BRIGHAM AND WOMEN'S HOSPITAL
The Lung Center

Harvard Medical School

Lung transplantation: state of the art

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Disclosures

•Co-PI/member of Clinical Coordinating Center for Genentech sponsored study of pirfenidone in autoimmune ILD

Overview

- Pre-transplant
  - -Evolution of candidate selection
  - -Allocation Policy
  - -Recipient management

- Post-transplant
  - -The changing face of transplant rejection

Pre-transplant

"It's good that you're eating more fresh fruit and vegetables, but be careful to chew more thoroughly."

"The handle on your recliner does not qualify as an exercise machine."

General selection criteria

Individuals with advanced lung disease

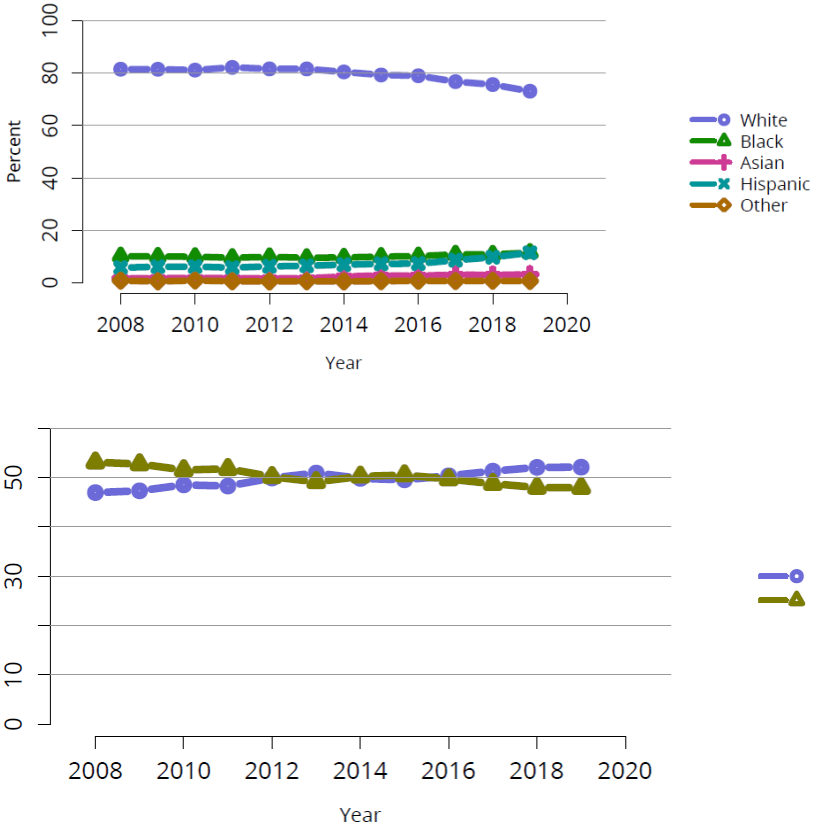
- -NYHA Class III - IV
- -Unacceptable quality of life
- -50% survival < 3 years despite maximal medical therapy
- Accelerated clinical course

Individuals with limited co-morbidities:

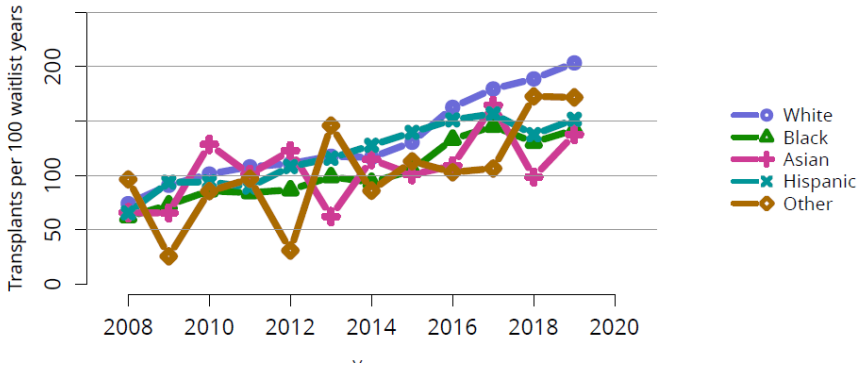
- CAD: unstable, inducible, uncorrectable
- Renal insufficiency
- Cirrhosis
- Connective tissue disease with skin or peripheral vessel involvement
- Malignancy
- Chronic Infection: Hepatitis, HIV

