Geert M. Verleden, MD, PhD, FERS
Medical Director
Leuven Lung Transplant Program

# CHRONIC LUNG ALLOGRAFT DYSFUNCTION: WHAT IS IT NOWADAYS?

# History of BOS ...

- **A working formulation for the standardization of nomenclature and for clinical staging of Chronic Dysfunction in Lung Allografts. International Society for Heart and Lung Transplantation.**

**TABLE I** Original and proposed classifications of BOS

| Original classification | | Current proposition | |
|---|---|---|---|
| BOS 0 | $FEV_1$ 80% or more of baseline | BOS 0 | $FEV_1$ > 90% of baseline and |
| BOS 1 | $FEV_1$ 66% to 80% of baseline | BOS 1 | $FEV_1$ 66% to 80% of baseline |
| BOS 2 | $FEV_1$ 51% to 65% of baseline | BOS 2 | $FEV_1$ 51% to 65% of baseline |
| BOS 3 | $FEV_1$ 50% or less of baseline | BOS 3 | $FEV_1$ 50% or less of baseline |

BOS, bronchiolitis obliterans syndrome; $FEF_{25-75}$, mid-expiratory flow rate; $FEV_1$, forced expiratory volume in 1 second.

Cooper J et al. J Heart Lung Transplant 1993; 12: 713-716.

# BOS update…

**TABLE I** Original and proposed classifications of BOS

| Original classification | | Current proposition | |
|---|---|---|---|
| BOS 0 | $FEV_1$ 80% or more of baseline | BOS 0 | $FEV_1 > 90\%$ of baseline and $FEF_{25-75} > 75\%$ of baseline |
| | | BOS 0-p | $FEV_1$ 81% to 90% of baseline and/or $FEF_{25-75} \leq 75\%$ of baseline |
| BOS 3 | $FEV_1$ 50% or less of baseline | BOS 3 | $FEV_1$ 50% or less of baseline |

BOS, bronchiolitis obliterans syndrome; $FEF_{25-75}$, mid-expiratory flow rate; $FEV_1$, forced expiratory volume in 1 second.

Estenne et al. J Heart Lung Transplant 2002; 21: 297-310.

# 2nd revised BOS update....

**AN INTERNATIONAL ISHLT/ATS/ERS CLINICAL PRACTICE GUIDELINE: *DIAGNOSIS AND MANAGEMENT OF BRONCHIOLITIS OBLITERANS SYNDROME***

**Chair:**

- Keith C. Meyer, MD, MS, University of WI School of Medicine and Public Health, Madison, WI, USA

**Co-Chairs:**

- Ganesh Raghu, MD, University of Washington School of Medicine, Seattle, WA, USA
- Geert Verleden, MD, University of Leuven, Belgium
- Paul Corris, MD, Freeman Hospital, Newcastle upon Tyne, UK
- Allan Glanville, Sydney, Australia
- Paul Aurora, MD, MRCP, PhD, Great Ormond Street Hospital for Children, London, UK
- Jim J. Egan, MD, Dublin, Ireland

Meyer KC, Raghu G, Verleden GM et al. Eur Respir J 2014; 44: 1479-503.

# Up to now…

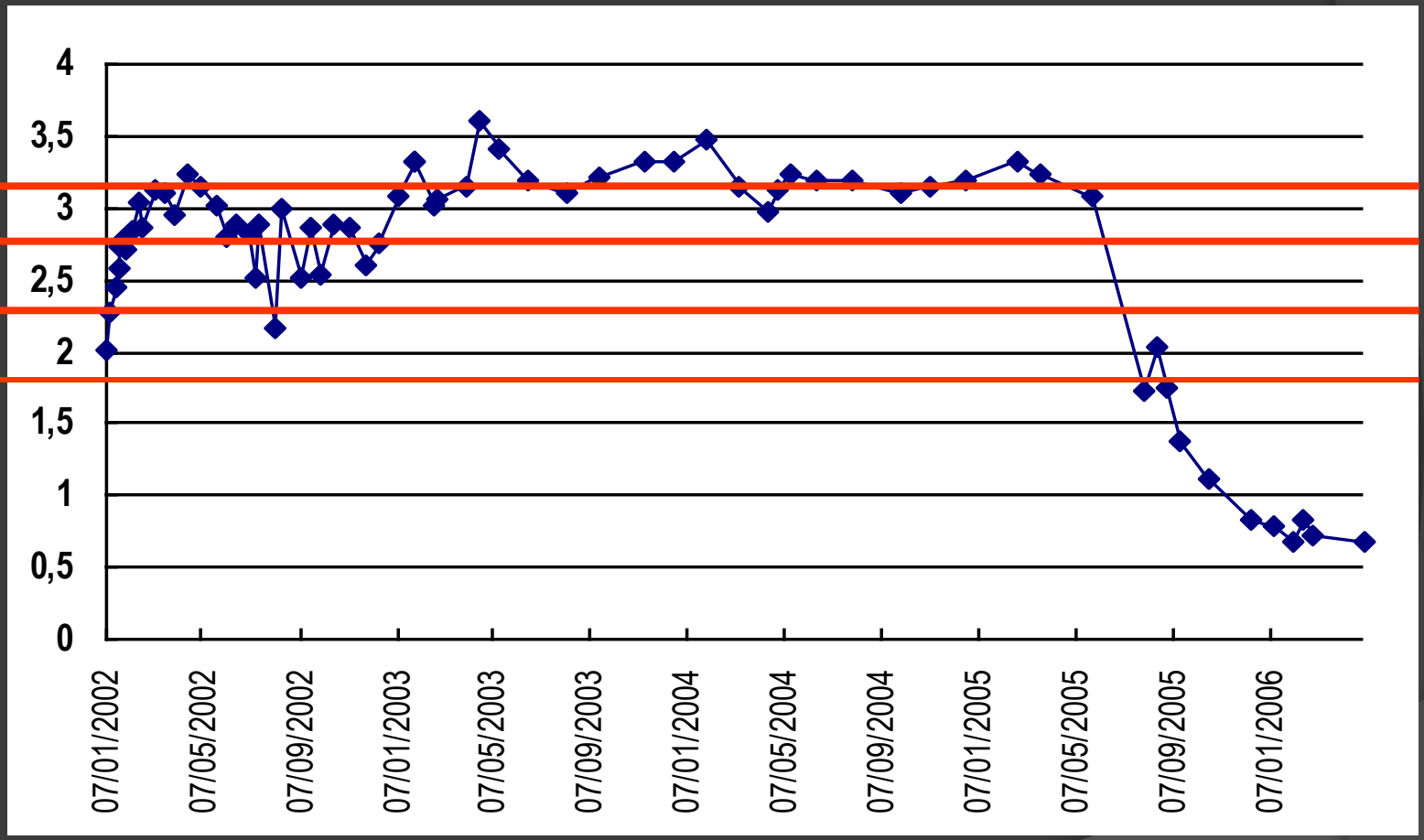
- BOS diagnosis based on
  - Obstructive spirometry
  - Usually non-reversible
  - Usually progressive
  - Several established risk factors

**Risk factors for the development of BOS**

Primary graft dysfunction
Acute cellular rejection
Lymphocytic bronchiolitis
Antibody-mediated rejection (e.g. de novo donor specific anti-human leukocyte antigen antibodies)
Gastro-oesophageal reflux and microaspiration
Infections/colonization
Persistent neutrophil influx and sequestration
Autoimmunity (e.g. collagen V sensitisation)
Air pollution
Genetic factors

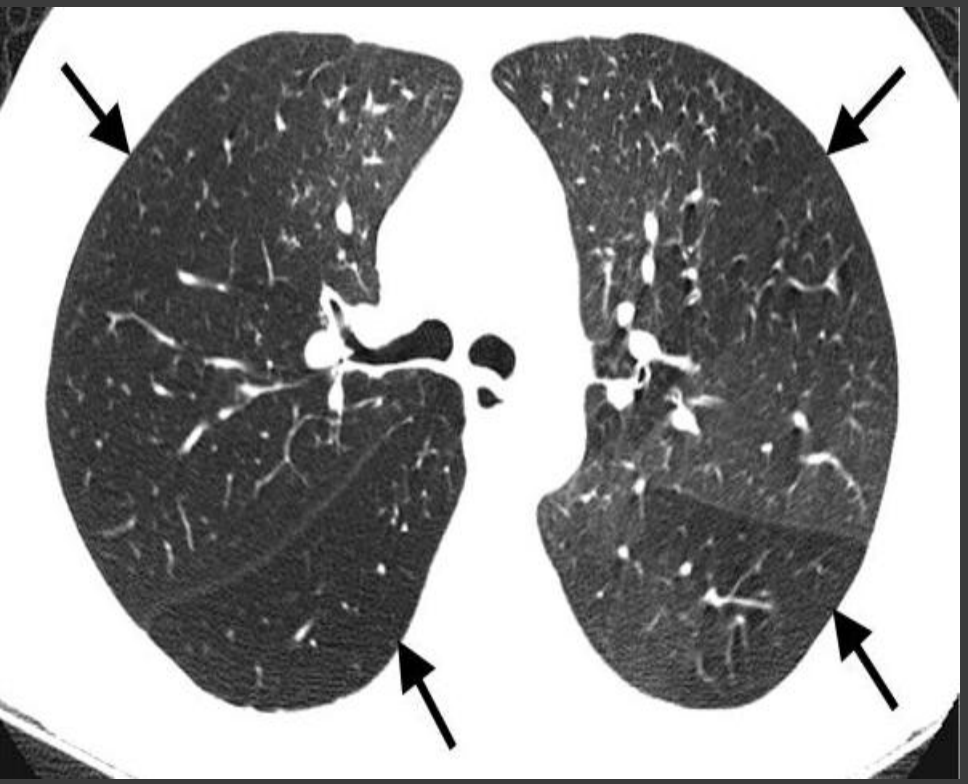
Verleden GM et al. Transplant Int 2015, in press

