspergillus infection (log-rank test, P=0.002)

„natural course“ of infections



Geltner, Respiratory Investigation,2016

Aspergillosis in LungTX

- **Nodular** versus **disseminated** invasive aspergillosis better outcome, lower immunosuppression, mortality 25 versus 64%!
  (Singh, Journal of infection 2013)

- **Immunoreconstitution syndrome (IRS)**
  often after SOT and invasive fungal disease, occurs after reduction of immunosuppression and enhances symptoms (esp IA)
  Mortality increased due to acute/chronic rejection
  (Singh, Geltner ea, Transplant Immunology 2013)

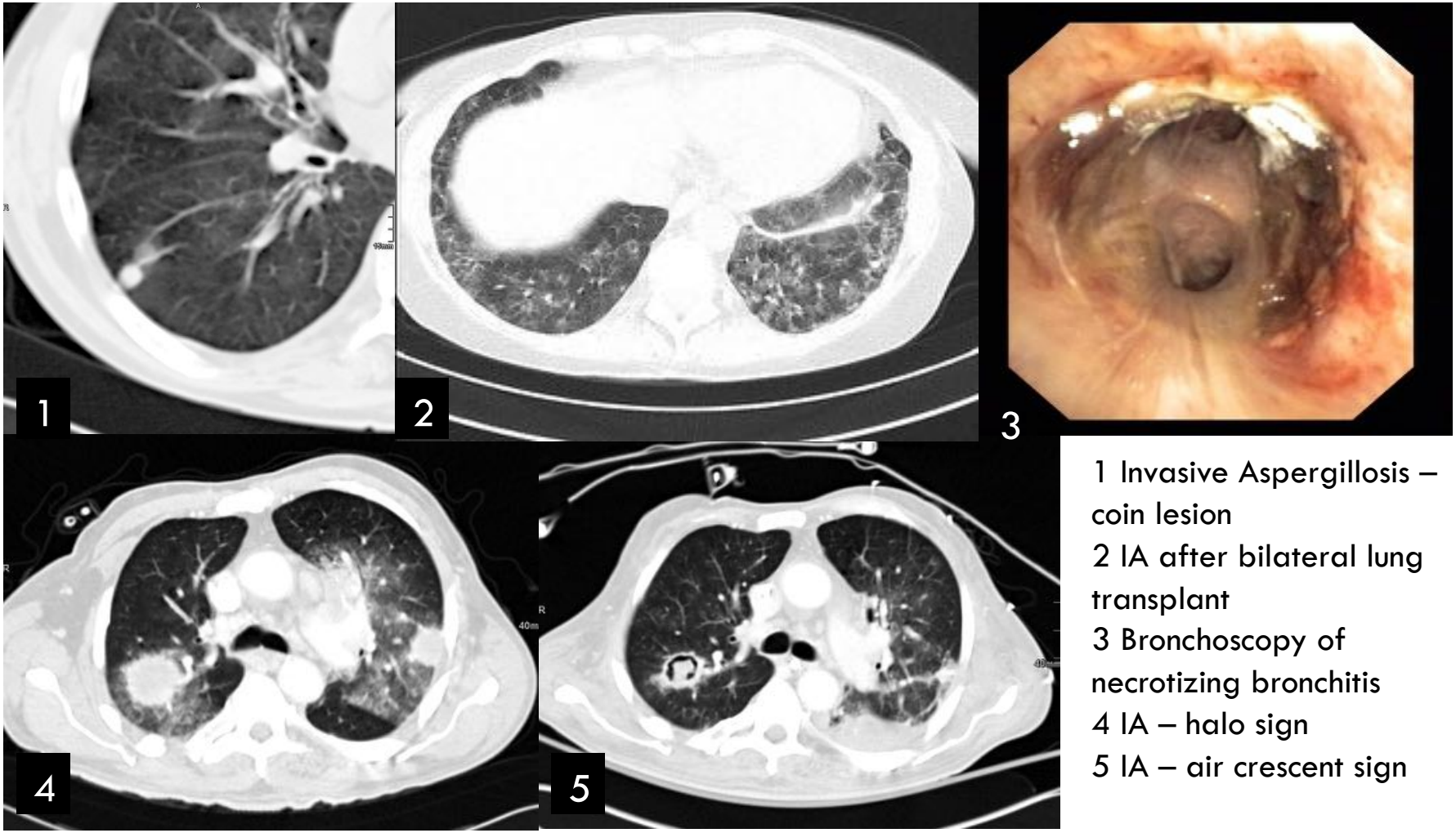
Clinical Appearance of Mycoses in lung transplanted patients

- **Colonization** of bronchial epithelium/anastomoses
  DD of early invasive disease

- **Invasive** Pulmonary Aspergillosis (mycosis)
  (EORCT)
  - Proven IA (biopsy)
  - Probable IA
  (host factor + clinical factor + microbiological)
  - Possible IA (host factor + clinical factor)

- (invasive) **Tracheobronchitis** (=clinical factor)
  Plaques, ulcerations, pseudomembranous bronchitis, granulations
  - anastomoses site „Anastomositis“

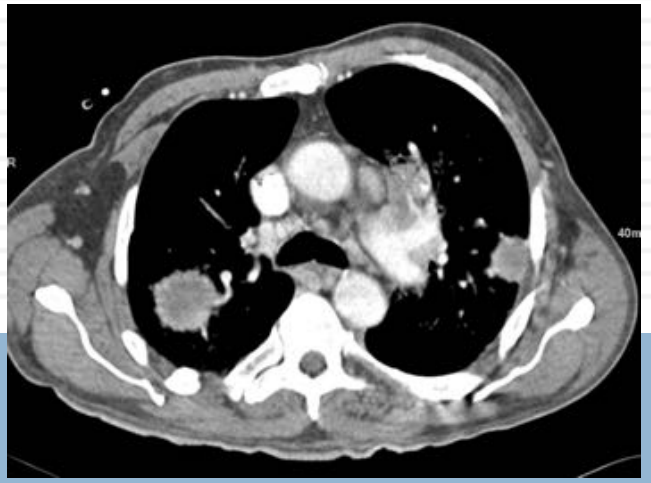
Features of Aspergillus in lung transplants



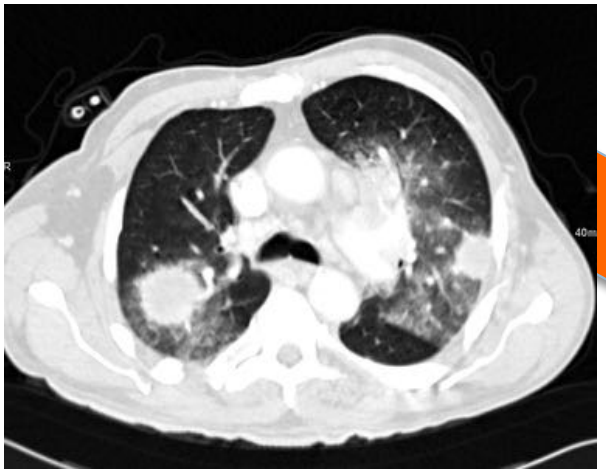
1 Invasive Aspergillosis – coin lesion
2 IA after bilateral lung transplant
3 Bronchoscopy of necrotizing bronchitis
4 IA – halo sign
5 IA – air crescent sign

Geltner, Respiratory Investigation,2016

Diagnosis



from suspicion to diagnosis



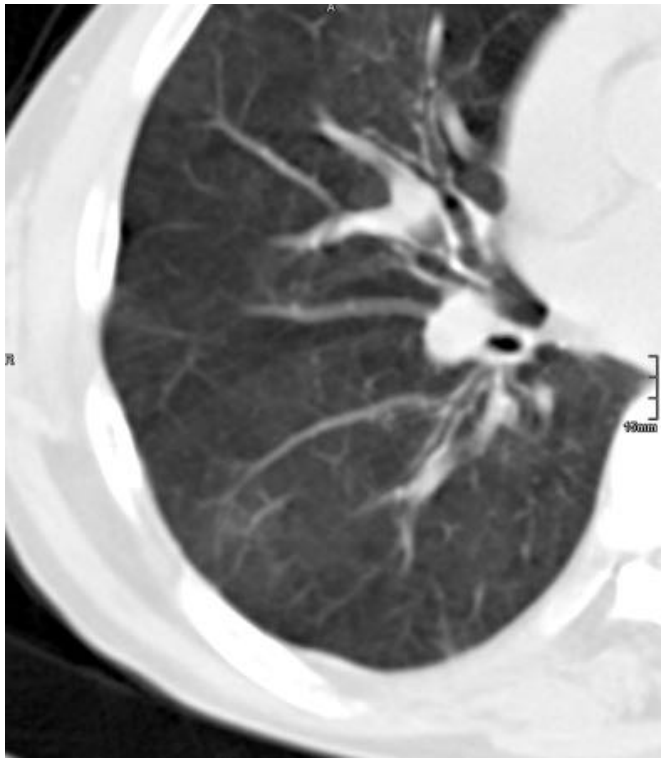
This is what you have

This is what your microbiologist wants

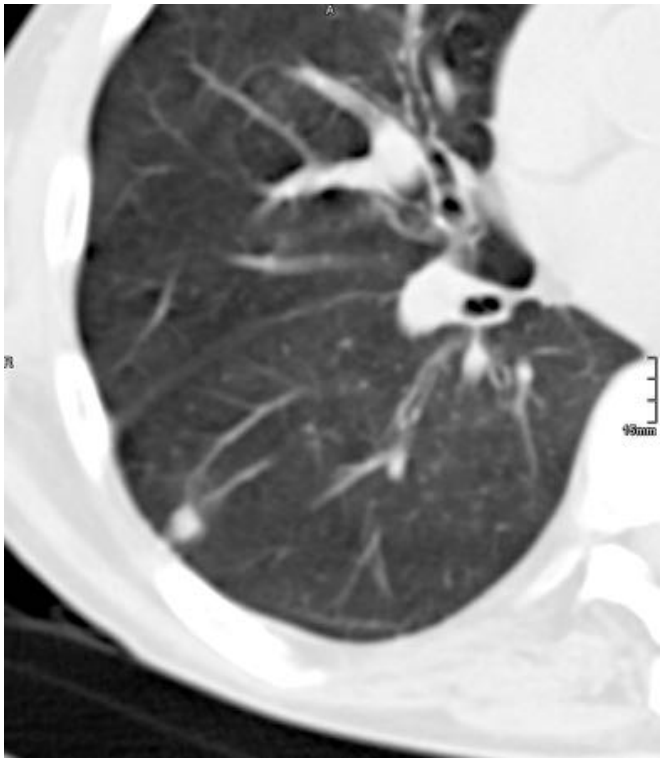
- How to get the material out of the lungs?
- How to make a diagnosis out of CT scan?