Demographics of lung transplantation

Candidate Listing



Transplantation



OPTN/SRTR 2019 Annual Data Report: Lung

Demographics of transplantation

- Improvements in survival in advanced lung disease impact men more than women
- minority populations represent a disproportionate number of patients with end stage lung disease
- Between 2016 - 2020, non-white patients represented 20-30% of lung transplant recipients in the United States.
- At present, Black candidates represent 12.6% of the national lung transplant waiting list, while Hispanic candidates represent 15.6%.
- While national policy changes have had an impact on racial disparities in the listed population, such efforts have limited impact on referrals and candidate acceptance rates

Am J Transplant 2006; 6: 2436
Res Health Sci 2020; 5: 48
J Heart Lung Transplant 2013; 32:684
J Heart Lung Transplant 2015; 34: 1
https://optn.transplant.hrsa.gov/data/view-data-reports/national-data/#

Equity Initiatives

Data - OPTN | OPTN Metrics | Equity in Access to Transplant

insights.unos.org/equity-in-access/

Equity in Access to Transplant

What is Health Equity?

Organ & Factor-Specific Trends

Organ:
- Kidney
- Liver
- Heart
- Lung

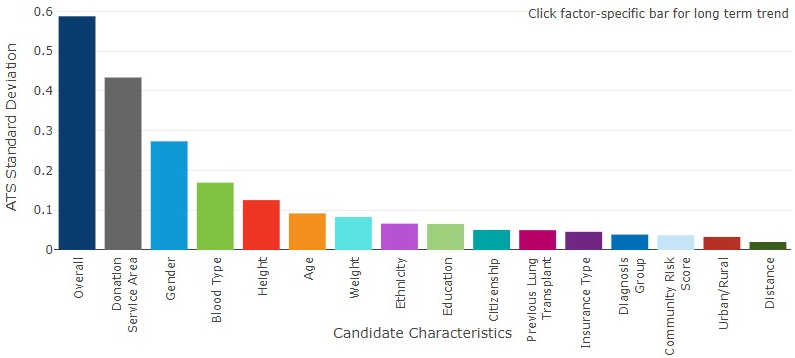
System-level Equity Trends

Equity Resources

dataproducts@unos.org

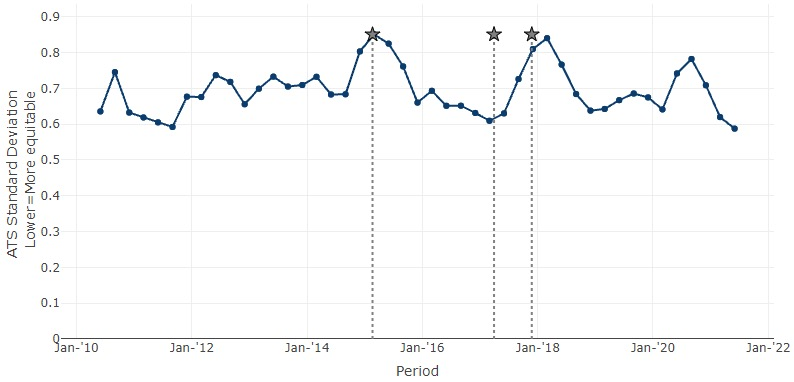
Lung Equity Dashboard

Variability in Access-to-Transplant Scores (ATS) Among Waitlisted Lung Candidates (01/01/2021 - 06/30/2021)



Download Candidate Characteristics Data

Overall Variability in Access-to-Transplant Score (ATS) (01/01/2010 - 06/30/2021)



Download Candidate Characteristic Trend Data

Though the overall disparity metric for access to deceased donor lung transplants among candidates on the waiting list has fluctuated over the past decade, the overall level of disparity in 2019 remains about the same as it was in 2010.
The overall lung ATS standard deviation has varied between 0.59 and 0.85 during this time period. The quarterly fluctuations may be at least partly attributable to random variation.

Since ATS standard deviations reflect patient-to-patient variability relative to different average waiting times among organ types (e.g., 3-5 years to receive a kidney transplant; <1 year for lungs), these standard deviations should not be used to conclude that allocation is more or less equitable for one organ type compared to another.

