Pulmonary Sessions
October 10, 2025

Chronic Lung Allograft Dysfunction (CLAD)

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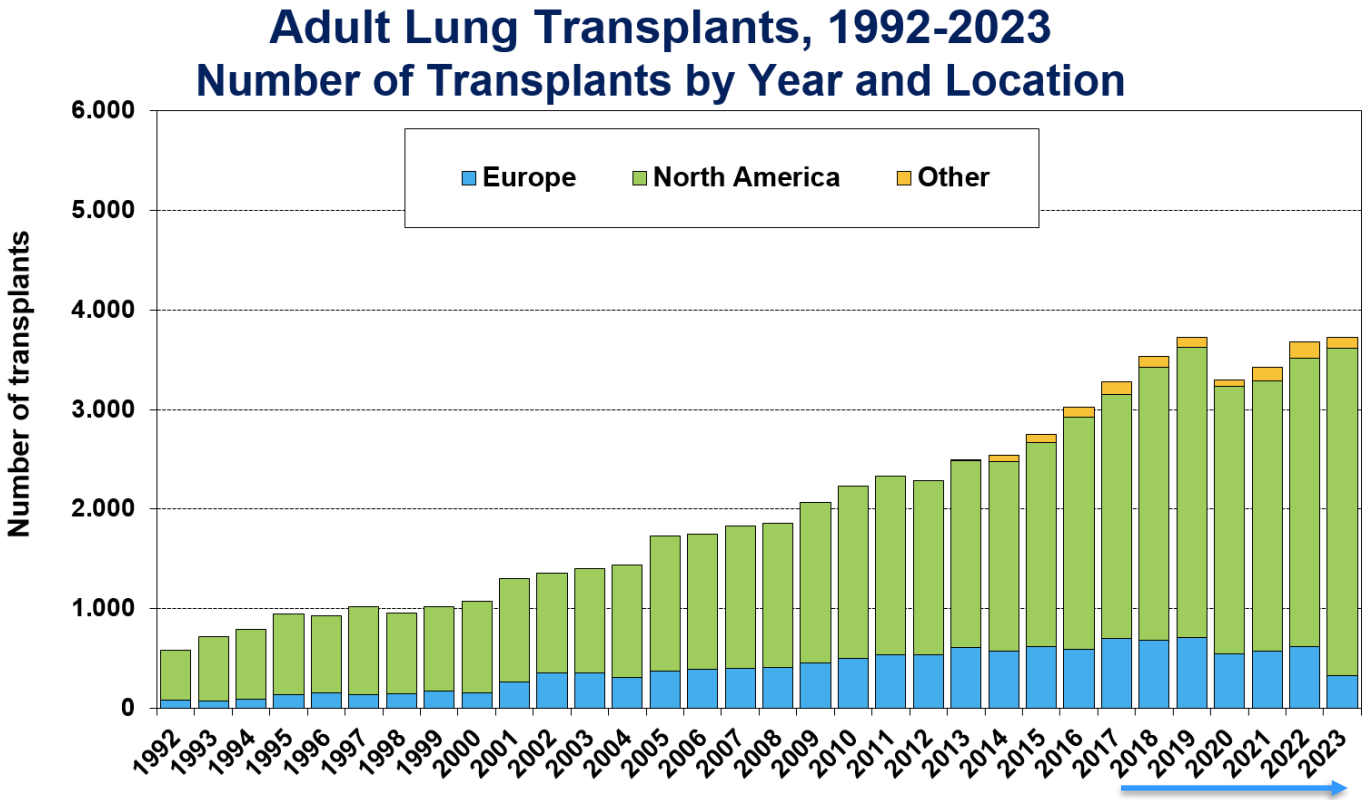
COI

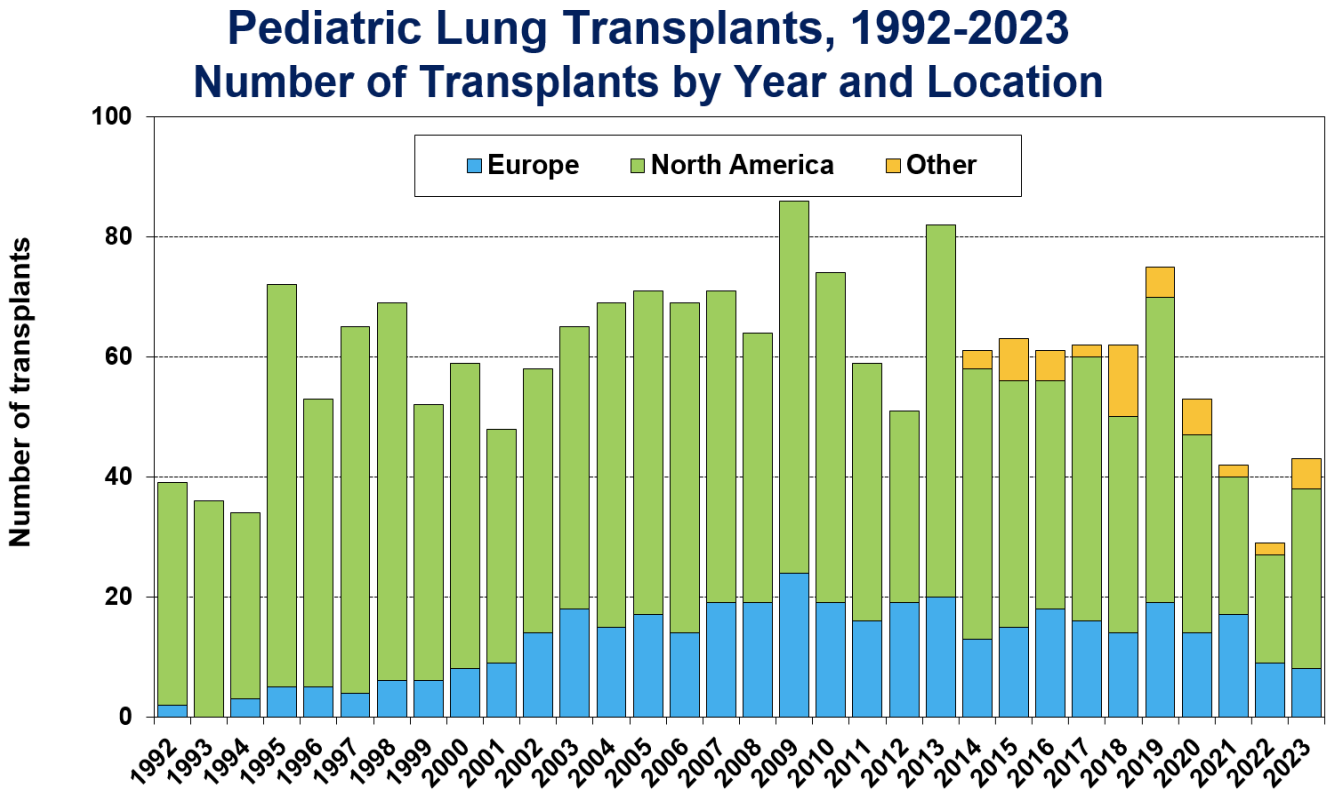
I here with declare the following paid or unpaid consultancies, business interests, grants and research support or sources of honoraria payments for the past three years, and anything else which could potentially be viewed as a conflict of interest:

Affiliation / Financial interest	Commercial Company
Grants/research support:	KU Leuven, FWO, CFF, AstraZeneca, Neovii
Honoraria or consultation fees:	Zambon, Sanofi, GSK, Takeda, Shionogi, Incyte
Participation in a company sponsored bureau:	/
Stock shareholder:	/
Spouse / partner:	/
Other support / potential conflict of interest:	Clinical Trial PI: Incyte, Zambon, Sanofi

Reported LTx for (chronic) lung diseases

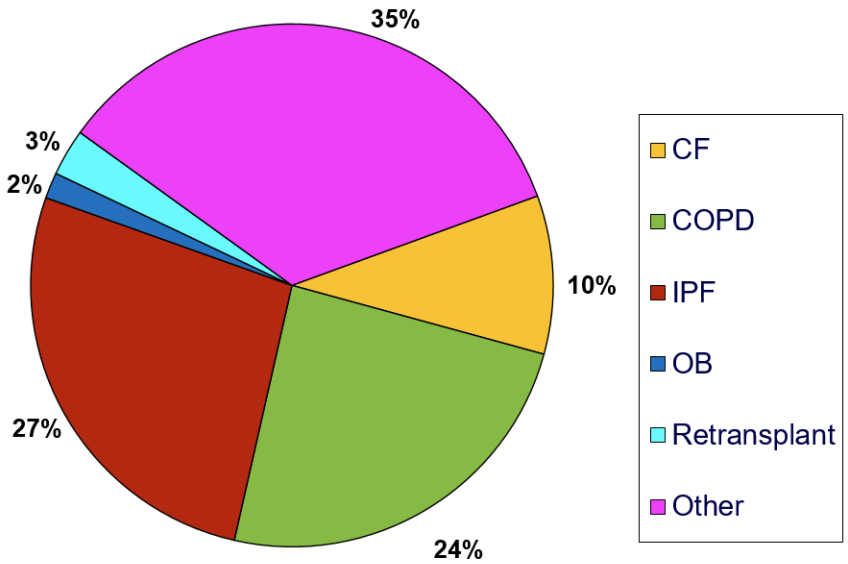


Reported LTx for (chronic) lung diseases

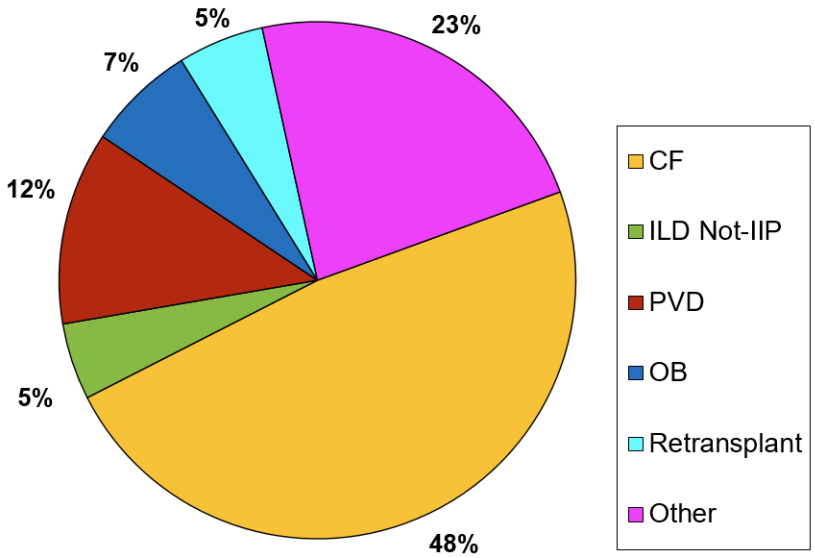


Reported LTx for (chronic) lung diseases

Lung Transplants by Diagnosis, 1992-2024



Adult Transplants



Pediatric Transplants

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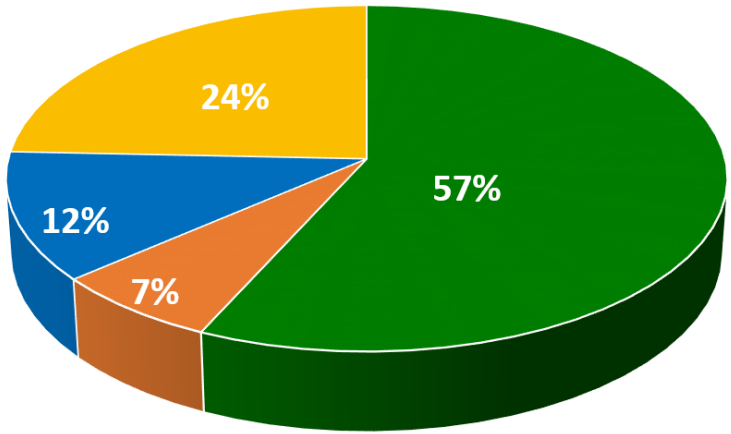
Leuven lung transplant indications 1991-2024 (n=1500)



59 (4%) redo-lung

OBSTRUCTIVE DISORDERS	VASCULAR	CF	RESTRICTIVE DISORDERS
Emphysema/COPD	PAH		Pulmonary Fibrosis (IPF, non-IPF)
LAM	Congenital heart disease		RAS
Bronchiolitis	PVOD		
BOS	PCH		

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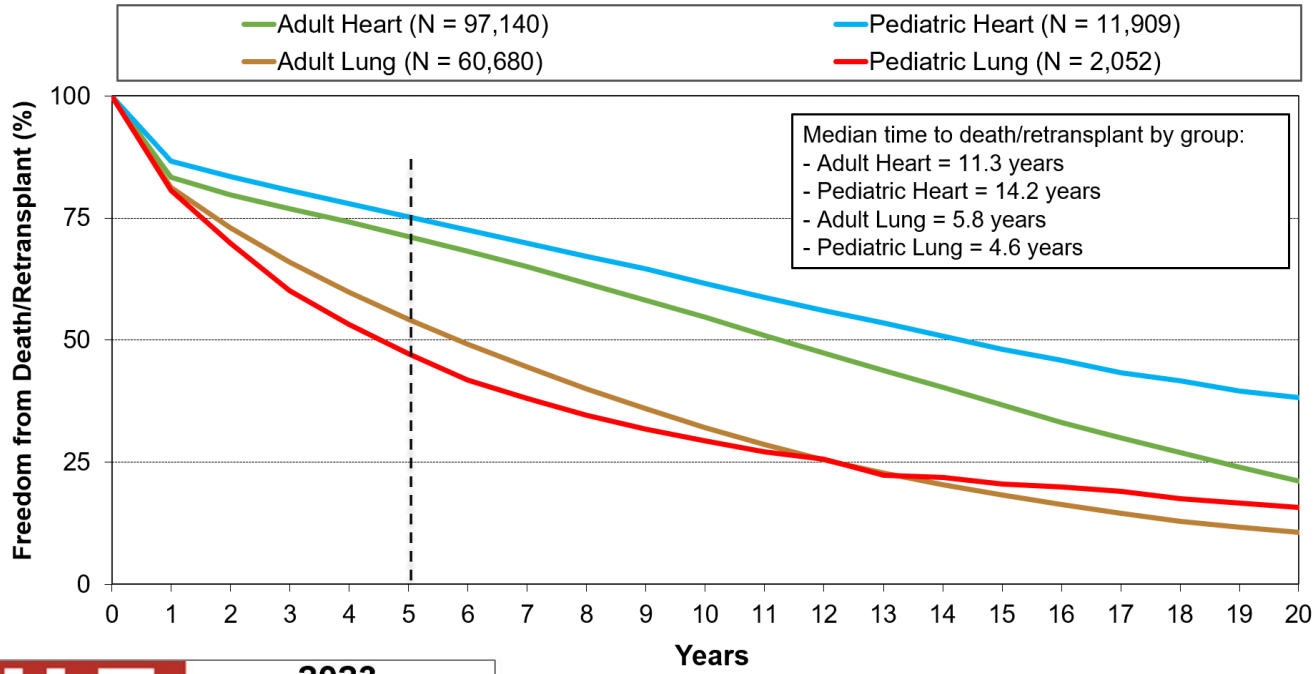
LTx: long-term outcome

Kaplan-Meier Freedom from Death/Retransplant by Age Group and Organ

(Deceased Donor Transplants: January 1992 – June 2017)



ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION
2023
JHLT. 2023 Oct; 42(10): 1321-1333

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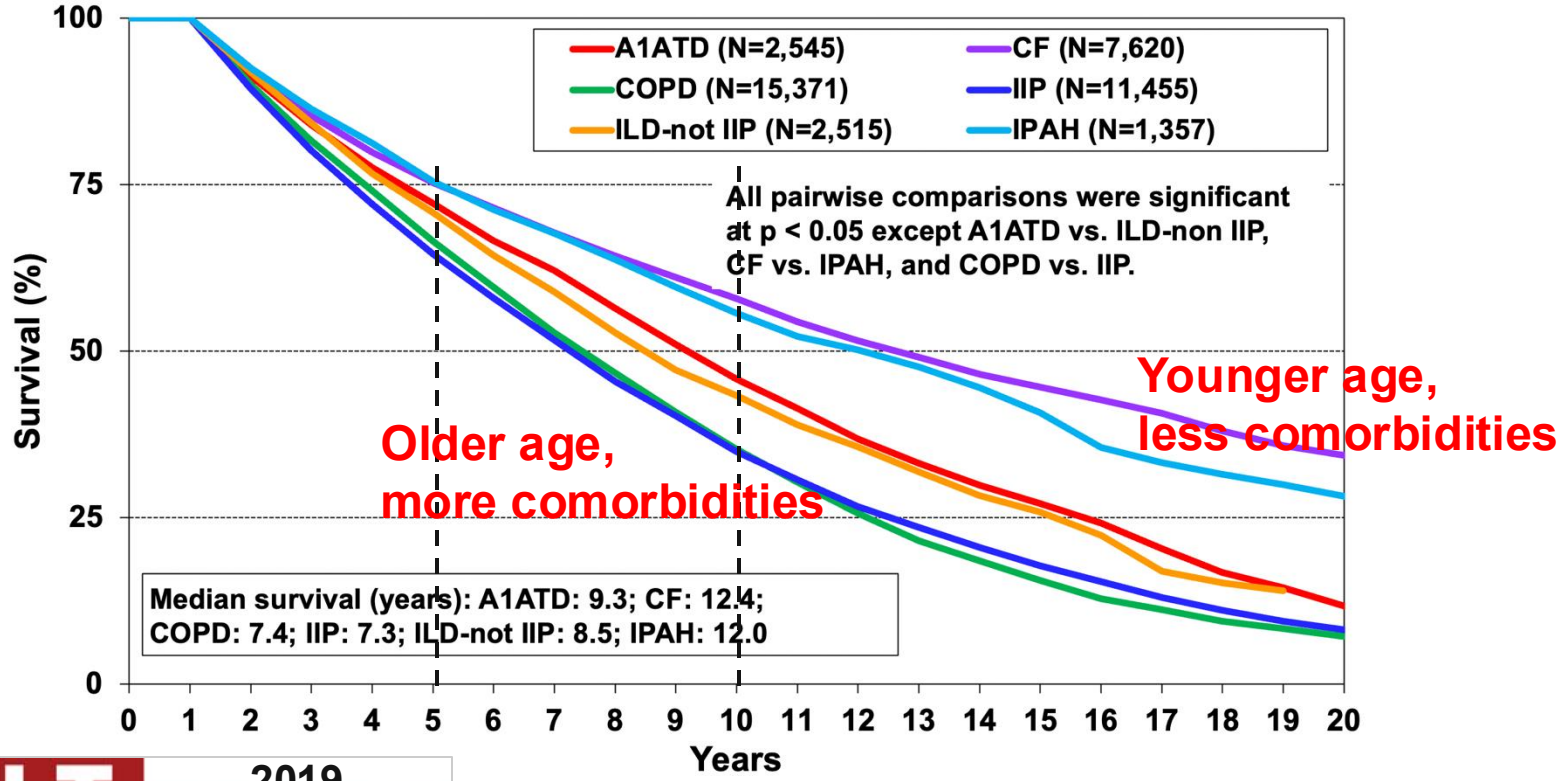
Survival by Diagnosis, Conditional on Survival to Year 1

Adult Lung Transplants

(Transplants: January 1992 – June 2017)



ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION 2019

JHLT. 2019 Oct; 38(10): 1015-1066

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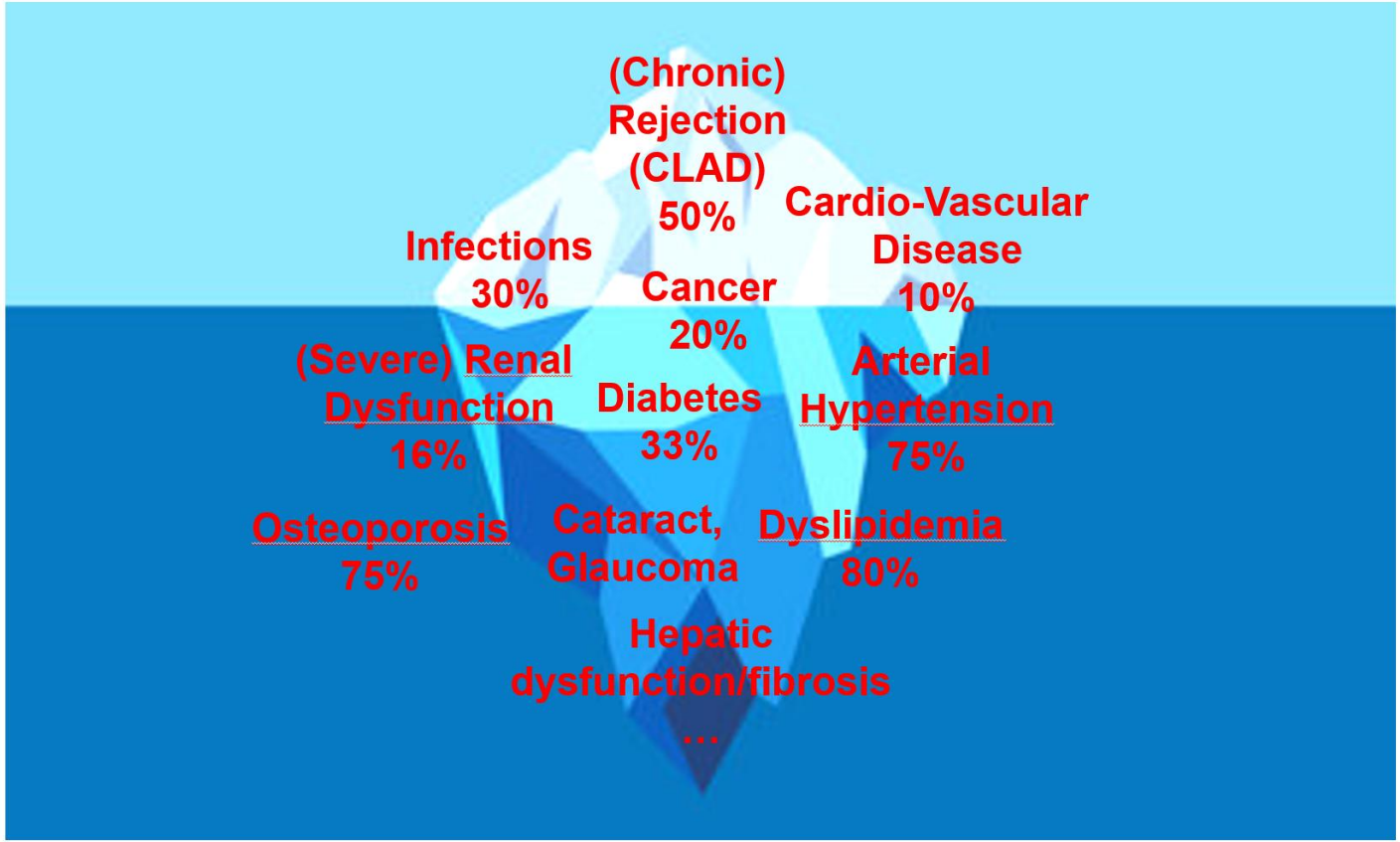
Long-term morbidities/complications (< 5 years post-LTx)



Based on ISHLT Registry data. Courtesy of Vos R.