Invasive Aspergillosis

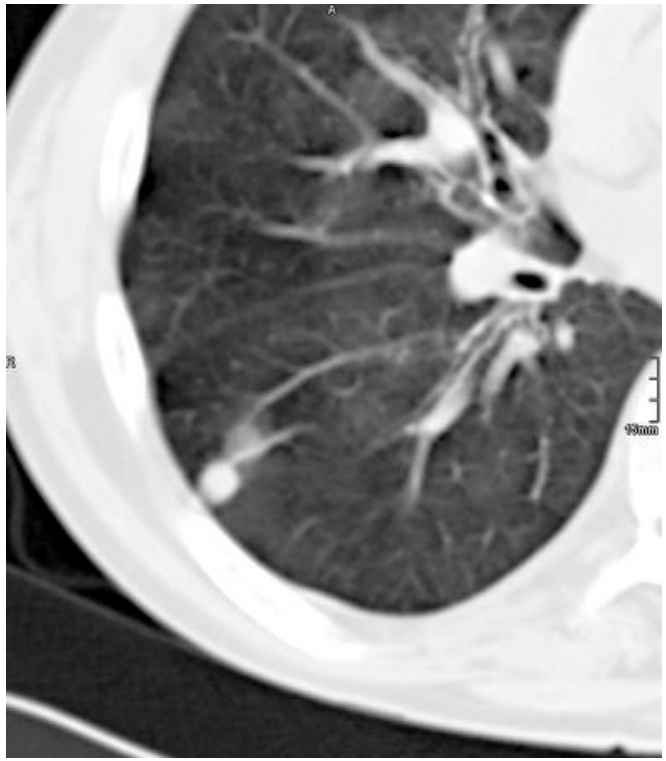
Pulmonary coin lesion – solitary nodule



6 month post TX

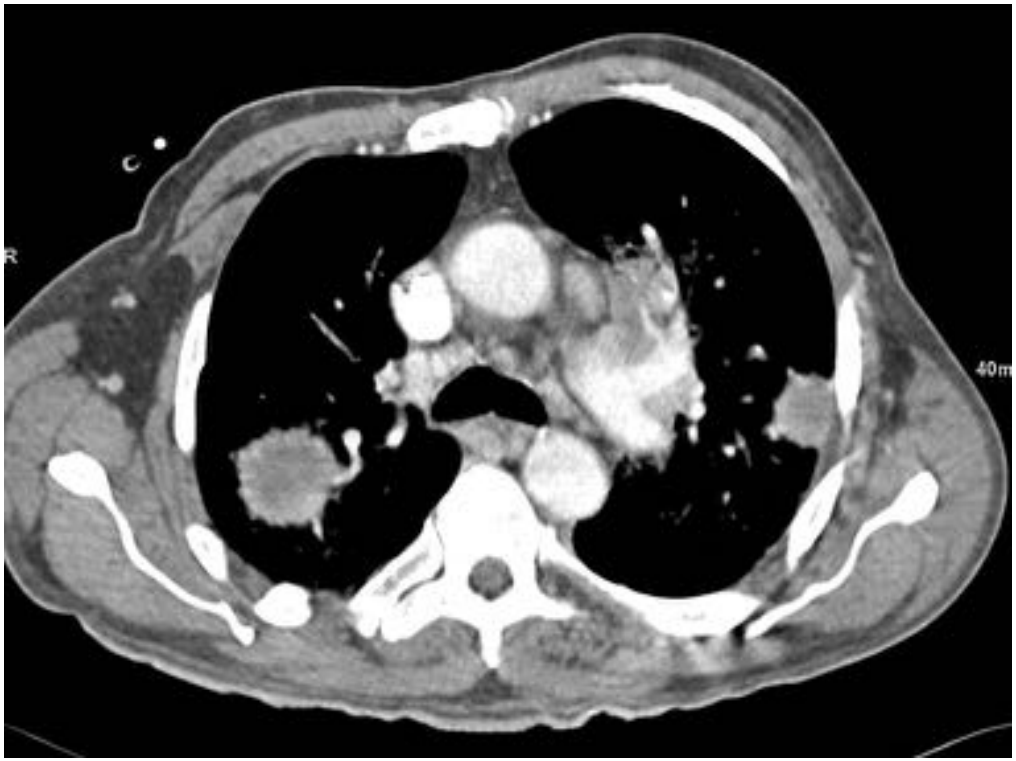


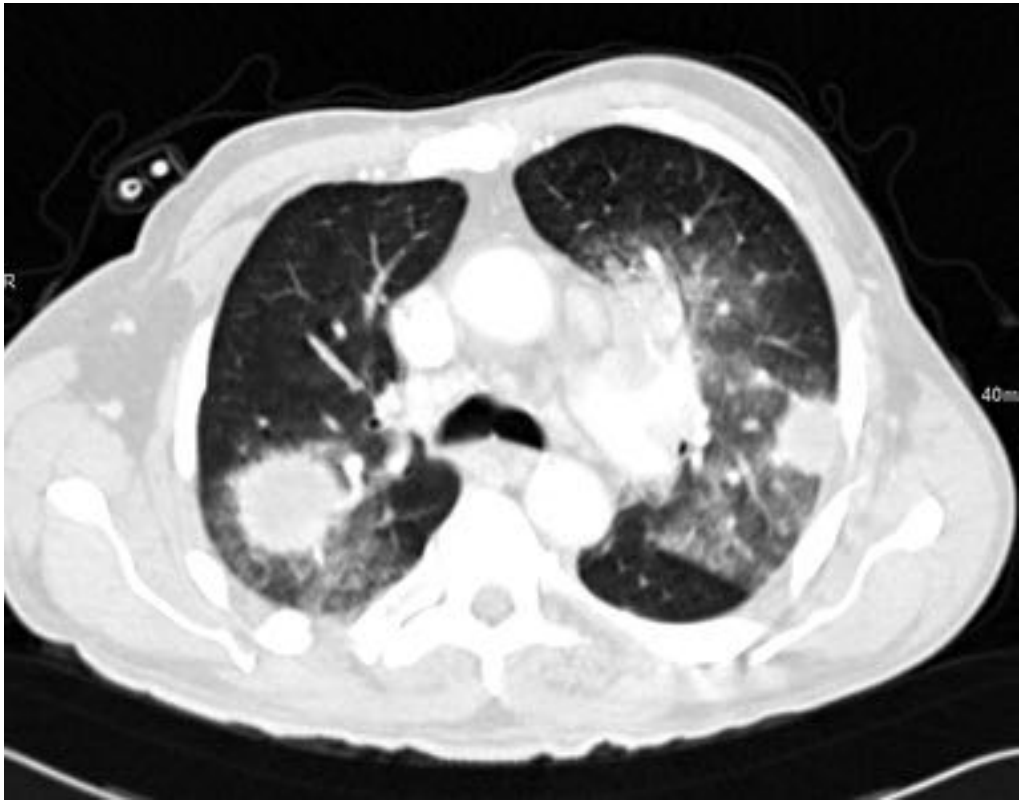
8 month post TX



9 month post TX

Invasive Aspergillosis - Coin lesion and halosign





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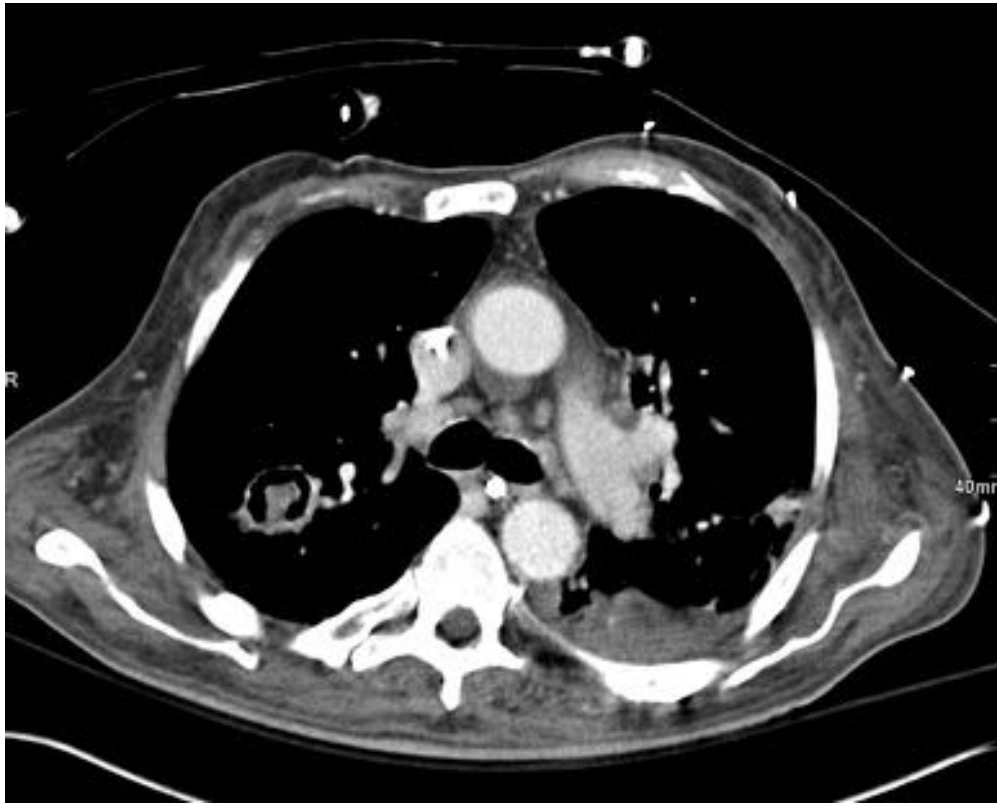
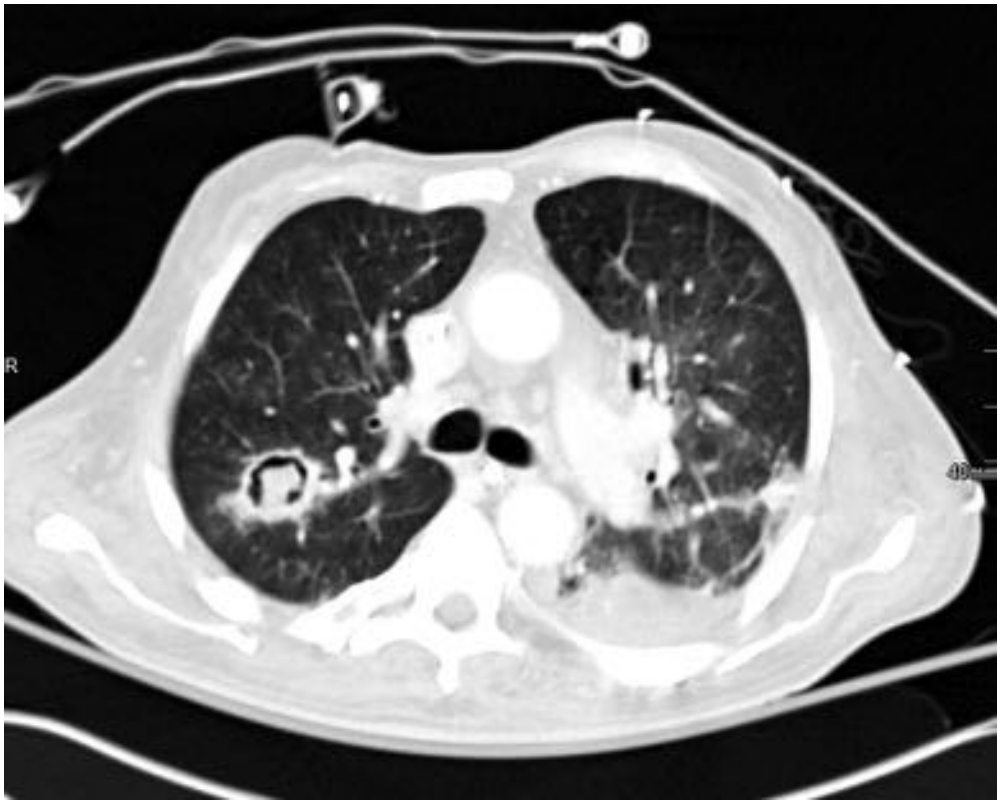
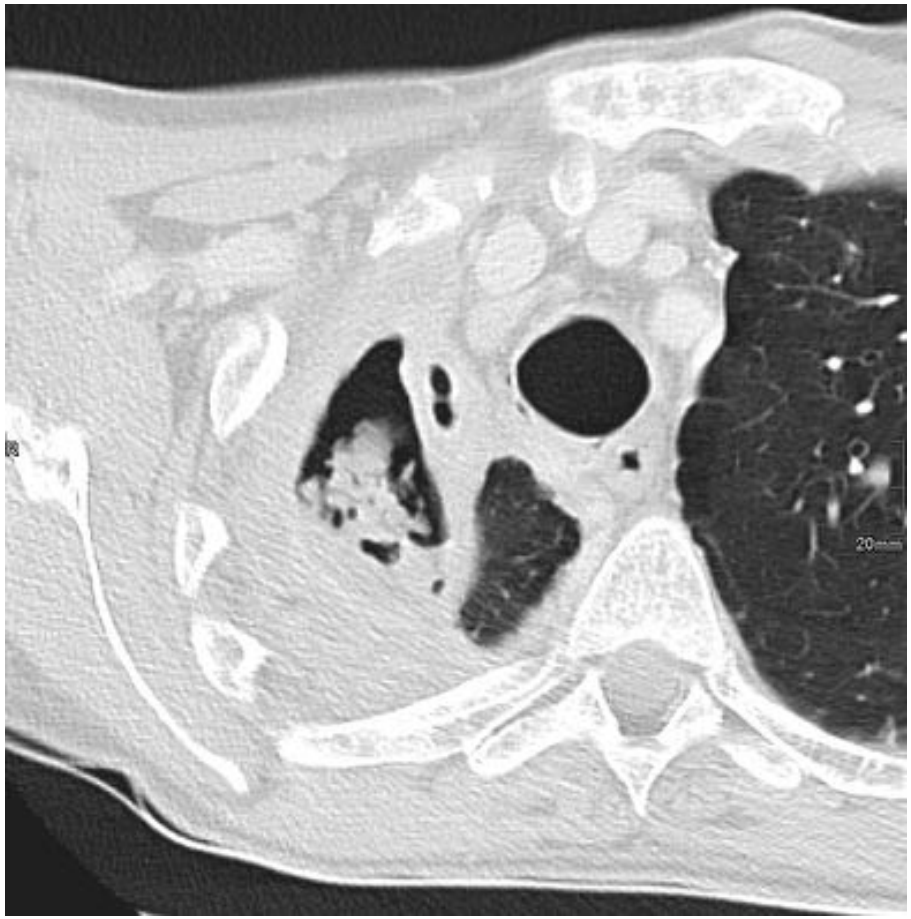
Invasive Aspergillosis - air crescent sign