The most noteworthy risk-adjusted differences in access to lung transplants correspond to four key factors:

- Donation service area, or DSA
- Gender
- Blood type

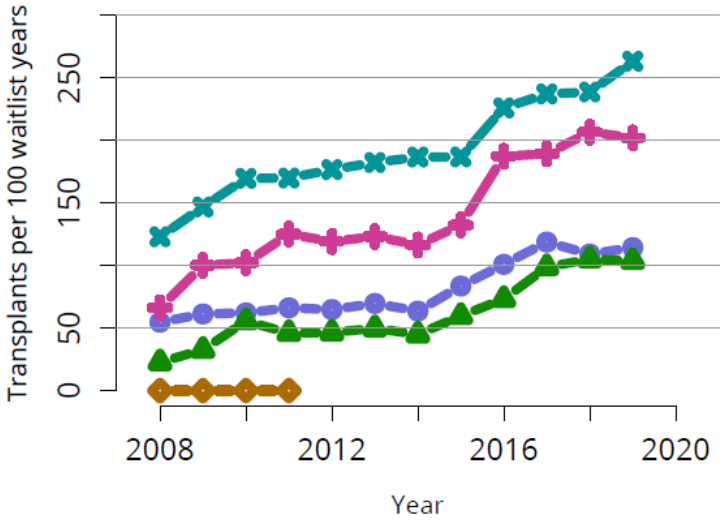
Type here to search | 74°F Mostly sunny | 2:57 PM 10/14/2021

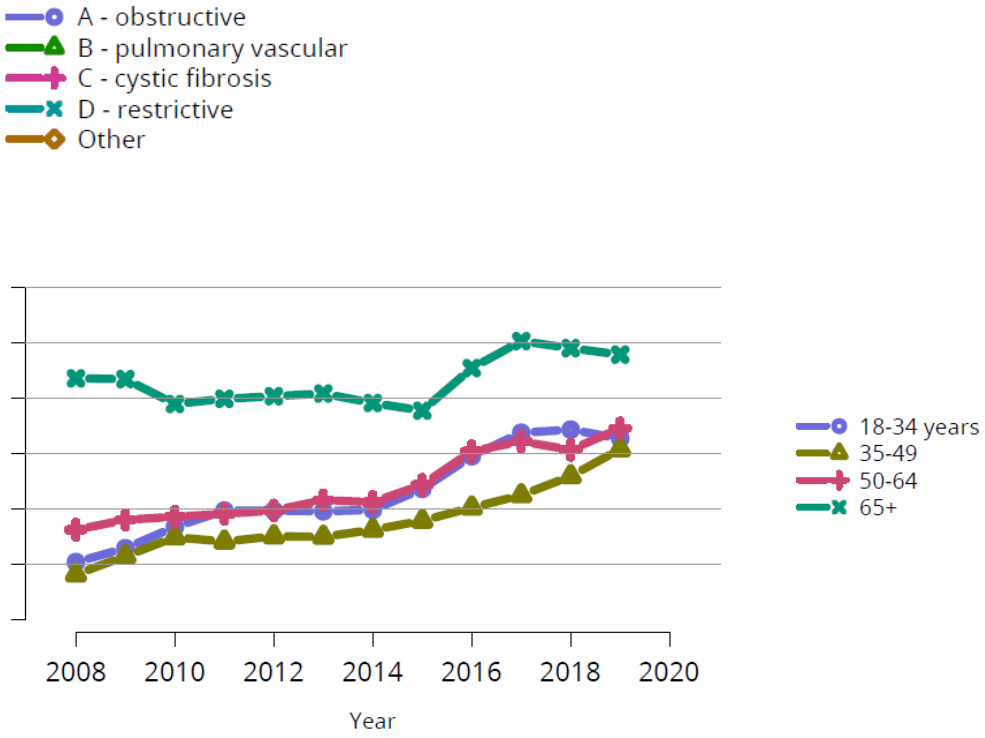
Describing the need

- Institution of the Lung Allocation Scoring System in 2005
  - Minimize waiting list deaths
  - (maximize post-transplant survival)

- Liberalization of recipient acceptance criteria
  - Increasing age
  - Increasing acuity