FEV1, L

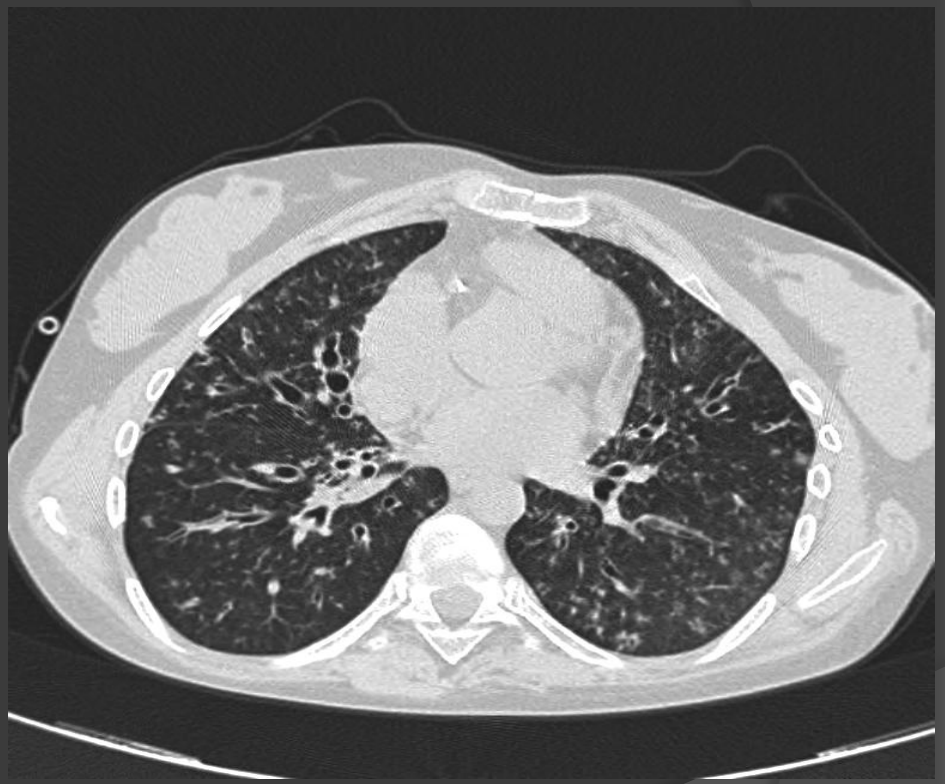



Postoperative time

# CAT scan

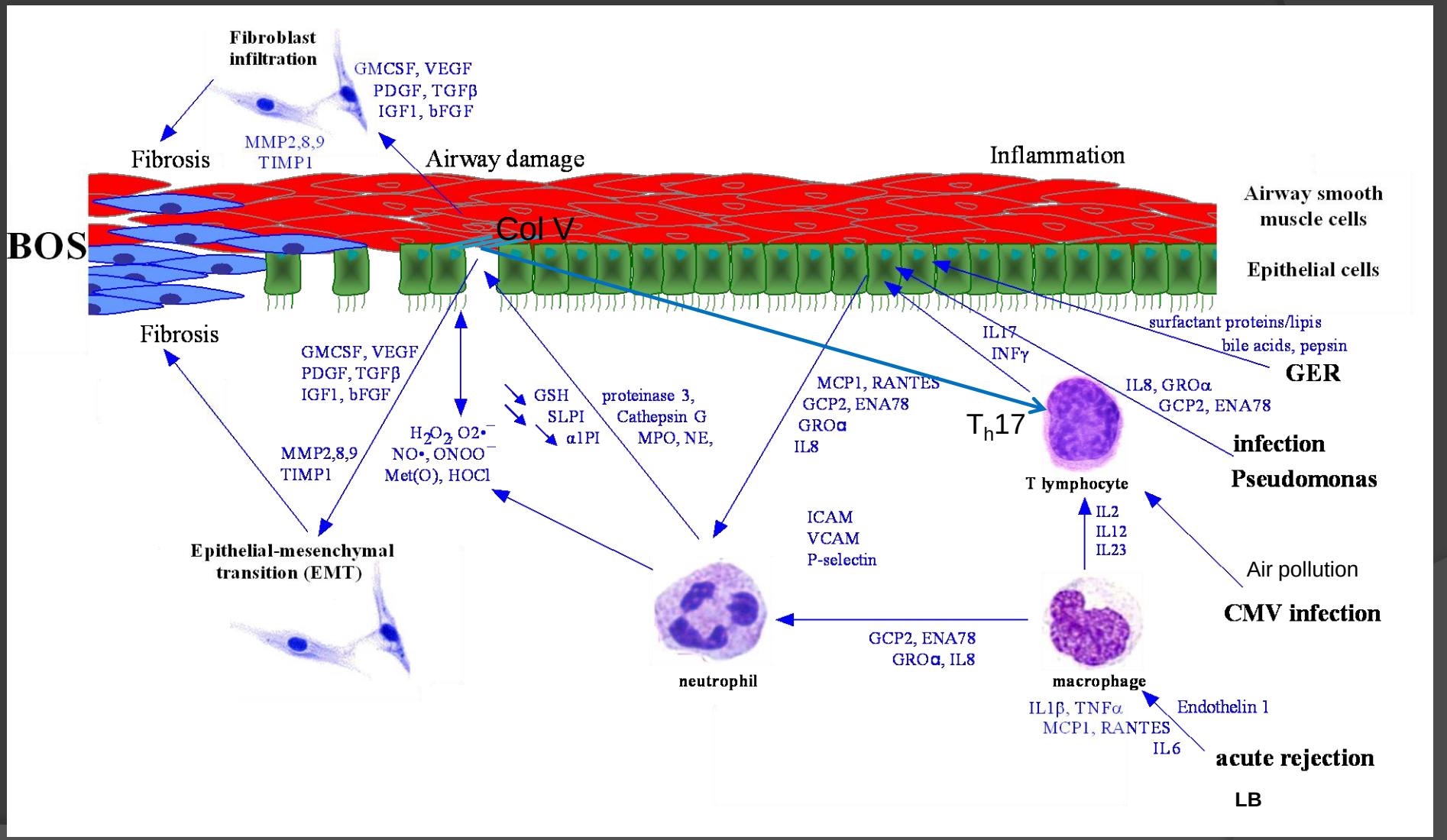


expiratory air trapping



bronchiectasis/tree-in-bud

# Pathophysiology of BOS

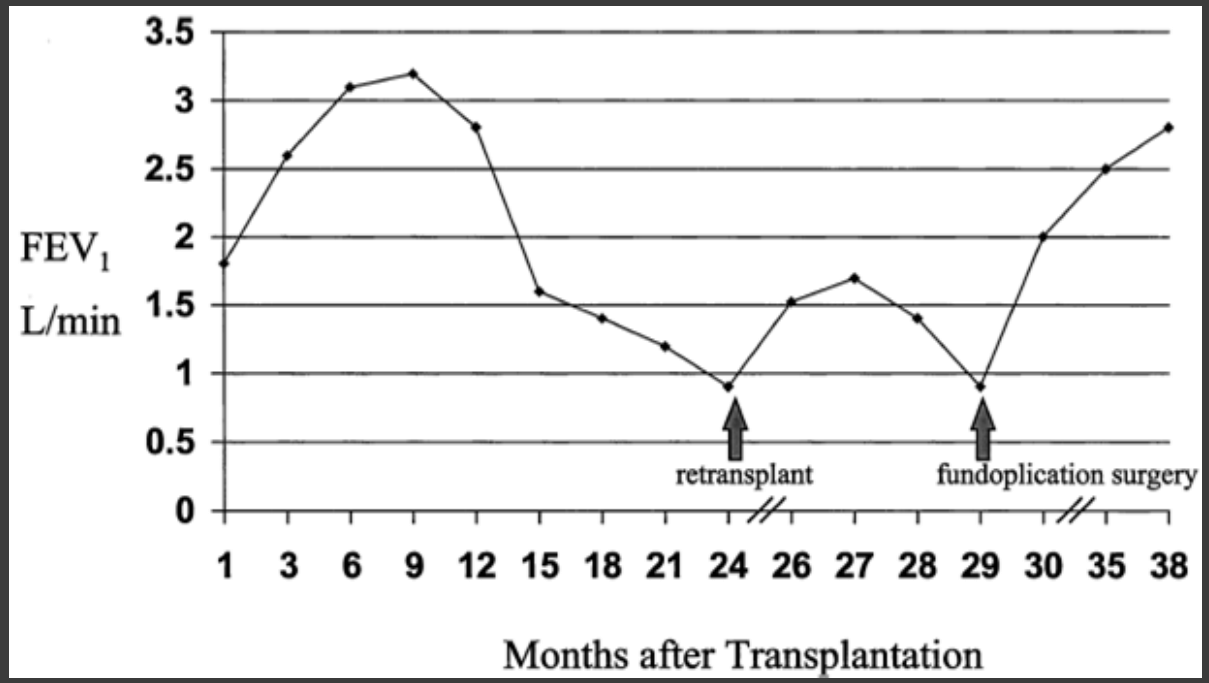



Adapted from Vanaudenaerde et al. Inflamm Allergy Drug Targets 2008;7:279-87.

# Upcoming problems with current BOS definition

- Reversibility/normalisation of pulmonary function with specific treatments resulting in survival differences after BOS diagnosis

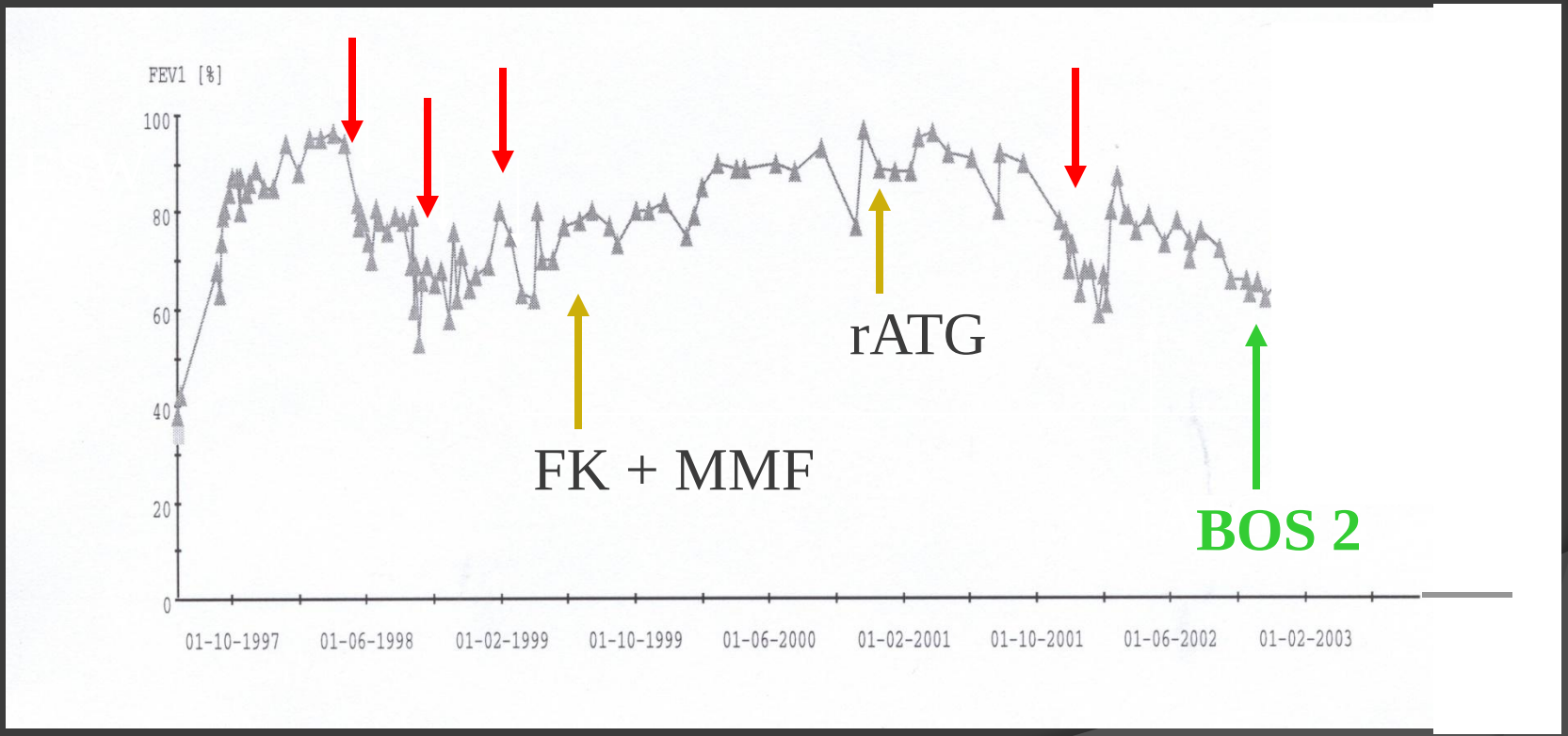
# Role of fundoplication




- case report of 23 y old male with CF
- reversible "allograft dysfunction"
  - bronchiectasis in lower lung lobes
  - **no OB on biopsy**

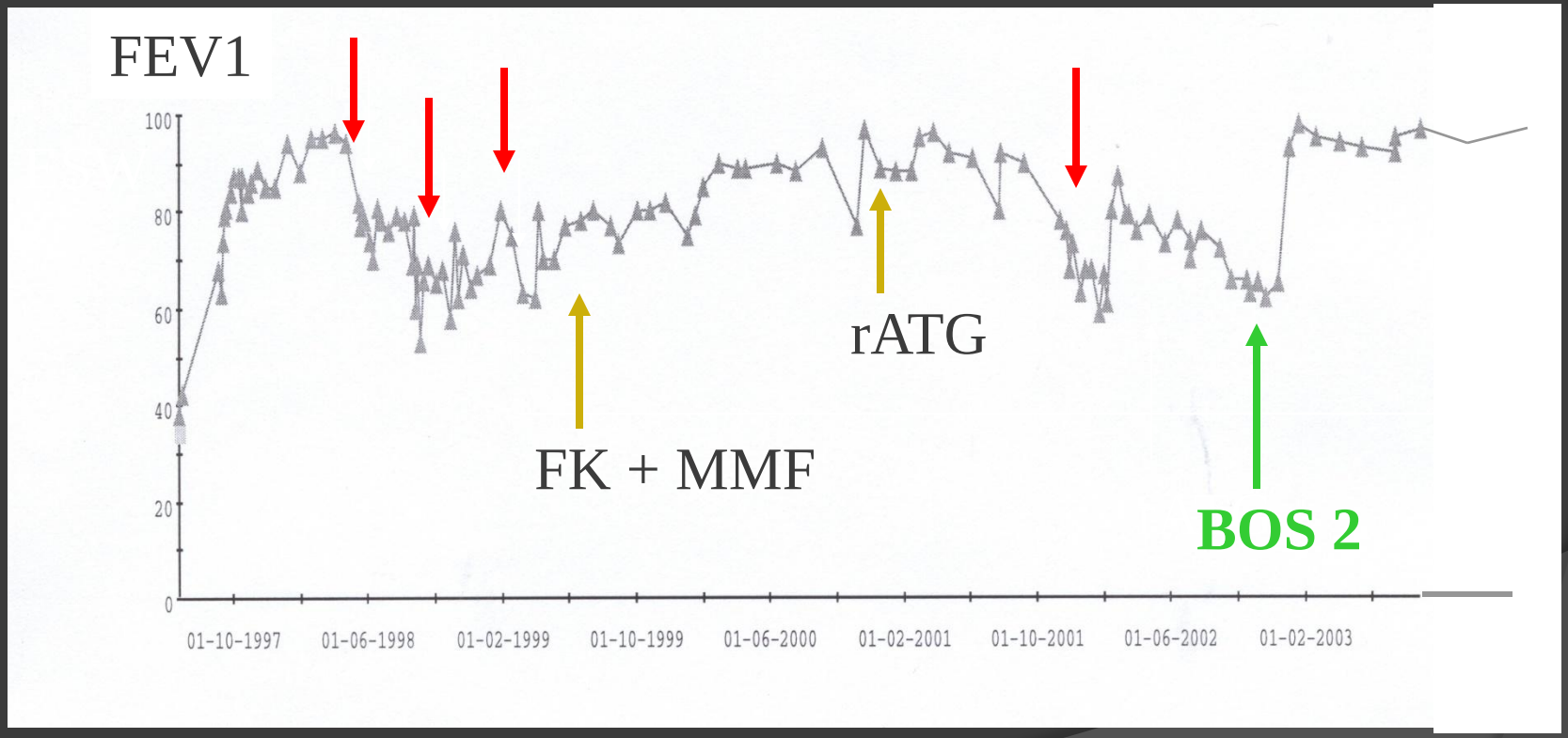
Palmer et al. Chest 2000.