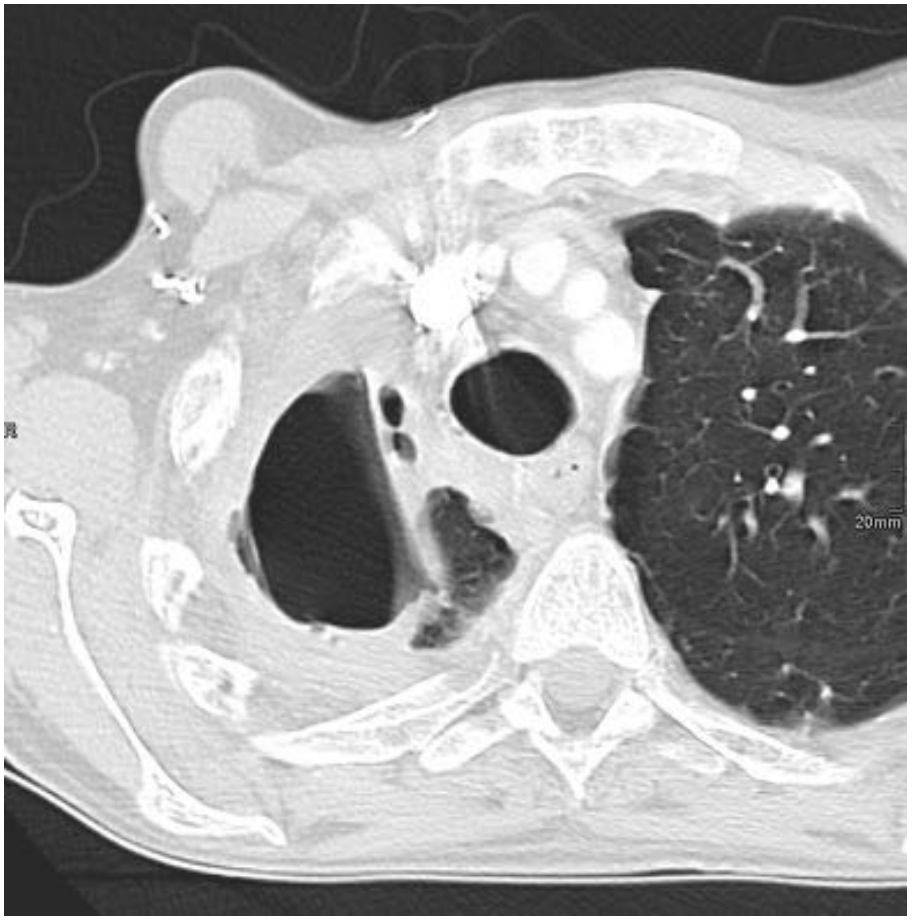




Saprophytic Aspergillosis

Aspergillus and posttuberculous cavernous lesion





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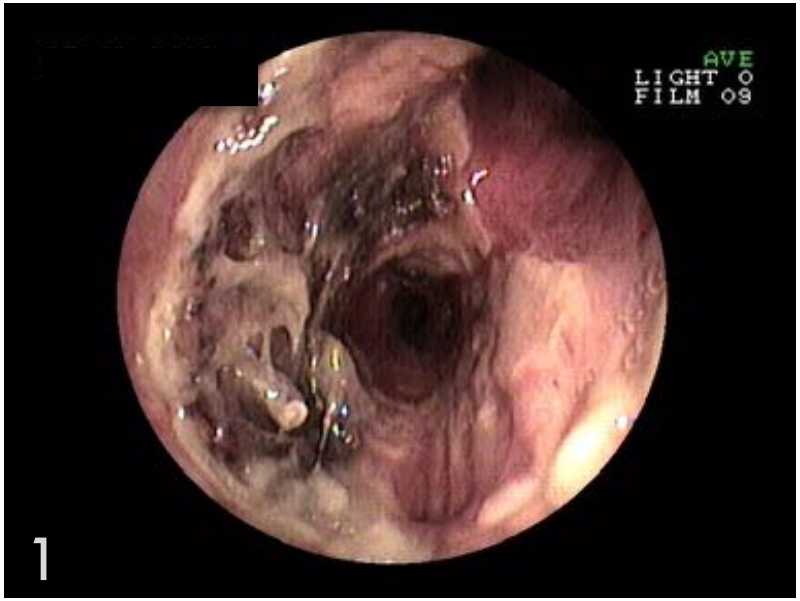
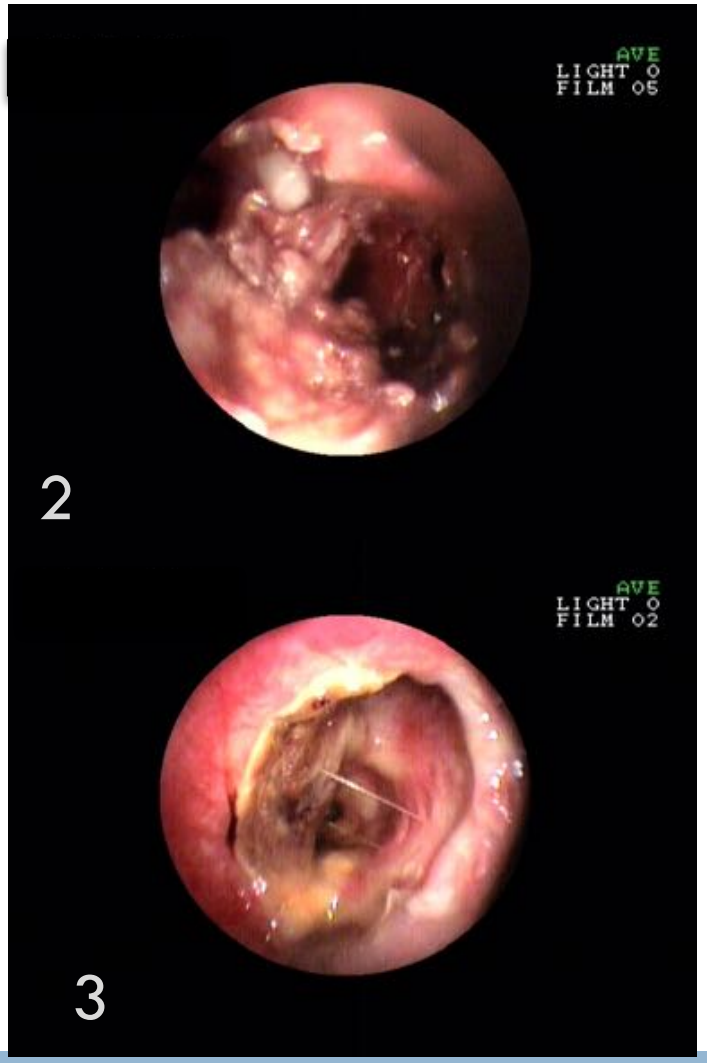
Anastomositis and Necrosis after LungTX
Colonization with A. fumigatus





1: Anastomositis left lung, 6 weeks postTX
2: Necrosis and infection (necrotizing bronchitis)
3: „normal“ 20 days post TX

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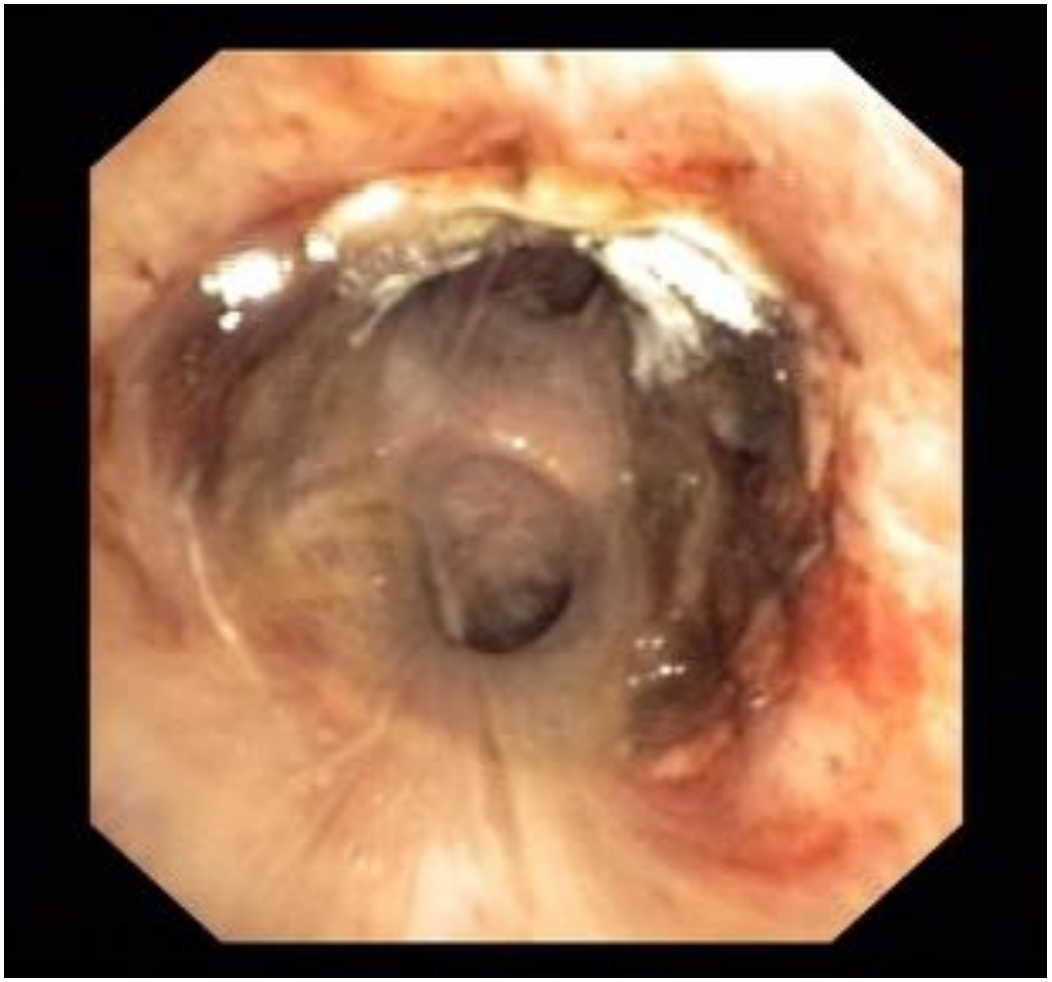
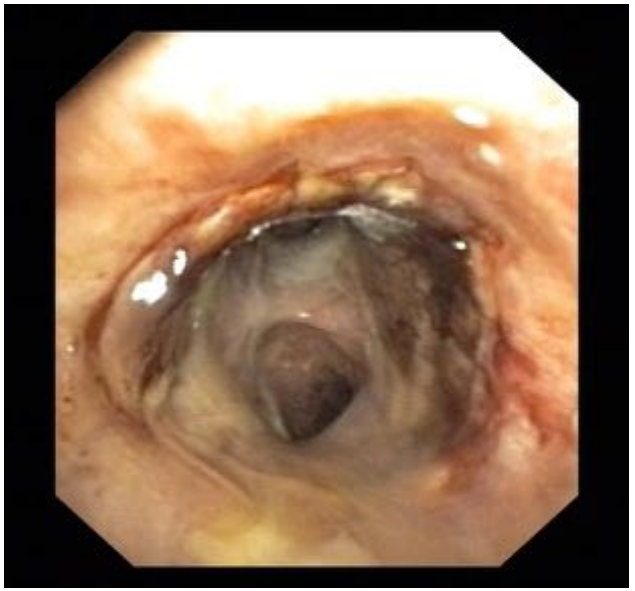
Necrotizing bronchitis after lungTX
Invasive bronchial Aspergillosis





BLUTX, anastomosis left, 14 days postTX
A. terreus
Prophylaxis:
inhaled Amphotericin B
Therapy:
Voriconazole, Caspofungin