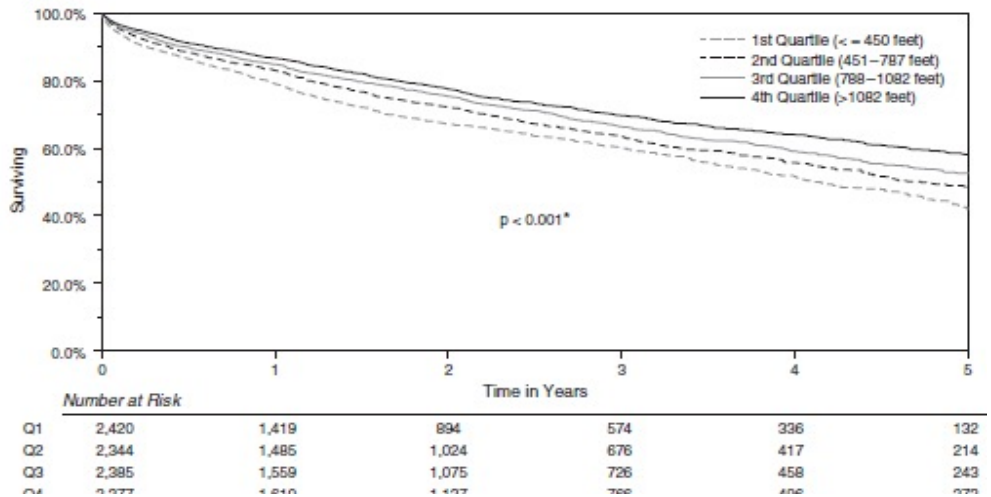
Describing the need



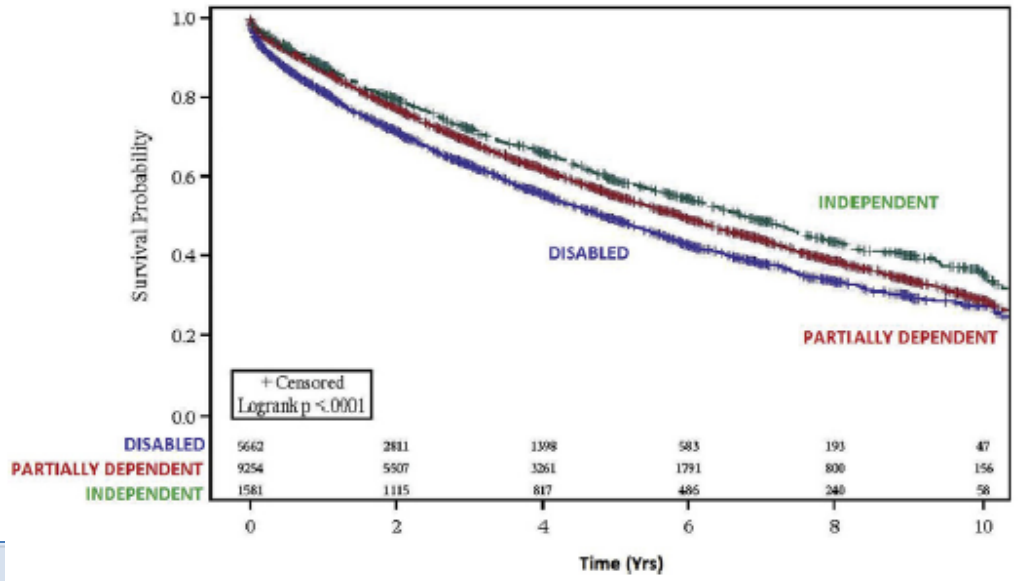


Am J Transplantation 2021; 21: 441

Functional status and lung transplant outcomes



Am J Resp Crit Care Med 2015: 192: 843
Ann Thor Surg 2018; 106: 79



The result – the waiting is the hardest part

Need to support the more acutely ill candidate:
-Increased age
-Increased disease severity
- Unchanged need to maintain functional status

Concurrent technological advances

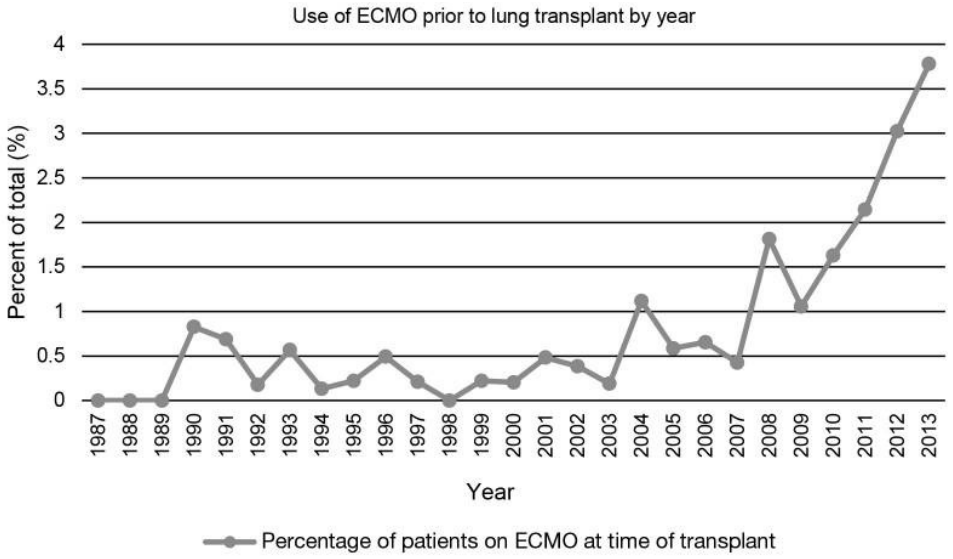


Table 2
Experience with ECLS as a bridge to lung transplant (series with more than 4 cases)