Spectrum of (chronic) lung disease post-LTx

Obstructive

Restrictive

CHRONIC LUNG ALLOGRAFT DYSFUNCTION (CLAD)

BRONCHIOLITIS OBLITERANS SYNDROME

MIXED/ UNDEFINED CLAD

RESTRICTIVE ALLOGRAFT SYNDROME

NON-CLAD ALLOGRAFT DYSFUNCTION

(CHRONIC) INFECTIONS

ABNORMAL PHYSIOLOGY

PLEURAL DISEASE

BRONCHIAL ANASTOMOTIC DISEASE

CARDIOVASCULAR DISEASE

NORMAL AGEING?

DRUG-INDUCED TOXICITY

MALIGNANCY

NEUROMUSCULAR OR THORACIC DISEASE

DISEASE RECURRENCE

OBESITY

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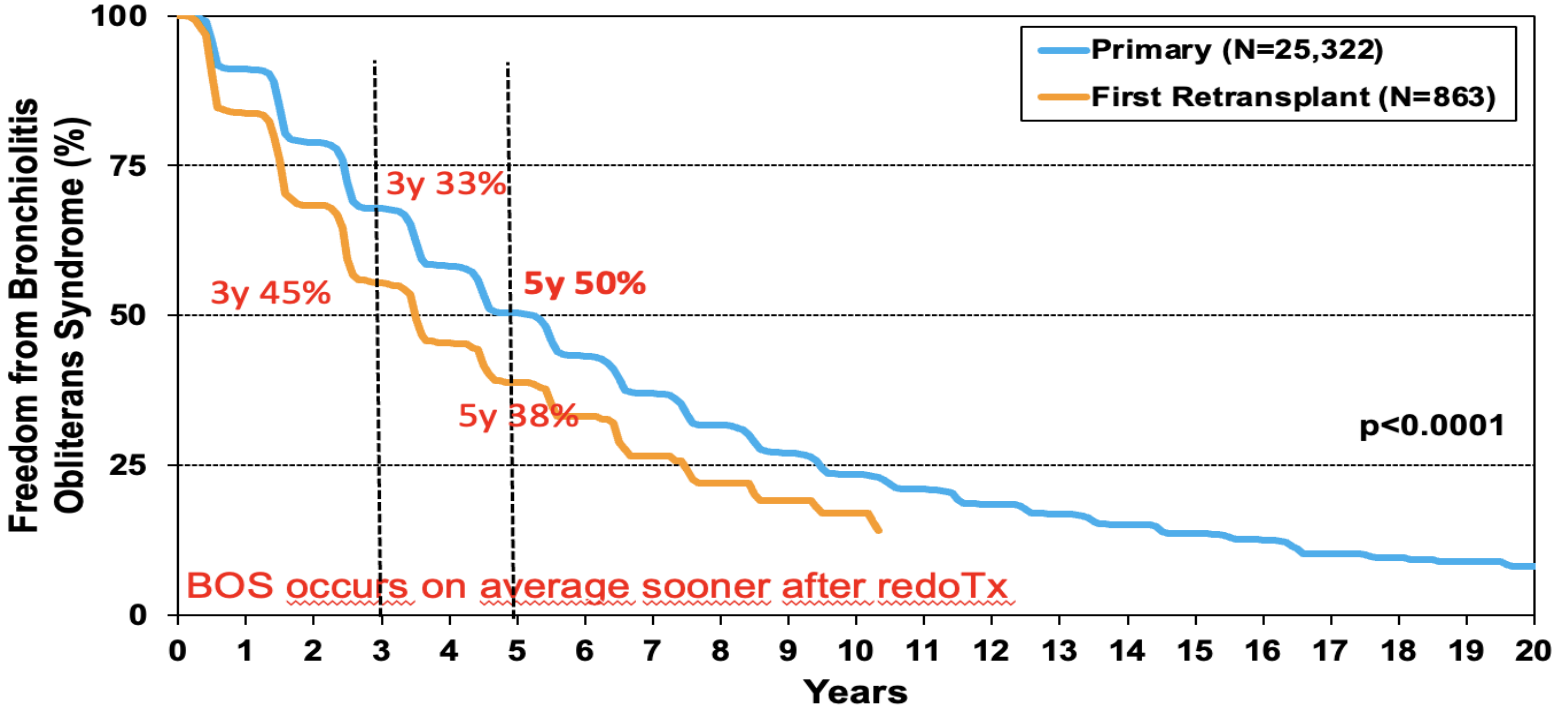
CLAD: a very prevalent complication

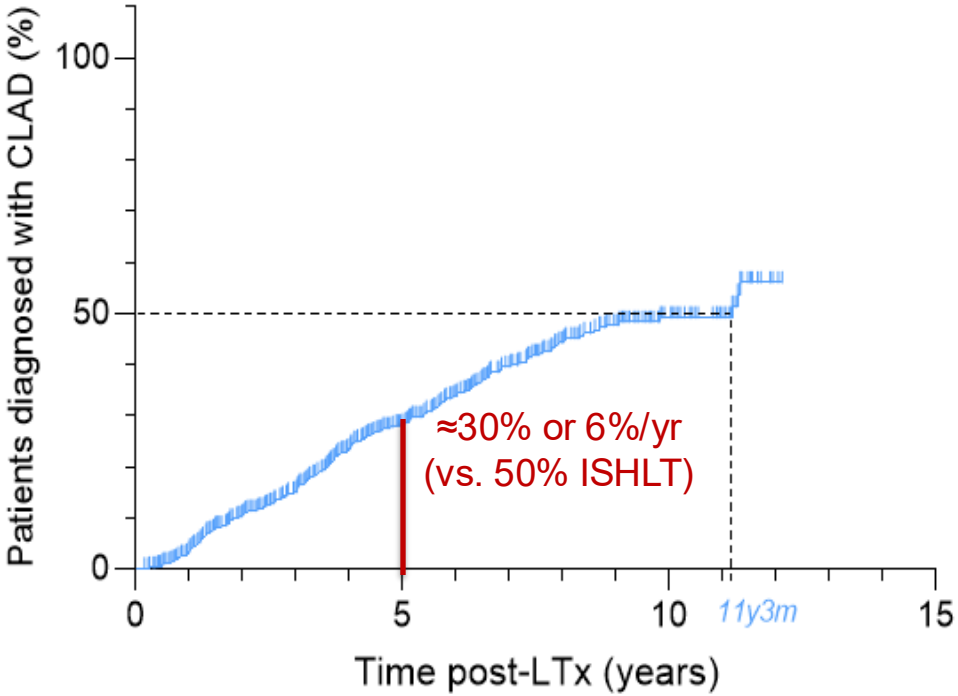
Adult Lung Transplants

Conditional on Survival to 14 days (Transplants: January 1995 – June 2017)



ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION 2019
JHLT. 2019 Oct; 38(10): 1015-1066

Chronic rejection/CLAD prevalence in Leuven (2010-2021, n=727)



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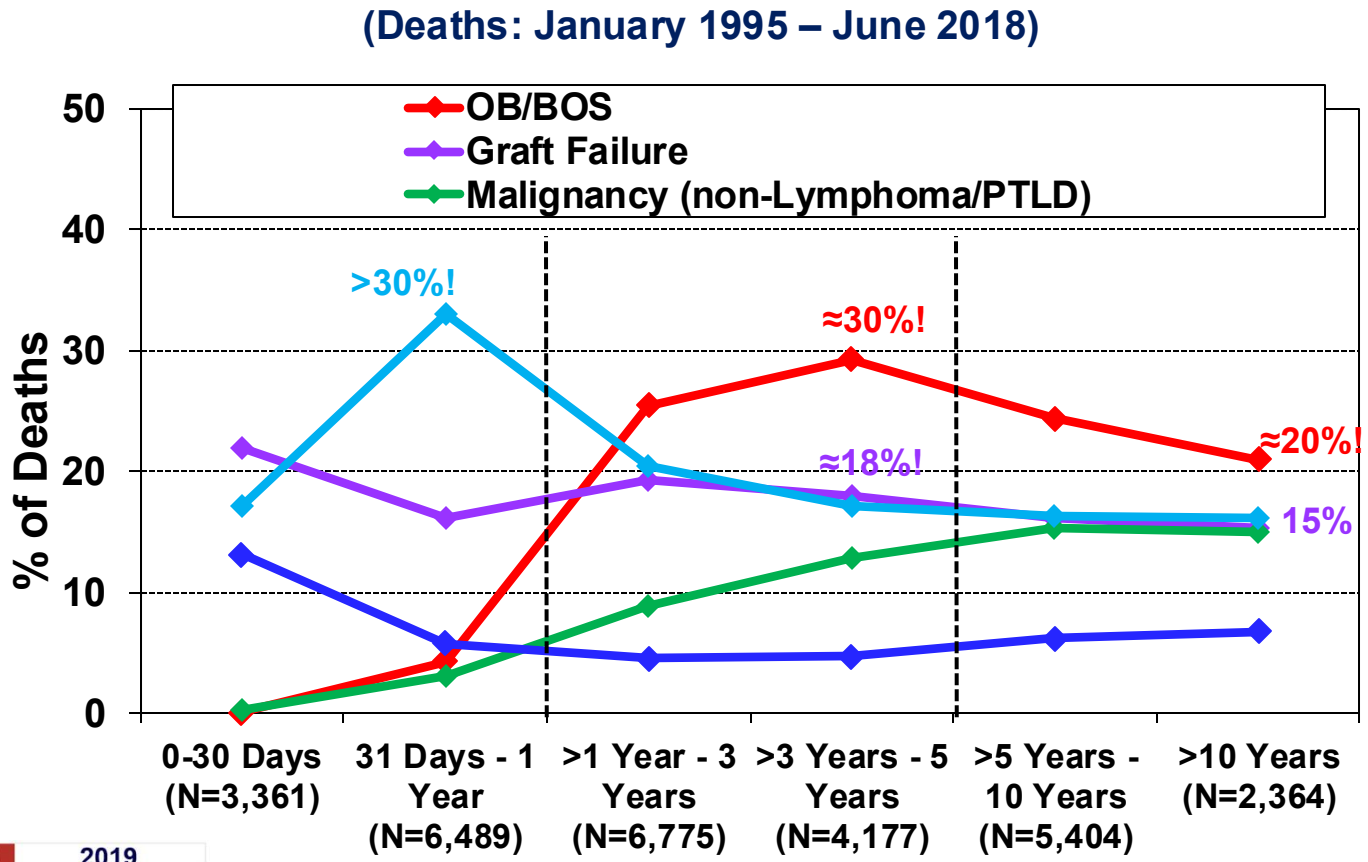
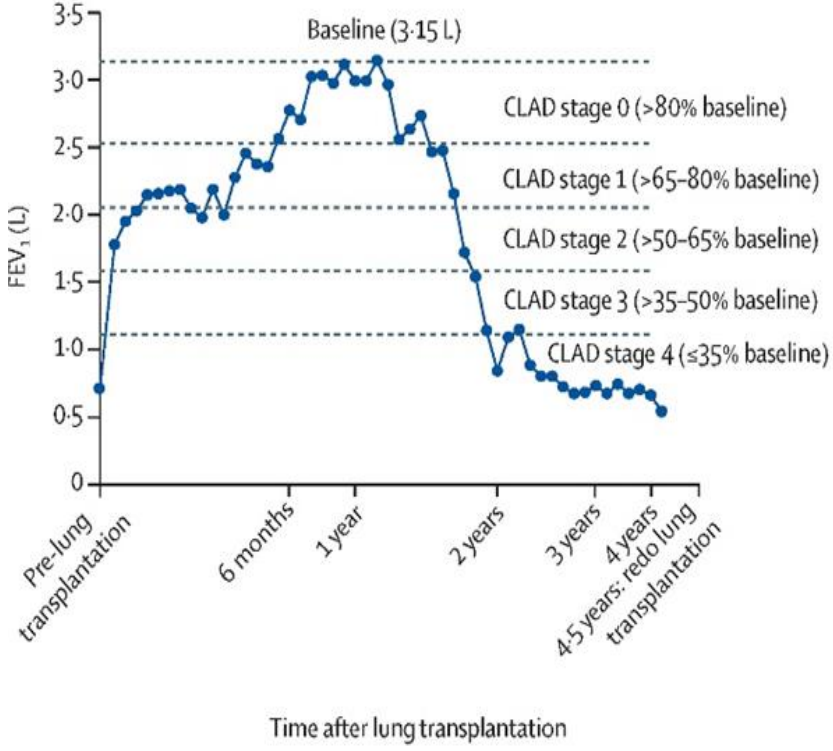
Leading Causes of Death in Adult Lung Transplants



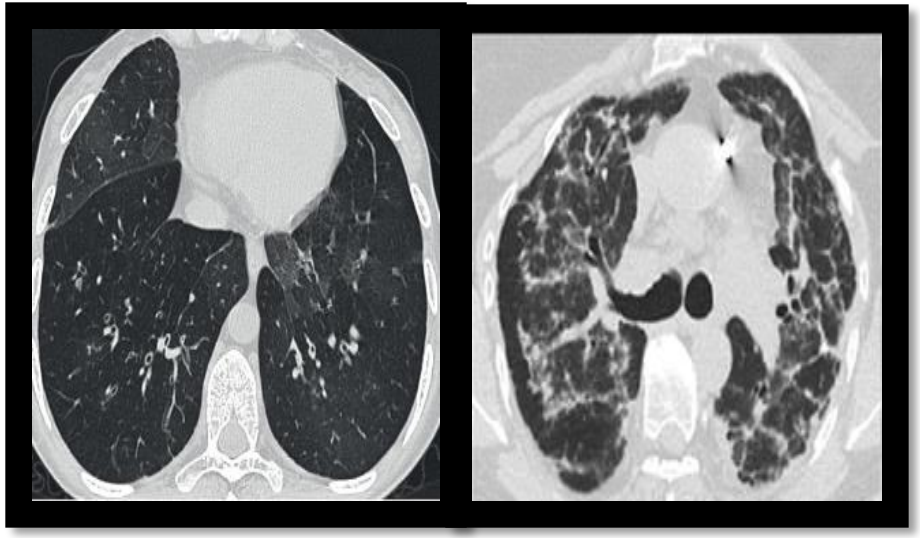
ISHLT • INTERNATIONAL SOCIETY FOR HEART AND LUNG TRANSPLANTATION 2019
JHLT. 2019 Oct; 38(10): 1015-1066

“Chronic Lung Allograft Dysfunction” (CLAD)

Functional



Radiological



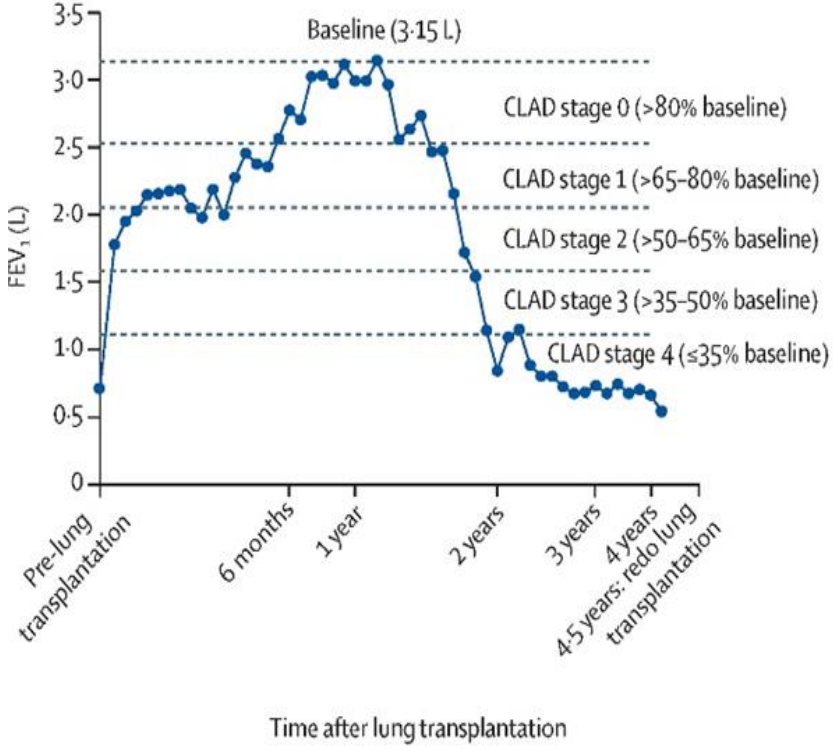
Airtrapping,
Bronchiectasis

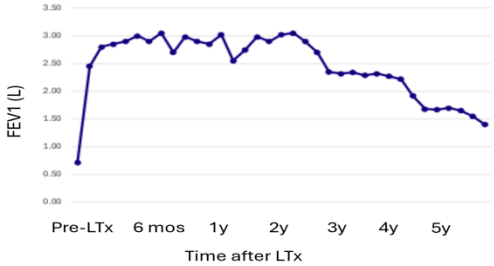
Parenchymal opacities,
Pleural thickening

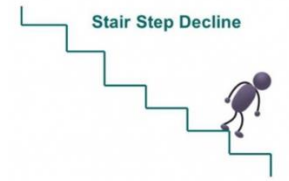
From Bos S, et al. Lancet Respir Med. 2022.