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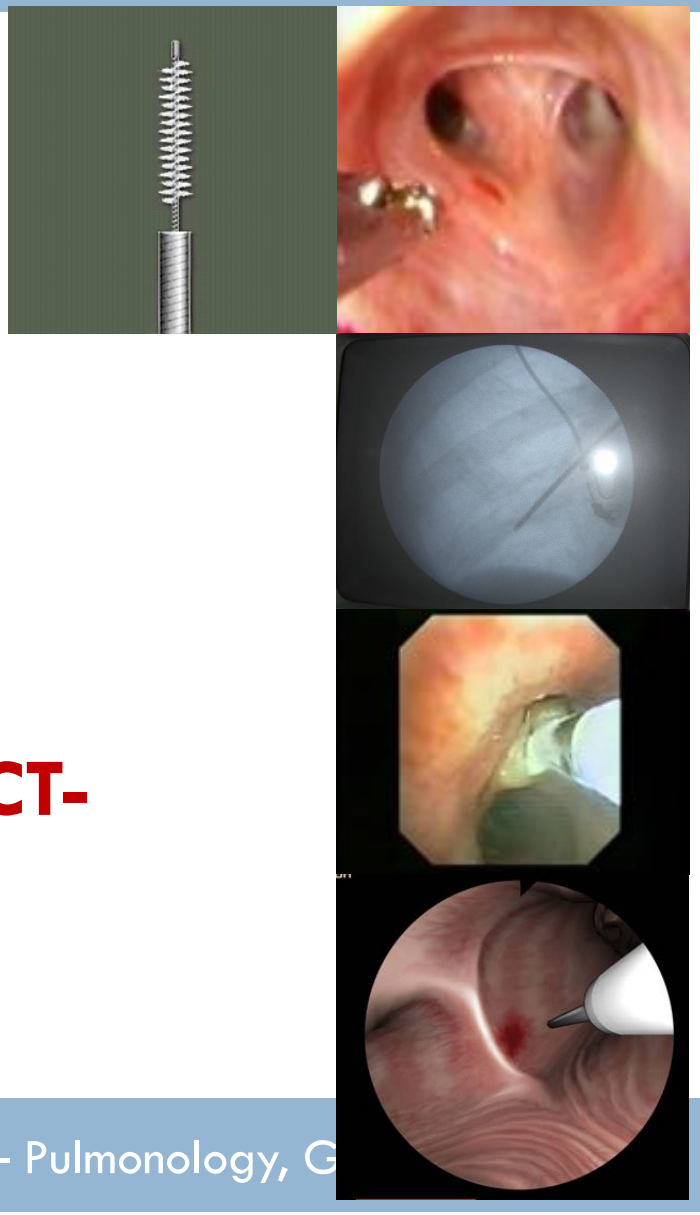
How to get material out of the lungs

- Sputum
- Tracheal aspirate
- Bronchial aspirate
- **Broncho-alveolar lavage (BAL)**
- Bronchial brush

- Bronchial biopsy (central)
- **Transbronchial biopsy (TBB)**
- Transbronchial needle aspiration (TBNA +/- EBUS)
- **Perthoracic needle aspiration (US/CT-guided)**
- Surgery (VAT, VATS, open surgery)

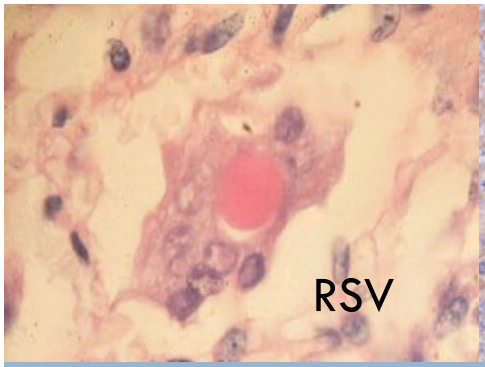


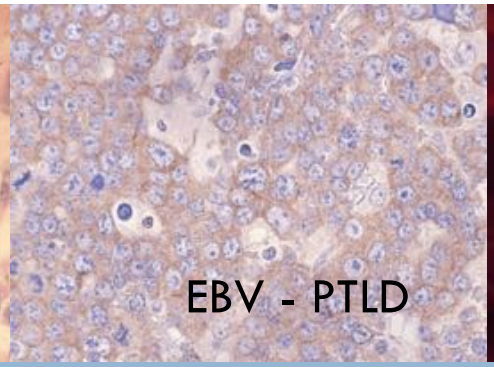
How to perform BAL

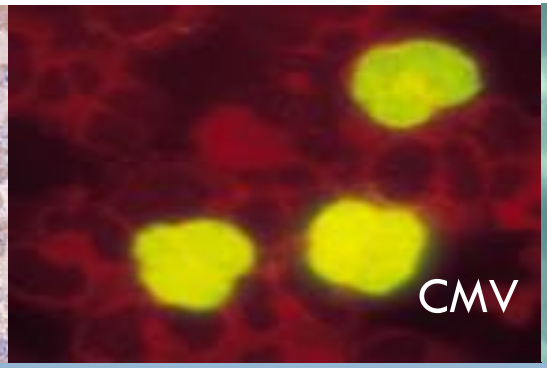
- Flexible bronchoscopy in local anesthesia +/- sedation or general anesthesia
- In diffuse lung disease, the middle or lingular lobe is recommended as a standard site. Localized disease naturally requires lavage of the radiographically involved area.
- Warm isotone saline is used as instillate in multiple fractions up to 100-300ml
- first fraction represents the central bronchial system whereas the last fraction allows the differentiation of alveolar disorders
- BAL is very safe and complications are mostly mild. Especially in immunocompromized patients fever (20% of patients) and an aggravation of infectious pneumonia can occur. The rate of severe complication is under 2%.
- Transport cooled, quick to the cytologic institute or cell culture medium

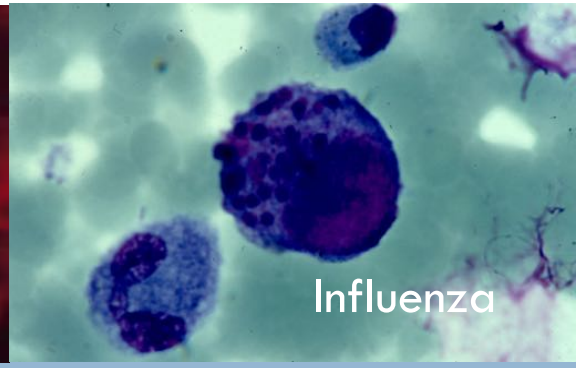
BAL – Cellular components

- Recovery volume (>40ml) centrifugated (non-cellular part)
- Cytospin-preparation
- May Grünwald Giemsa staining for cell differentiation
- Special stainings:
  PAS – fungi
  iron, silver – PCP, fungi
- PCR, GM, IGRA
- Intracellular viruses and pathogens (IF, PCR)



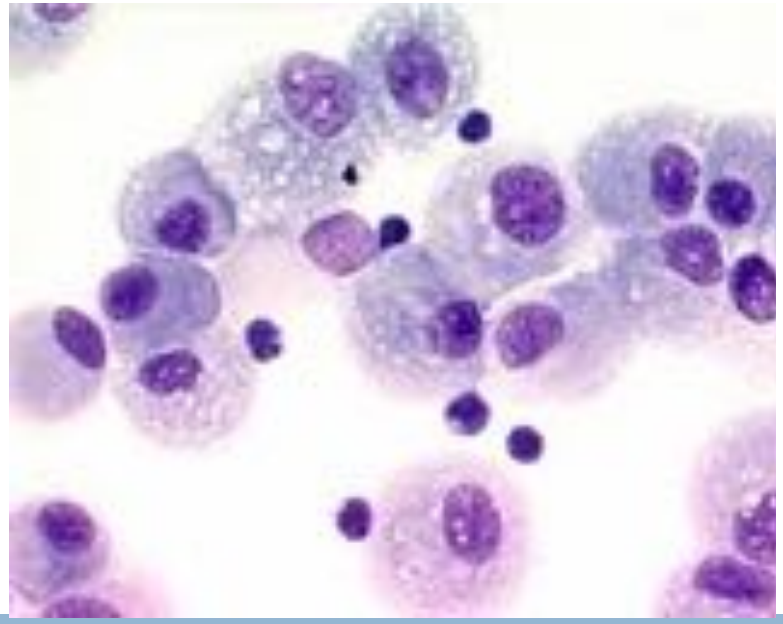




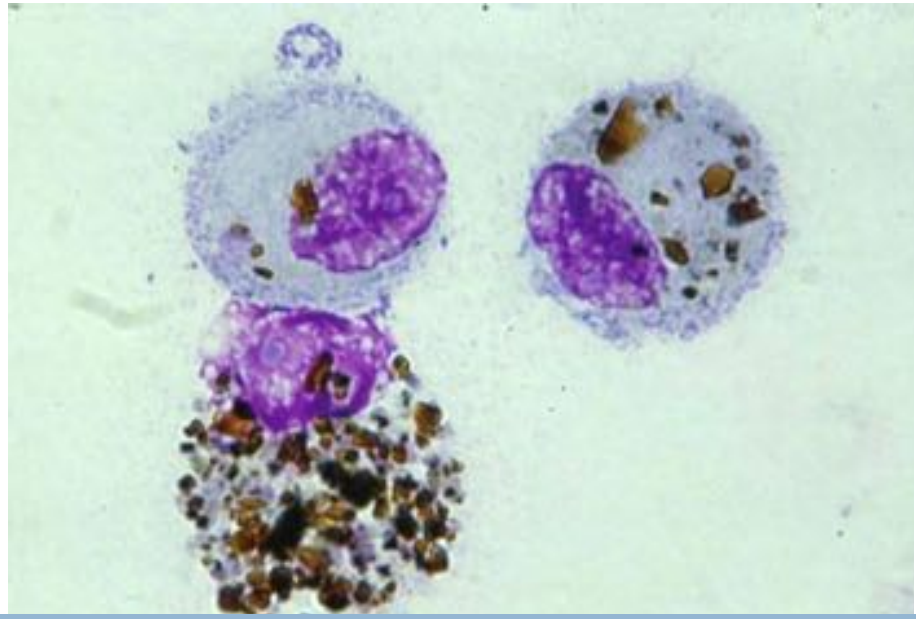


Cellular – normal findings

- Normal (Nonsmoker)
  lymphocytes <7%
  neutrophiles <3%
  eosinophiles <0,5%,
  alveolarmacrophages > 80%



- BAL smoker
  smoking pigments
  lymphocytes up to 12%



Neutrophilic BAL

Neutrophilic Pattern

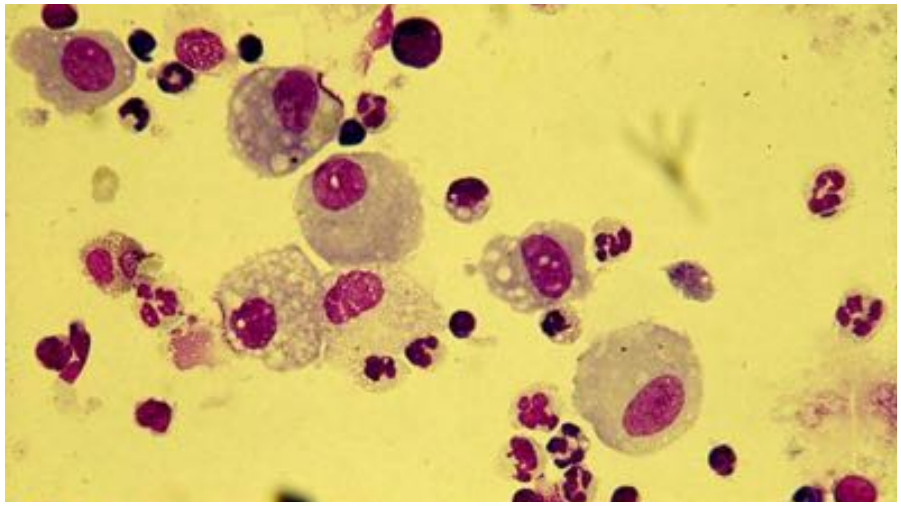
IPF
ARDS
MCTD
Pneumoconiosis

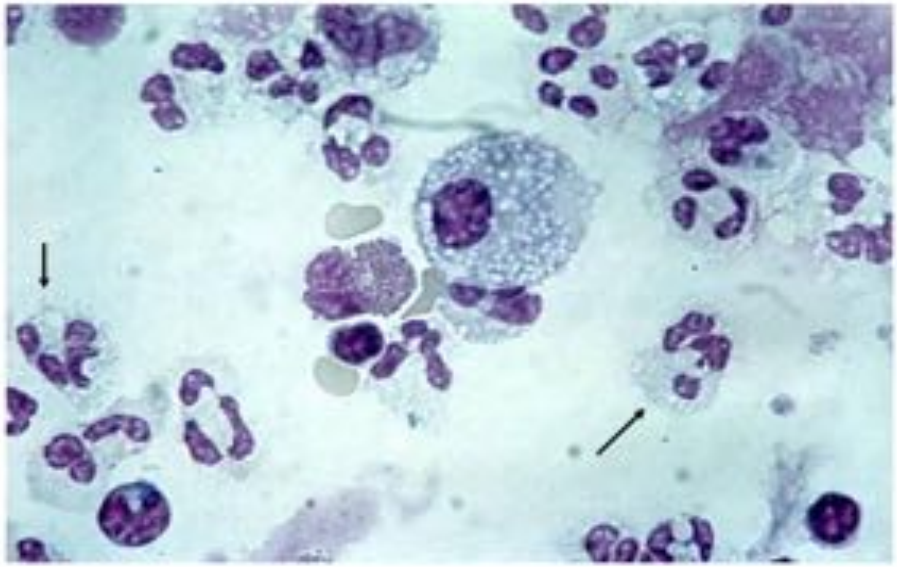
EGPA granulomatosis
Lower respiratory tract infections