# Introduction of azithromycin



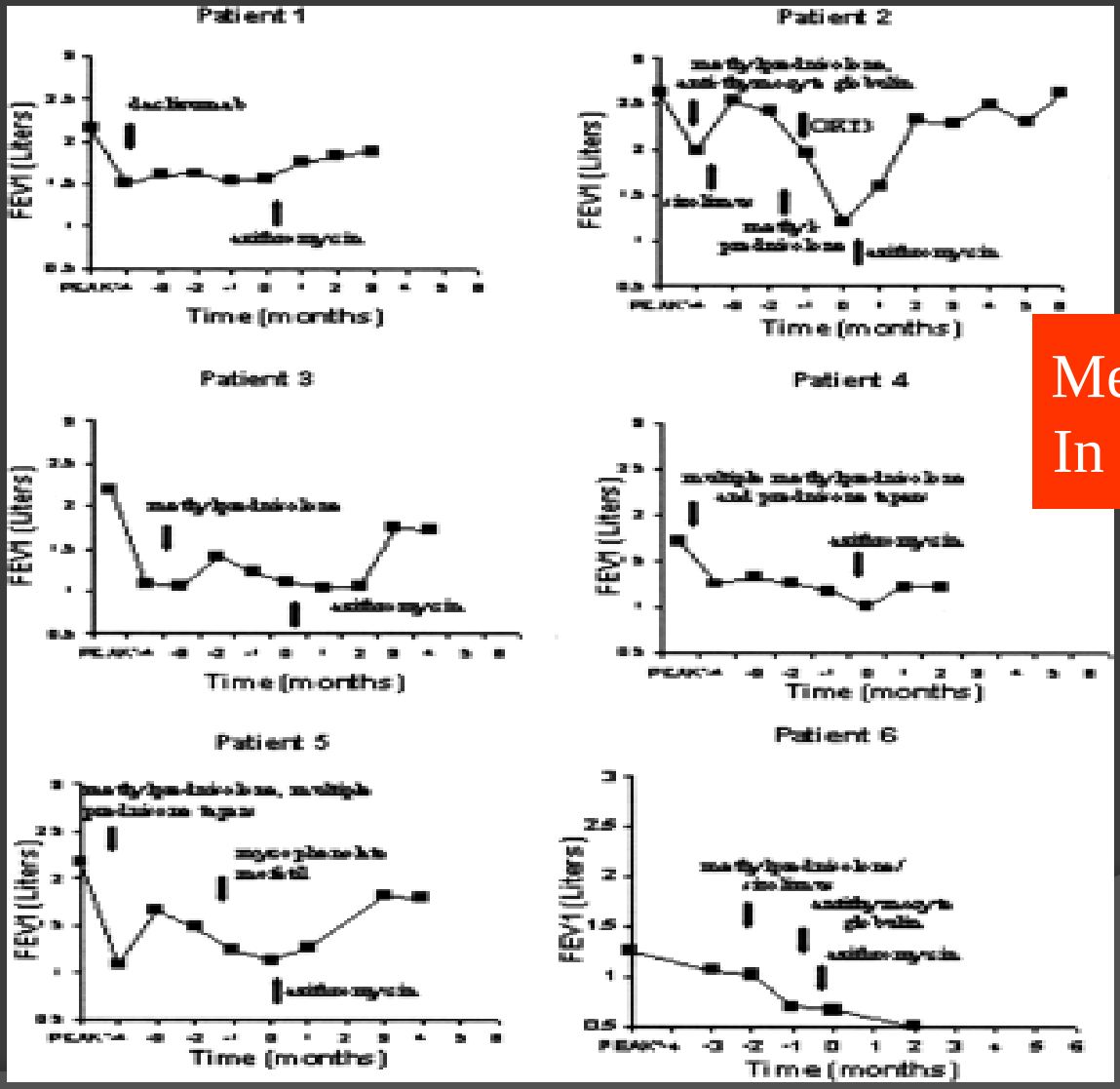

Time after HLTx

Verleden et al. Eur Respir J 2005




Time after HLTx

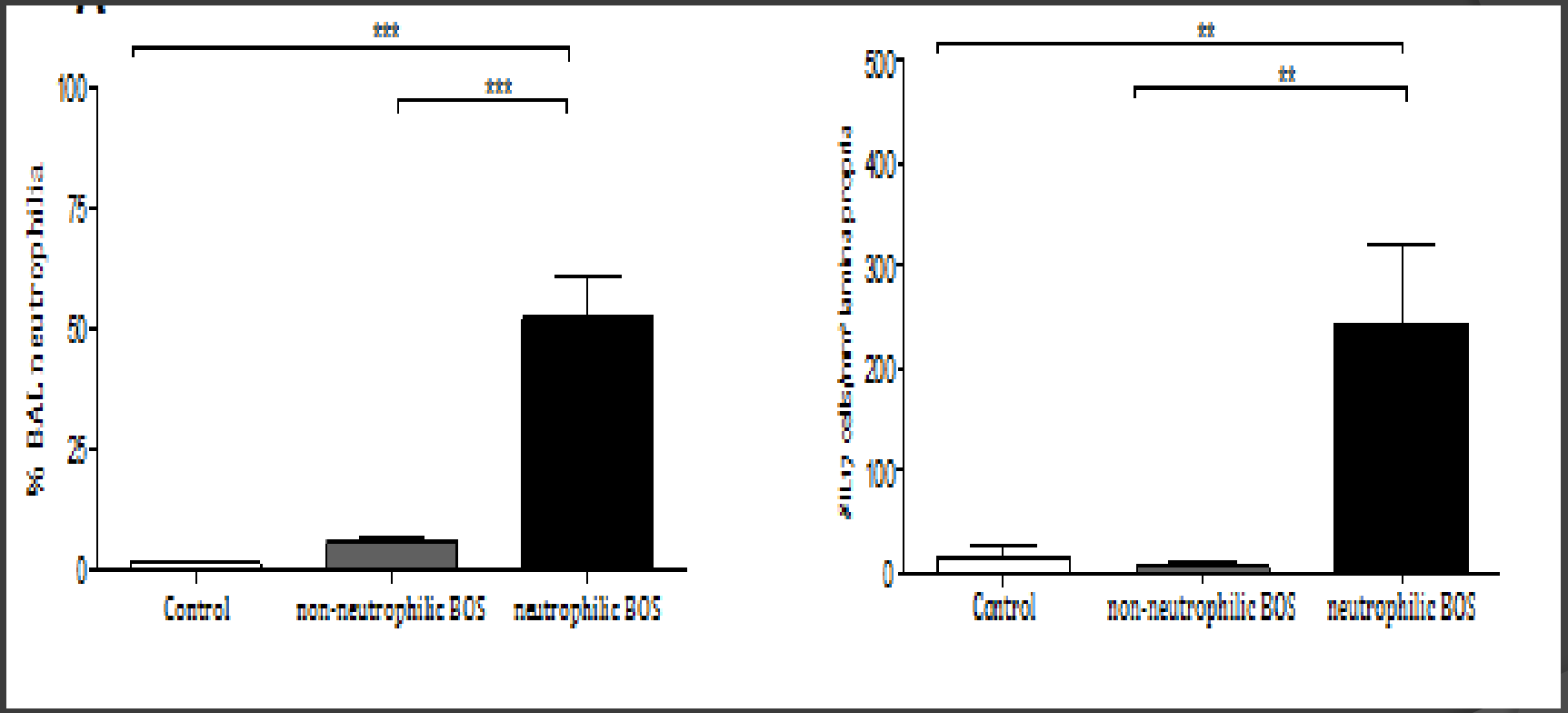
# Role of azithromycin




Mean increase
In FEV1: **17%**

Gerhardt et al. AJRCCM, 2003

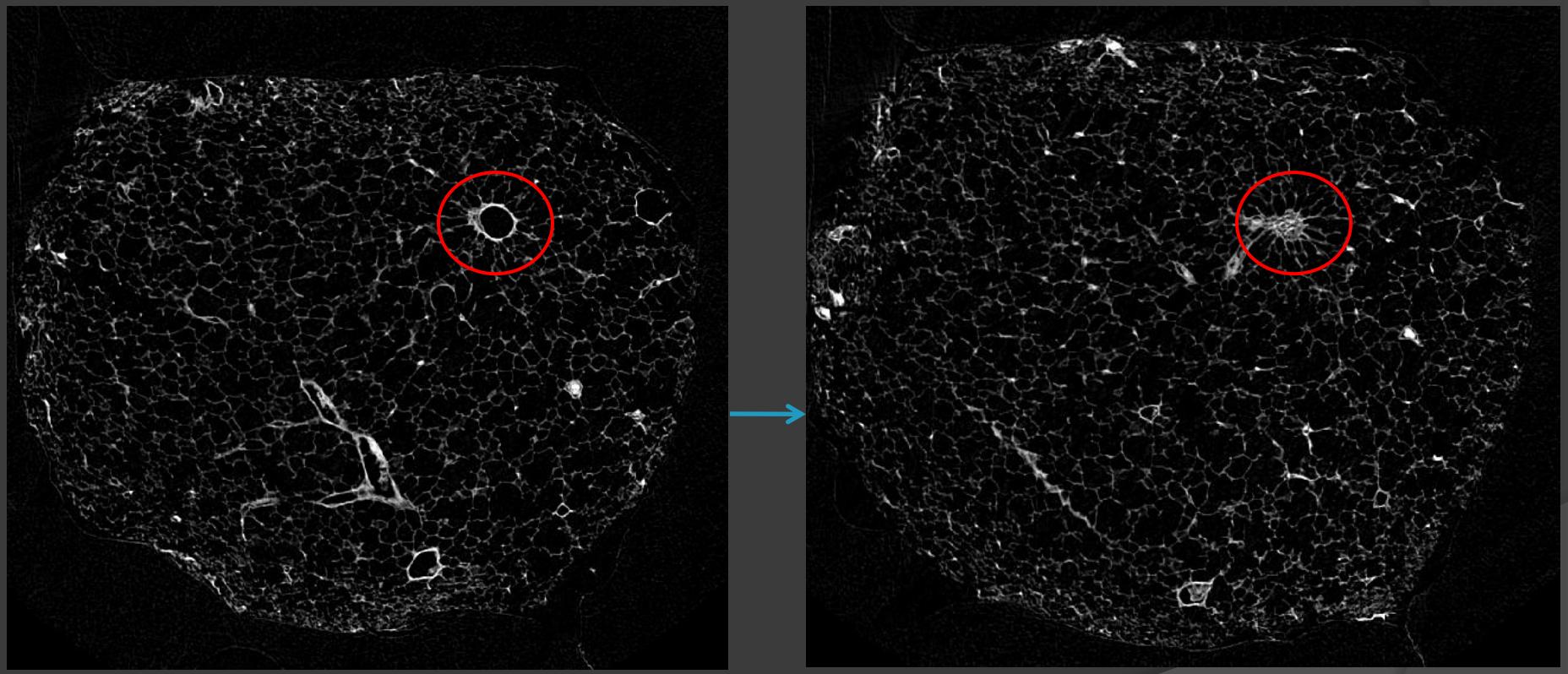
# Role of BAL NF and IL17 in BOS




Correlation % BAL NF and IL-17 + Cells
R=0.39
P=0.03

Verleden S et al. JHLT 2013; 32:447–453

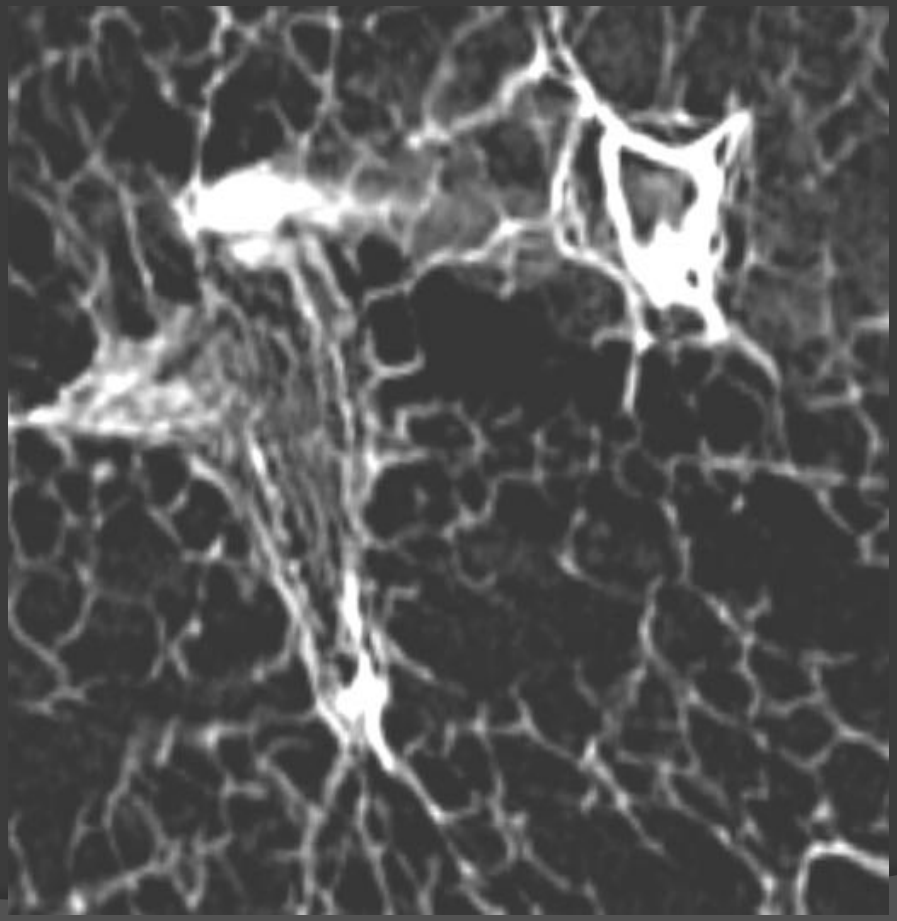
# BOS/OB
# microCT analysis



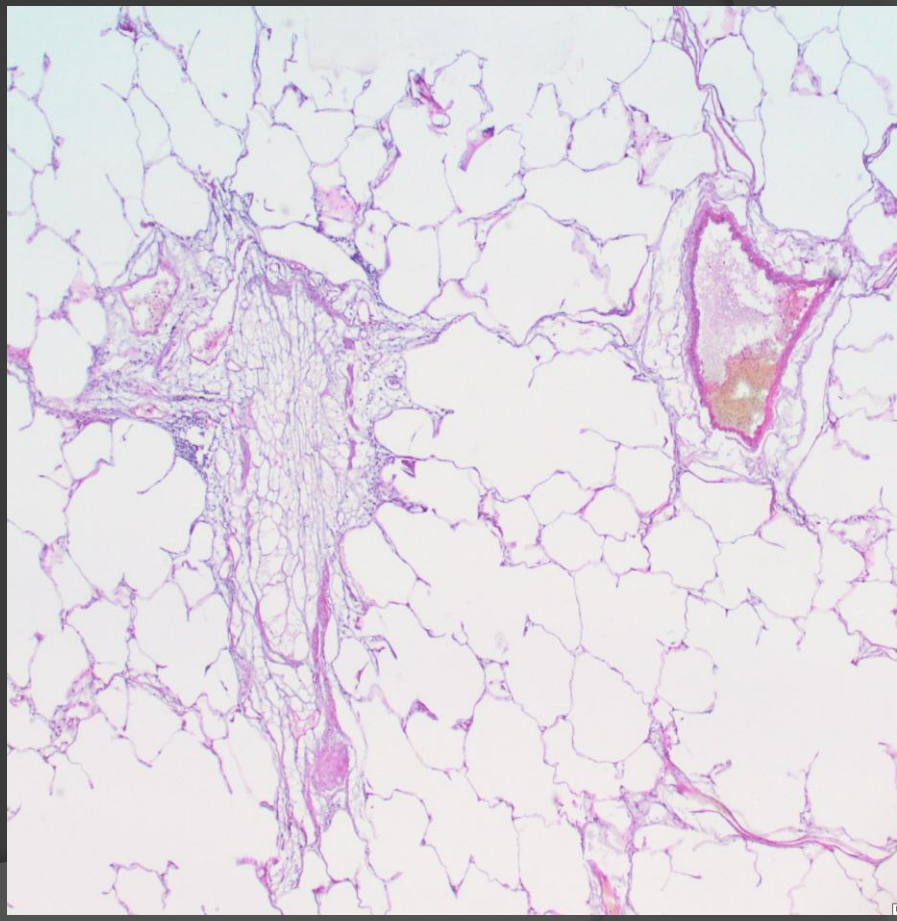
Courtesy of S. Verleden

# BOS/OB

microCT



Pathology

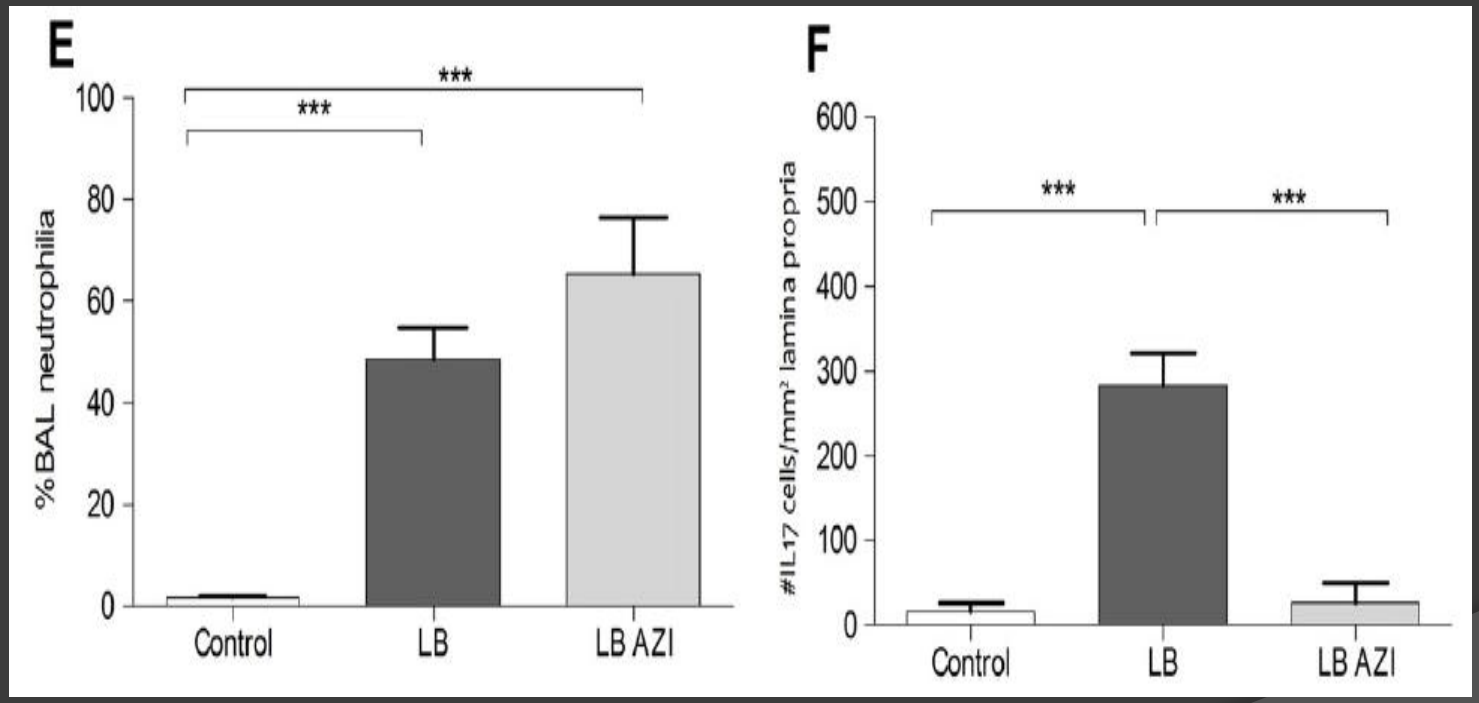


# BOS Phenotypes

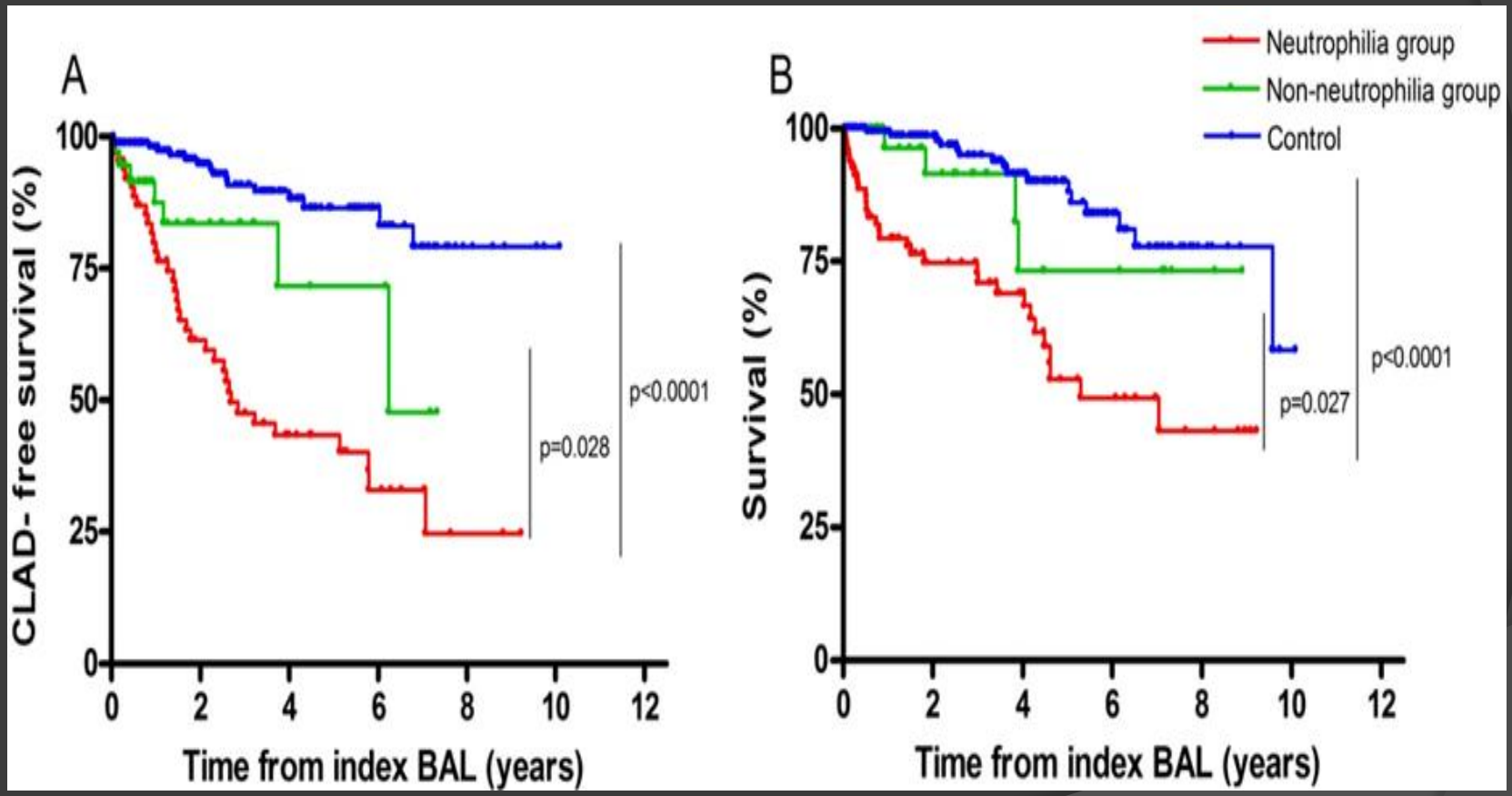
| Characteristic | Neutrophilic reversible allograft dysfunction (NRAD-ARAD) | Non-neutrophilic BOS |
|---|---|---|
| **Bronchoalveolar Lavage** | Excess neutrophils (>15%) | Neutrophils < 15% |
| **Clinic** | Coarse crackles, increased sputum production | No crackles, no sputum |
| **Time of Onset** | Early after transplantation (<1y) | Later (> 1y) |
| **Progression** | Slow (several years) | Rapid (<6-12 months) |
| **Histology** | Inflammatory, ends up in fibrosis | Pure fibrosis (?) |
| **Radiology** | airway wall thickening, mucus plugging, bronchiectasis | Air trapping, consolidation |