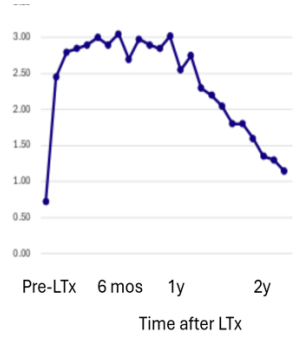
“Chronic Lung Allograft Dysfunction” (CLAD)

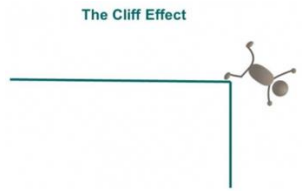
Functional

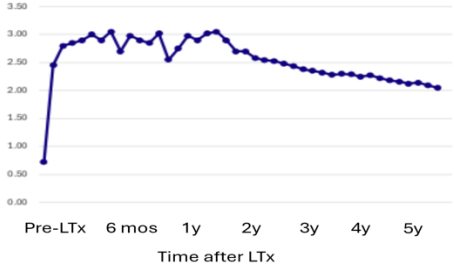






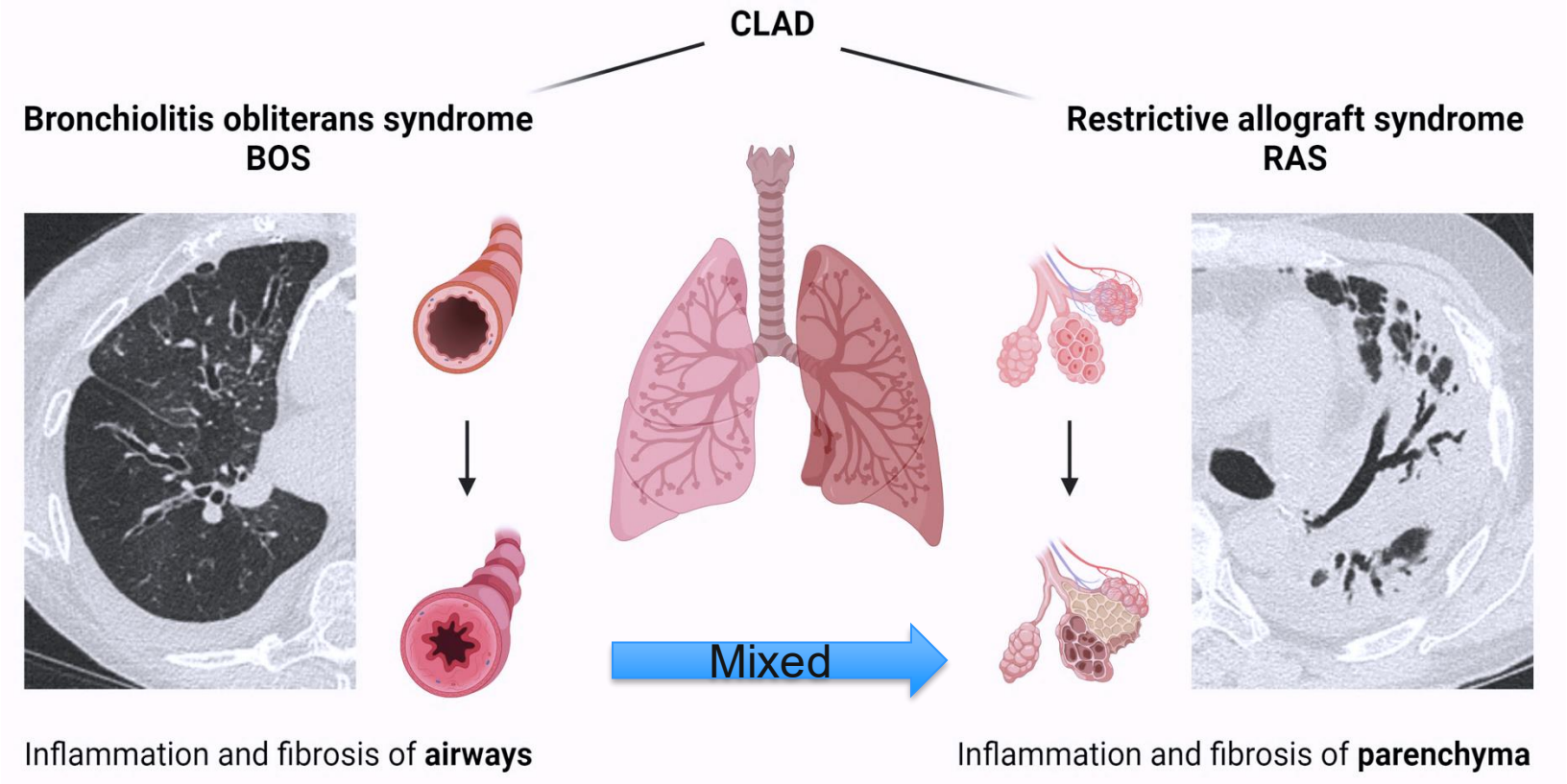






Bos S, et al. CRC. 20225

”CLAD”:
Clinical Syndrome and Phenotypes

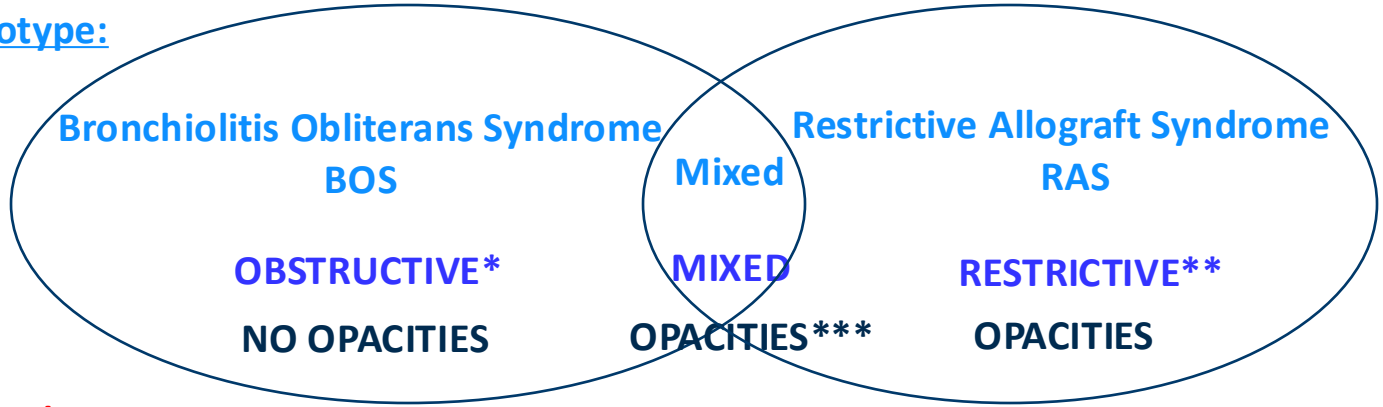


Adapted from Bos S, et al. Lancet Respir Med. 2022.

2019 ISHLT consensus definition

Umbrella term: **Chronic Lung Allograft Dysfunction** *(without clear other cause)*

CLAD



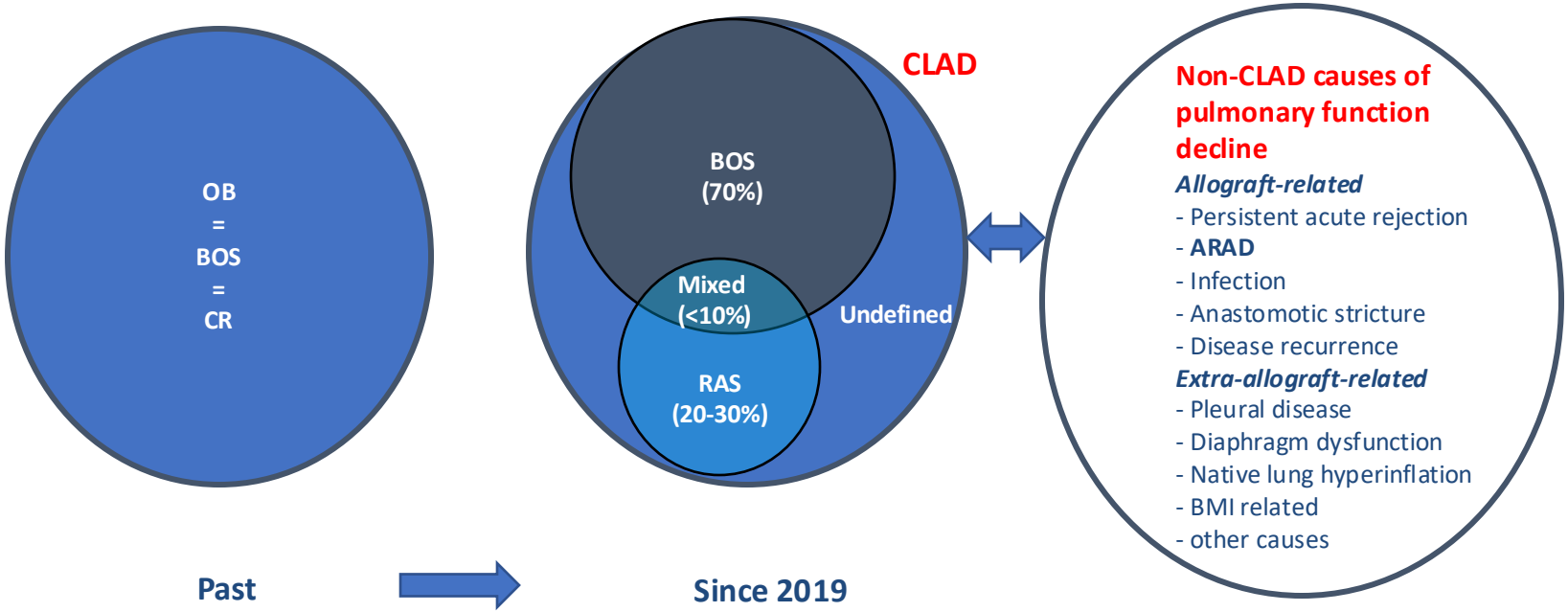
Conditions:

**Obstruction:* FEV1/FVC <0.7 ***Restriction*: TLC decline ≥10% from baseline

****Opacities*: parenchymal opacities and/or increasing pleural thickening consistent with a diagnosis of pulmonary and/or pleural fibrosis

Verleden GM, et al. J Heart Lung Transplant. 2019

CLAD Anno 2025



2025:
Diagnostics: biomarkers missing
Therapeutics: targeted therapies missing

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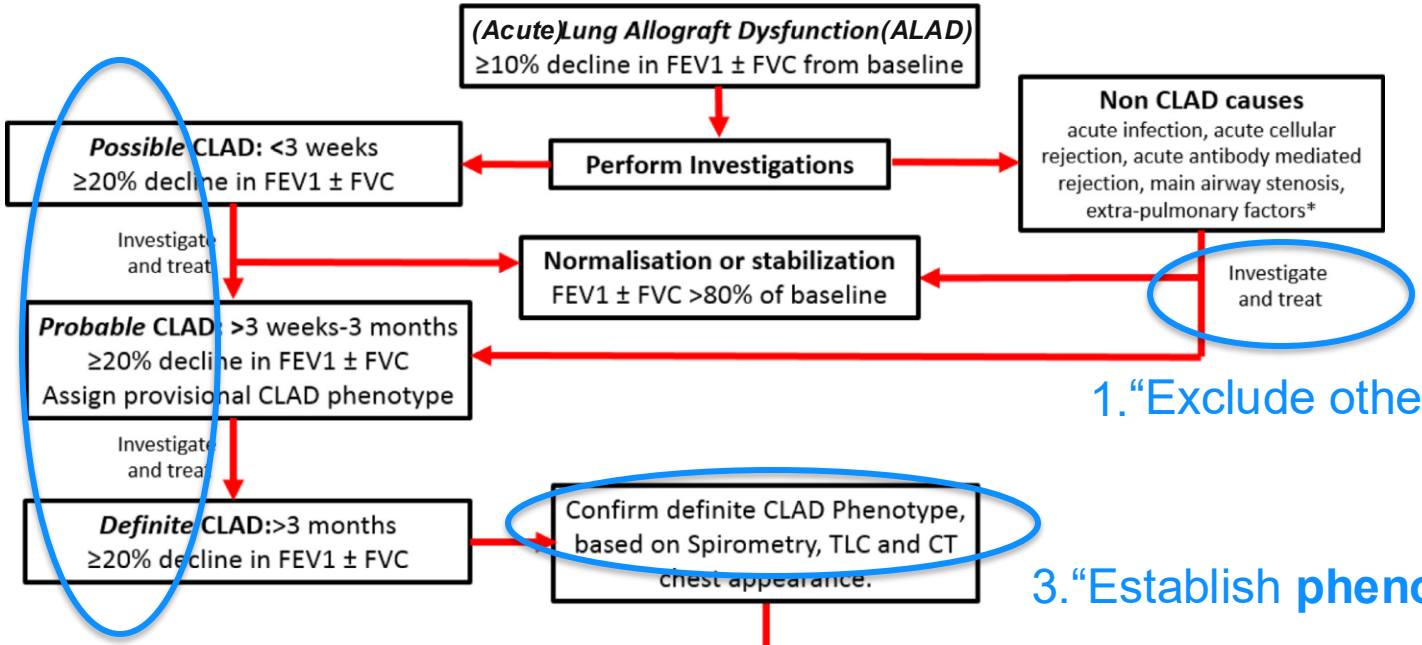
Clinical Approach of (suspected) CLAD?



1. "Exclude other **causes**"

2. "Document **chronicity**" (persistent decline)

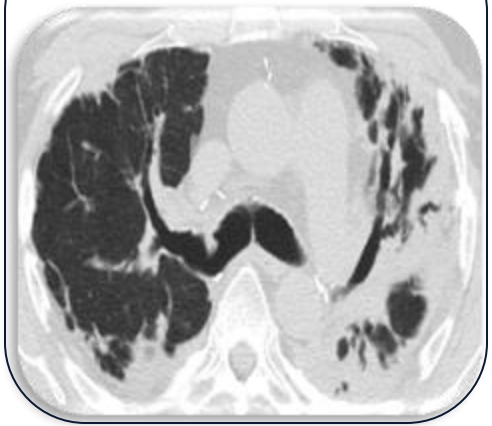
3. "Establish **phenotype**"

4. "Establish **stage**" (disease severity)

5. "**Evolution**: reassess type/stage"

Adapted from Verleden GM, et al. JHLT. 2019

Definite CLAD: establishing the phenotype

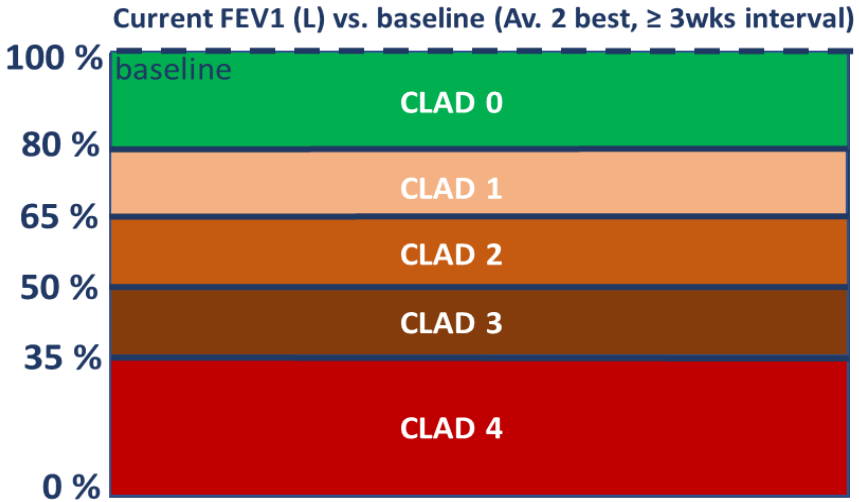
	BOS	Mixed	RAS
PFT	FEV1/FVC <0.7 + TLC >90% of baseline* +	FEV1/FVC <0.7 + TLC ≤90% of baseline* +	FEV1/FVC ≥0.7 + TLC ≤90% of baseline* +
CT**	No opacities: 	Persistent opacities: 	Persistent opacities: 

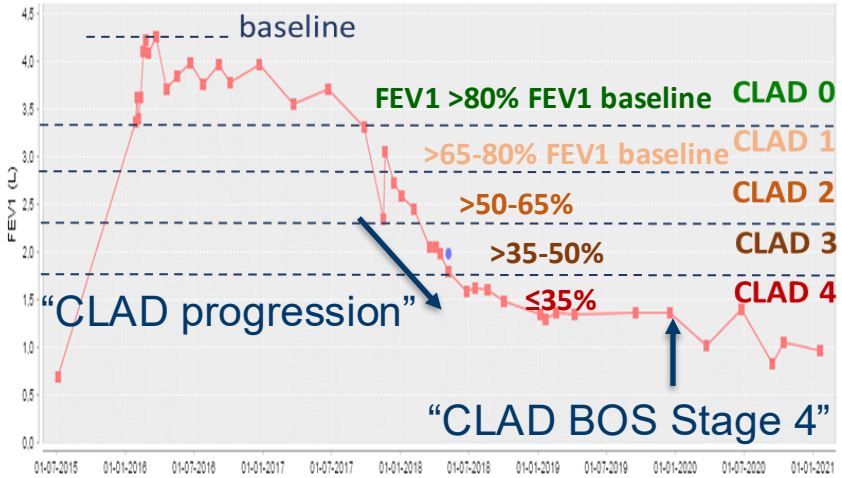
* *Baseline* TLC = TLC at 3 and 6 months post-transplant

** *Baseline* CT = (HR)CT at 6 months post-transplant (in/expir. sections)

Adapted from Verleden GM, et al. JHLT. 2019

CLAD Severity Staging and Progression





"CLAD Progression" *(definition not yet established!)* =

- ✓ FEV1 decline to more severe CLAD stage (CLAD1>2>3>4) (may be >15% decline)
  or
- ✓ FEV1 (± FVC) decline of >10% ?
- ✓ *or*? (i.e. new infiltrates? BOS -> RAS? Oxygen need? Symptoms/ PROMS? …)

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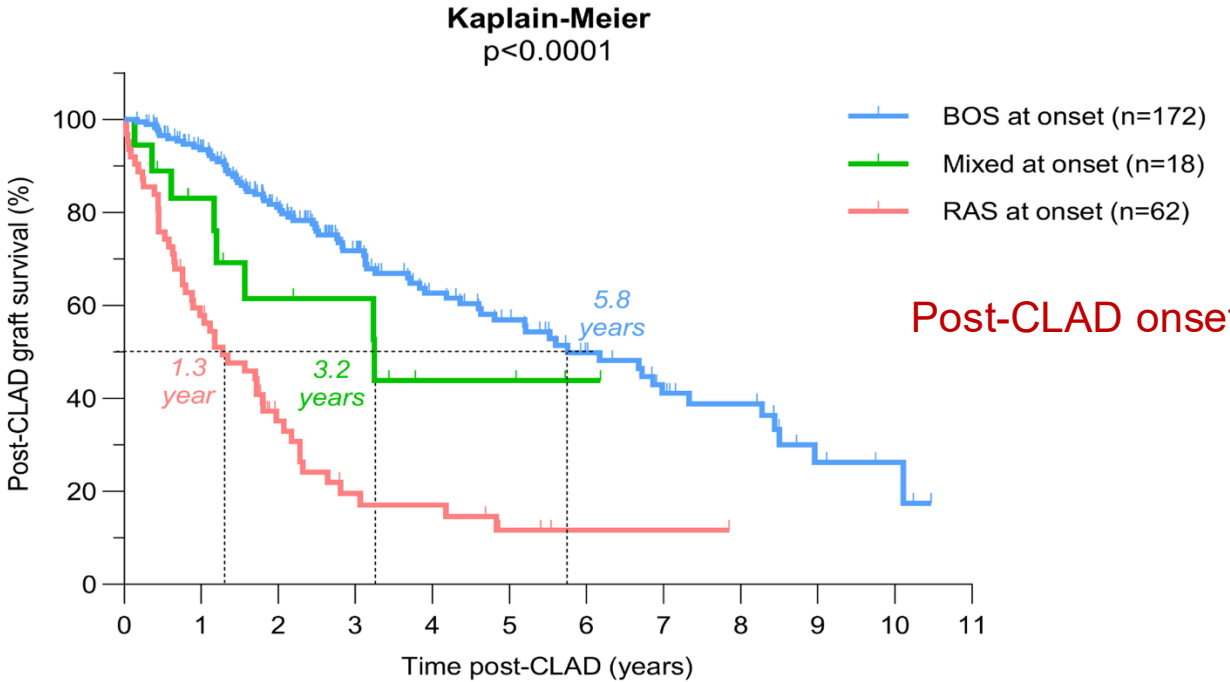
Why does phenotyping matter?
Post-CLAD graft survival in Leuven (2010-2022, n=252/918, 27.5%)

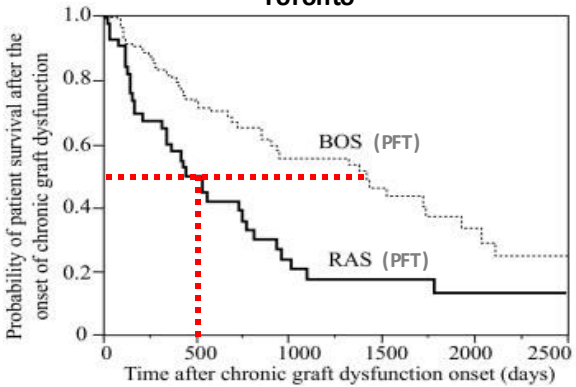


Post-CLAD onset survival ≈ 2.3y !

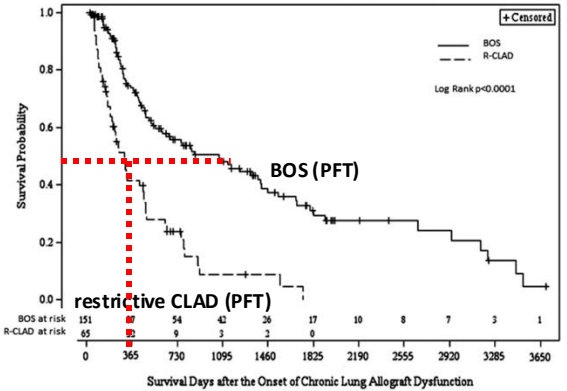
Beeckmans H, Zajacova A, et al. CLAD phenotype determines post-CLAD outcome: a contemporary single center analysis. Eur Respir J. 2024;64(Suppl 68):PA591. doi:10.1183/13993003.congress-2024.PA591.

Importance of CLAD phenotypes?