Toxic alveolitis

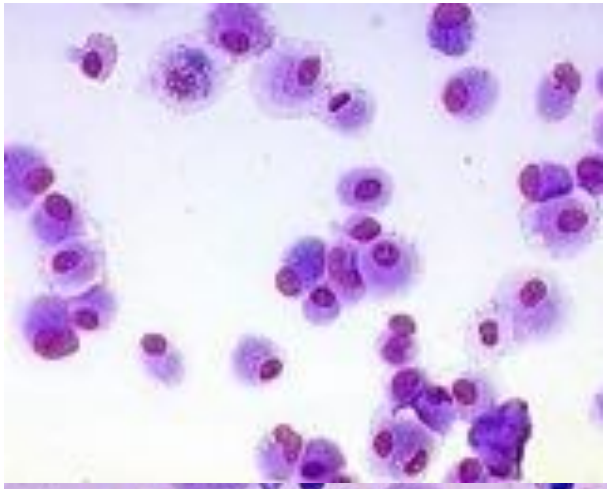
Acute interstitial pneumonitis
Desquamative interstitial pneumonitis

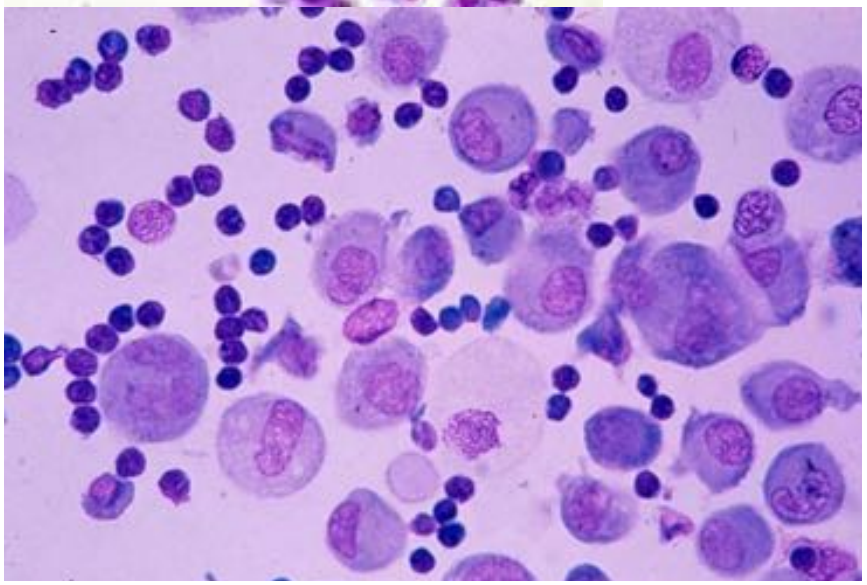
Bronchiolitis obliterans
TX- Bronchiolitis obliterans (OP)





Lymphocytic BAL





Lymphocytic pattern

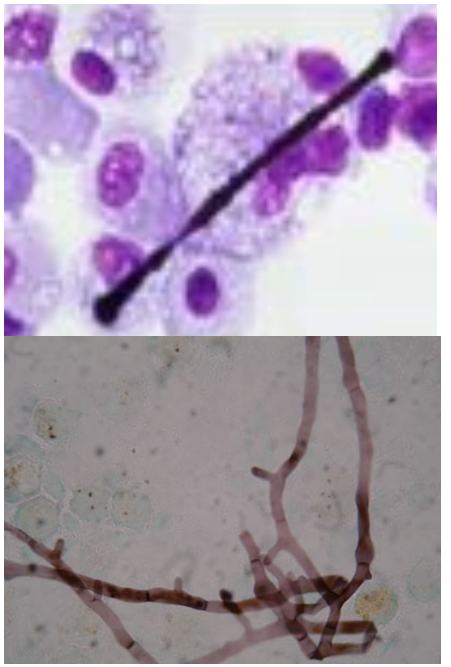
Hypersensitivity pneumonitis
Sarcoidosis
Beryllium-lung

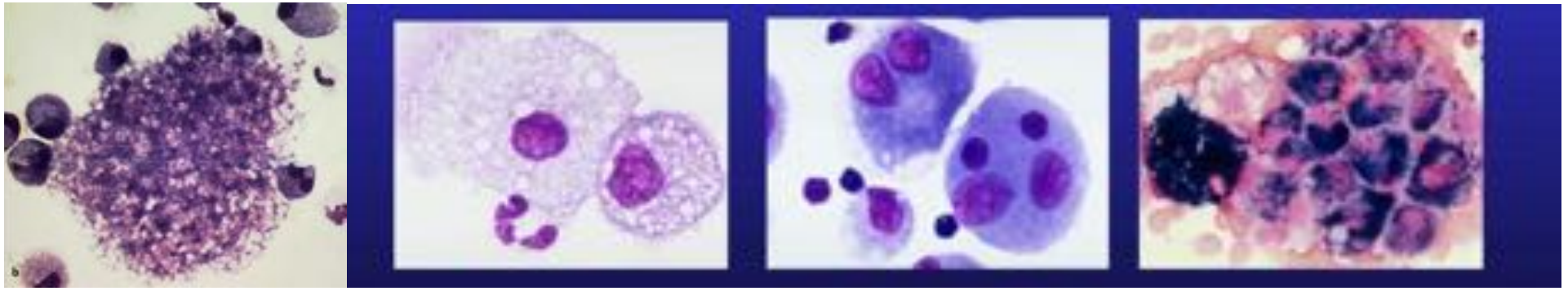
Tuberculosis
Lymphangiosis carcinomatosa
Acute allograft rejection

TX: **Viruses**
PTLD

Other diagnosis (made easily)

- Asbestosis
- Molds
- Malignant tumor cells
- Proteinosis (PAS)
- Pneumocystis jiroveci
- Ironloaded macrophages
- Activated pneumocytes

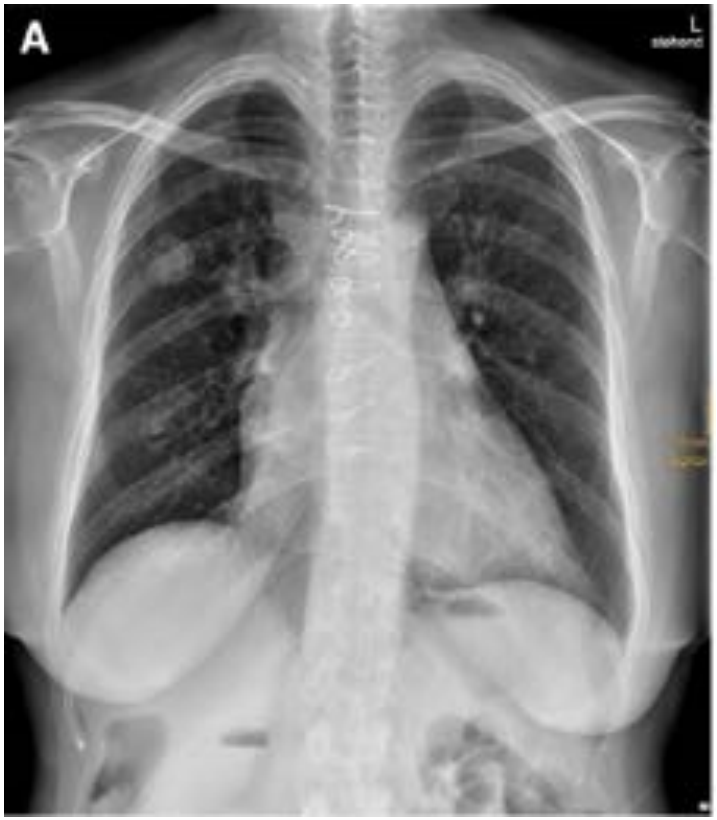


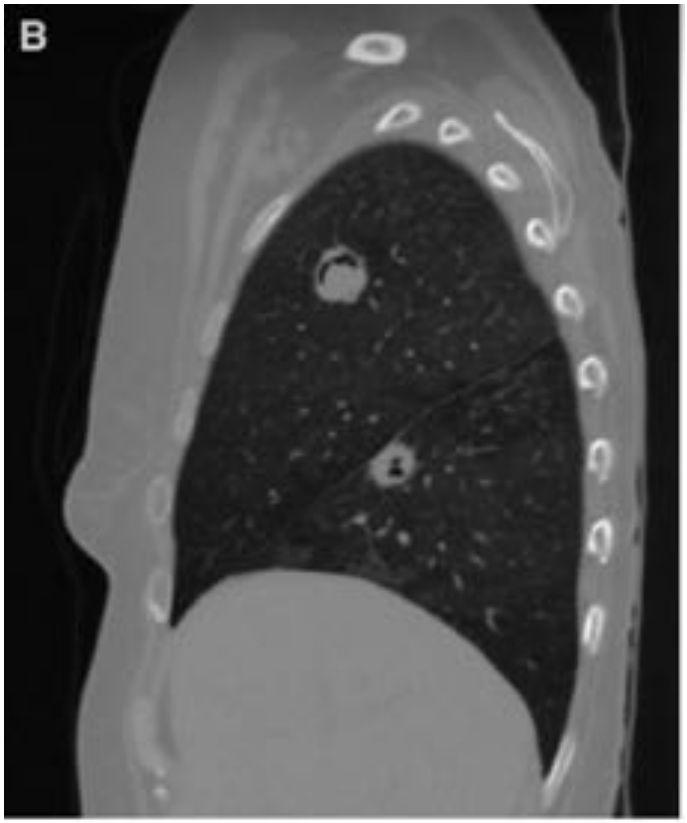


GM/PCR

- Galactomannan in BAL
  remains unclear, Sens 86%, Spez. 96% (Luong, 2010)
- PCR in BAL, similar
- Combination (Sens 97%, Spez 96%), (Avni, JCM, 2012)
- Compared to EORCT criteria critical (Affolter, AJRCCM, 2014)
- Not clear recommendation in case of surveillance in lung TX

CT guided biopsy





Lass-Flörl, Infection 2017

CT guided biopsy

Time period	2003–2006	2007–2010	2011–2014
Number of patients with proven lung infection	55[a]	43	29
Fungal pathogens identified			
Aspergillus species	42	38	5
A. terreus complex	24	19	1
A. fumigatus complex	18	16	1
A. flavus complex	0	1	1
Other species	0	2	2
Mucorales	5	12	18
Others	0	1	6
Main antifungal treatment strategies applied	Empirical and pre-emptive treatment[b]	Empirical and pre-emptive treatment[c]	Anti-mold prophylaxis[d]
Laboratory blood screening tests performed	*Aspergillus*-specific PCR	GM *Aspergillus*-specific PCR Panfungal PCR	None

GM galactomannan testing, *PCR* polymerase chain reaction

[a] Data obtained from few patients have been reported earlier in 2007 [9]

[b] Mainly, empirical treatment was undertaken applying amphotericin B or caspofungin