| **Effect of azithromycin** | Improvement of $FEV_1$ (reversible) | No effect on $FEV_1$ (irreversible) |

Adapted from Vanaudenaerde et al. Eur Respir J 2008; 32: 832-43

# AZI-resistant BAL neutrophilia?



# Neutrophilic Azi-resistant BOS / NAR: prognosis



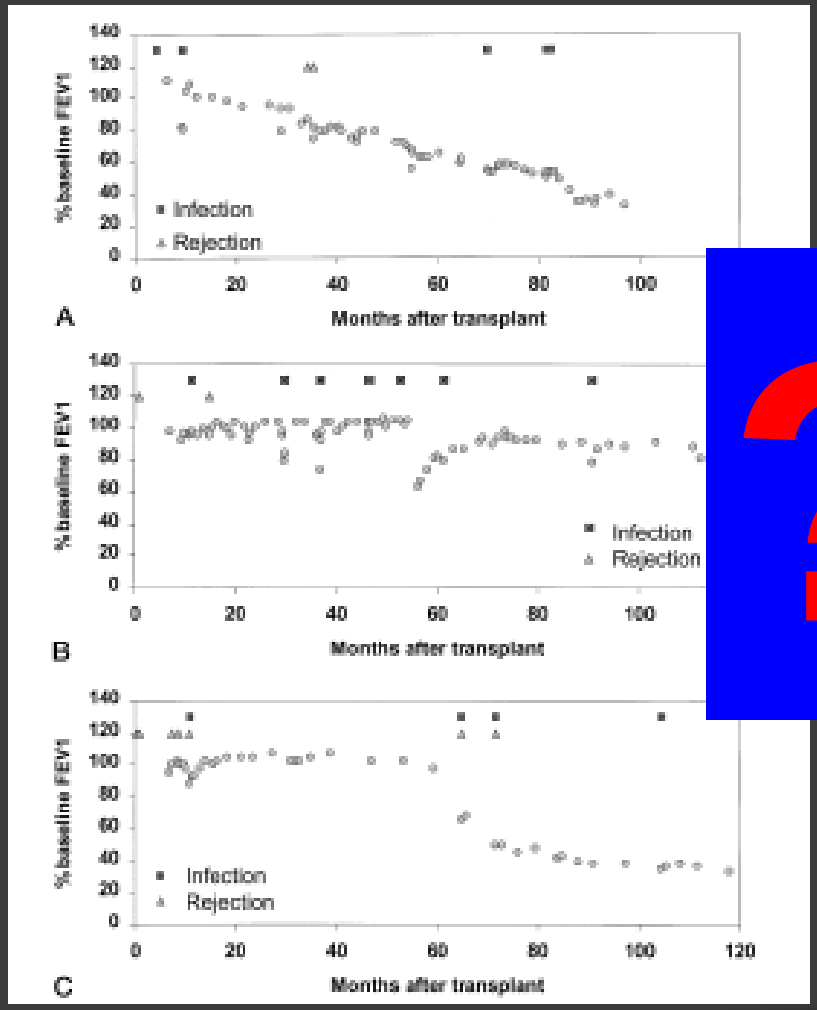

Vandermeulen et al; ERS 2013.

# BOS phenotypes

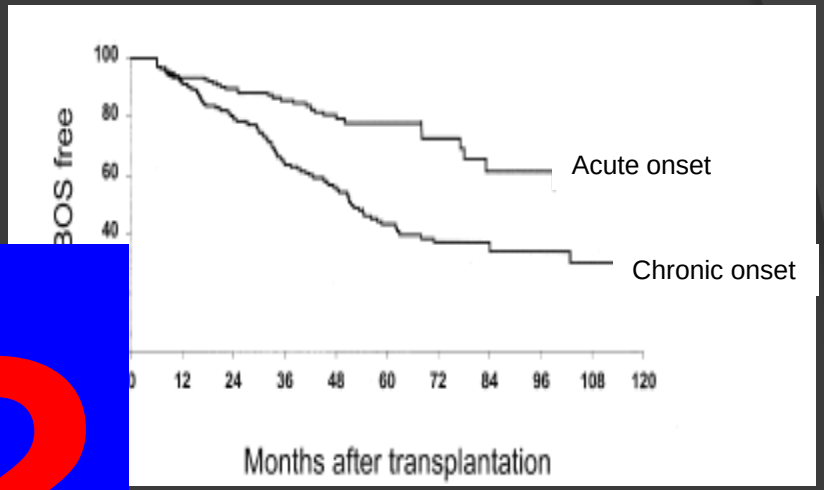
| Characteristic | NRAD/ARAD | AZI-resistant neutrophilic BOS | Non-neutrophilic BOS |
|---|---|---|---|
| **Bronchoalveolar Lavage** | Excess neutrophils (>15%), IL-17 dependent | Excess neutrophils (> 15%) IL-17 independent | Neutrophils < 15% |
| **Clinic** | Coarse crackles, increased sputum production | Crackles, velcro rales, sputum production | No crackles, no sputum |
| **Time of Onset** | Early after transplantation (<1y) | Later > 1 y) | Later (> 1y) |
| **Progression** | Slow (several years) | Moderate, fast | Rapid (<6-12 months) |
| **Histology** | Inflammatory, ends up in fibrosis, LB | Inflammation, fibrosis, LB | Pure fibrosis (?) |
| **Radiology** | airway wall thickening, mucus plugging, bronchiectasis | TIB, mucus plugging, brect | Air trapping, consolidation |
| **Effect of azithromycin** | Improvement of $FEV_1$ (reversible) | No effect on $FEV_1$, role of ECP? | No effect on $FEV_1$ (irreversible) |

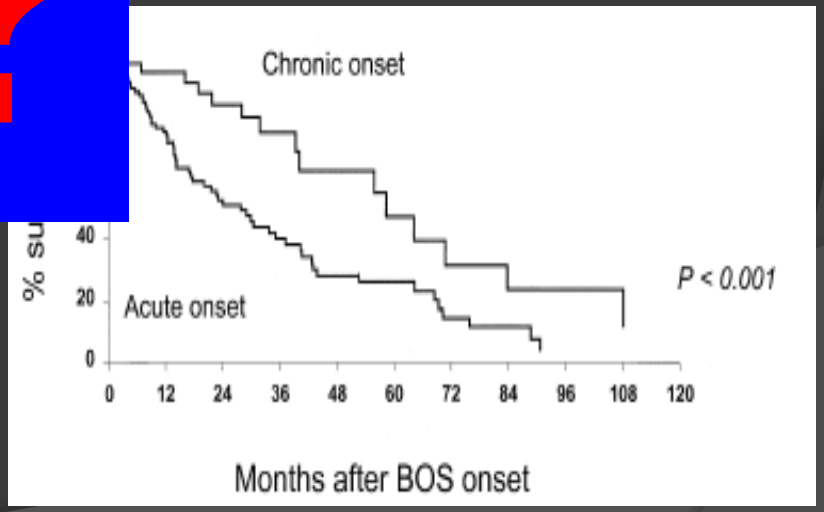
Adapted from Vanaudenaerde et al. and Vandermeulen et al.