Toronto

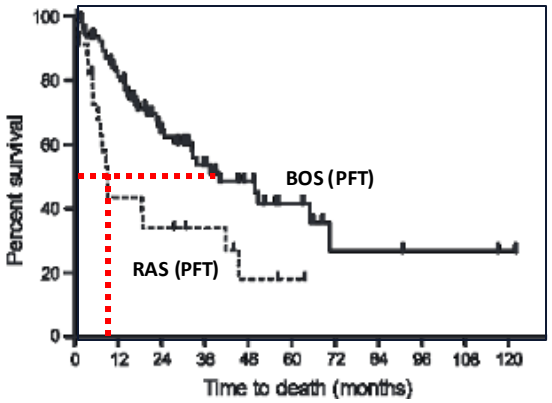


Duke

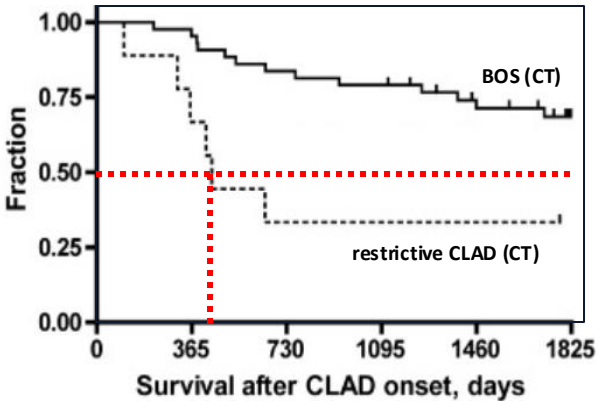


CLAD/RAS is more deadly than most lung cancers

Leuven

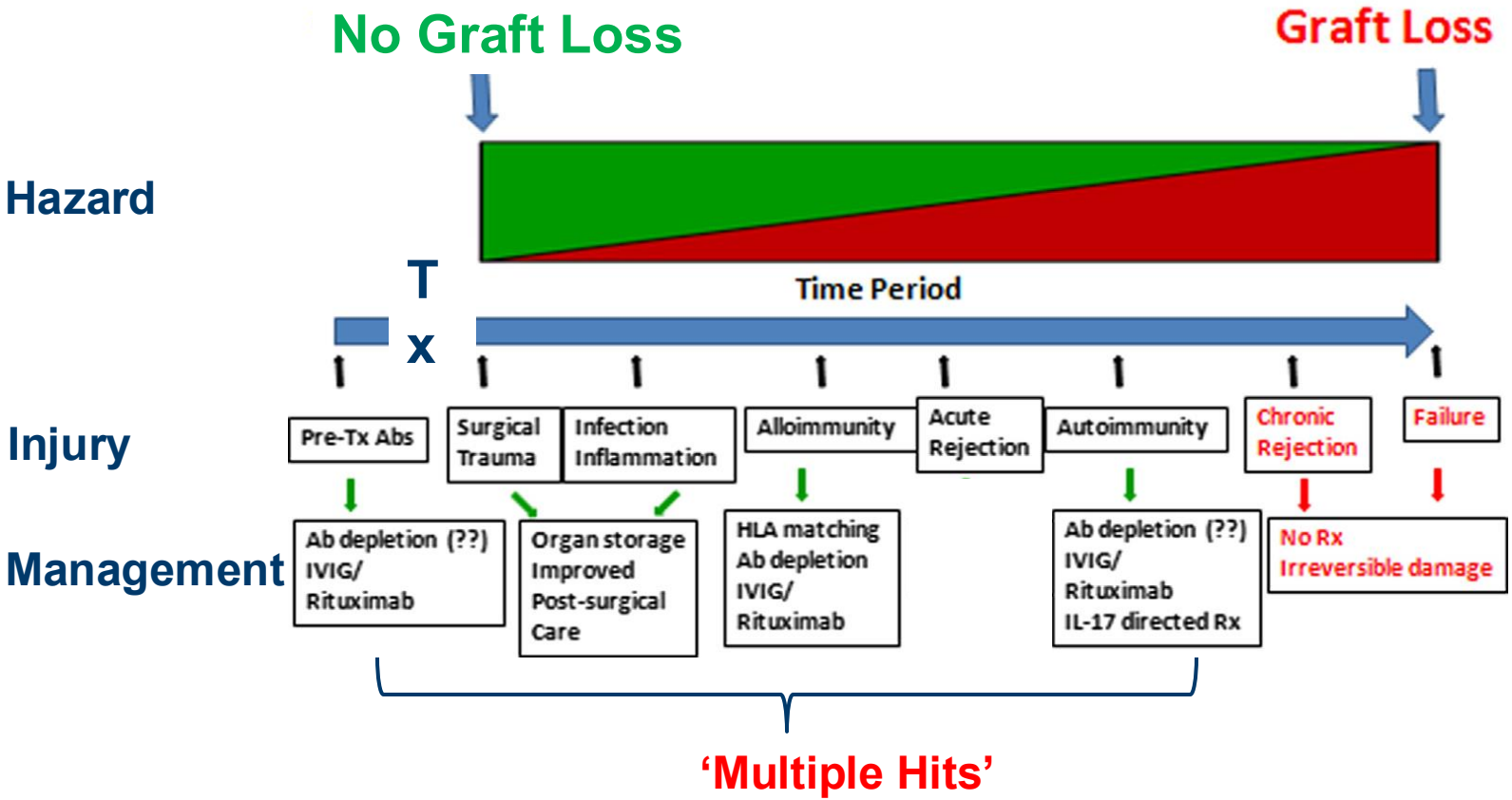


Hannover



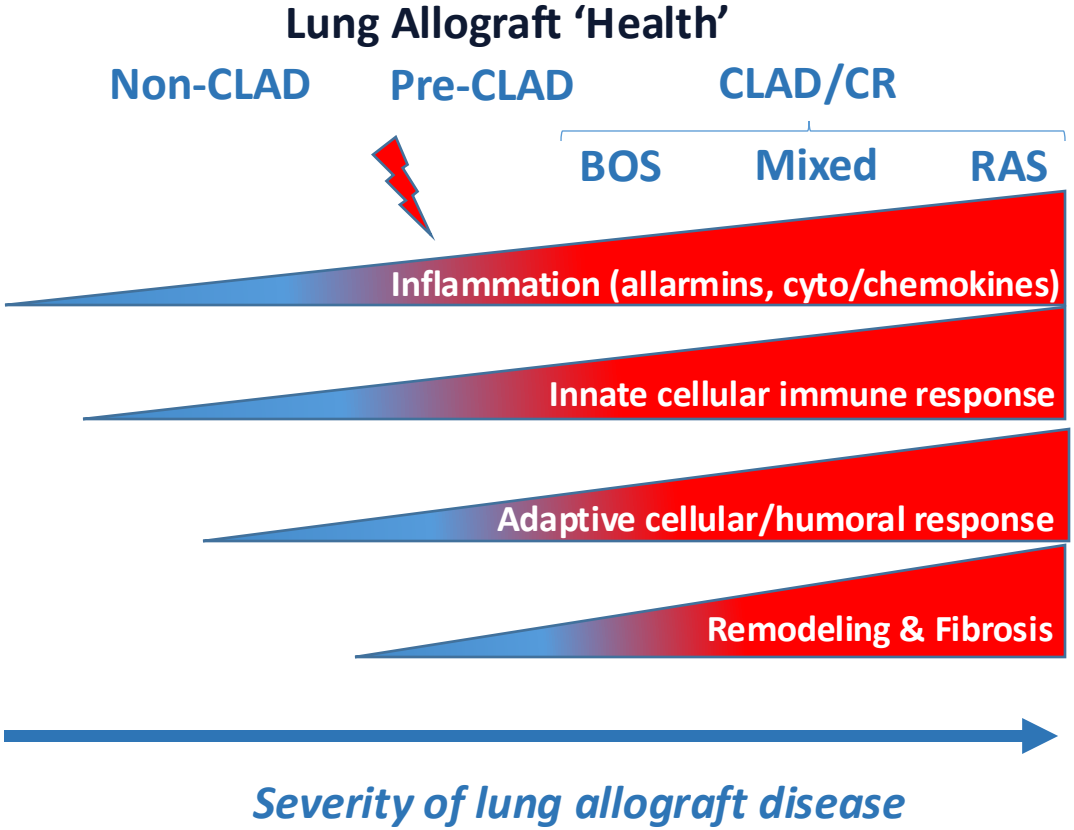
Sato, et al. JHLT, 2011. Verleden, et al. Transplantation, 2011. Todd, et al. AJRCCM, 2014. Dettmer, et al. Eur J Radiol, 2017.

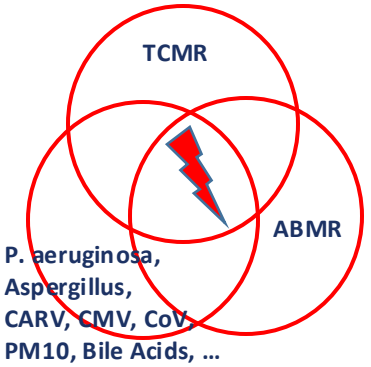
CLAD Etiology ?
'Multiple hits'–Theory



Adapted from Angaswamy, et al. Hum Immunol. 2013.

CLAD: dynamic multi-modal process

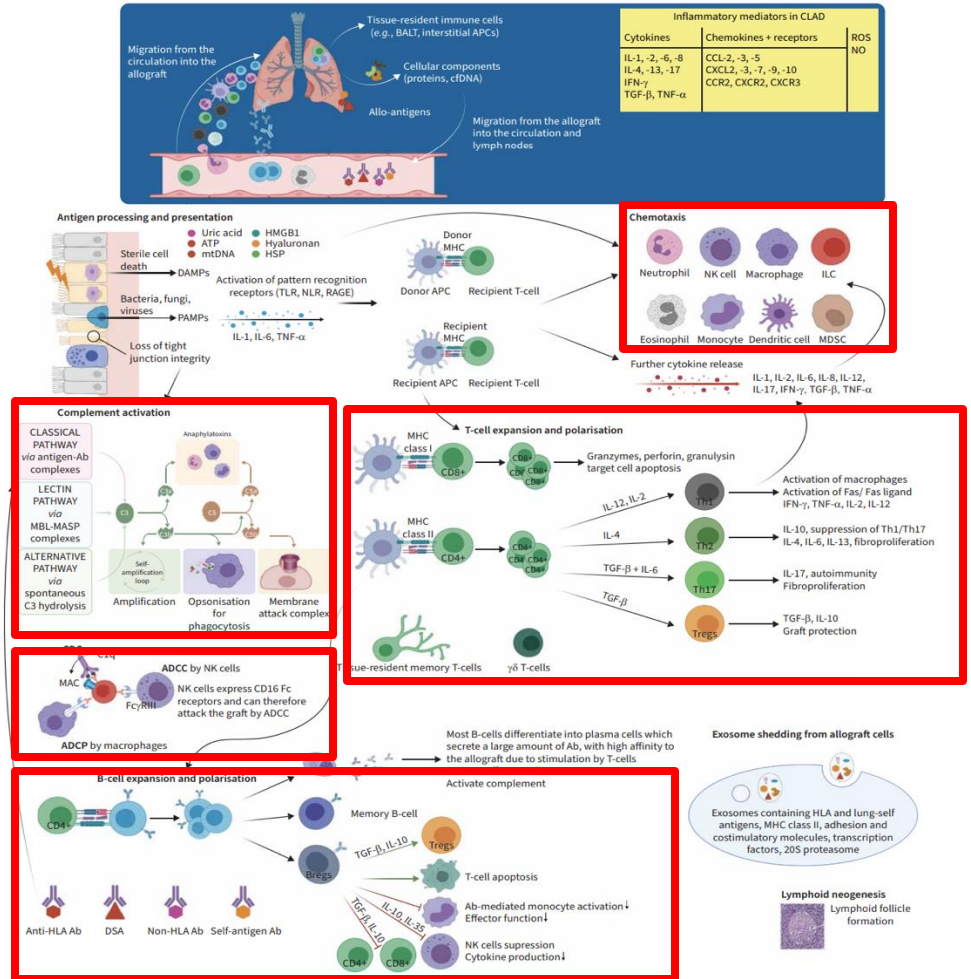




Beeckmans H, et al. Clin Chest Med. 2023

Complex immune activation

No specific biomerkers !



CHRONIC

TISSUE INJURY & NON-SELF

EARLY PHASE
Innate Immune Response

LATE (EFFECTOR) PHASE
Adaptive Immune Response / Autoimmunity

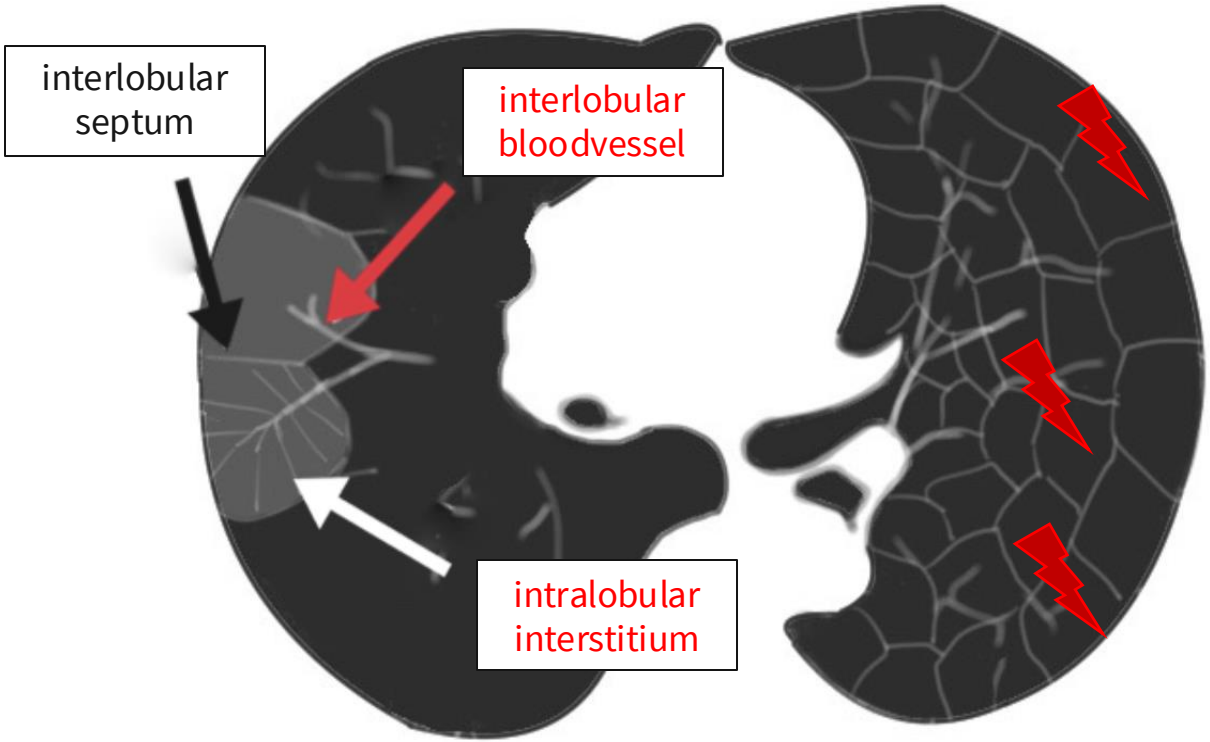
'REPAIR' PHASE
Extracellular matrix, sclerosis/fibrosis

"CLAD"

CHRONIC

Bos S, et al. Eur Respir Rev. 2022.

CLAD: pathologic changes in the secondary pulmonary lobulus

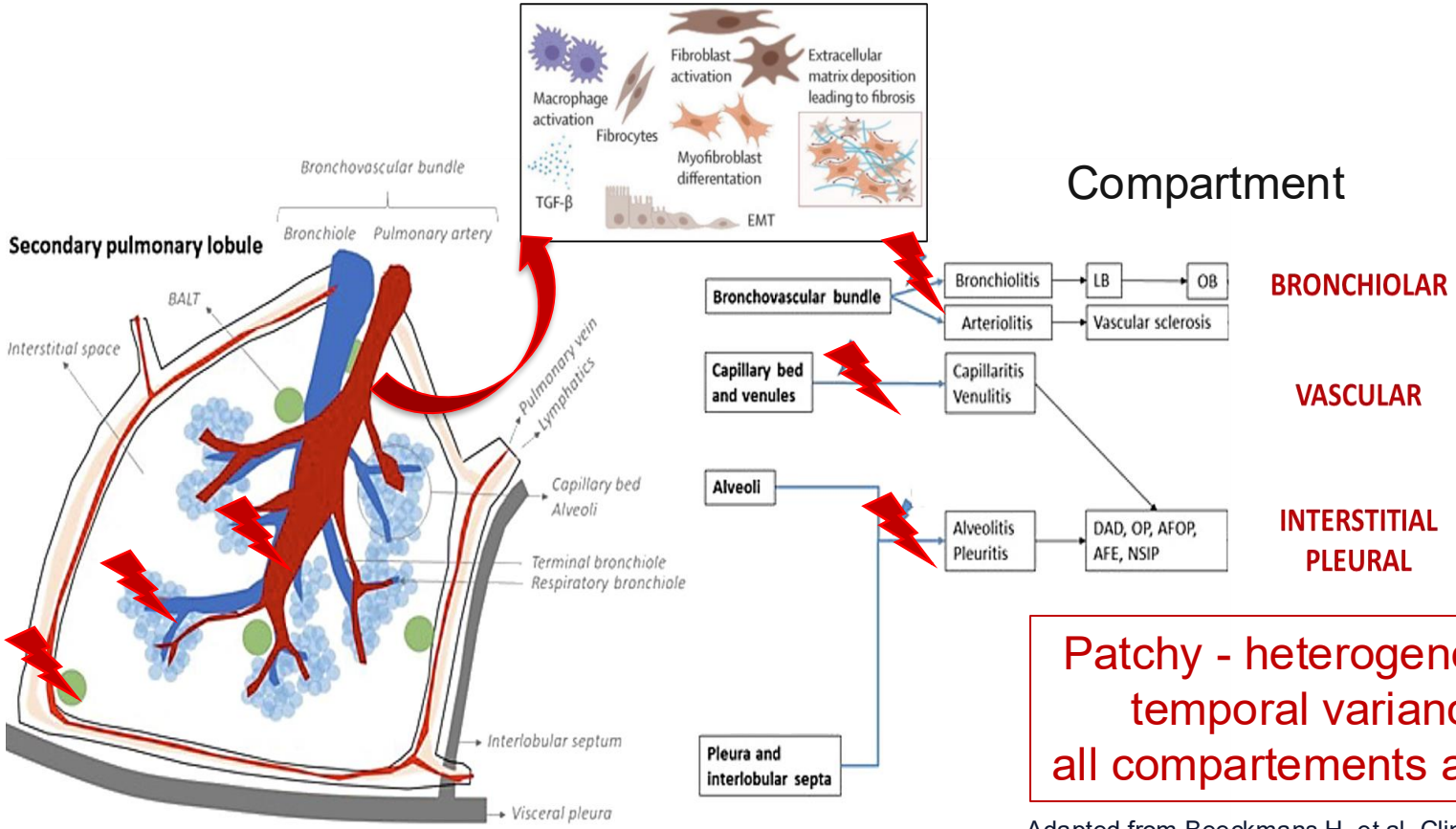


Distribution of pulmonary lobules

Patchy - heterogeneous - temporal variance - all compartements affected

Adapted from Zhao D, et al. *Authorea*. June 08, 202

Inflammatory-induced changes in the secondary pulmonary lobulus

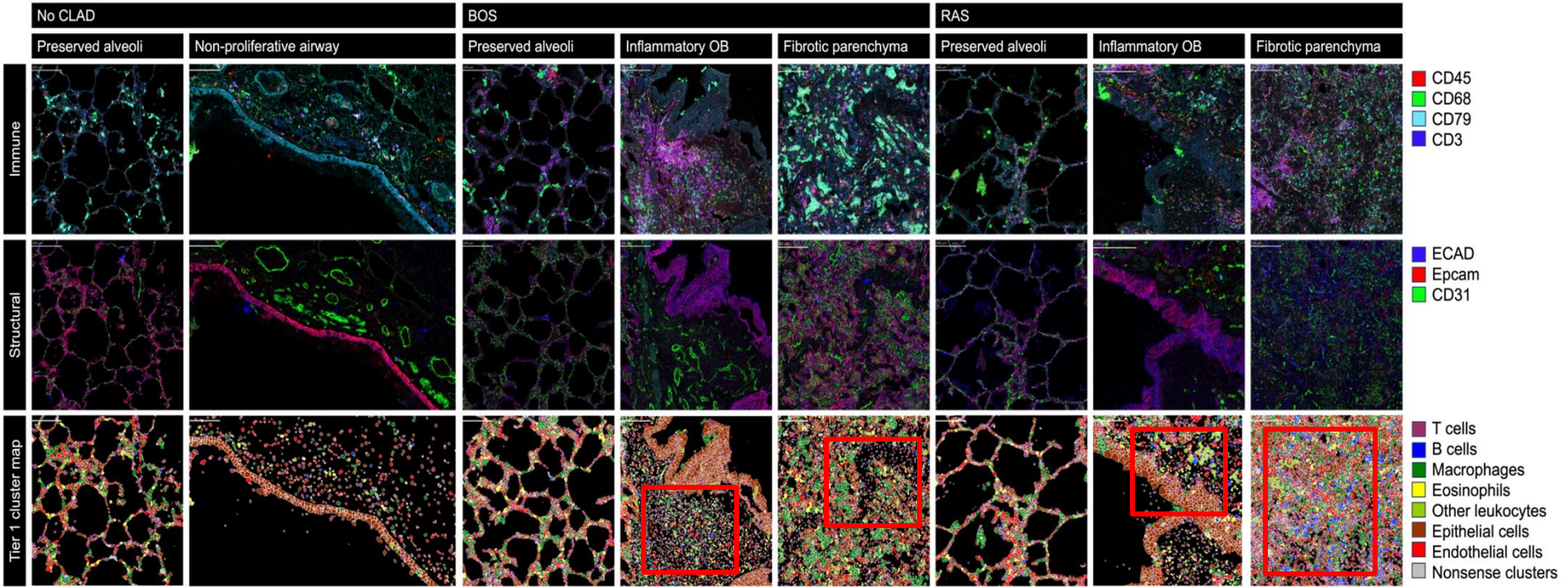


Patchy - heterogeneous - temporal variance - all compartements affected

Adapted from Beeckmans H, et al. Clin Chest Med. 2023.

Lymphoid inflammation in end-stage CLAD lungs

Explant lung tissue
end-stage CLAD vs. Ctr = non-CLAD LTx



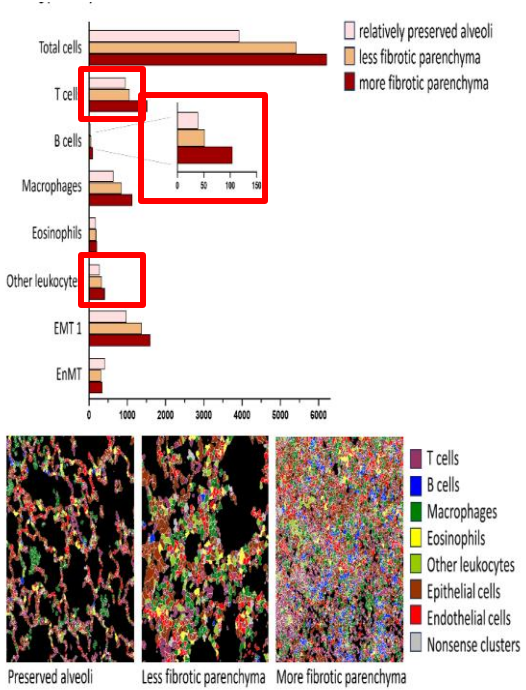
Imaging Mass Cytometry: heavy metal tagged Abs -> laser-abation -> multidimensional images

Bos S, et al. JHLT 2025.