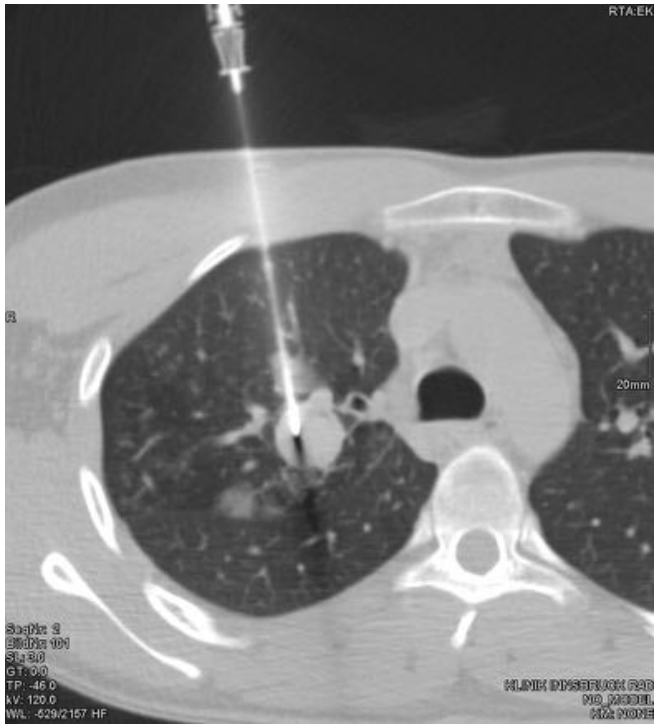
[c] Due to the extensive performance of polymerase chain reaction assays (various protocols) and GM blood screenings, pre-emptive treatment strategies with voriconazole and/or caspofungin were applied

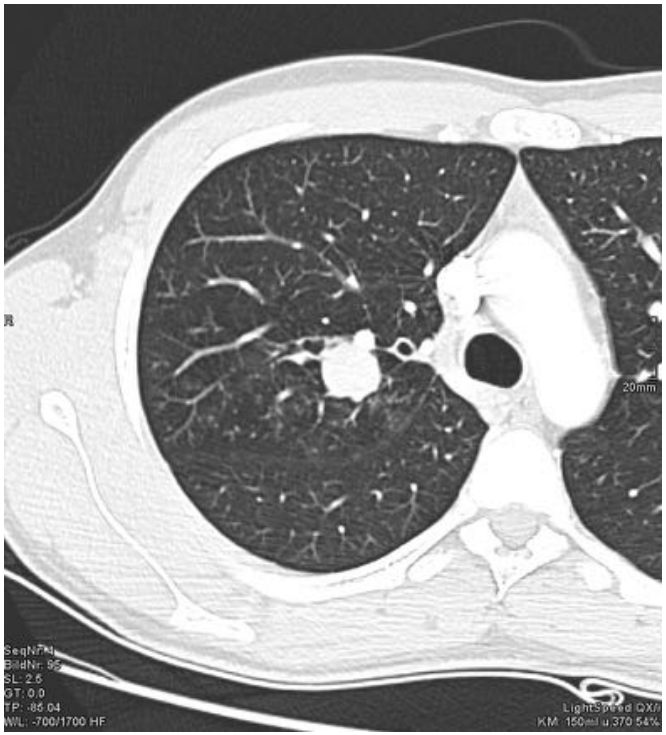
[d] Antifungal mold prophylaxis with micafungin and posaconazole was administered to patients at risk

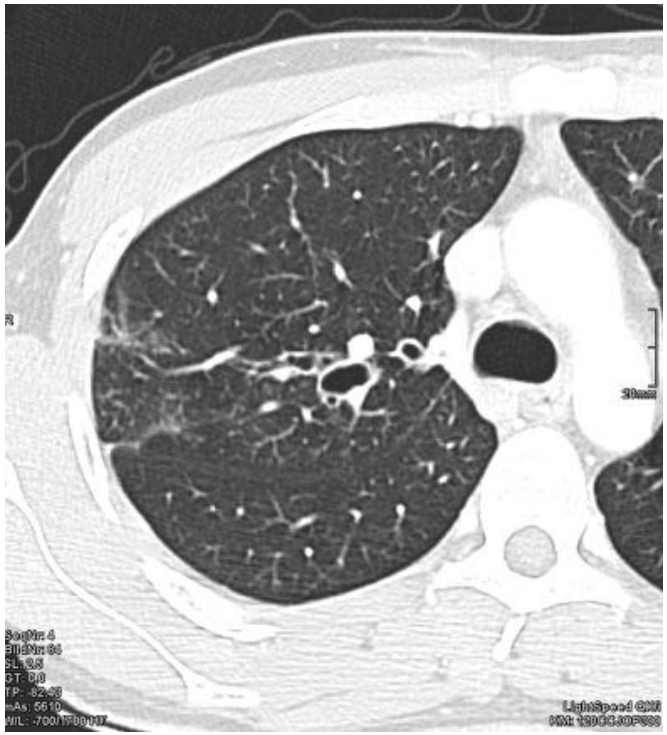
Lass-Flörl, Infection 2017

Saprophytic Aspergillosis

Aspergillus ball and bronchiectasis







CT guided biopsy

- High diagnostic value
- Low side effects
- Microscopic and cultural specimen
- Antigen and molecular based test on hyphae positive samples with high accuracy

Table 2 Genus and species identification from 127 fungal-positive lung biopsies obtained by CT-guided procedures

Species	No. of patients (%)
Aspergillus fumigatus complex	35 (27.5)
Aspergillus terreus complex	44 (34.6)
Aspergillus flavus complex	2 (1.5)
other *Aspergillus* species	4 (3.1)
Mucor sp.	11 (8.6)
Rhizomucor sp.	9 (7.0)
Rhizopus sp.	5 (3.9)
Lichtheimia corymbifera	6 (4.7)
Cunninghamella sp.	4 (3.1)
Scedosporium sp.	2 (1.5)
Penicillium sp.	3 (2.3)
Trichosporon sp.	2 (1.5)

Genus and species identification was obtained by culture and micromorphology typing or by applying PCR targeting the ITS techniques

Lass-Flörl, Infection 2017

Diagnostic accuracy

Table 3 Performance of various diagnostic assays in relation to fungal-positive lung biopsies obtained from invasive CT-guided interventions

Test assays	% Sensitivity	% Specificity	% PPV	% NPV
CT scan	100	44	80	100
Aspergillus PCR[a]	89	58	88	58
Broad-range fungal PCR[b]	90	83	95	90
GM[c]	94	83	95	90

PPV positive predictive value, *NPV* negative predictive value

CT-guided lung samples resulted from 127 patients and 24 control (negative) patients

[a] Over the last 12 years, we used various *Aspergillus*-specific PCR assays targeting the 18S ribosomal RNA

[b] We applied a broad-range PCR using the internal transcribed spacer region

[c] GM testing defined a cutoff value of 0.5

Lass-Flörl, Infection 2017

Registry – data
Innsbruck Lung Transplantation Program

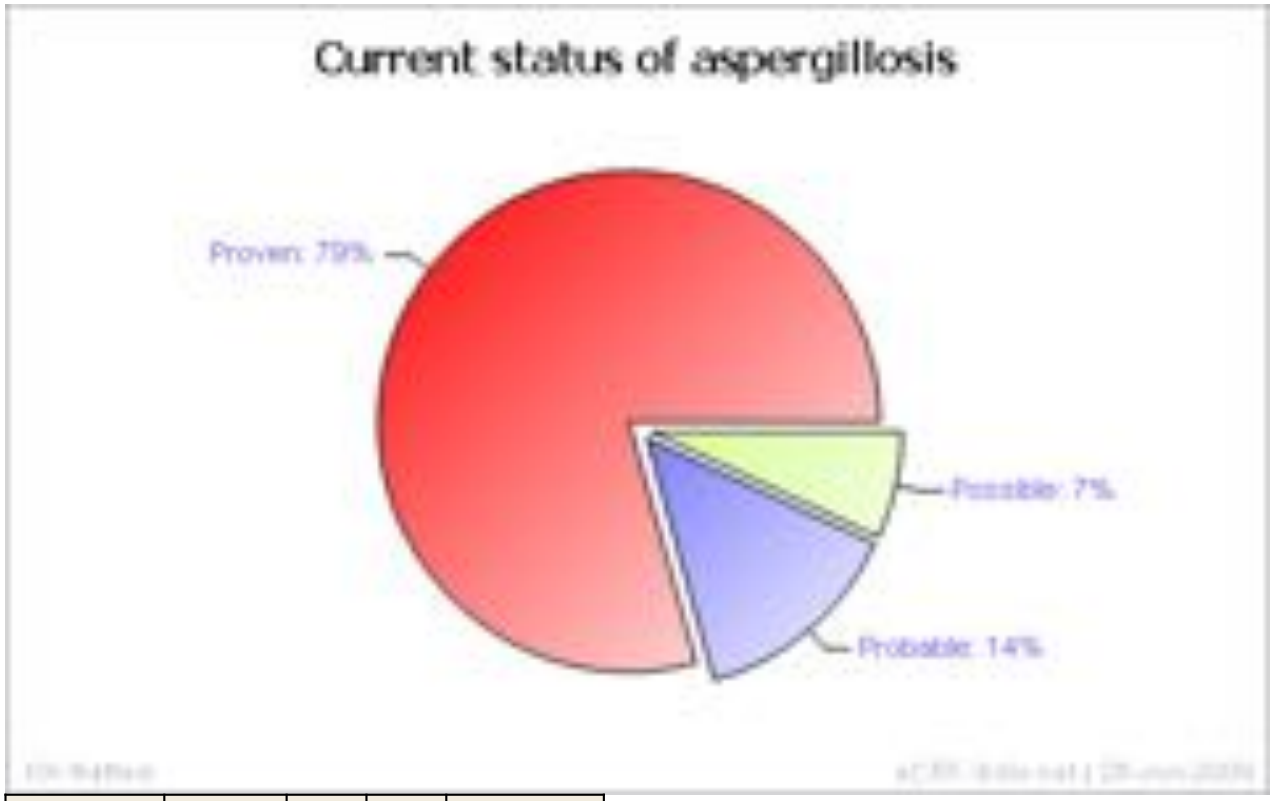
- 01/2008 bis 05/2009

- LungTX: 178
  von 01/2008 bis 05/2009: 21

- Immunsuppression: (routine)
  Daclizumab, Cyclosporin A (C0 300 – 350, after 3 mon 200 – 250)
  or tacrolimus,
  Mycophenolate mofetil (1g q12h)
  Prednisolon tapering

- Standard antimicrobial prophylaxis:
  Cephalosporines 4th generation/Tazobactam
  GCV, VGCV and immunoglobulin (Cytotect) 3 month after TX
  Inhalative Ampho B/ Liposomal Amphotericin
  trimethoprim/sulfa for 1 (to 5) year after TX

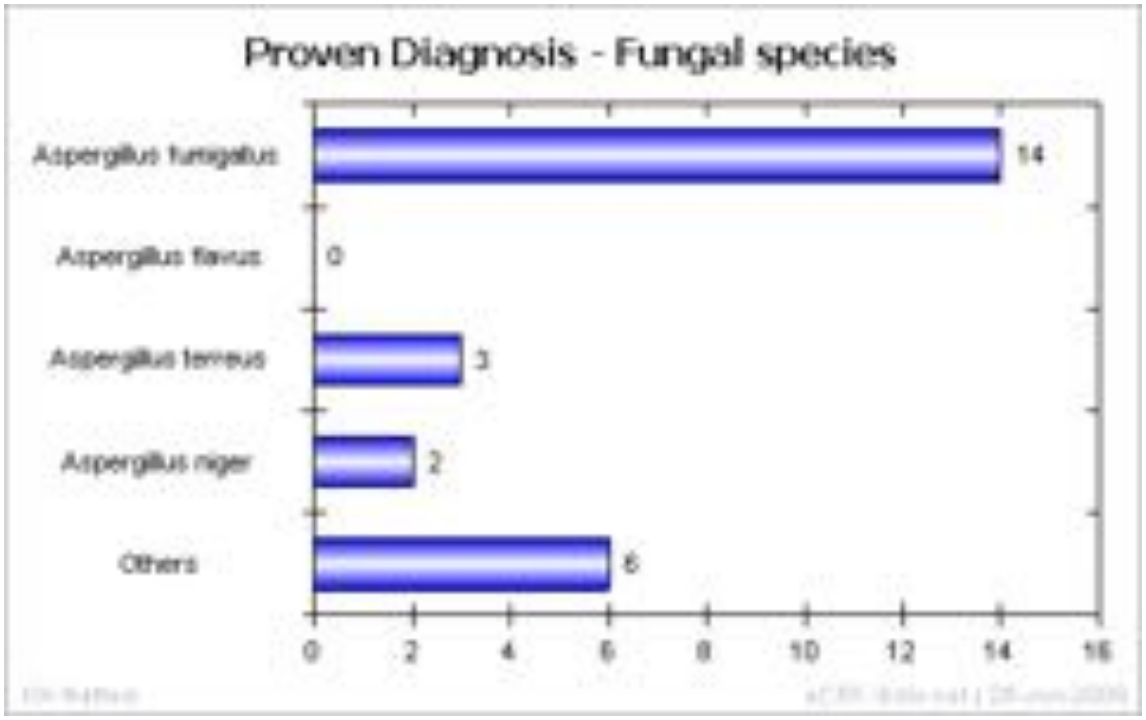
Status of IA



Label	Value	F	M	%
Possible	2	0	2	6,90%
Probable	4	3	1	13,79%
Proven	23	7	16	79,31%
Total	**29**	**10**	**19**	**100,00%**