# Variations in BOS




?



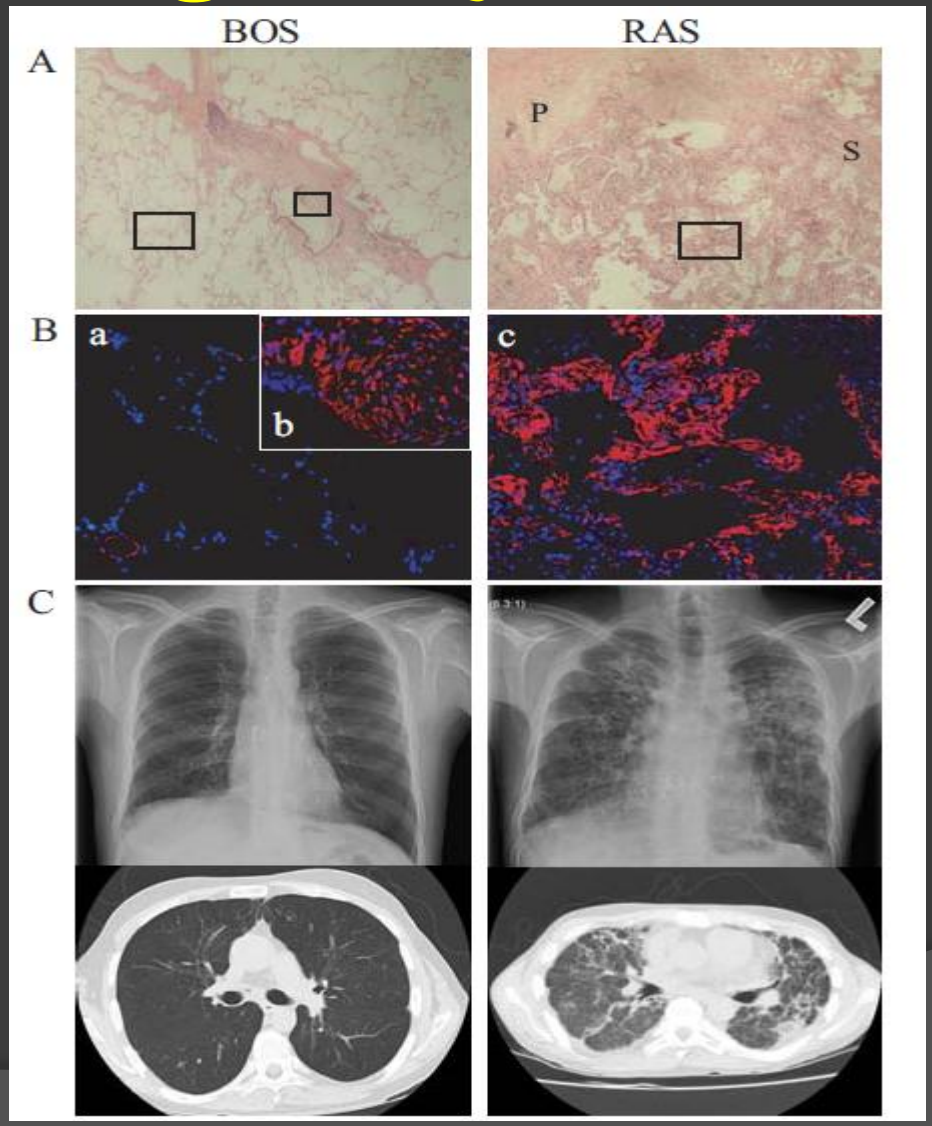




Jackson CH et al. J Heart Lung Transplant 2002;21: 658-66

# Upcoming problems with current BOS definition

- Reversibility/normalisation of pulmonary function with specific treatments resulting in survival differences after BOS diagnosis
- Other CAT findings, so far not explained In combination with a restrictive pulmonary function defect

# RAS: a new phenotype of lung allograft dysfunction




Sato et al. JHLT 2011

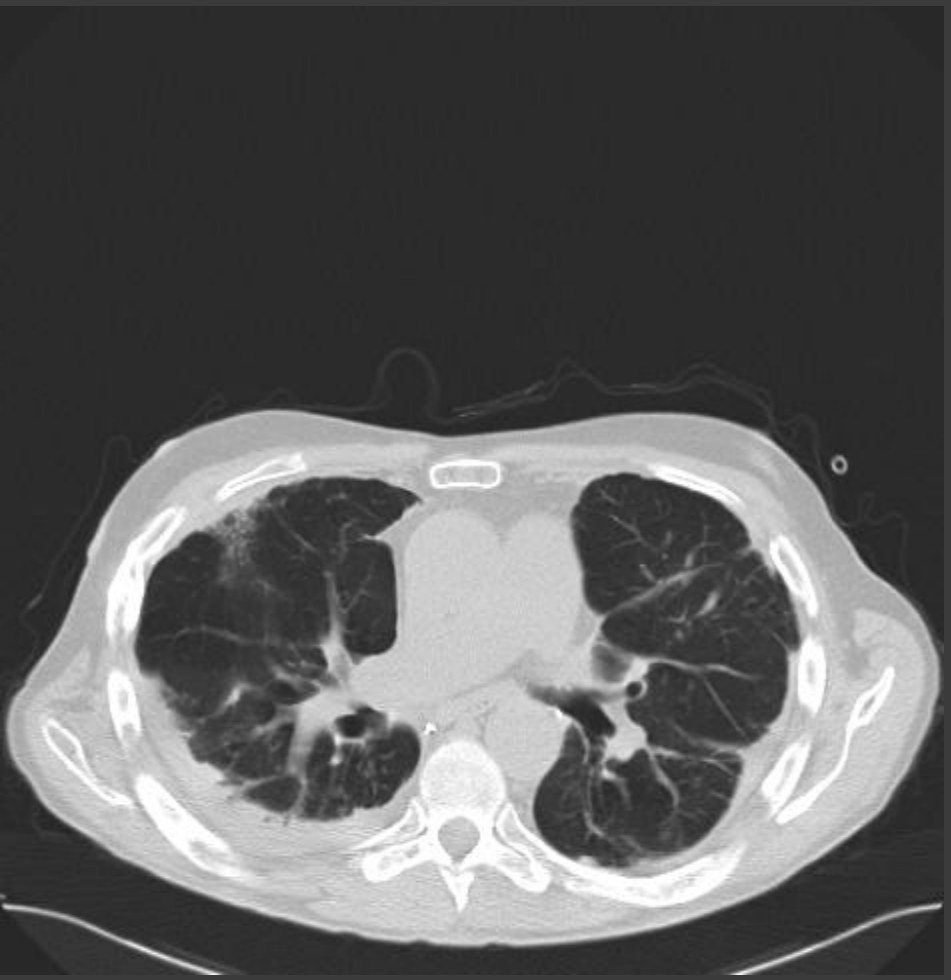
# Diagnosis of RAS: an unsolved problem?

**Table 2** Overview of Different Tools Used to Diagnose rCLAD

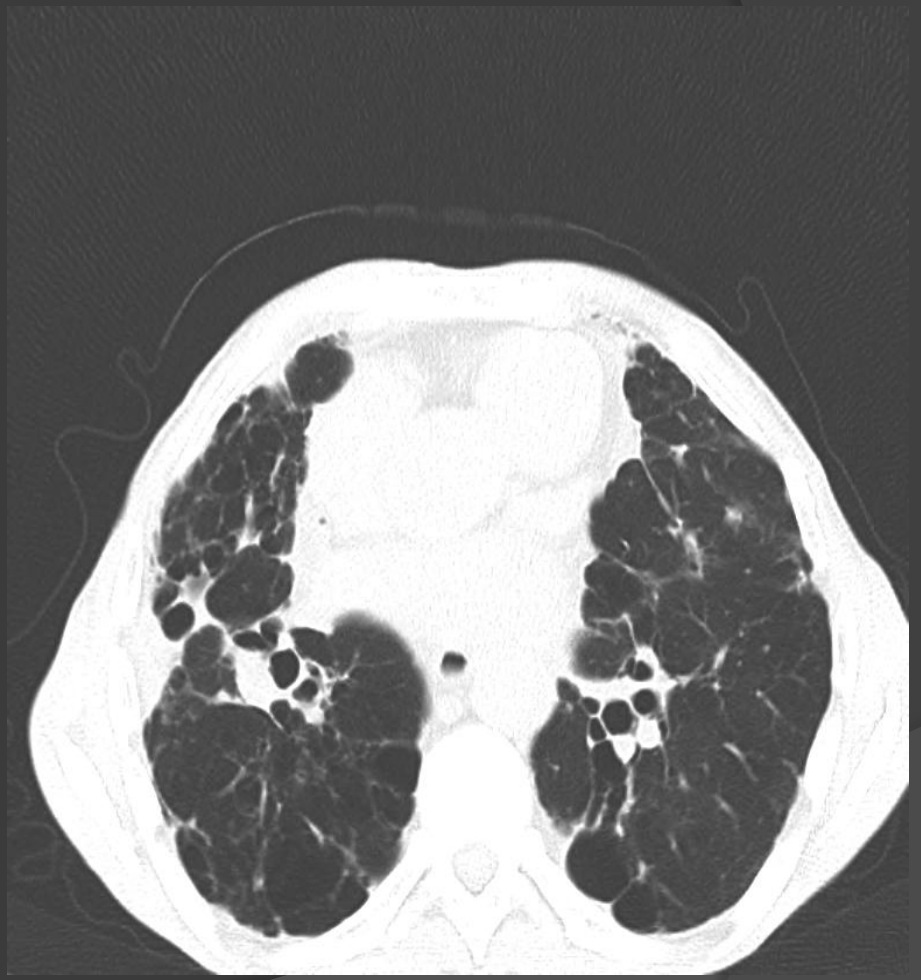
| Tool | Criterion | Advantage | Disadvantage |
|---|---|---|---|
| Plethysmography | TLC decline $\geq 10\%$[12] | Easy-to-use criterion | Higher cost for repeat measurement<br>Patient claustrophobia and additional oxygen requirement may prohibit TLC measurement<br>In retrospect, many centers have no TLC data available; prospective follow-up of TLC necessary |
| Spirometry | $FEV_1/FVC \geq 0.70$[13] | Serial measurements available<br>Low cost<br>Implicated in regular patient follow-up | Specificity unclear (e.g., FVC drop may allude to gas trapping) |
| | $FVC/FVC_{best} > 0.80$[14] | | |
| Imaging | Persistent infiltrates and pleural thickening[11,18] | Phenotyping possible in single lung Tx<br>Possible in sicker patients<br>Easy to perform | Radiation exposure<br>Specificity unclear (e.g., differential diagnosis with infections) |
| Histopathology | AFOP[16] and late-onset (>3 months) DAD on TBB[21,22] | Very direct evidence | Representative biopsy is necessary<br>Risk of complications<br>Interpretation by experienced pathologist<br>Specificity of AFOP for rCLAD not clear |

Verleden SE et al. J Heart Lung Transplant 2015, in press.