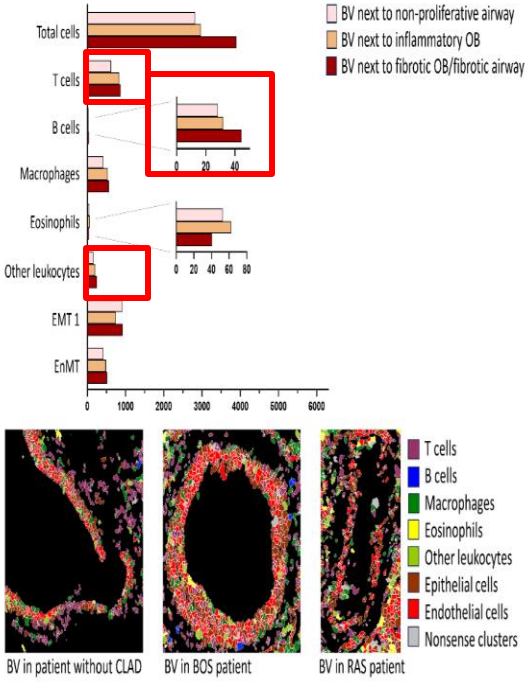
Lymphoid inflammation ~ fibrosis in CLAD lungs

Explant lung tissue
end-stage CLAD vs. Ctr = non-CLAD LTx

PARENCHYMA



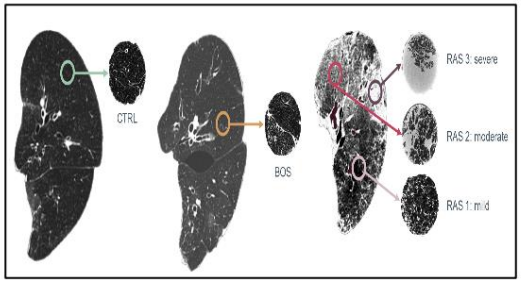
BLOOD VESSELS

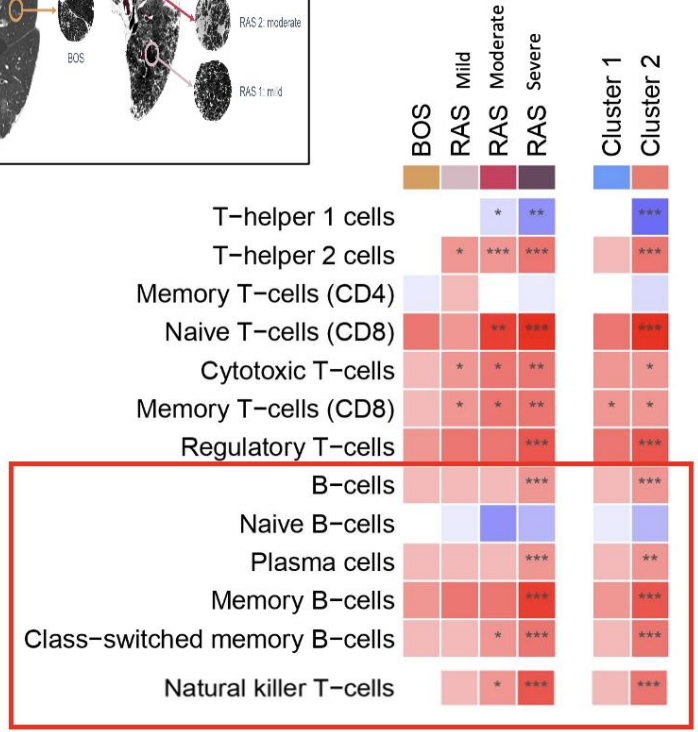


Bos S, et al. JHLT 2025.

Linking phenotypes, fibrosis and molecular endotypes

Explant lung tissue RNAseq
(end-stage disease, BOS vs. RAS vs. non-CLAD LTx)

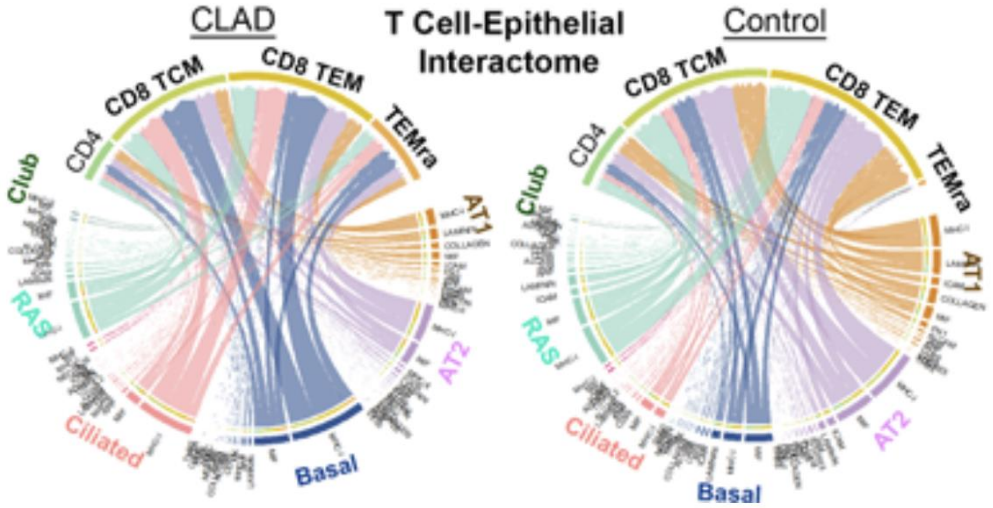


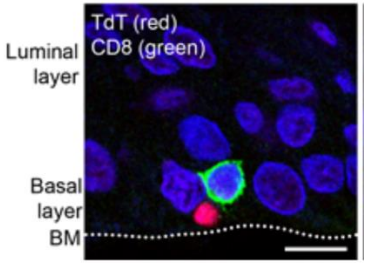


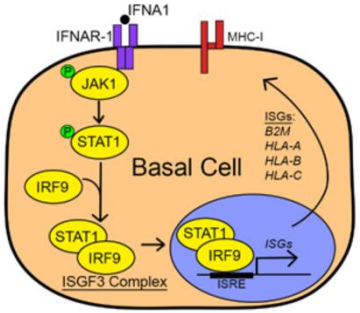
Beeckmans H, et al. Presented at ERS 2022. In preparation.

Immune cell dynamics in CLAD: pathway and cell-cell interaction discovery

SSRNAseq in 4 CLAD and 3 donor control lung samples



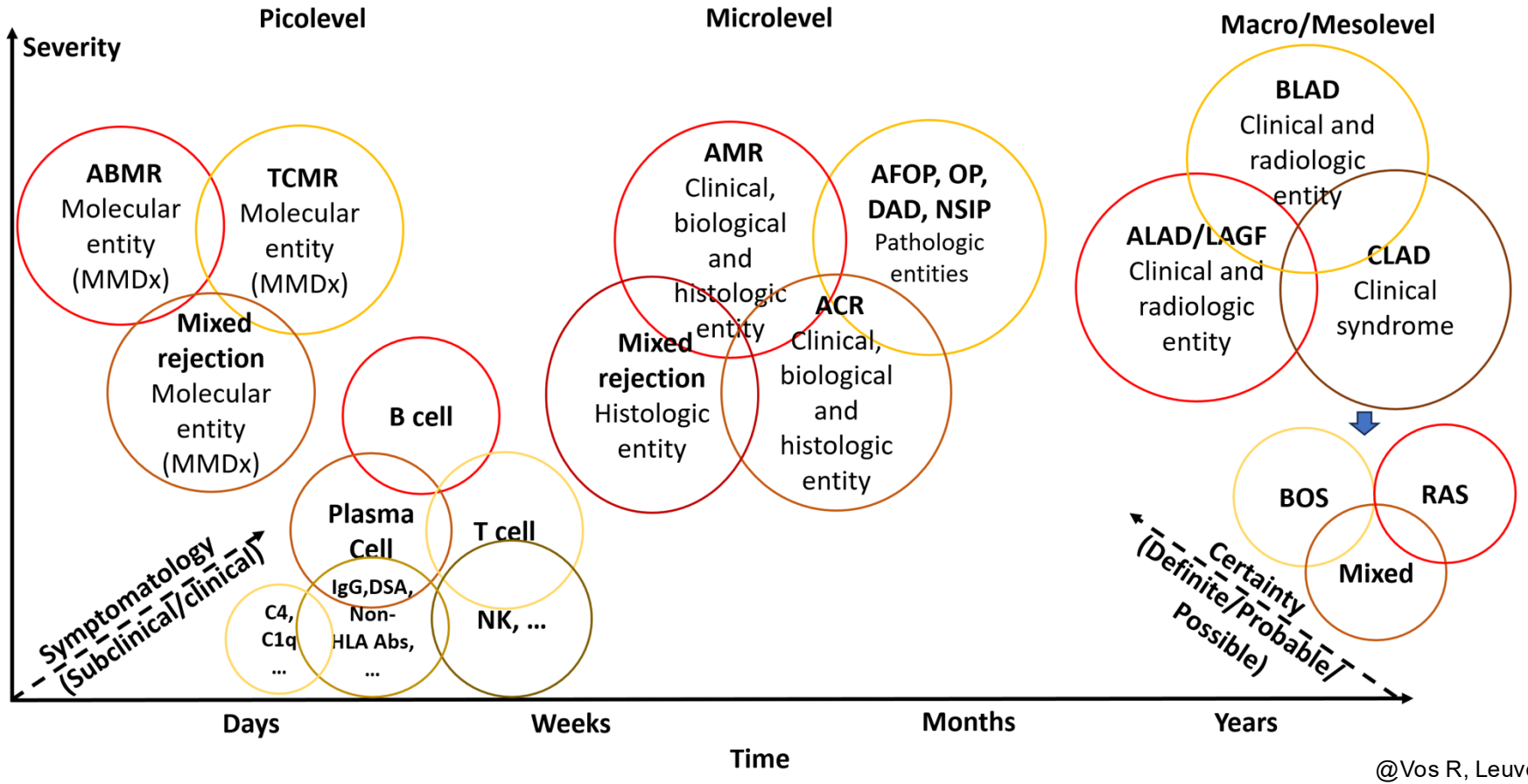




Activation of JAK-STAT signaling leads to upregulation of MHC-I in airway basal cells and contributes to cytotoxic CD8+ T cell–mediated basal cell death in CLAD

Khatri Y, et al. JCInsight 2023

The molecular complexity of CLAD

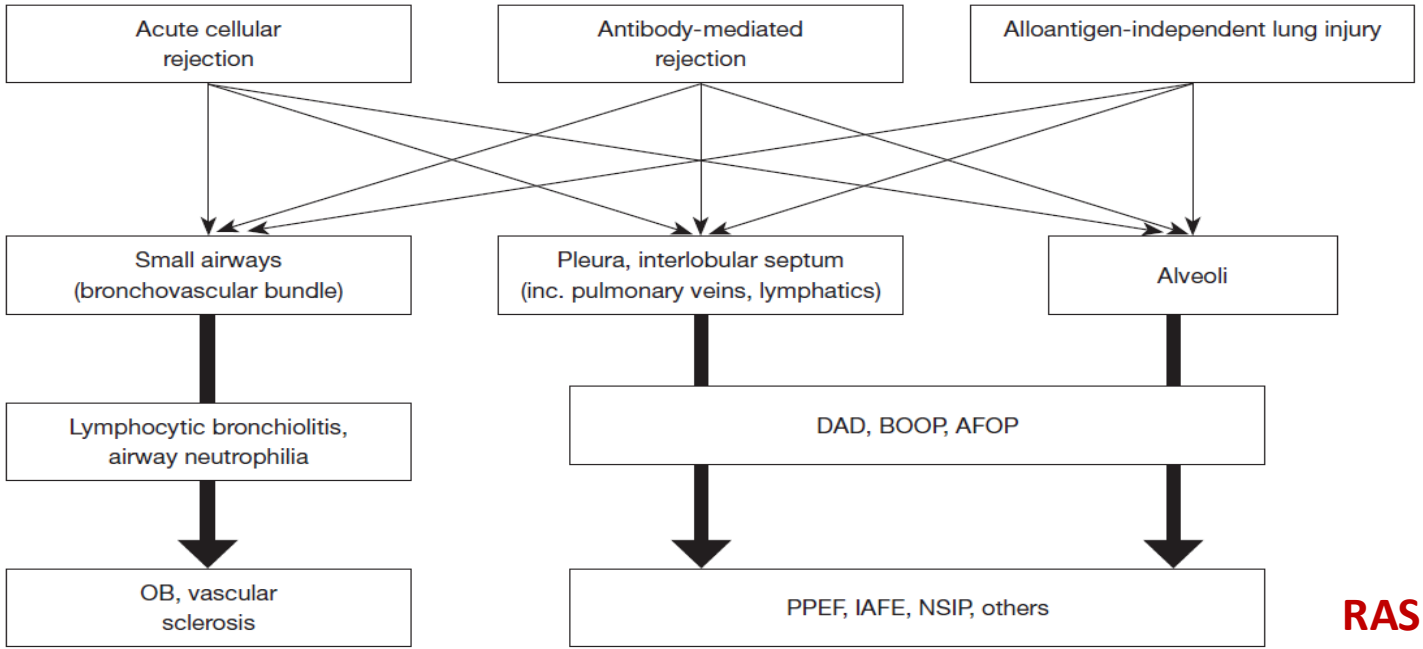


@Vos R, Leuven

Lung allograft injury: 'multiple-hits theory'

"Preventable/Treatable Traits?"

Non-adherence, Suboptimal IS, HLA-sensitization/mismatch/DSA P. aerug, CMV, CARV, Asperg, GERD, PM10



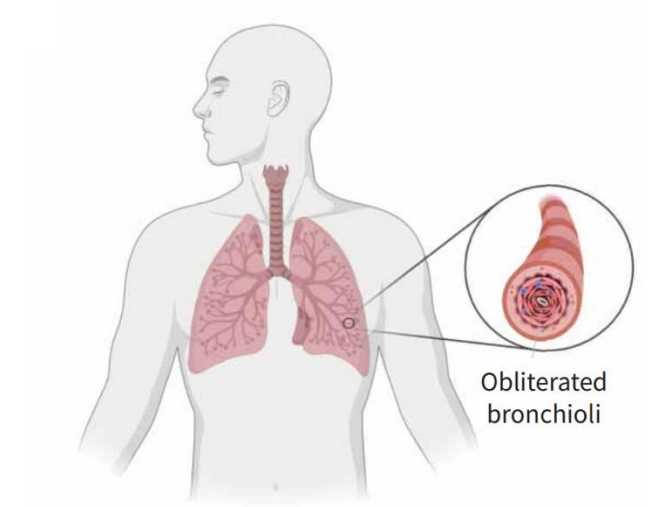
BOS

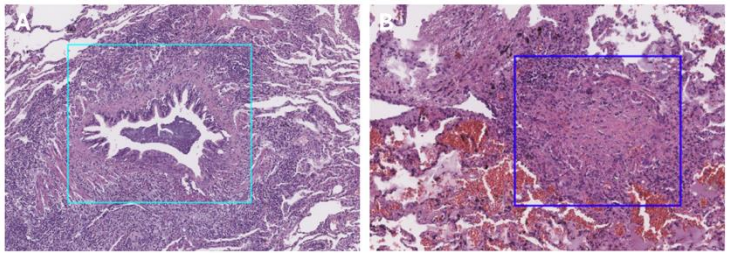
RAS

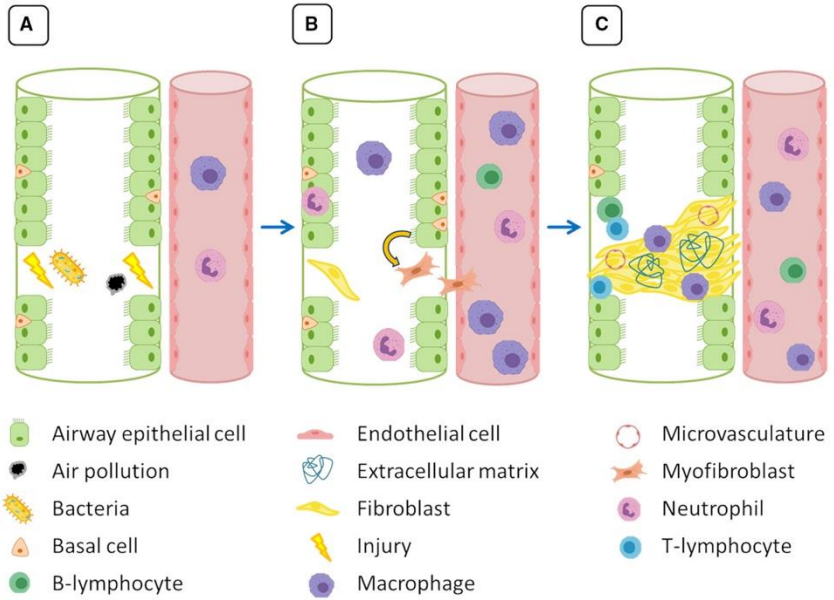
'CLAD' ≃ all equally responsive to treatment (?)

Adapted from Sato M. Ann Transl Med 2020.

Bronchiolitis Obliterans Syndrome (BOS)

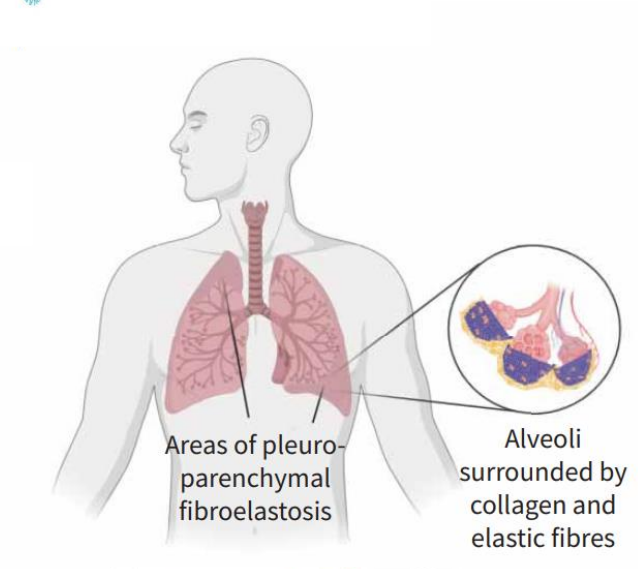


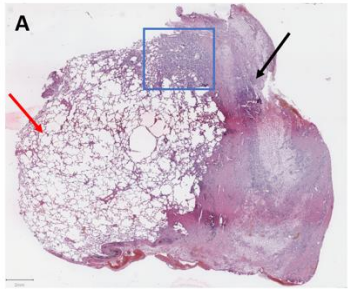


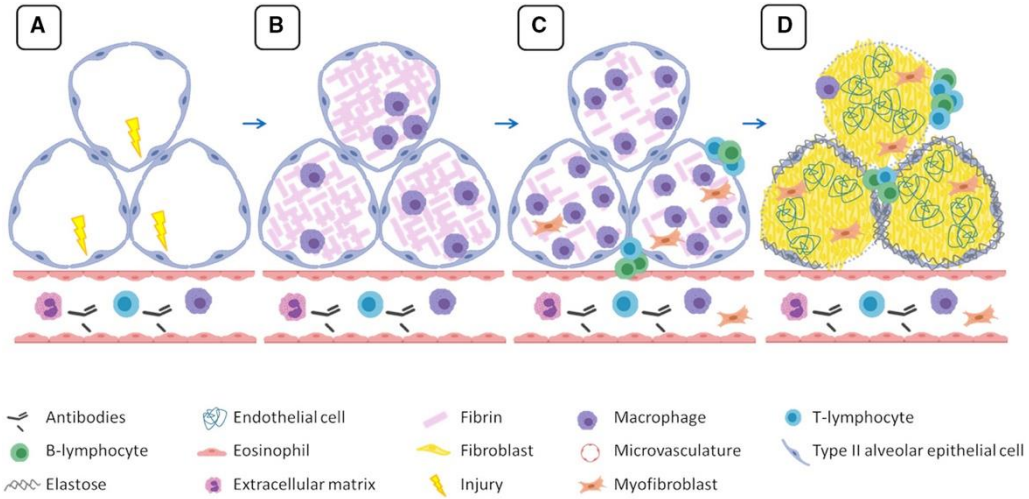


Adapted from Verleden SE, et al. *Am J Transplant*. 2020;20(10):2644-2651 and BOS S, et al. CRC Press.2025.

Restrictive Allograft Syndrome (RAS)

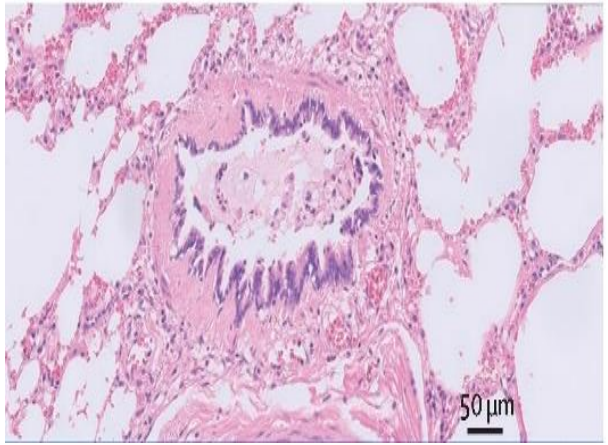


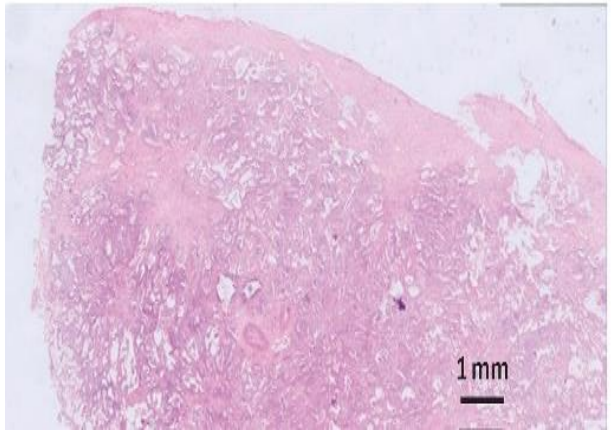




Adapted from Verleden SE, et al. *Am J Transplant*. 2020;20(10):2644-2651 and BOS S, et al. CRC Press.2025.