Registry – Data – Innsbruck lung transplant program

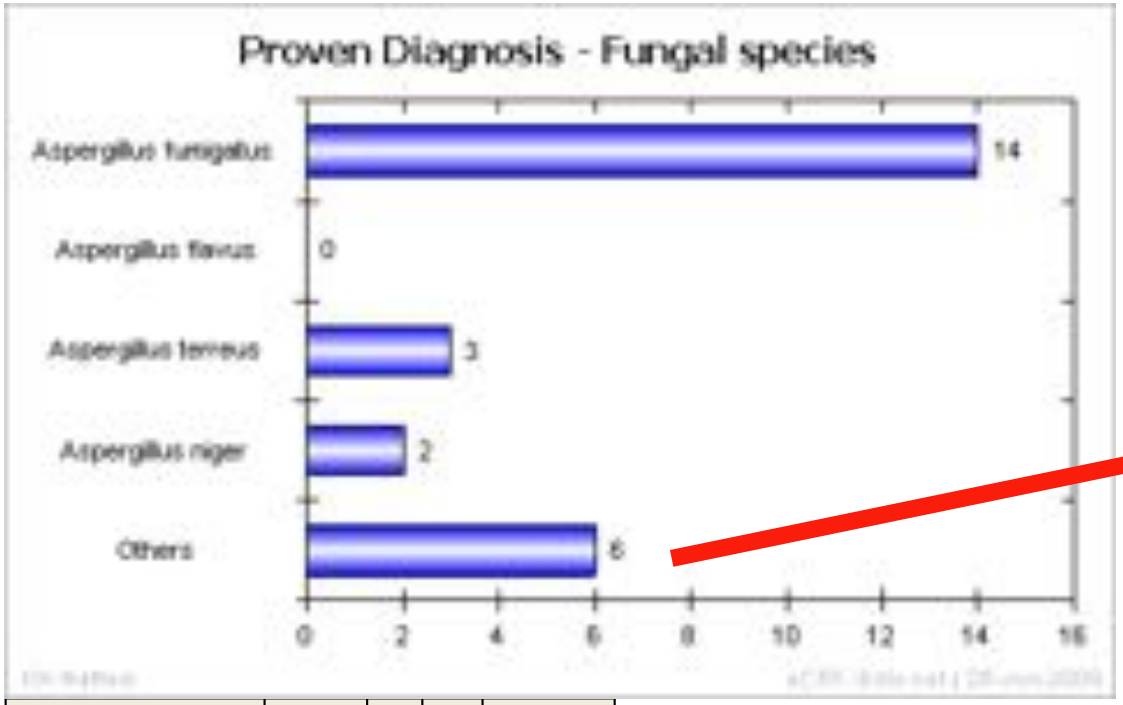
fungal species



Label	Value	F	M	%
Aspergillus fumigatus	14	0	0	56,00%
Aspergillus flavus	0	0	0	
Aspergillus terreus	3	0	0	12,00%
Aspergillus niger	2	0	0	8,00%
Others	6	0	0	24,00%
Total	**25**	**0**	**0**	**100,00%**

(22 Patients, 25 Rows)

fungal species – Non Aspergillus

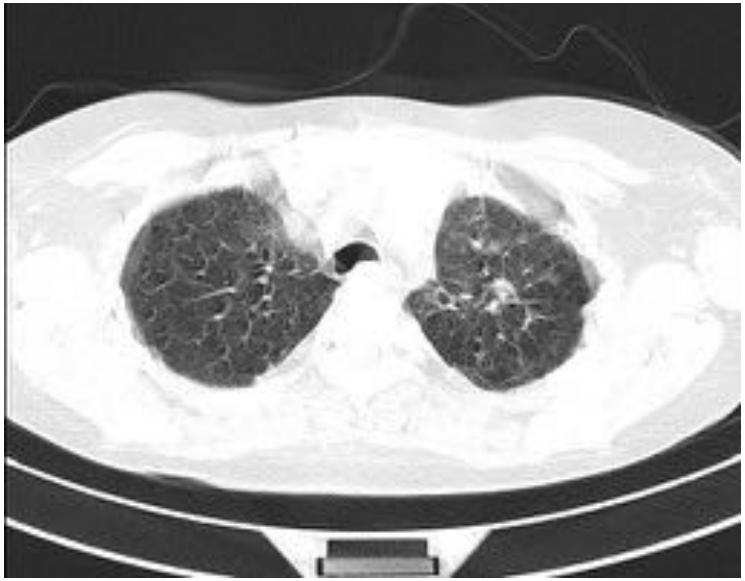


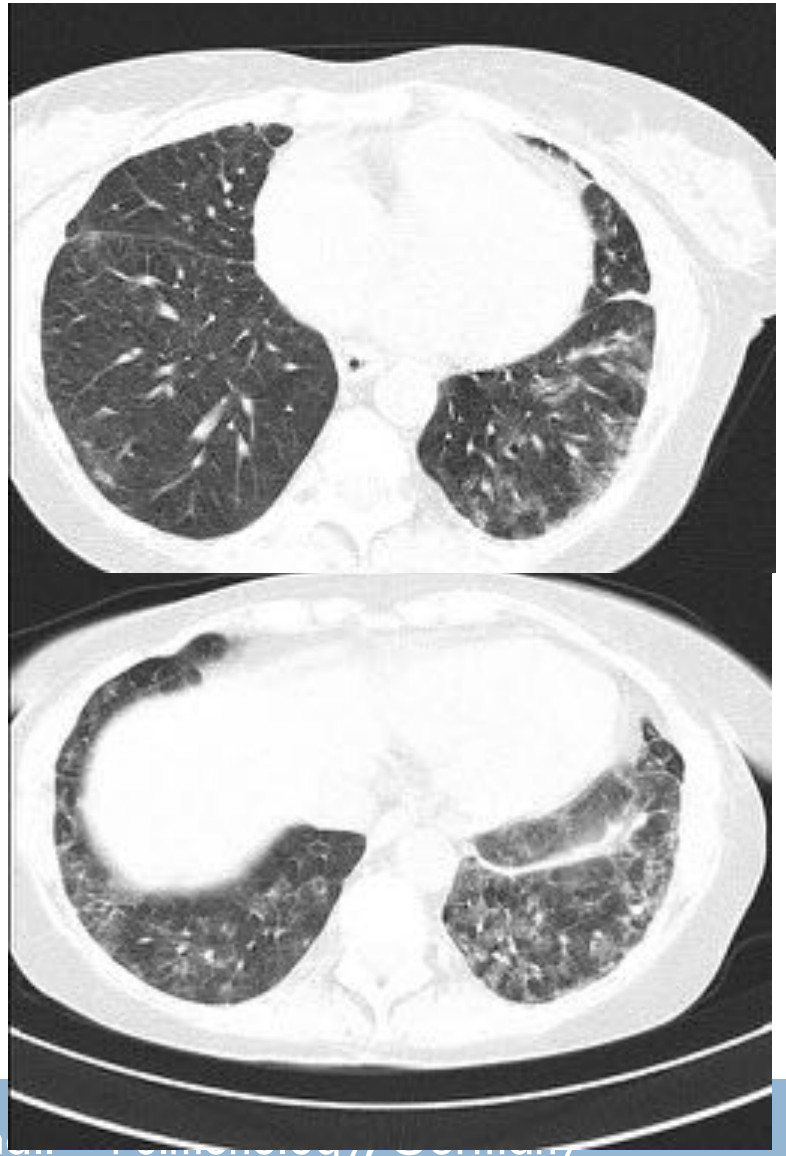
Label	Value	F	M	%
Aspergillus fumigatus	14	0	0	56,00%
Aspergillus flavus	0	0	0	
Aspergillus terreus	3	0	0	12,00%
Aspergillus niger	2	0	0	8,00%
Others	6	0	0	24,00%
Total	**25**	**0**	**0**	**100,00%**

(22 Patients, 25 Rows)

Penicillium crysogenes
Penicillium spp.
Absidia corymbifera
Scedosporium
Mucor

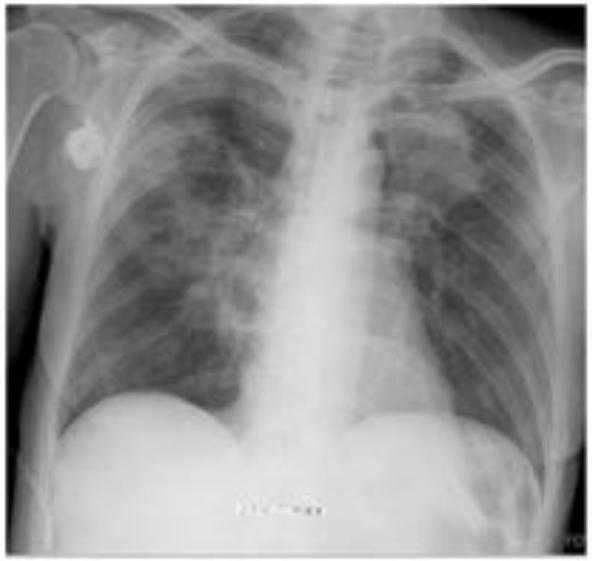
Proven IA after BLUTX

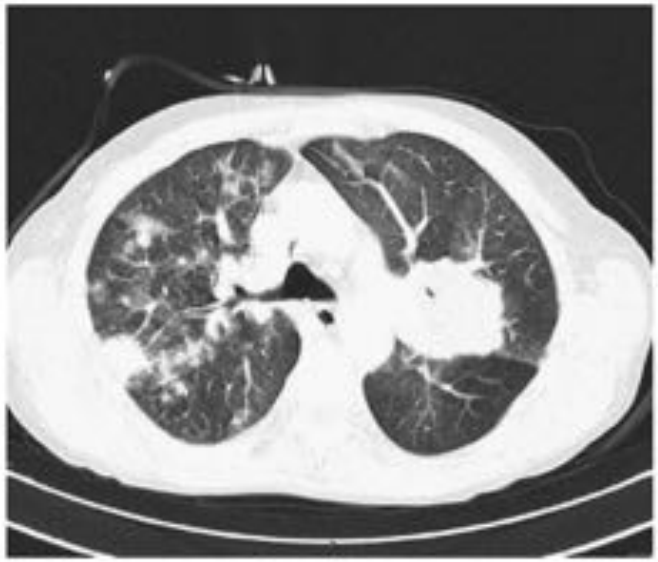




Pat., 49yrs, fem, BLUTX 01/2007, COPD,
steroidresistant rejection
Steroids and alemtuzumab (Mabcampath)
IA with A. fumigatus

„breaktrough infection“





Pat., 52yrs, fem, BLUTX 01/2008, COPD, 3 yrs after TX,
PTLD, treatment with rituximab 4 cycles, prophylaxis with posaconazole 3x 200mg,
Invasive mycosis (Absidia corymbifera)

Geltner, Respiratory Investigation,2016

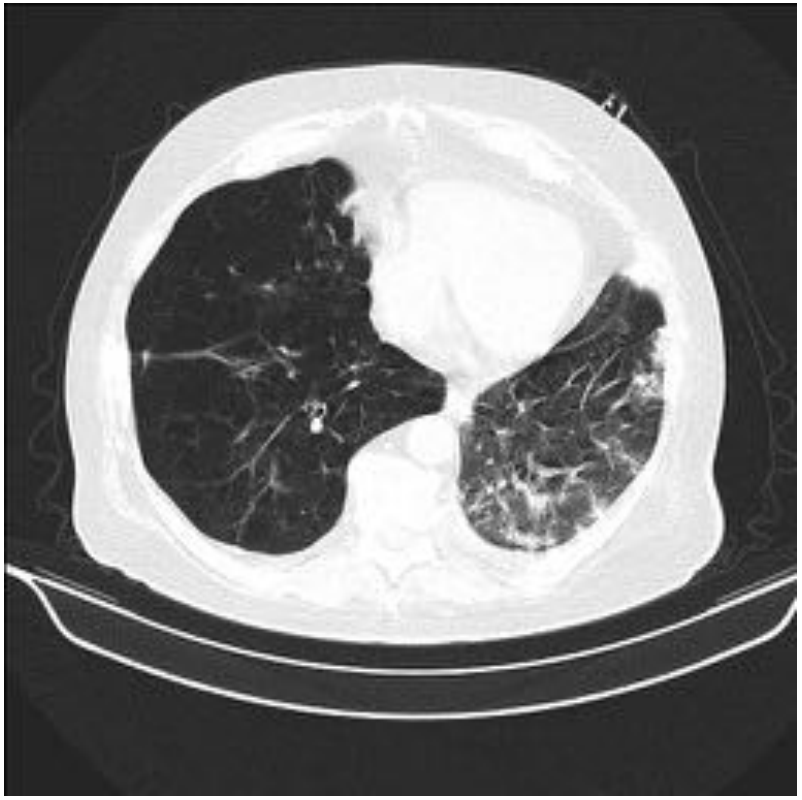
Non-Aspergillus fumigatus fungal Infections