# CT scan in RAS

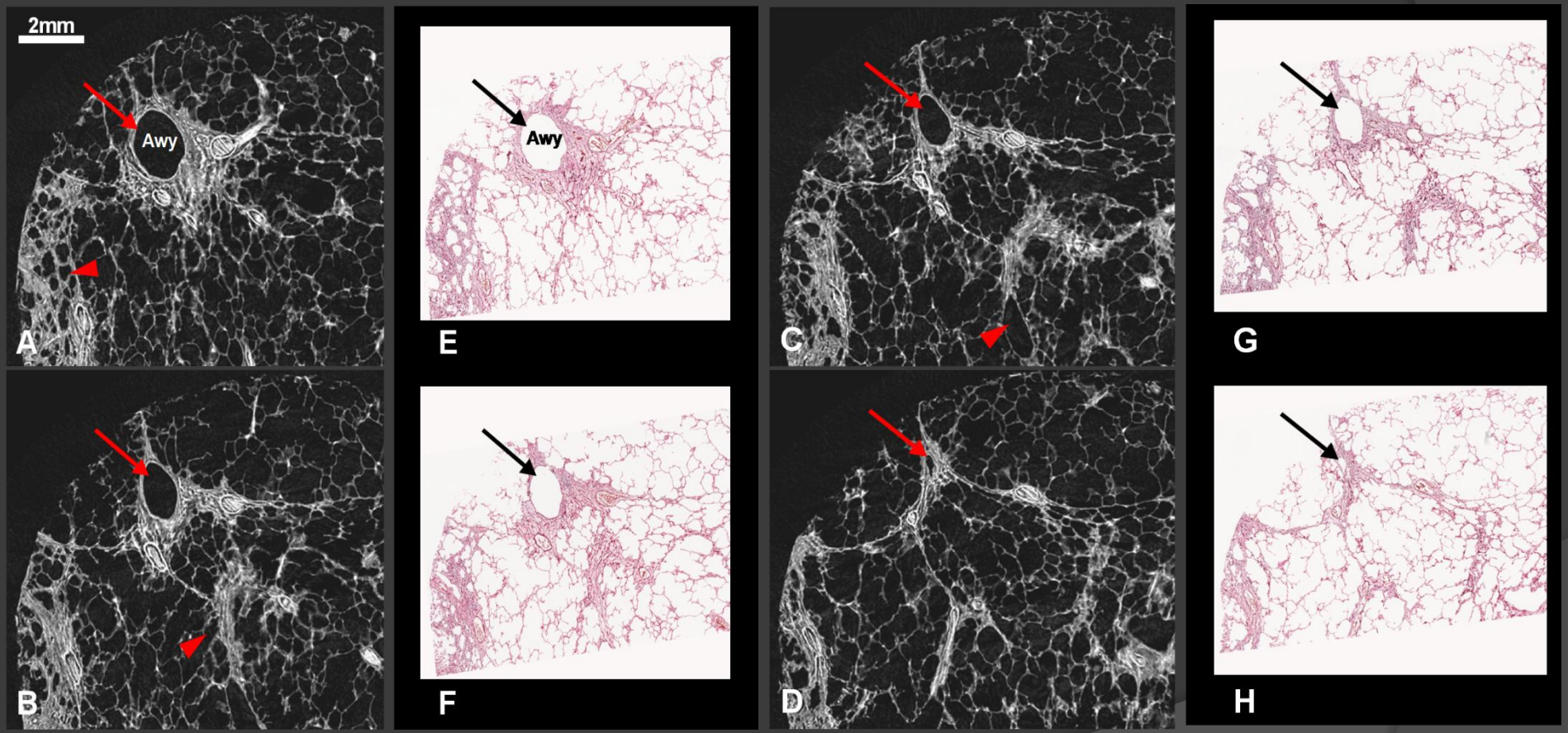


Pleuro parenchymal fibro-elastosis like



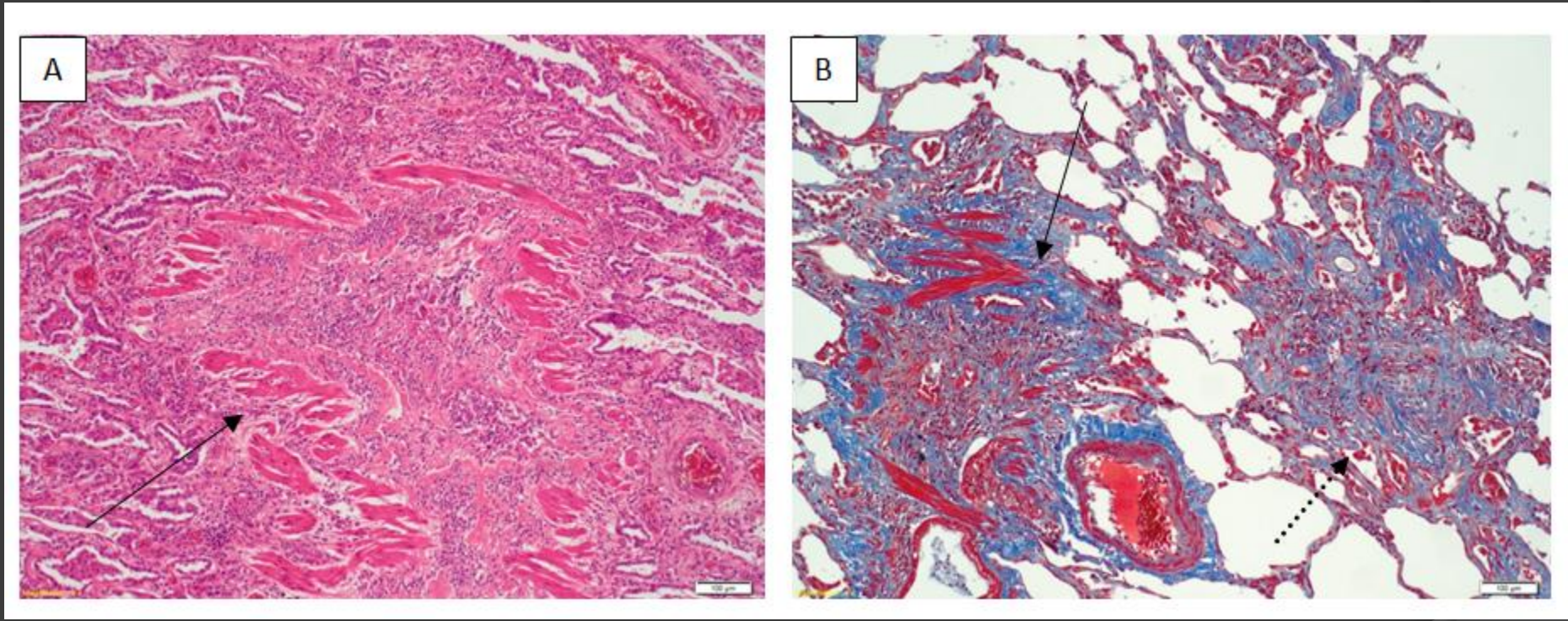
interstitial fibrosis like

# Micro-CT vs histology: RAS



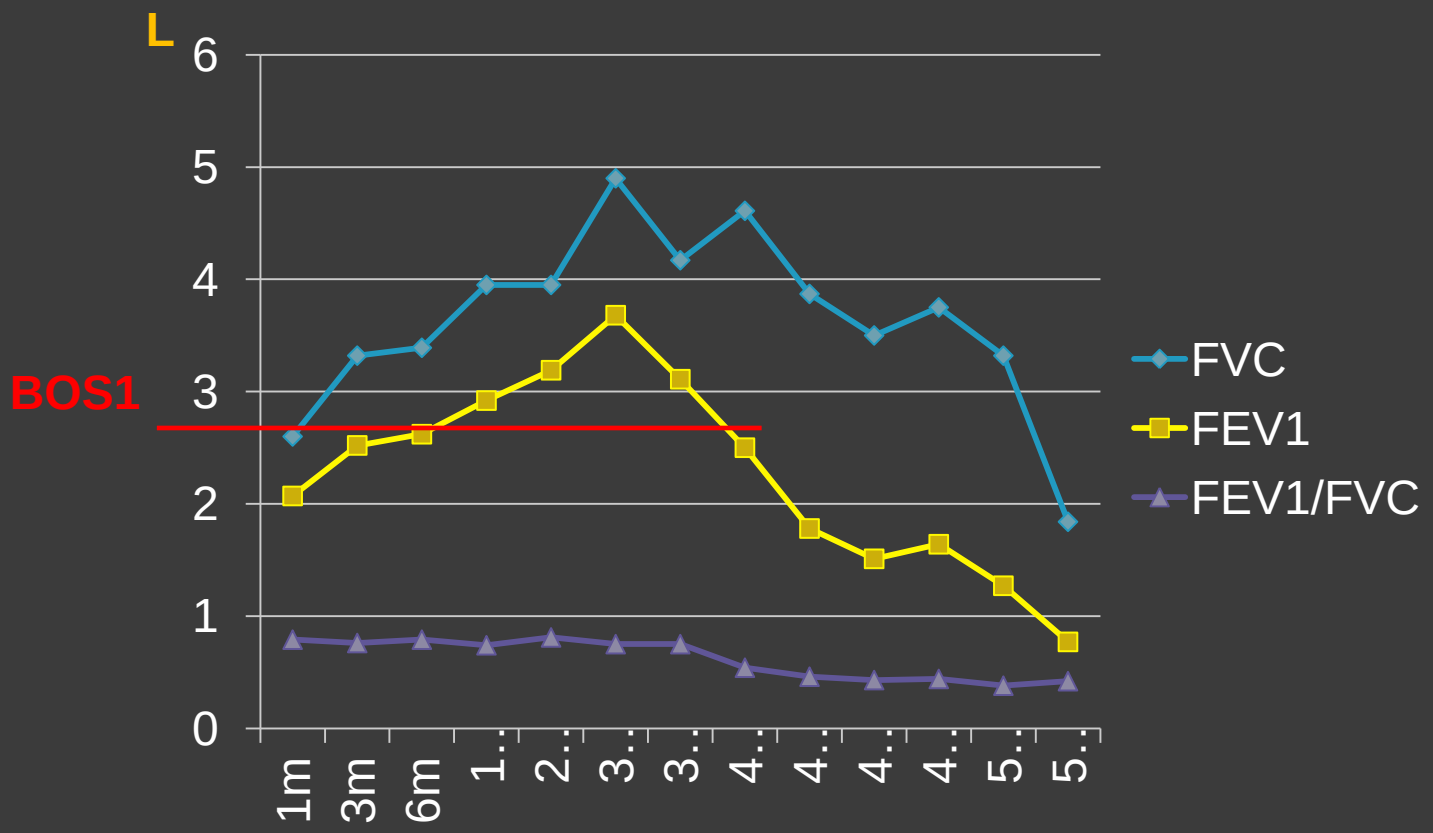

Courtesy of S. Verleden

# Pathology of RAS

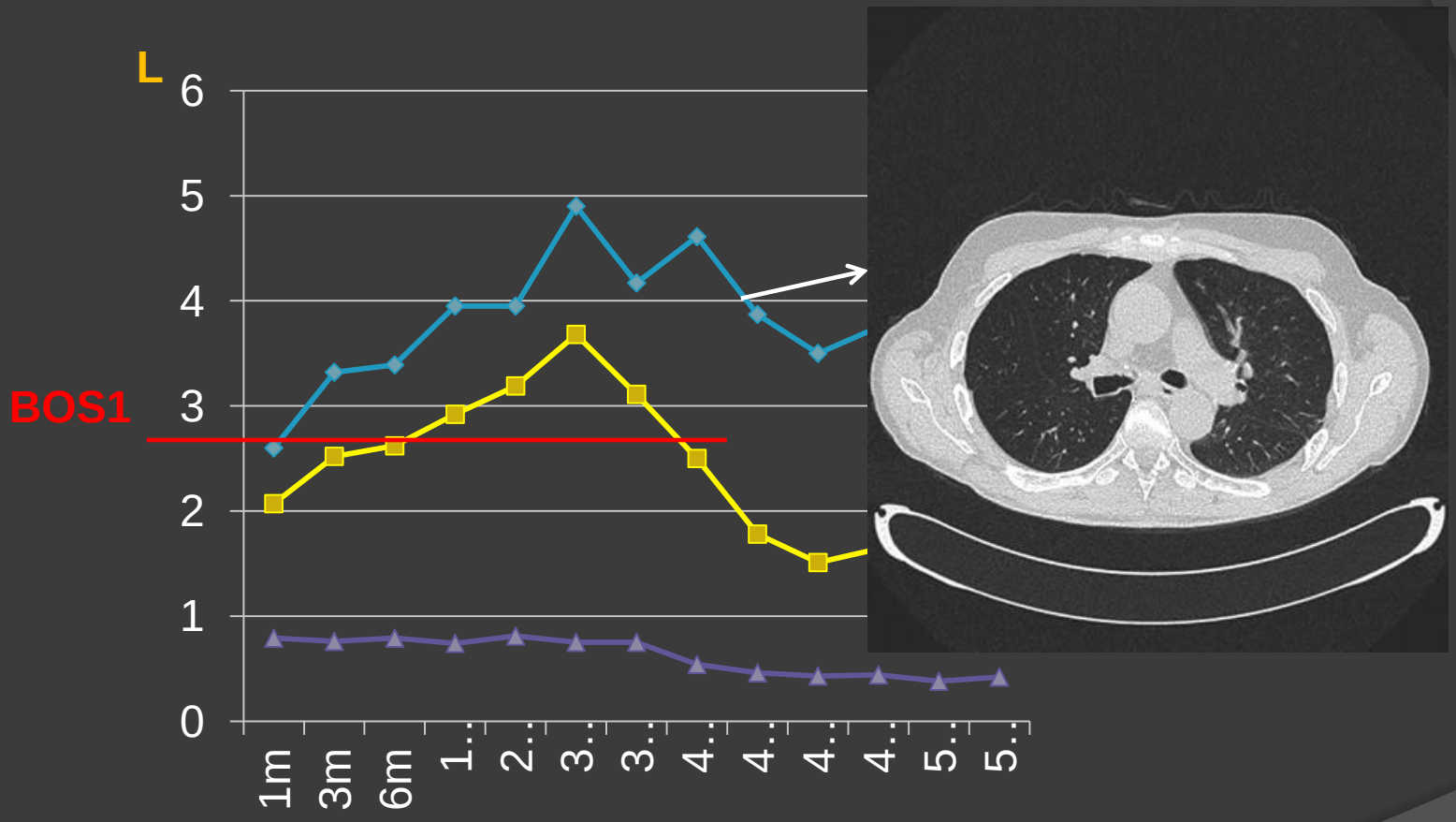



Verleden S et al. Sem Respir Crit Care Med 2013, 34: 352-60

# BOS may preceed RAS



# BOS may preceed RAS



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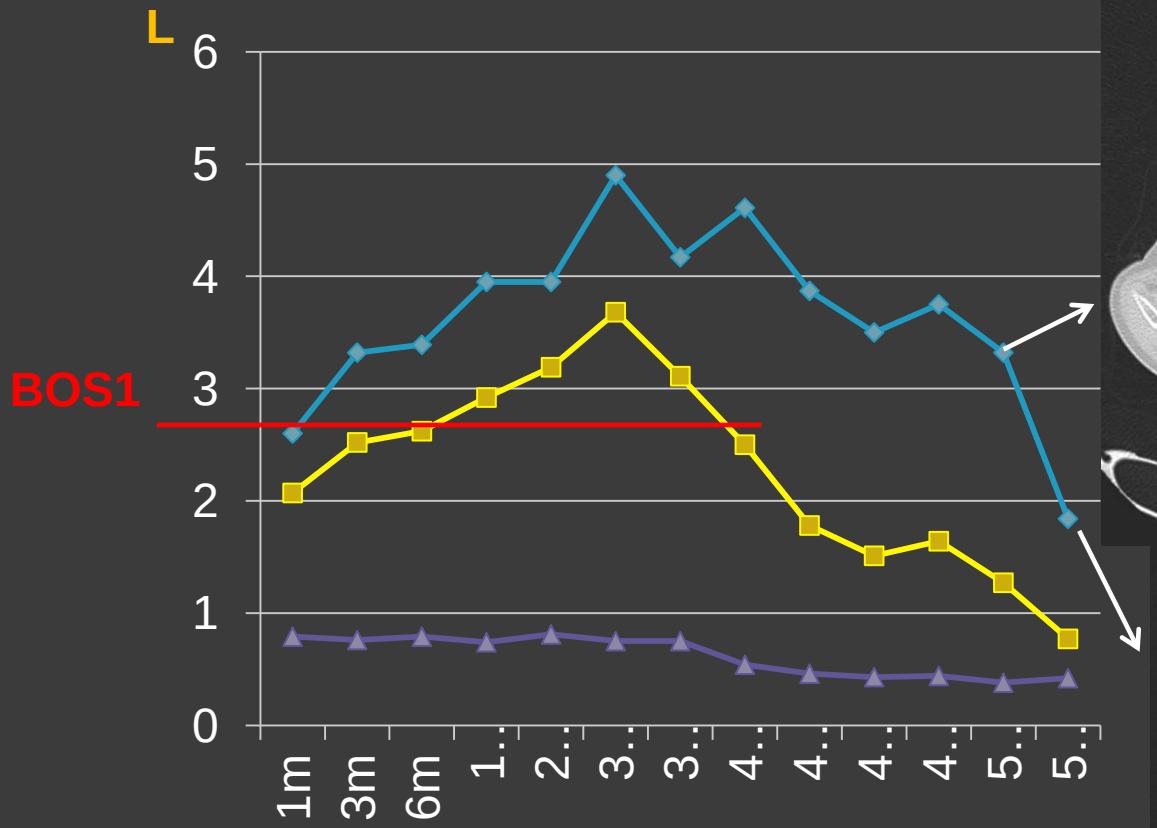
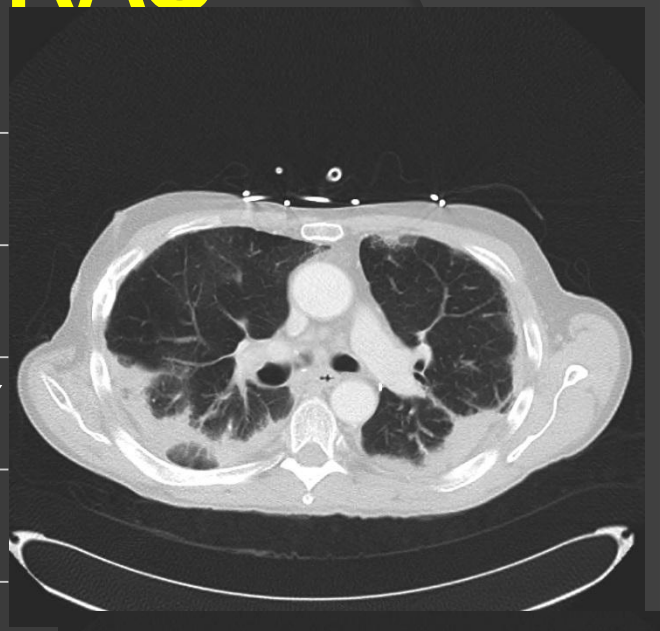
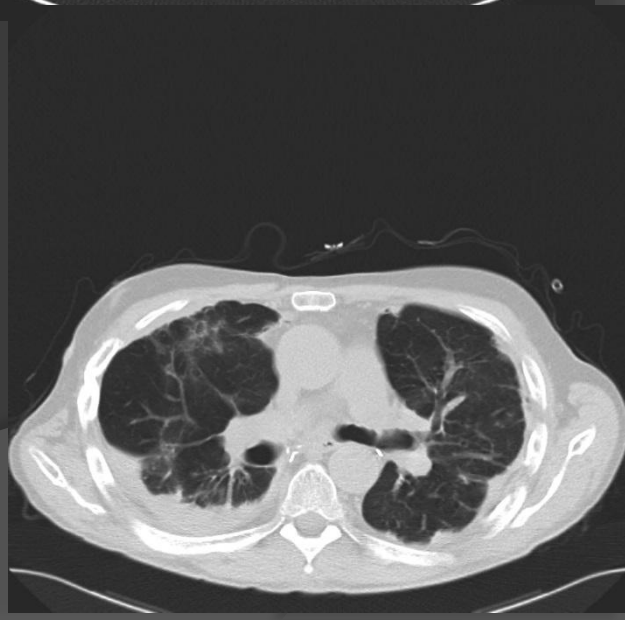
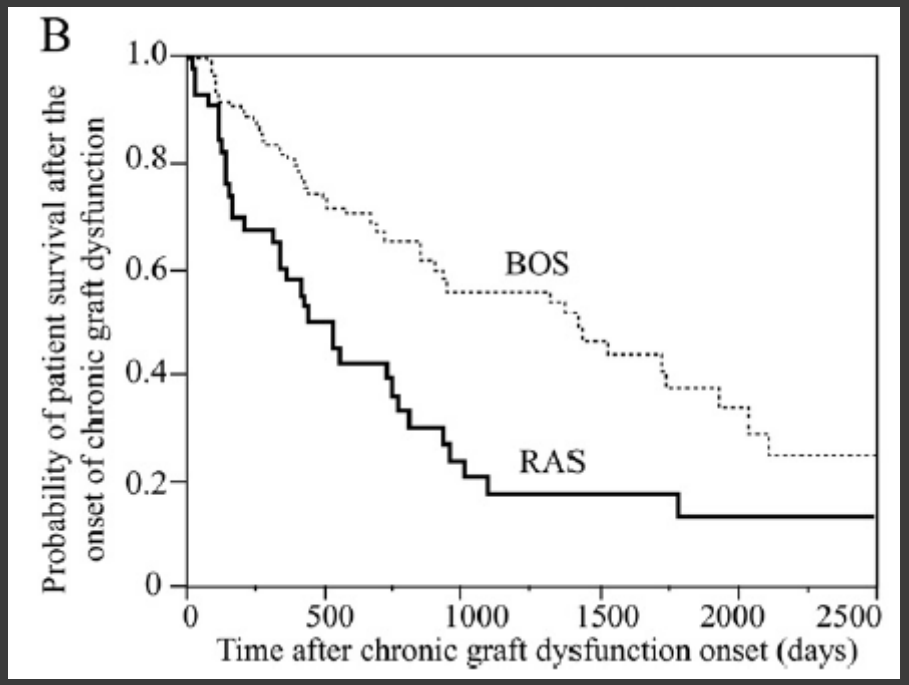
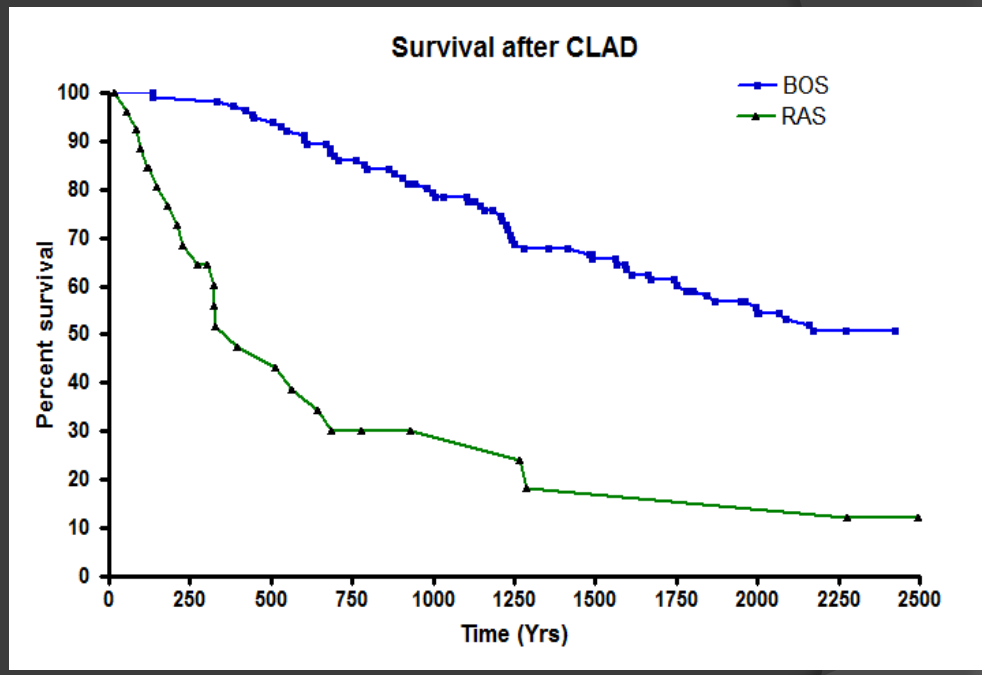




# Prognosis of different phenotypes



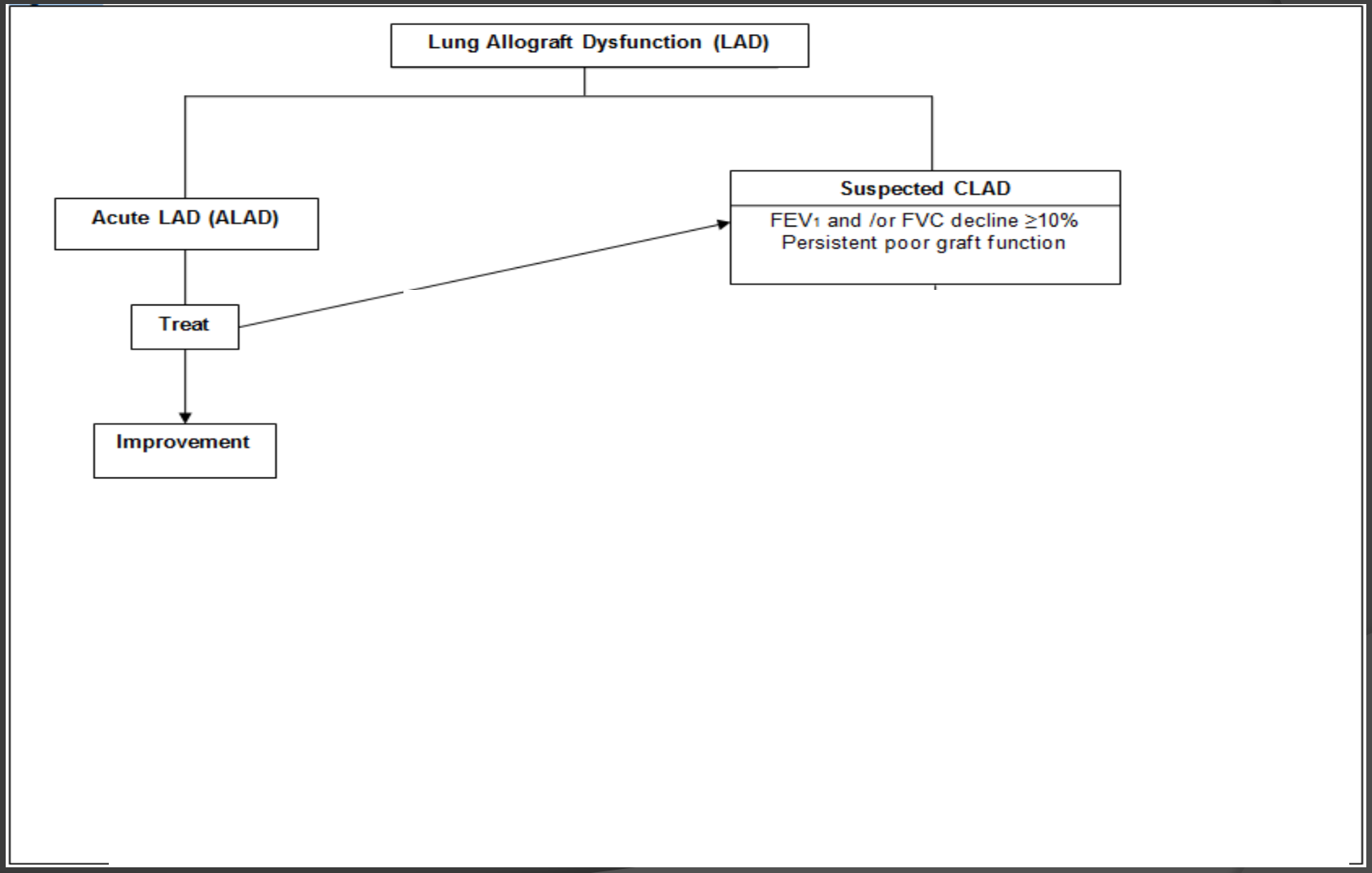

Sato et al. J Heart Lung Transplant 2011; 30:735-42

Verleden et al. Transplantation 2011; 92: 703-8