Irreversible tissue remodeling in CLAD



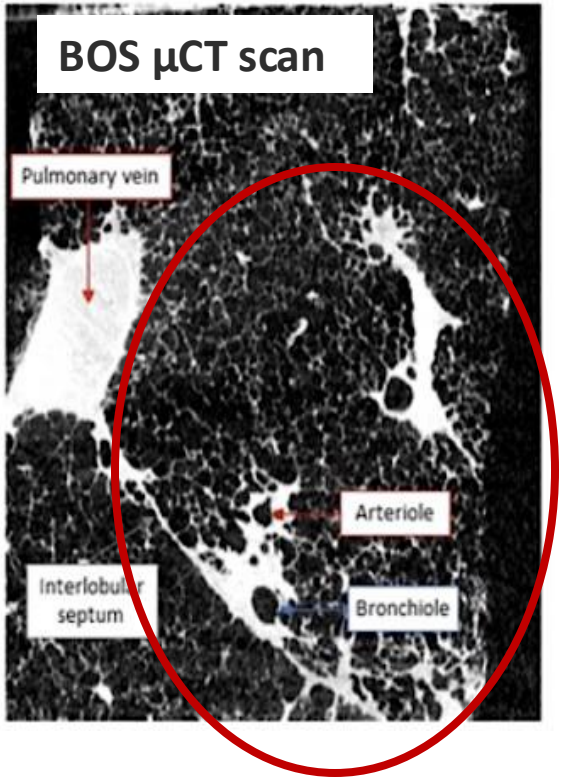


Constrictive Bronchiolitis (CB) / Obliterative Bronchiolitis (OB)

Mixed

Interstitial lung disease:
DAD, AFE, NISP, AFOP, (C)OP, interstitial fibrosis

AND **CB/OB!**



Bos S, et al. Lancet Respir Med. 2022. Beeckmans H, et al. Clin Chest Med. 2023.

Small airways disease

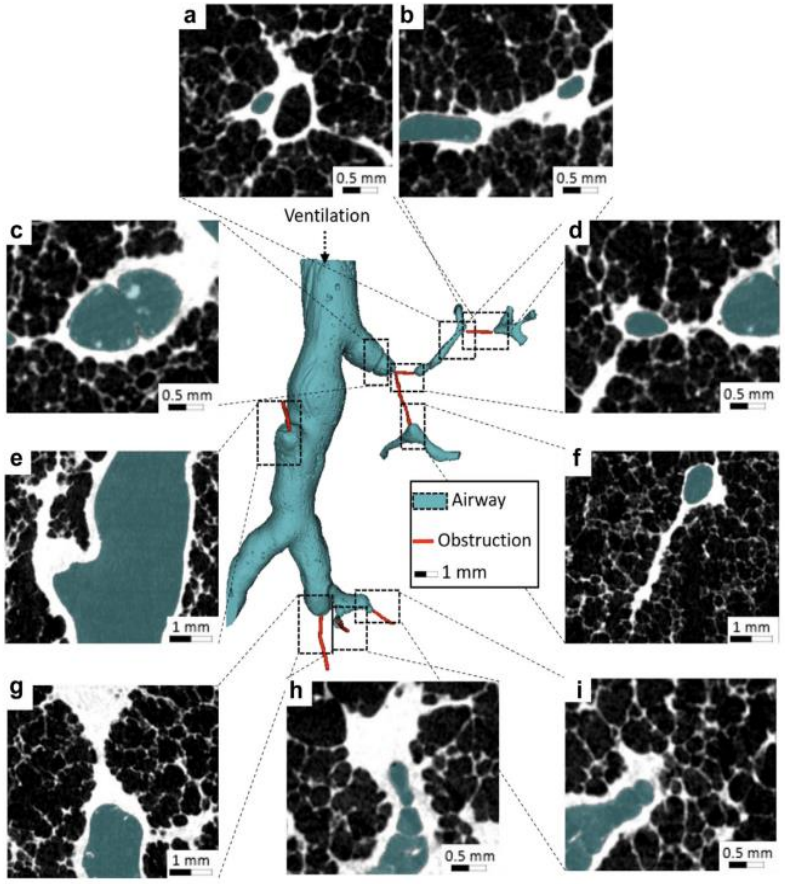
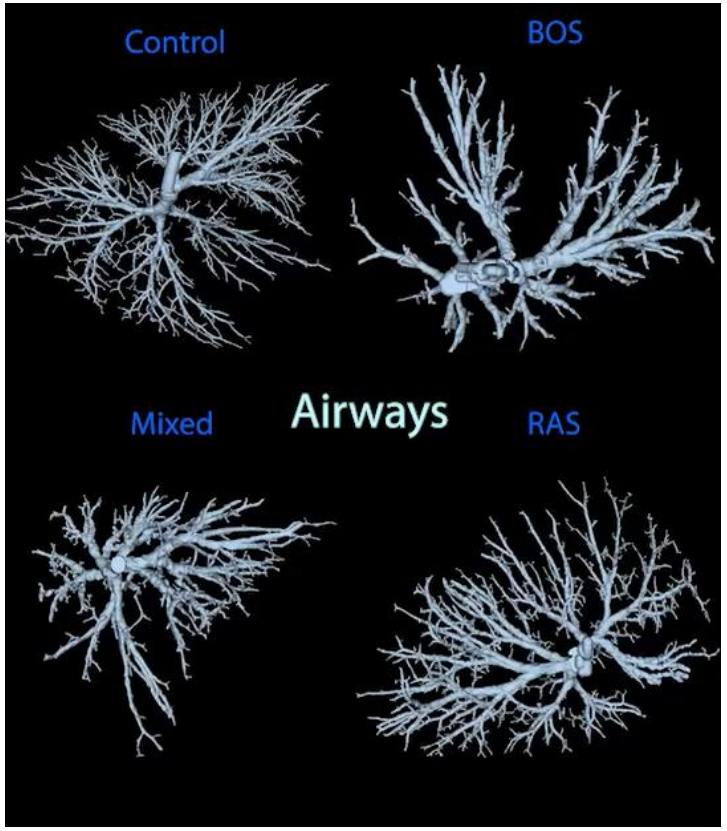


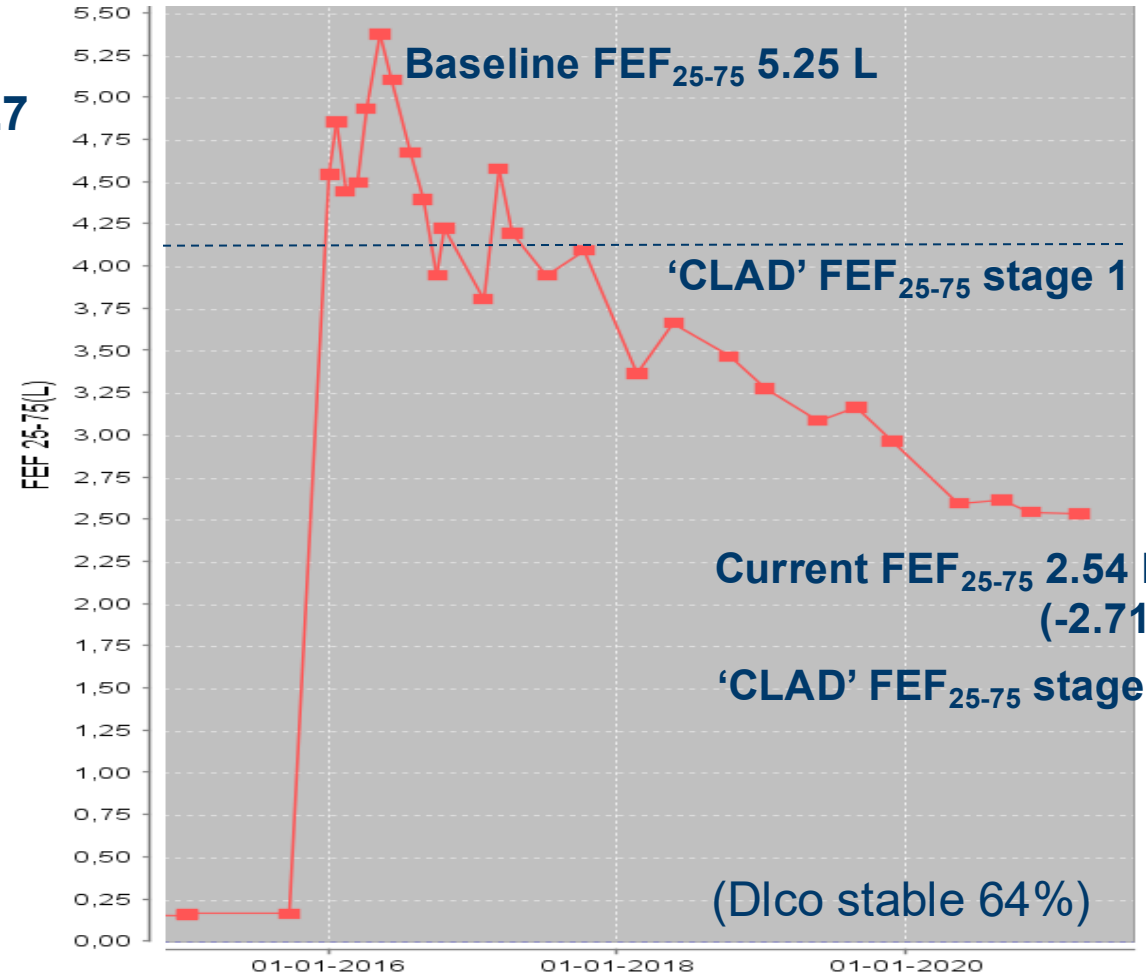
Fig. 8: **Airway tree from a BOS core with CT images of all observed lesions.** (a) Narrowed airway (CB). (b) Example of CB. (c) Example of a web. (d) Example of CB. (e) Example of CB in a relatively large airway. (f–i) examples of CB with some webs in h-i.



Kerckhof P, et al. eBiomedicine. 2024.

Diagnosing ‘CLAD’: why are small airways left out?

FEV1/FVC >0.7

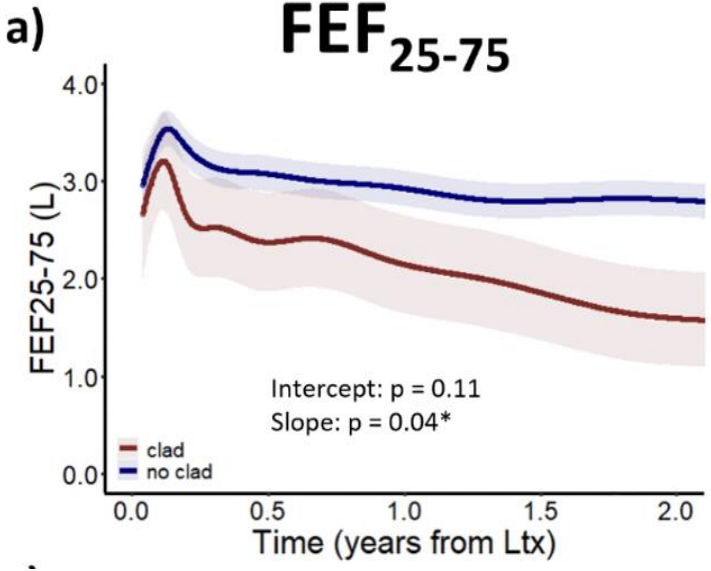


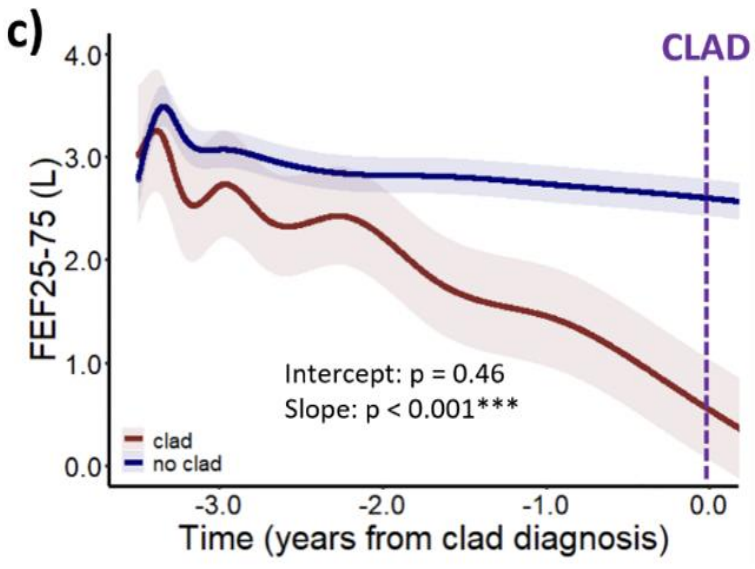
@5Y: No CLAD per ISHLT 2019

Diagnosing ‘CLAD’: why are small airways left out?

CLAD: Diagnosis 2-5y after transplantation, n=39

No CLAD: No diagnosis in first 5y after transplantation, n=305





Kerckhof P, et al. ISHLT Abstract 2025.

Shortcomings of 2019 CLAD Consensus Definition

- CLAD is a retrospective diagnosis ('the damage is done') - prevention is key
- CLAD treshold ('80%' of $FEV1_{best}$)) - misses early disease (≈'BOS 0p')
- Accurate phenotype assessment difficult
- Phenotype changes not accounted for/defined
- Other causes are not always fully excludable (i.e. persistently ongoing ACR/AMR)
- 'Definite' but still 'variable' evolution

- Spirometry is not sensitive or specific
- 'Obstruction' based on FEV1/FVC <0.7 vs. LLN (vs. 'abnormal physiology')
- Bodyplethysmography (TLC) is not always possible/available
- Small airways function (FEF25-75) is not included
- 'Normal decline' (ageing) not accounted for
- 'Baseline Allograft Dysfunction (BLAD)' not accounted for (i.e. higher CLAD risk)
- 'Opacities' = 'parenchymal opacities and/or increasing pleural thickening' (same importance?)

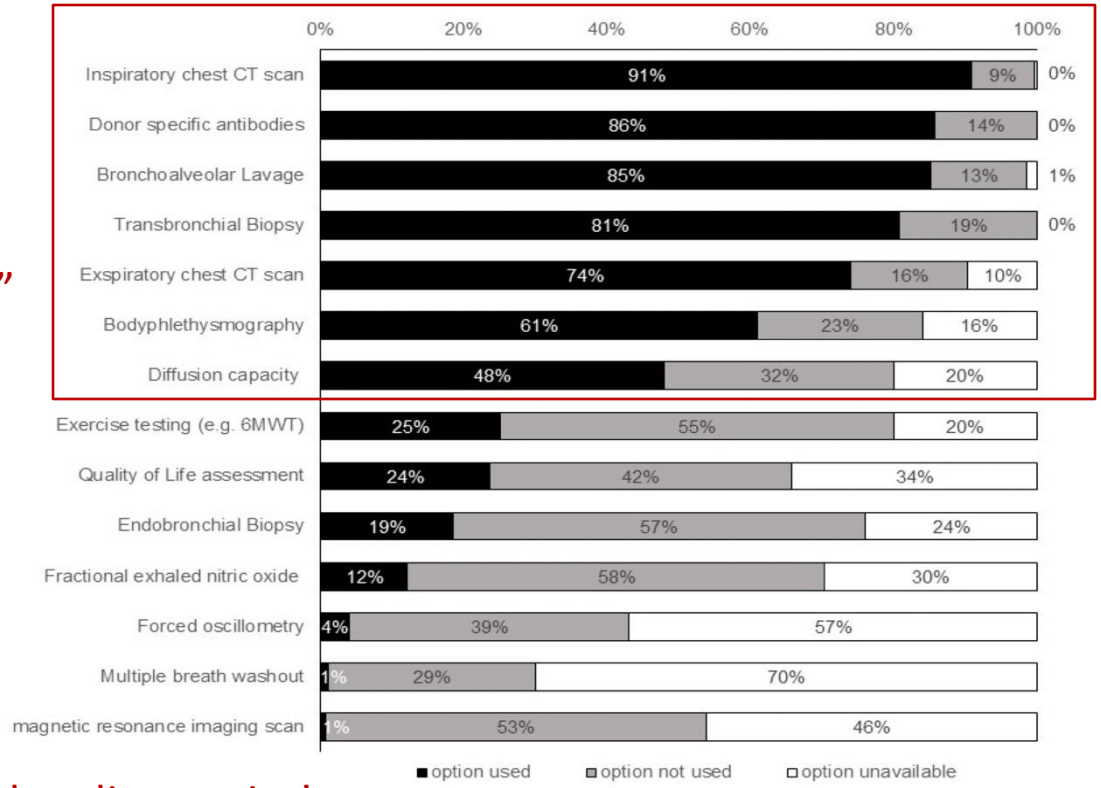
Diagnostic testing for possible CLAD

EU practices

n=44 centers, n=20 countries,
74% all Tx in EU

Practice variation!

despite ISHLT 2019:
”exclude other cause”



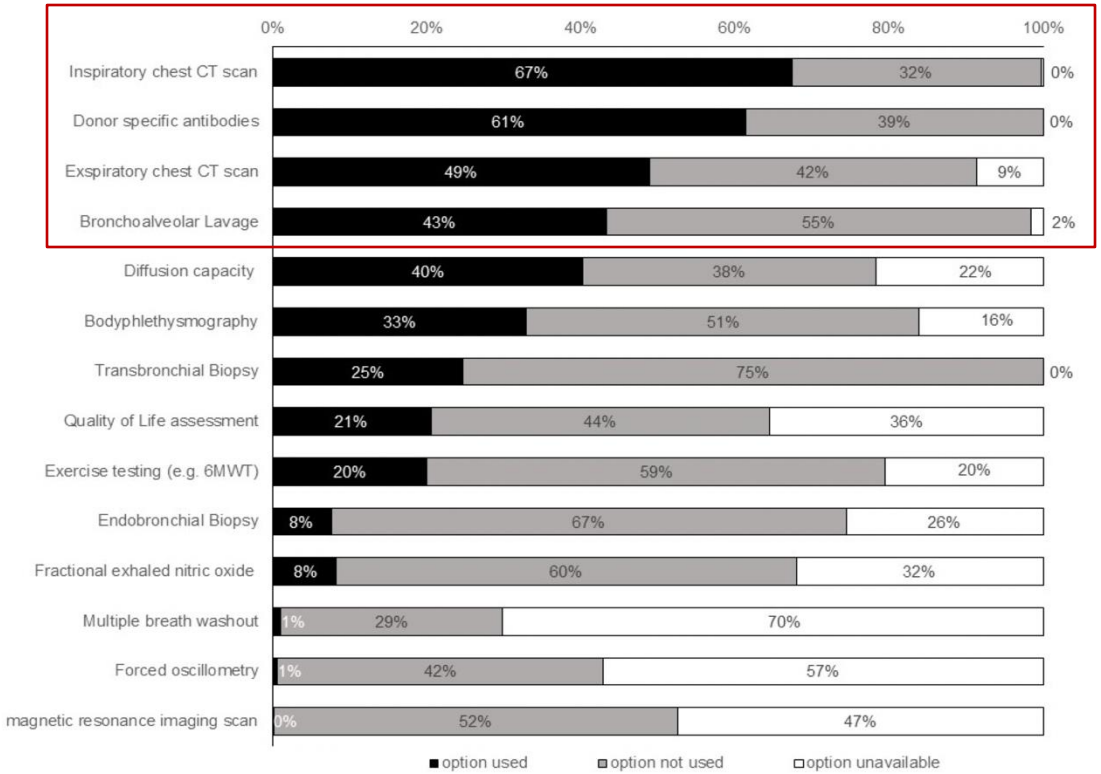
No molecular/biomarker diagnostics!

Gottlieb J, et al. Eur Respir Rev. 2025

Monitoring of pts with definite CLAD (ex. spirometry)

No guidelines on
'minimal KPI'
in established CLAD

EU practices



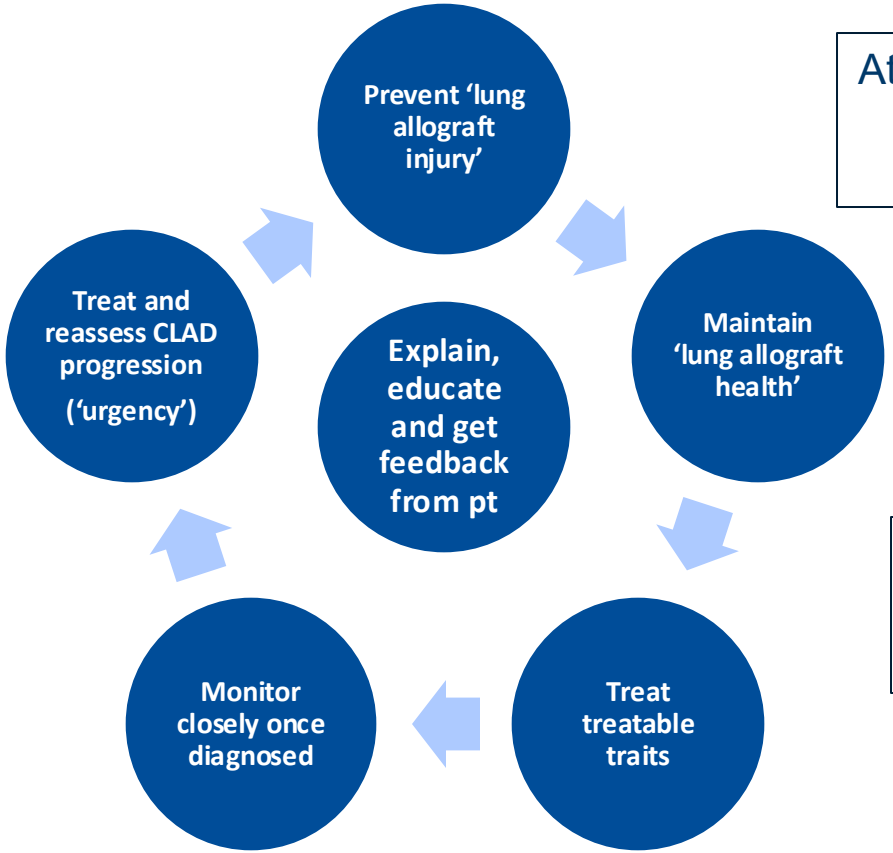
Gottlieb J, et al. Eur Respir Rev. 2025

CLAD Management

General Principles

Reduce symptoms and avoid respiratory failure

Attenuate/prevent imune activation



Attenuate fibrosis formation

Decrease lung inflammation

Courtesy of R. Vos, Leuven

CLAD Prevention?