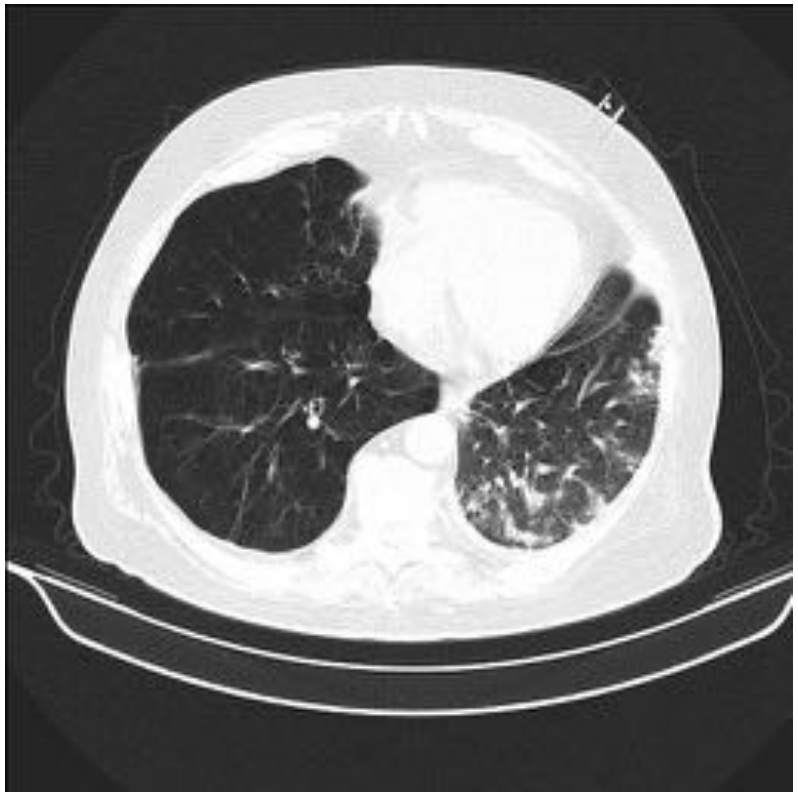
New fungi – new problems – shift to non-aspergillus species

- Stelzmüller, *Transplant International 2008*
  11/2898 SOT with non AFFI (0,4%)
  - Alternaria, Pseudoallescheria, Trichoderma
  - Zygomycets: Absidia, Mucor

- Geltner, *Abstract ERS 2009*
  Penicillium sp., Penicillium crysogenes
  Scedosporum
  Absidia corymbifera
  Mucor
  Trichoderma
  7 cases/6 Patients invasiv probable/proven
- Mattner, *ISHLT 2008*
  LungTX Hannover
  Emergence of Zygomycosis invasive, Penicillium sp mostly colonization (65 cases/580 LuTX !)

Proven IA after SLUTX





Pat., male, 54yrs: SLuTX left, Alpha 1 ZZ, NHL-PTLD 4 mo post TX,
Mabcampath (aemtuzumab)
Invasive mycosis with penicillium

Geltner, Transplantation 2013

Case: Penicillinosis after lungTX

- 54yr, male, SLUTX left, coin lesion, IA after inital therapy
- Microbiology:
  PENICILLIUM CRYSOGENUM
  invitro resistency (according to EUCAST methodology): amphotericin B 16 g/ml; voriconazole 0.025 g/ml; caspofungin 0.019 g/ml; posaconazole 0.025 g/ml.
- Therapy:
  Posaconazole und caspofungin
- Outcome:
  early improvement for 2 months, than worsening, recurrent disease and death

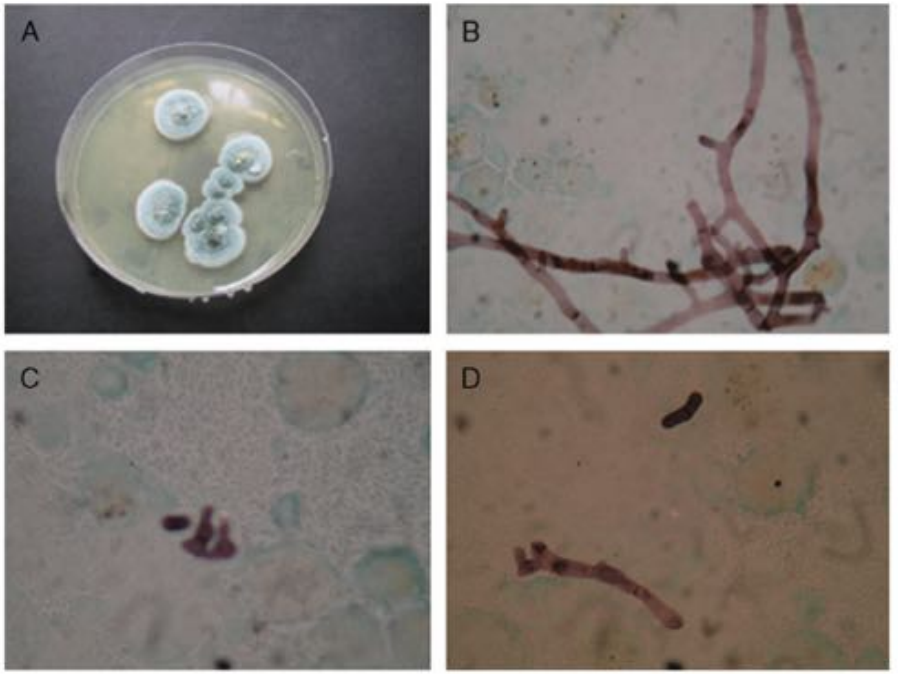


FIGURE 2. A, *P. chrysogenum* colonies on Sabouraud glucose agar. B–D, bronchoalveolar lavage with Grocott-Gomori's methenamine silver stain (magnification, ×400). Fungal elements appear as hyalin, thick, and septated mycelial fragments with 3–5 μm in diameter.

Geltner, Transplantation 2013

Zygomycoses

- Early reports:
  Rhinocerebral Mucormycosis (RCM)
  1995 kidneyTX (RCM)
  2003 Shift on lungTX (50% RCM)
  Hussain, Clin Infect Dis 2003
- High alert situation:
  - higher immunosuppression
  - emergence after introdution of voriconazole und echinocandines (mucormycetes are naturally resistent)
  - Therapy with Ampho + posaconazole
  - increasing azole resistance
- New developments: Isovuconazole

Prophylaxis in LuTX/SOT

- **Prophylaxis inhalative**
  Inhaled Antimycotics – LuTX
  (conventional ampho B, liposomal ampho B – ABLC)

  durance:
  - Standard (21d, 30d, **100d**, 365d)
  - till healing of anastomoses
  - augmented immunosuppresion (alemtuzumab, rituximab, OKT3)
- **Prophylaxis peroral** all SOTs ?
  Voriconazole (4mg/kg/bid) for 3 to 12 month
  (Itraconazole)
  Posaconazole (interaction with immunosuppressive drugs)
  fluconazole not recommended
- **INTENSIVE MONITORING**
  Bronchoscopy – BAL +/- TBB
  PCR questionable, GM
- Prophylaxis at time of infection (34%), emergence of resistant molds and breakthrough infections

Therapy

Therapeutic considerations

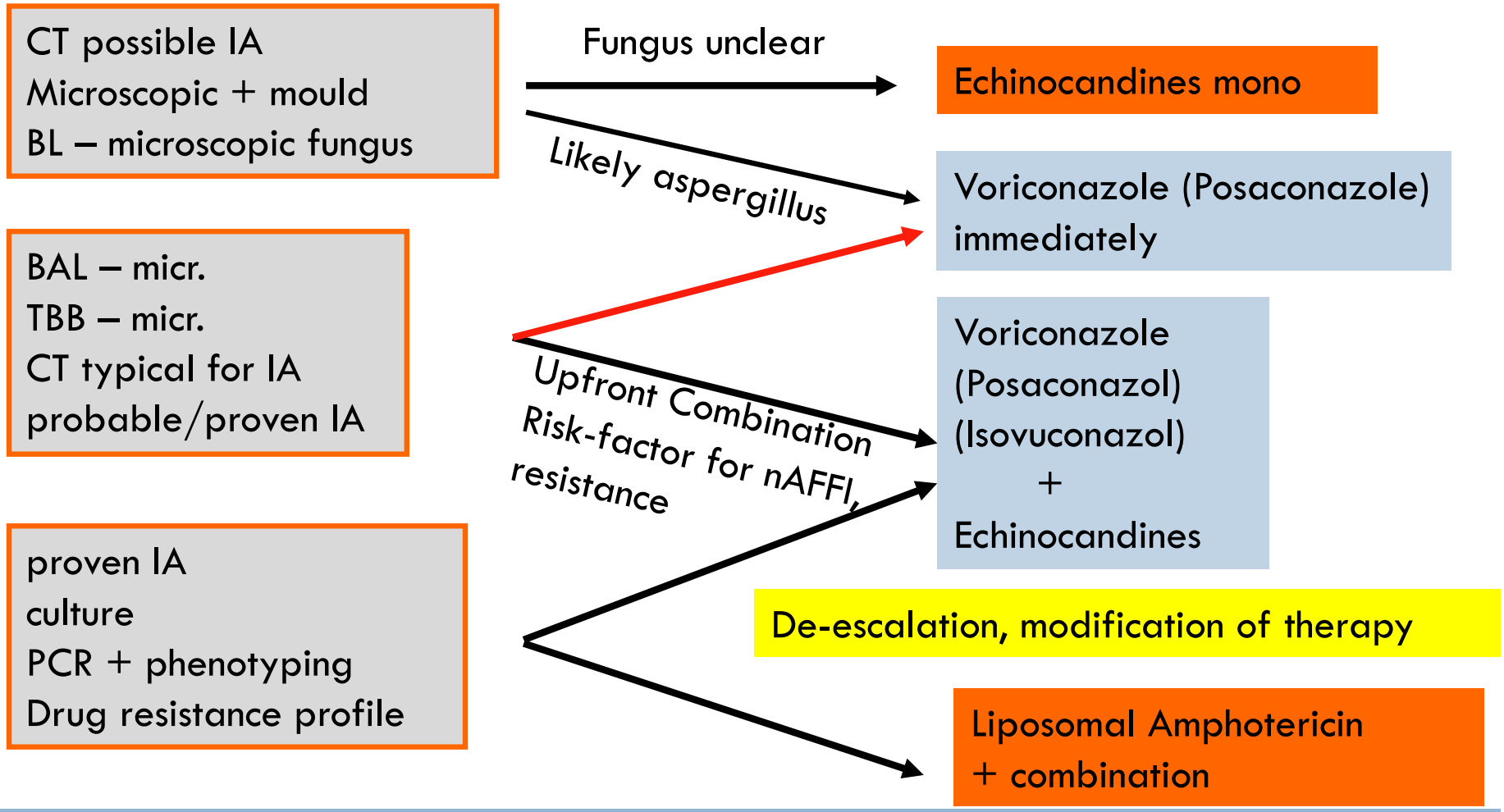
- Depending on local epidemiology

  i.e.: Innsbruck:
  24% non-aspergillus fumigatus molds
  high incidence of aspergillus terreus, zygomycetes

  i.e: Hannover (Mattner, 2007, 2008)
  20-30% Non-Aspergillus
  high incidence of aspergillus flavus

- Strategy of prophylaxis
- Incidence of resistant molds (stategy of previous therapy)

Therapeutic - algorythm



Conclusions

- Incidence of aspergillosis in patients:
  LuTX > AlloHSCT > AutoHSCT > SOT (kidney, liver, heart)
- Risk factors: Viral infection (CMV), Rejection, augmented immunotherapy
- Incidence in Lung transplants: up to 30%
- Lung transplants: necrotizing bronchitis is a unique entity
- Mortality in lung transplants 16% (– 30%)
- Shift to non-aspergillus molds and azole resistant molds (Mucormycosis, Penicillium)
- **Local epidemiology !!**
- **Surveillance !!!**

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