# CLAD phenotypes

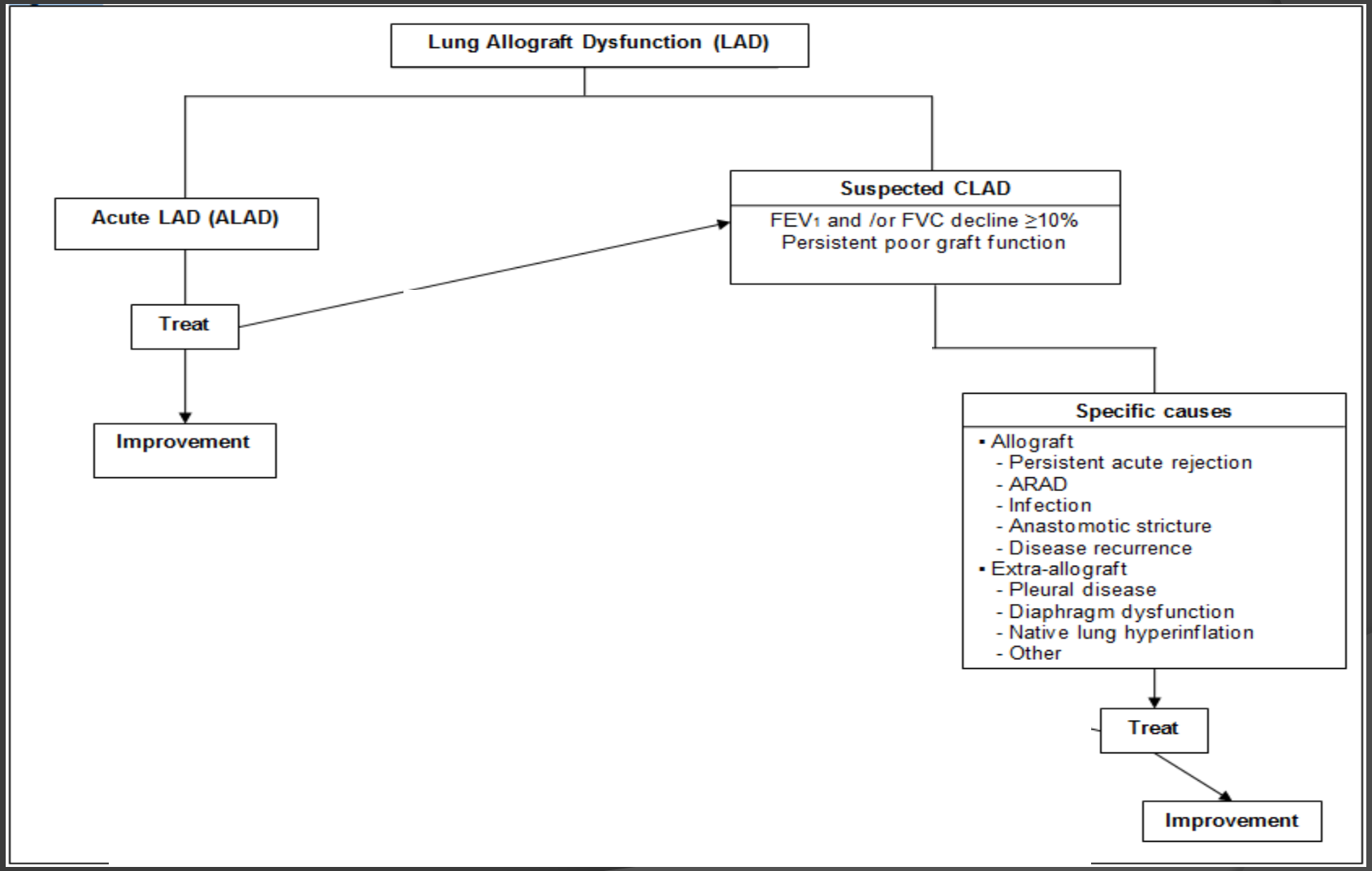
| Characteristic | BOS | | RAS |
|---|---|---|---|
| | AZI-resistant neutro BOS / NAR | Non-neutrophilic BOS | |
| **Bronchoalveolar Lavage** | Excess neutrophils (> 15%) IL-17 independent | Neutrophils < 15% | Varying neutrophilia (mostly increased), eosinophilia? |
| **Clinic** | Crackles, velcro rales, sputum production | No crackles, no sputum | Normal/velcro rales |
| **Time of Onset** | Later '> 1 y) | Later (> 1y) | Later (>1-2 y) |
| **Progression** | Moderate, fast | Rapid (<6-12 months) | Very rapid in most pts |
| **Histology** | Inflammation, fibrosis, LB | Pure fibrosis (?) | OB/fibrosis |
| **Radiology** | TIB, mucus, brect | Air trapping, consolidation | Air trapping, persistent infiltrates |
| **Effect of azithromycin** | No effect on $FEV_1$, role of ECP? | No effect on $FEV_1$ (irreversible) | No effect |