No Standard Practice Guidelines!

Induction IS

Lymphocyte depletion
ATG, Alemtuzumab, Rituximab?

IL-2 Receptor antagonist
Basiliximab

Maintenance IS

Calcineurin Inhibitor
Tacrolimus*#Dellgren > Cyclosporine

Cell cycle inhibitor
Mycophenolate*, Azathioprine

mTOR inhibitors
Everolimus*, Sirolimus

Corticosteroids

Immunomodulators

Azithromycin*#Vos

ECP*#Benazo

***RCT**

#proven benefit

HLA crossmatch and DSA-directed treatment

Reduction of Ischemia-Reperfusion-Injury
Hypo/Normothermic preservation devices

Microbial prophylaxis
Vaccinations (Influenza, COVID-19, RSV), CMV
Fungi/Aspergillus, Pneumocystis

Microbial treatment
Viruses / Bacteria (P. aeruginosa) / Fungi (Asp.)

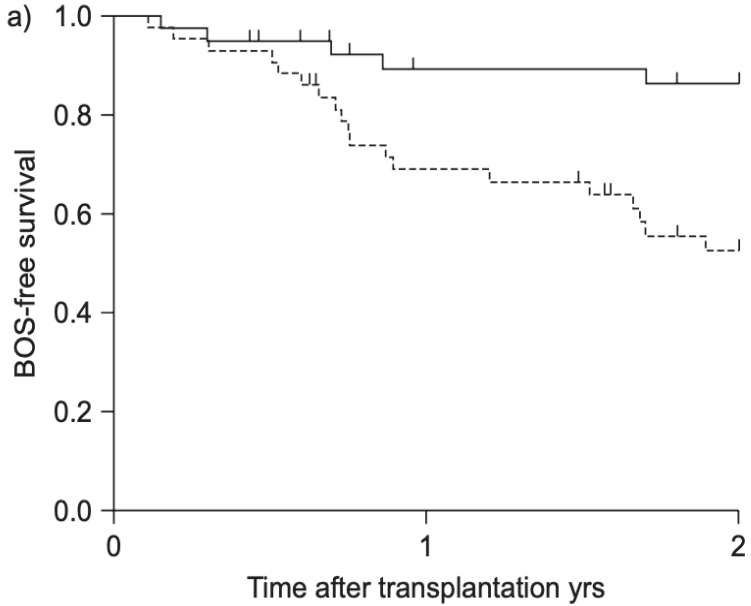
GERD detection and treatment
PPIs / Gastroprokinetics

Avoidance of inhaled toxins/particulate mattter

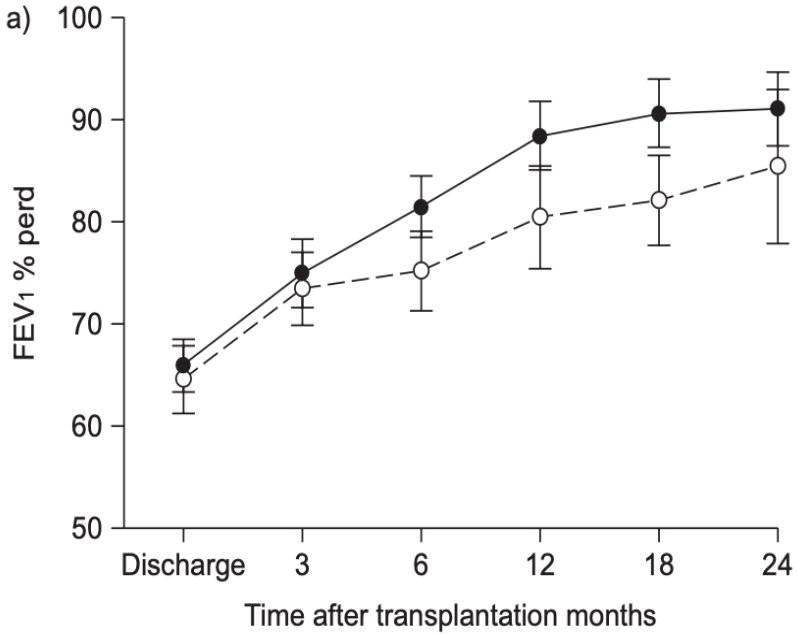
Detection and treatment of subclinical ACR

Check and adjust medical adherence

CLAD Prophylaxis: Azithromycin



At risk n					
Placebo	43	41	29	27	18
Azithromycin	40	37	31	31	28

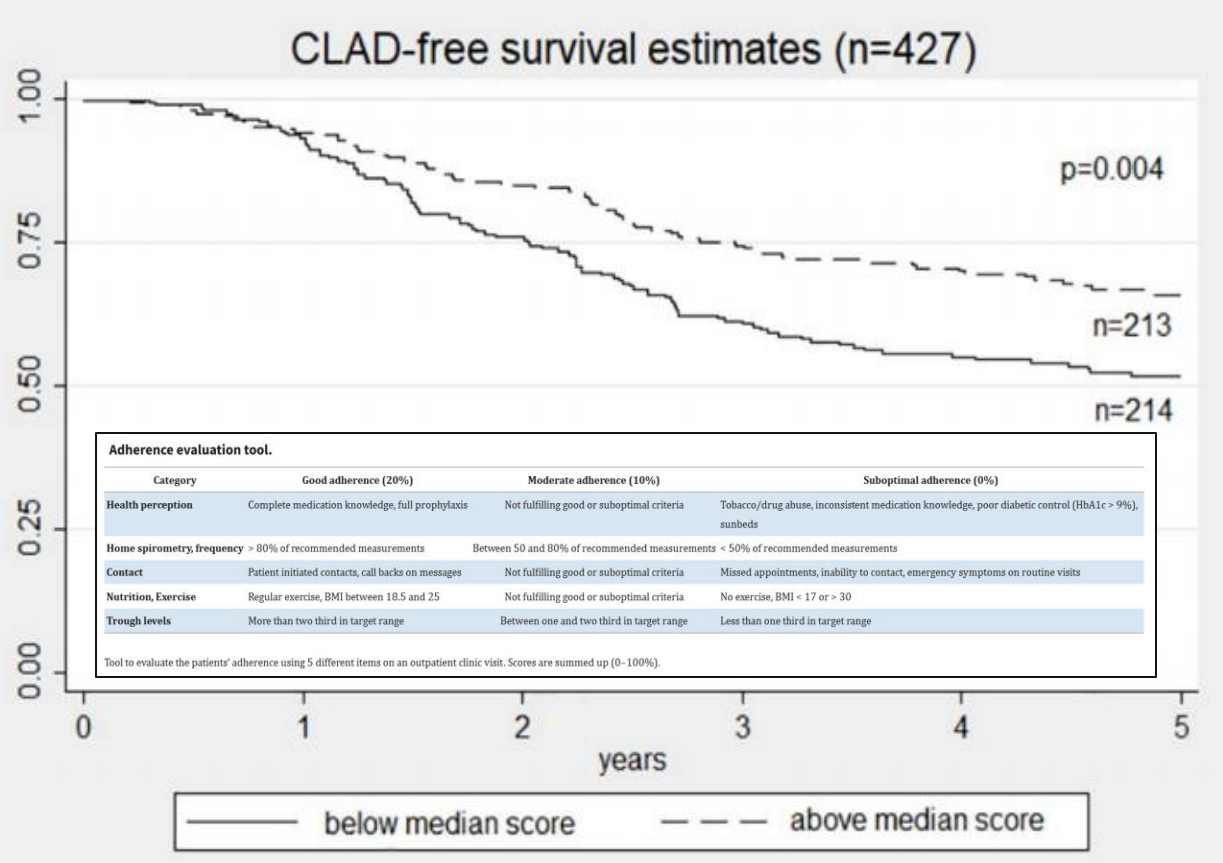


Placebo n	36	40	38	29	27	18
Azithromycin n	36	38	37	31	28	27

No difference in ACR, LB or infections. Less pulmonary and systemic inflammation w AZI.

Vos R, et al. Eur Respir J. 2011

CLAD Prophylaxis: Adherence



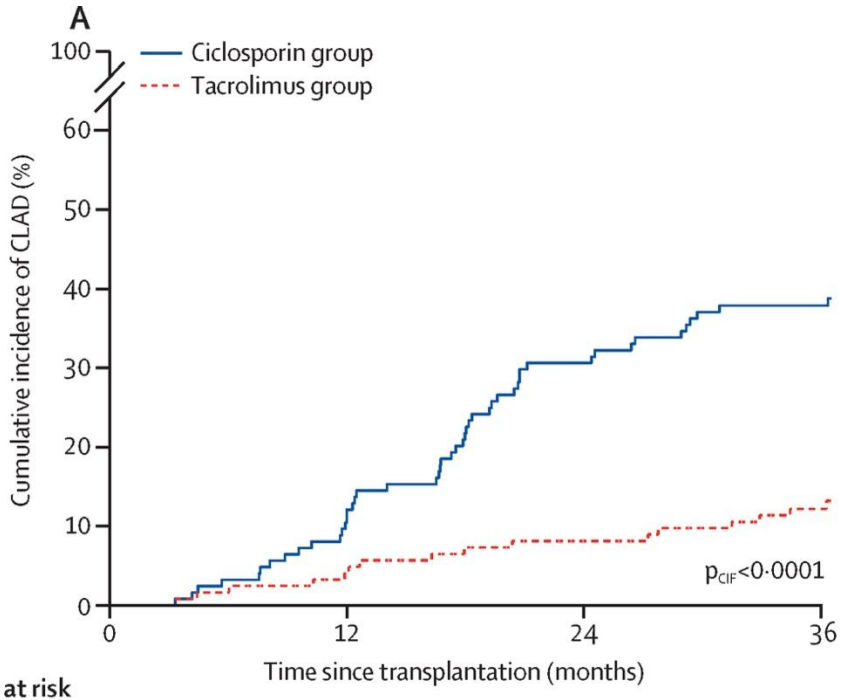
Adherence evaluation tool.

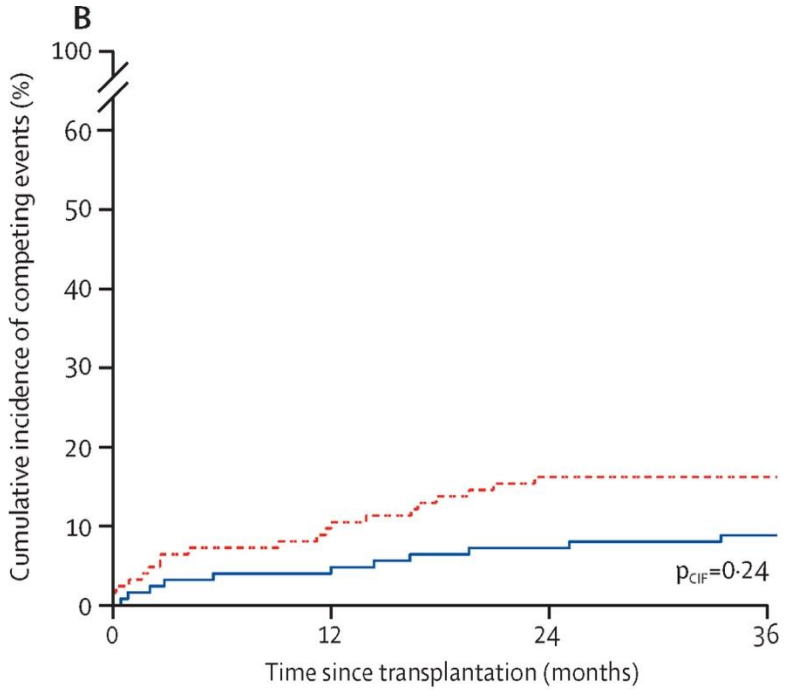
Category	Good adherence (20%)	Moderate adherence (10%)	Suboptimal adherence (0%)
Health perception	Complete medication knowledge, full prophylaxis	Not fulfilling good or suboptimal criteria	Tobacco/drug abuse, inconsistent medication knowledge, poor diabetic control (HbA1c > 9%), sunbeds
Home spirometry, frequency	> 80% of recommended measurements	Between 50 and 80% of recommended measurements	< 50% of recommended measurements
Contact	Patient initiated contacts, call backs on messages	Not fulfilling good or suboptimal criteria	Missed appointments, inability to contact, emergency symptoms on routine visits
Nutrition, Exercise	Regular exercise, BMI between 18.5 and 25	Not fulfilling good or suboptimal criteria	No exercise, BMI < 17 or > 30
Trough levels	More than two third in target range	Between one and two third in target range	Less than one third in target range

Tool to evaluate the patients' adherence using 5 different items on an outpatient clinic visit. Scores are summed up (0–100%).

Bertram A, et al. PLoS One. 2019

CLAD Prophylaxis: OD tacrolimus

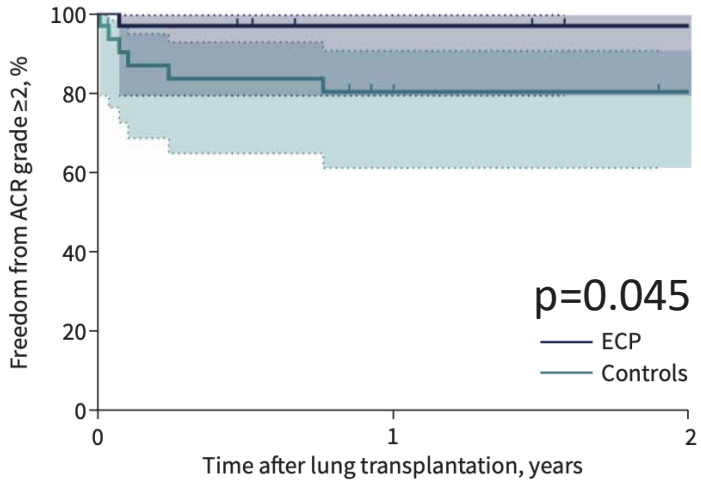




Dellgren, et al. Lancet Resp Med, 2024.

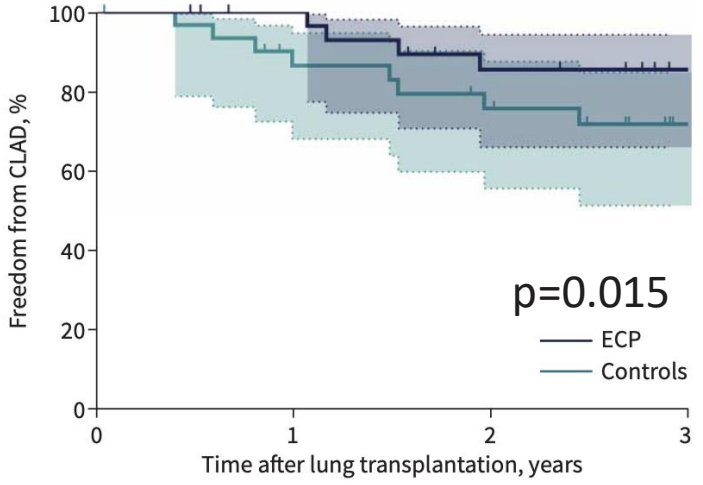
CLAD Prophylaxis: ECP

COPD LTx recipients
Primary outcome = composite of high-grade ACR incidence, CMV infection or CLAD <24 months
19.3% ECP vs. 61.3% CTR (p<0.001)



At risk, n:

ECP	31	28	26
Controls	31	22	20



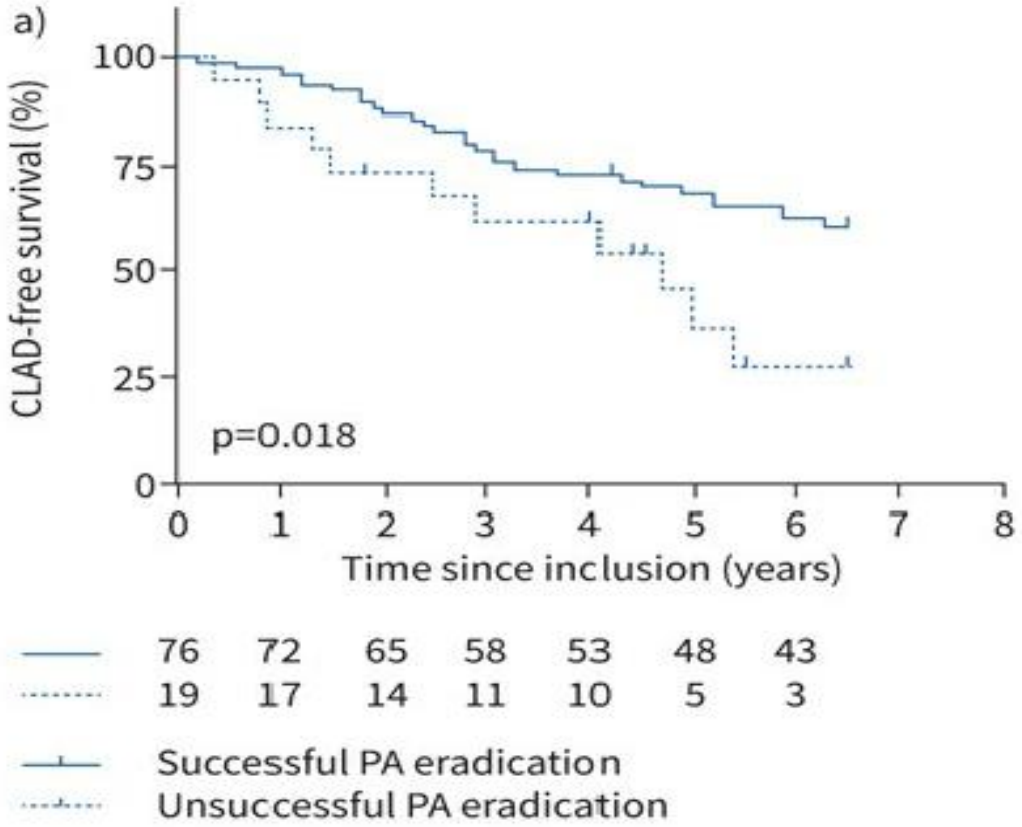
At risk, n:

ECP	31	29	23	18
Controls	31	25	21	13

Infection Rate p=0.002 (CTR>ECP)

Benazzo A, Eur Respir J, 2024.

CLAD Prophylaxis: Anti-microbial treatment

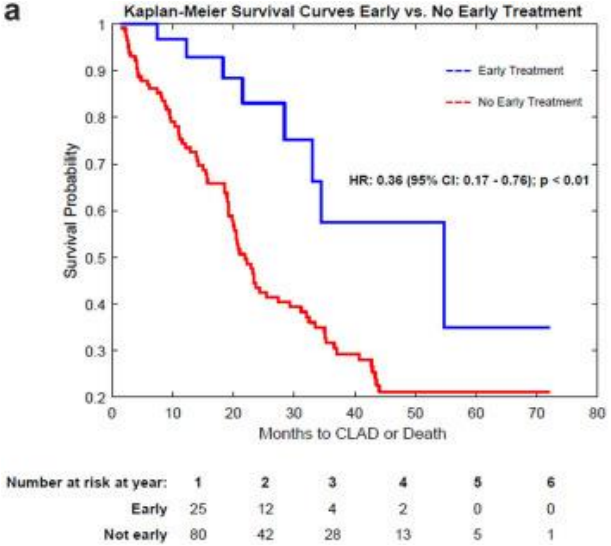


De Muynck B, et al. Eur Respir J. 2020.
Vos R, et al. Eur Respir J 2021.

CLAD Prophylaxis: Preemptive treatment of dnDSA?