# CLAD and different rejection phenotypes: a proposal




Verleden GM et al. J Heart Lung Transplant 2014; 33: 127-33

# CLAD and different rejection phenotypes: a proposal



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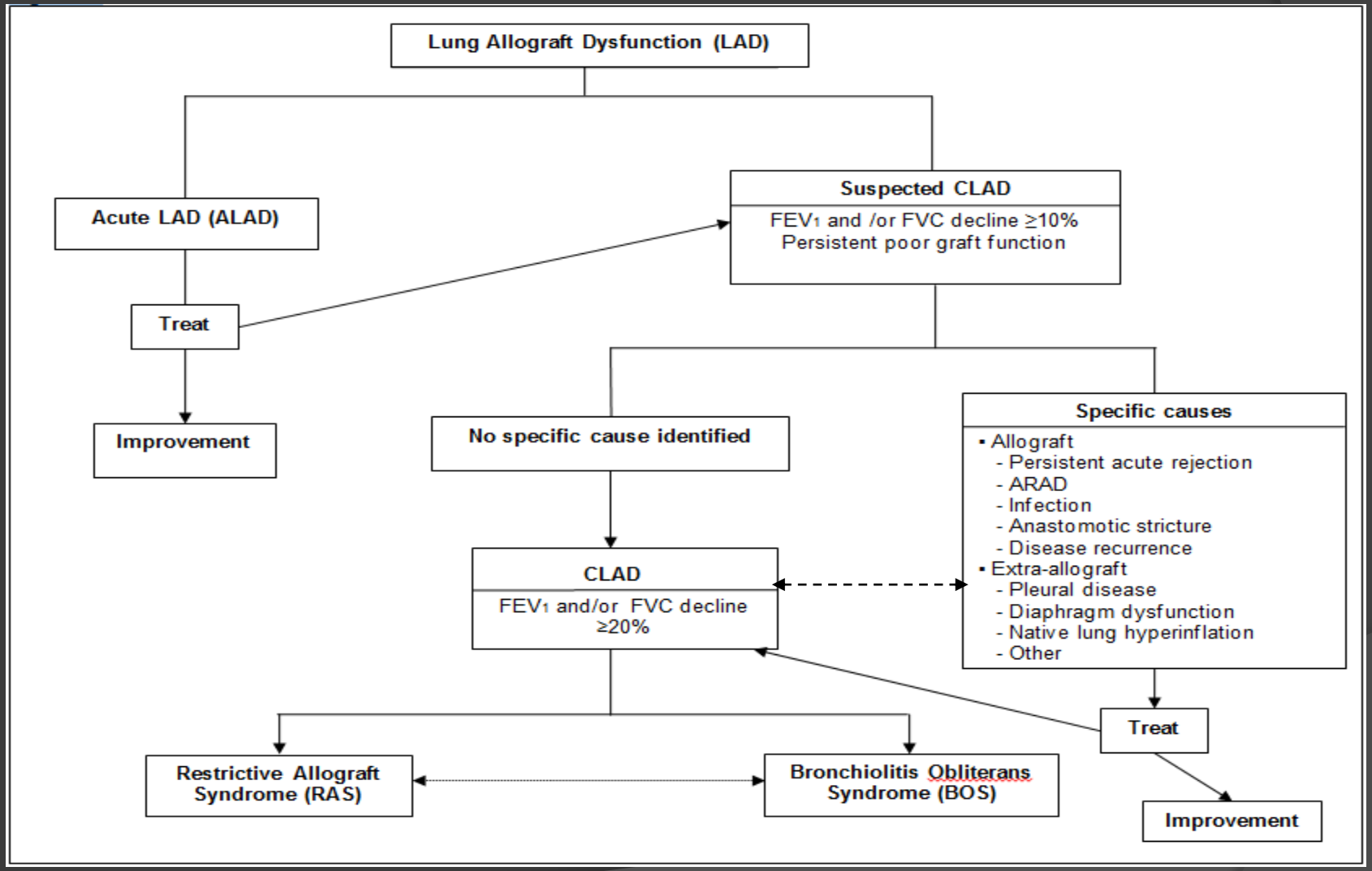
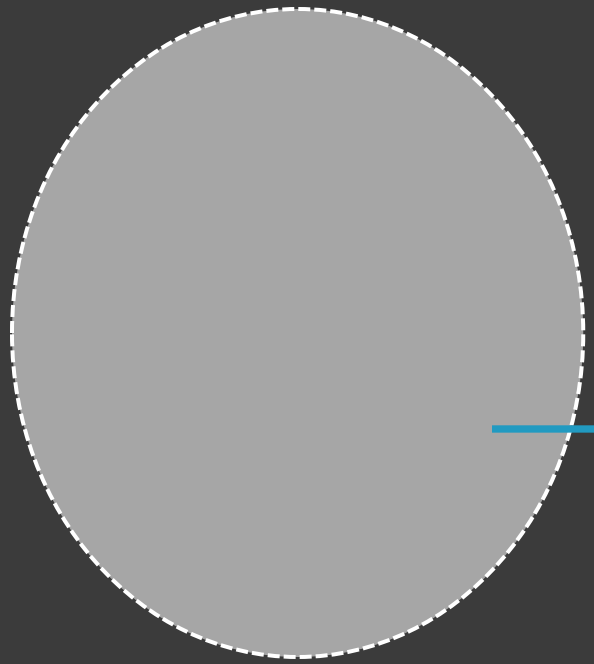



Verleden GM et al. J Heart Lung Transplant 2014; 33:127-33

# Schematic CLAD overview



**CLAD due to specific non-rejection causes**

***Allograft-related***

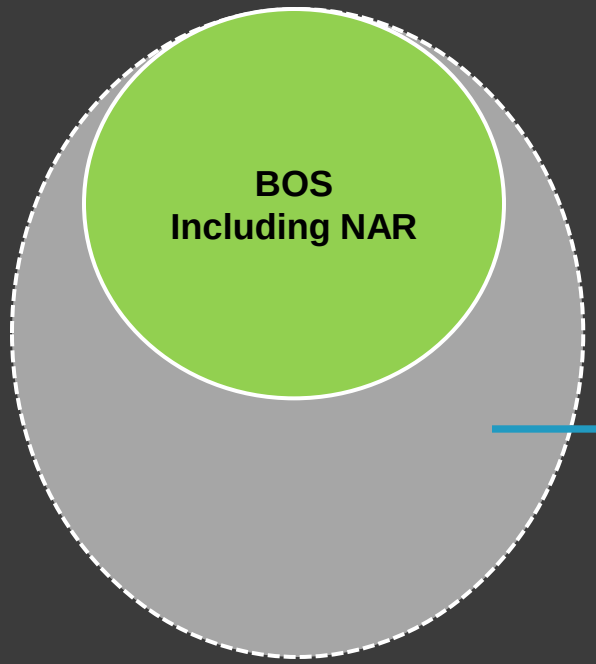
-Persistent acute rejection
-Infection
-Anastomotic stricture
-Disease recurrence

***Extra-allograft-related***

-Pleural disease
-Diaphragm dysfunction
-Native lung hyperinflation
-Other causes

CLAD= Persistent >20% decrease in $FEV_1$ and/or FVC, compared to the best postoperative baseline and despite a trial with azithromycine for at least 2-3 months

# Schematic CLAD overview

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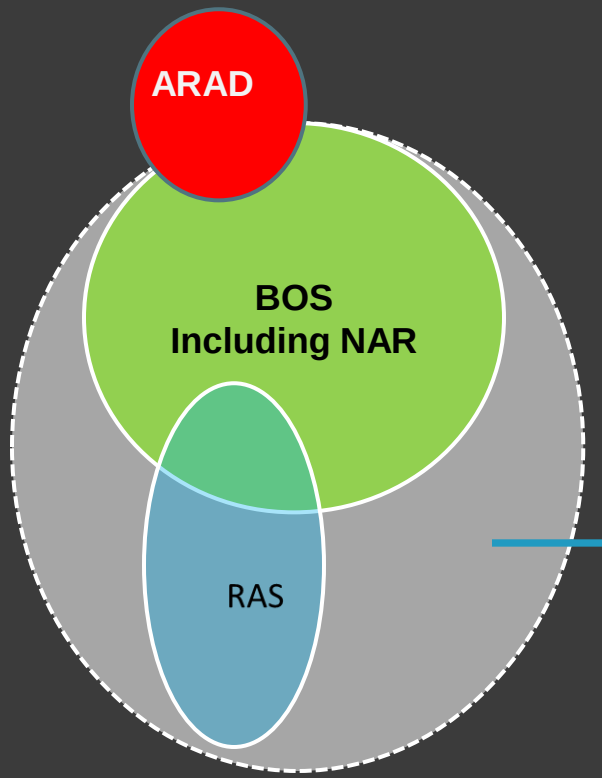


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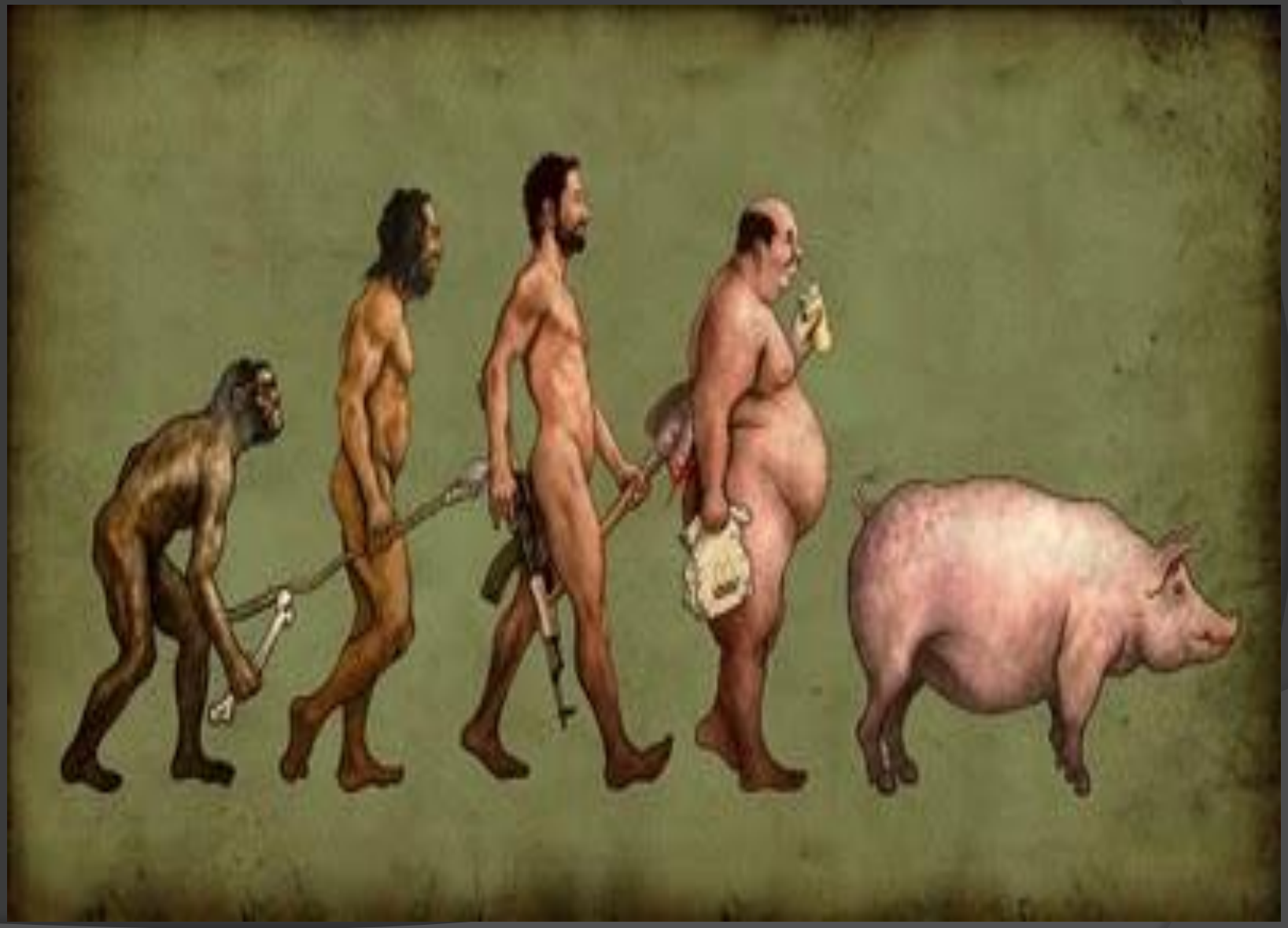
# Phenotypes might still change



# Conclusions

- CLAD is better than BOS to describe chronic $FEV_1$ decline after lung transplantation
- Further subphenotyping using BAL (neutrophilia), extended pulmonary function testing and CT scan is very important
- Identifying NRAD/ARAD may imply restoration of $FEV_1$ after adequate treatment with azi and should always be attempted when CLAD is suspected
- Exact diagnostic phenotype of CLAD may determine survival with RAS having the worst prognosis
- This proposal will need constant adaptation

# Thanks …

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