445 LTx recipients (GTD + GRAft + JH cohorts)
n=145/**32.5% dnDSA** (76% HLA II, **61% DQ**)
n=**30 early** treatment vs. n=**115 no** treatment

a



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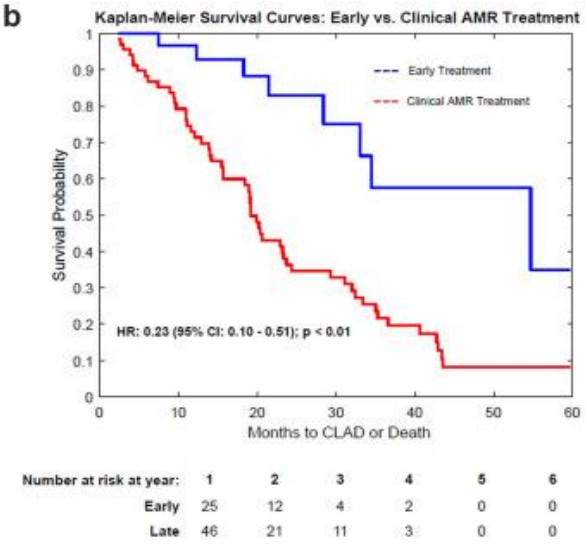


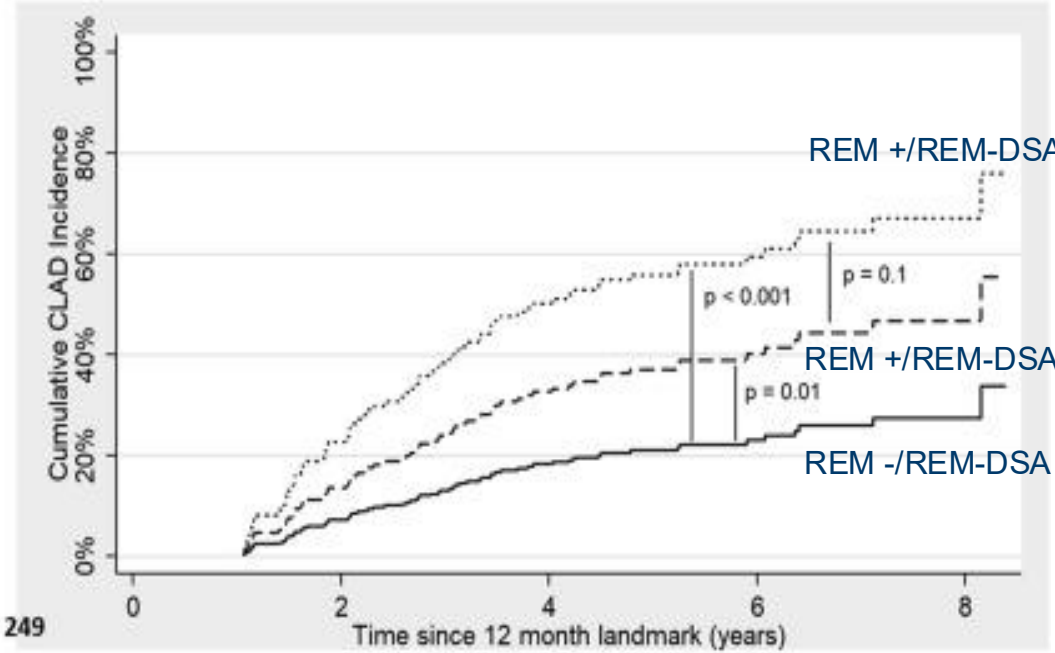
Treatment Regimens for Early dnDSA	
Treatment Regimen	**Number**
IVIG Alone	10
IVIG + Rituximab	8
IVIG + Rituximab + PLEX	4
PLEX + Bortezomib	3
IVIG + Rituximab + Tocilizumab	1
PLEX + Rituximab	1
Rituximab + Methylprednisone	1
Methylprednisone alone	1
IVIG + PLEX	1

Preemptive treatment of dnDSA in LTx patients may reduce subsequent CLAD or death
Preferred treatment strategy?

Keller M, et al. Am. J Transplant. 2023

CLAD Prophylaxis: time for HLA (DQ) matching?

REM = D/R mismatch at DQA1∗05-DQB1∗02 (serologic equivalent DQ2) and/or DQA1∗05-DQB1∗03:01 (serologic equivalent DQ7)



Number at Risk = 249					
No DQ REM	144	128	75	29	4
DQ REM and DSA absent	62	51	35	17	2
DQ REM and DSA present	20	14	5	1	0

Avoid Risk Epitope Mismatches and/or DQA chain mismatch during organ allocation

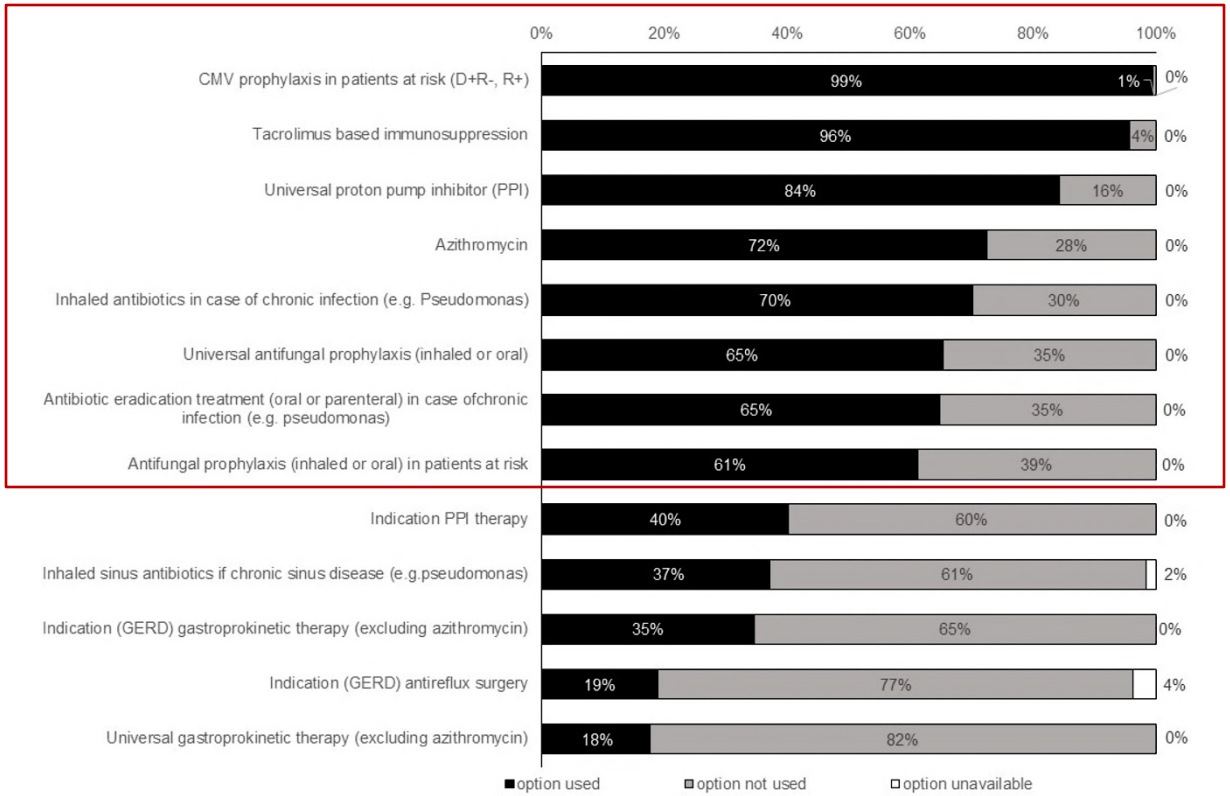
Ennis SL, et al. AJT, 2023.

CLAD Prevention

EU practices

Practice variation!

No guidelines



Gottlieb J, et al. Eur Respir Rev. 2025

CLAD Prevention

Open Questions & Uncertainties

Inhaled IS ?

Inhaled (liposomal) Cyclosporine:

NCT01334892 (Ph 2/3 MC RCT): study failed to meet its primary endpoint (low recruitment, 130/180 pts) *(Neurohr C, Am J Transplant 2022)*

NCT00755781 (Ph 3 MC open-label): results not available (284 pts) *(USA-based PC)*

(**Inhaled Tacrolimus:** Only preclincial data)

Immunomodulators ?

Tociluzimab (IL-6 RA):

NCT06033196 (Ph 2 MC RCT): study ongoing (350 pts, 2028) *(Madsen J)*

Belumosudil (Rho-kinase inhibitor):

NCT06476132 (DAIT CTOT-47, "High risk" for CLAD= AR/LB/OB/ALI, Ph 2 MC RCT) study ongoing (234 pts, 2028) *(Palmer S)*

CLAD Treatment

No Standard Practice Guidelines!

Augmented IS

- **Addition of inhaled steroids**
- **Pulse corticosteroids (IV, po)**
- **Optimize maintenance IS**
  - Cyclosporine to Tacrolimus
  - Azathioprine to Mycophenolate
  - Switch to/add mTOR inhibitor?
- **Lymphocyte depletion**
  - ATG, Alemtuzumab, Rituximab?
  - Total Lymphocyte Irradiation (TLI)

Immunomodulators

- **Azithromycin*#Corris**
- **Montelukast***
- **ECP*ongoing**

Supportive measures

- Vaccinations (Influenza, COVID-19, RSV,…)
- Microbial treatment (Viruses / Bacteria / Fungi)
- GERD treatment (PPI / Prokinetics / Nissen)
- Inhaled LABA/LAMA
- Long-term oxygen treatment
- Pulmonary rehabilitation
- Best supportive care

Redo-transplantation

- BOS > RAS

Defintion of ‘first’ line > ‘second’ line > etc?

***RCT**

#proven benefit

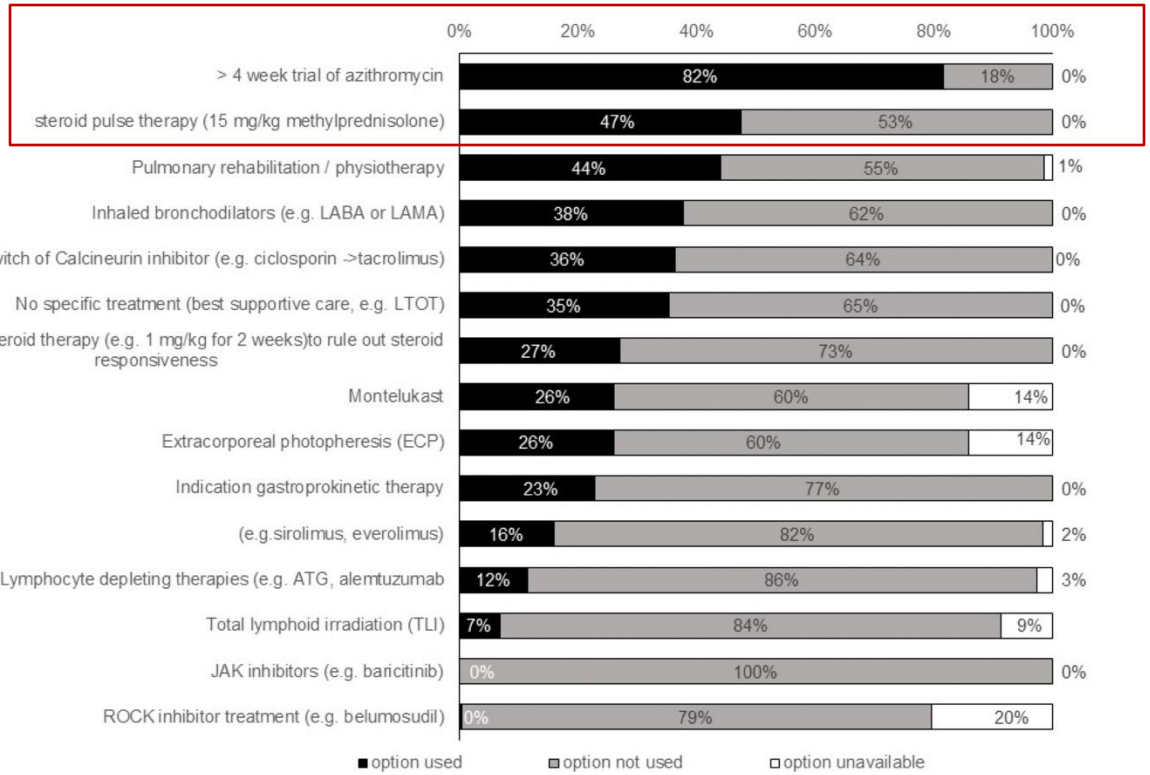
R. Vos, Leuven

CLAD Treatment

EU practices

Practice variation!

No guidelines



Gottlieb J, et al. Eur Respir Rev. 2025

CLAD Treatment

EU practices

1st line therapy	N	of all centers (n=40)
azithromycin	19	48%
steroid pulse intravenous	9	23%
steroids oral increase	4	10%
Photopheresis	3	8%
switch calcineurin inhibitor	3	8%
bronchodilators	3	8%
montelukast	2	5%
steroids inhaled	2	5%
total lymphoid irradiation	1	3%
increase immunosuppression	1	3%
rehabilitation	2	5%
best supportive care	1	3%

2nd line therapy	n	of all centers (n=40)
photopheresis	7	18%
switch to mTOR inhibitor	6	15%
steroid pulse intravenous	6	15%
azithromycin	5	13%
switch calcineurin ininhibitor	4	10%
reflux therapy	3	8%
montelukast	3	8%
antithymocyte globulin	3	8%
bronchodilators	2	5%
total lymphoid irradiation	1	3%
increase immunosuppression	1	3%
rituximab	1	3%
nintedanib	1	3%
intravenous immunoglobulines	1	3%
include in clinical trial	1	3%

3rd line therapy and beyond	n	of all centers (n=39)
photopheresis	19	49%
consider re-do transplantation	8	21%
best supportive care	7	18%
total lymphoid irradiation	6	15%
montelukast	5	13%
switch to mTOR inhibitor	4	10%
steroids oral increase	4	10%
steroid pulse intravenous	1	3%
reflux therapy	3	8%
antithymocyte globulin	3	8%
alemtuzumab	3	8%
switch calcineurin inhibitor	2	5%
bronchodilators	2	5%
include in clinical trial	2	5%
increase immunosuppression	2	5%
mesenchymal stem cells	2	5%
azithromycin	1	3%
nintedanib	1	3%
rehabilitation	1	3%
steroids inhaled	1	3%

Practice variation!

No guidelines

Gottlieb J, et al. Eur Respir Rev. 2025

CLAD Treatment

Open Questions & Uncertainties

Antifibrotics? = Not effective?

Pirfenidone

NCT02262299 (EPOS / BOS, ph 3 MC RCT):

no benefit of pirfenidone (n=48) vs. placebo (n=42) regarding FEV1-decline at 26 mo.
(Perch M, JHLT 2020; Vol. 39; iss. 4; pp. S12 - S12 - abstract)

NCT03473340 (STOP-CLAD / CLAD, ph 2 SC RCT):

study failed to meet its primary endpoint (low recruitment, 23/60 pts)
(Combs MP, JHLT 2024)

NCT03359863 (PIRCLAD / RAS, ph 2, SC open-label)

tolerability-study, no data on FEV1 (8 pts)
(Venado A, Chest 2020; Vol. 158; iss 4, pp. A2389-2390 - abstract)

Nintedanib

NCT03283007 (INFINITx-BOS / BOS, ph 3 SC RCT): recruiting (80 pts, 2026) *(Brugière O)*

CLAD Treatment

Open Questions & Uncertainties

Inhaled IS?

Inhaled liposomal cyclosporine

NCT03657342 / NCT03656926 / NCT04039347 (BOS stage 1/2, ph 3 MC RCT)
study results not yet available (≃300 pts, 2025) *(EU-based PC)*

Immunomodulators?

Itacitinib (JAK-inhibitor)

NCT03978637 (BOS stage 1/2, ph 1/2 MC open label):
FEV1 response was observed in 5/23 pts (21.7%), grade ≥3 AEs occurred in 60.9%
(Diamond J, JHLT 2022; Vol. 41; iss. 4; pp. S113 - abstract)

Belumosudil (Rho-kinase inhibitor)

NCT06082037 (CLAD stage 1/2, ph 3 MC RCT): study ongoing (180 pts) *(EU-based PC)*

CLAD Treatment

Open Questions & Uncertainties

Immunomodulators

Extracorporeal photopheresis (ECP):

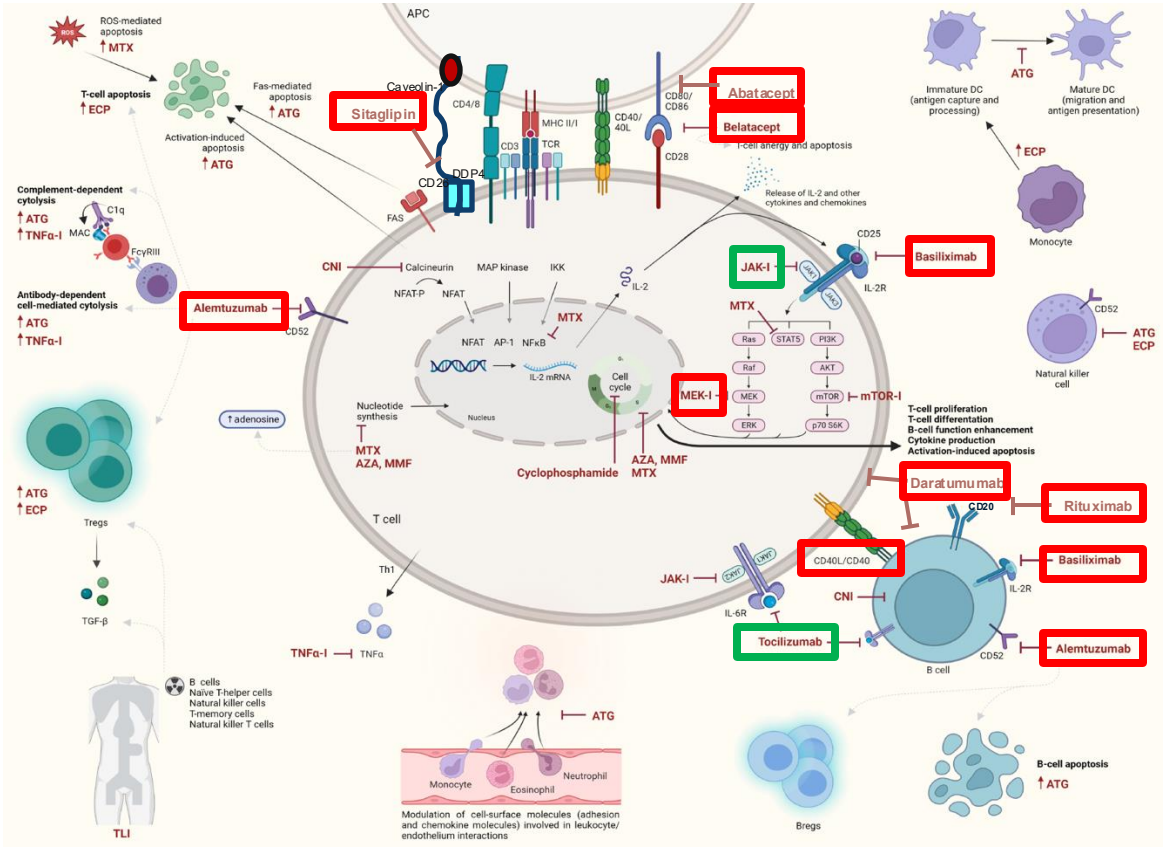
NCT02181257 (BOS stage 1-4, ph 2 MC RCT, refractory (258 pts) + new onset BOS (22 pts)):
enrollment hold 2022, study results not yet available *(Washington U)*

2022-002659-20 (E-CLAD UK, CLAD stage 1/2/3, ph 2 MC RCT):
study results not yet available (90 pts, 2027) *(Fisher AJ)*

Mesenchymal stem cells

NCT02709343 (ASSIST-CLAD/BOS 1/2, ph 2 MC RCT): BM-derived MSC in new onset CLAD
study results not yet available (64 pts, 2024/5) *(Chambers D)*

Future CLAD Therapies?



mABs and small molecules:

- ✓ Alemtuzumab (anti-CD52)
- ✓ Rituximab (anti-CD20)
- ✓ Daratumumab (anti-CD38)
- ✓ Belatacept (anti-CD80/86)
- ✓ Abatacept (ant-CD80/86)
- ✓ CD26/dipeptidyl peptidase 4 (CD26/DPP-4) inhibitors
- ✓ Tyrosine kinase inhibitors (Ibrutinib, Imatinib)

Cellular therapies:

- ✓ CAR-T, MSC, RMC, Treg

Gene editing therapies?

Adapted from BOS S, et al. Pharmacol Rev. 2023.

Upcoming guidelines on CLAD

- ***ISHLT Endpoints in Lung Transplantation Clinical Trials (2025)***
  (Greenland J, Todd K, Perch M, et al.)

  CLAD Section (Vos R, Halloran K, Combs M, Vibha L, Palmer S, Schultz HH)
  - ✓ Expert consensus recommendations on (clinical) endpoint assessments (single/composite, primary/secondary) in CLAD prevention and treatment trials
  - ✓ 13 statements, General: 7 - Prevention: 2 - Treatment: 4

*Clinical trials for CLAD prevention and treatment are an **unmet clinical need**.*

*CLAD prevention trials should use **time from initiation of study intervention to CLAD onset as the primary endpoint**, with **death and retransplant reported and analyzed as competing risks** for CLAD or in a **composite endpoint** with CLAD onset.*

*CLAD treatment trials should use **time from treatment assignment to CLAD progression (defined by FEV1 ± FVC decline of >10%) as the primary endpoint**, with **death and retransplant reported and analyzed as competing risks** or in a **composite endpoint** with CLAD progression.*

Developing guidelines on CLAD

- ***ESOT Clinical Practice Guideline on Prevention and Treatment of CLAD (2025)***
  (Vos R, Gottlieb J, Bos S, Hellemons M, et al.)

✓ Steering Committee (n=12, incl. Allied Health Repr and Pt Representative)
✓ Evidence-based (GRADE) recommendations on therapies for CLAD
✓ 'Best practices'
✓ 8 PICO-based recommendations + Additional expert considerations
✓

Prevention:	Treatment:
1. AZI	1. ATG
2. TAC>CsA	2. Alemtuzumab
3. MMF>AZA	3. Antifibrotics
4. ECP	4. MLK

- ***German-Austrian Recommendations Lung Transplantation (2025)***
  (Gottlieb J, Jaksch P, et al.)

Conclusions

- CLAD **identification, phenotyping, severity assessment, and monitoring of progression** are key in follow-up care after LTx
- (Better) identification of **patients at (higher) CLAD risk** is essential
- (Better) identification of **underlying (molecular) disease mechanisms and drugable targets/pathways** in CLAD are key – biomarkers are emerging
- **Early intervention** is essential to avert disease progression/graft failure&loss
- **Practice harmonization** and **evidence-based management** are largely lacking
- **RCTs are needed** to assess promising therapies for CLAD prevention and treatment (i.e. 1st line 'study treatment'-principle)

Muchas Gracias!

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