Author	Number of Cases	Days on Device (Mean)	Mode ECLS	Bridged to LTx (%)	30-d Survival After LTx (%)	1-y Survival (%)
Fischer et al,[7] 2006	12	15.0	A-V pumpless	83	80	80
Olsson et al,[8] 2010	5	21.0	V-A	80	100	NA
Strueber et al,[10] 2009	4	17.0	PA-LA pumpless	100	100	75
Cypel et al,[11] 2010	12	7.0	V-A (3), V-V (1), A-V (4), PA-LA (4)	100	100	83
Yun et al,[33] 2010	7	7.0	V-V (5) V-A (2)	86	83	NA
Ricci et al,[34] 2010	12	13.5	A-V pumpless	25	NA	NA
Nosotti et al,[35] 2010	4	9.0	V-V	100	75	NA
Hämmäinen et al,[36] 2010	16	17.0	V-V (7) V-A (6)	81	100	92

Thor CV Surg 2013; 145: 862

Clin Chest Med 2011; 32: 245

Ex vivo lung perfusion

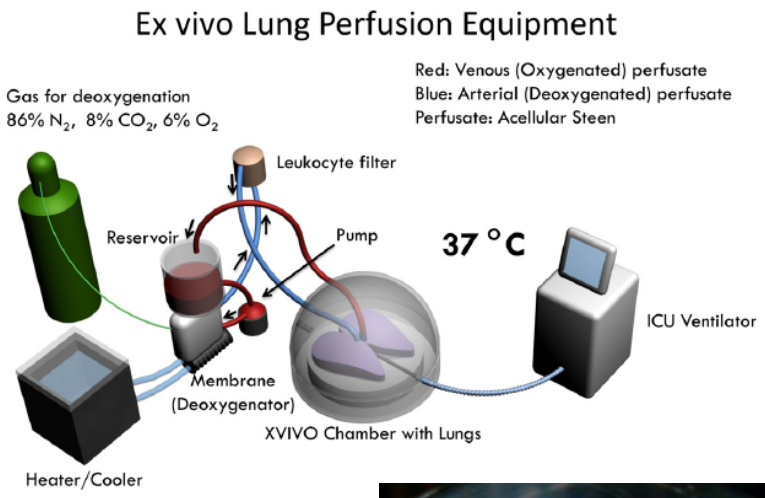


Table 3 Ventilatory and perfusion strategy for EVLP	
Ventilation	
Tidal volume	7 mL/kg
PEEP	5 cm H_2O
Frequency	7 breaths/min
I/E ratio	1/2
Recruitment	1 every hour to PawP 20 cm H_2O
Perfusion	
Pump flow	40% estimated donor cardiac output
Pulmonary artery pressure	7–13 mm Hg[a]
Left atrial pressure	3–5 mm Hg[b]
Perfusate exchange	250 mL every hour
Perfusate composition	Steen solution, heparin, antibiotics, solumedrol
Perfusate pH	6.8–7.4
Perfusate Pco_2	35–45 mm Hg

Clin Chest Med 2011; 32: 233-44

Ex vivo lung perfusion

Table 2. Outcomes in the EVLP and Control Groups.*

End Point	EVLP Lungs (N=20)			Control Lungs (N=116)	Absolute Difference†	P Value‡
	Donors without a Heartbeat (N=9)	Brain-Dead Donors (N=11)	Total (N=20)		*percentage points (95% CI)*	
Primary end point§						
PGD grade 2 or 3 at 72 hr (%)	11	18	15	30	15 (−3 to 33)	0.11
Secondary end points§						
PGD grade 2 or 3 at ICU arrival (%)	33	18	25	30	5 (−15 to 26)	0.30
PGD grade 2 or 3 at 24 hr (%)	11	18	15	36	21 (3 to 39)	0.07
PGD grade 2 or 3 at 48 hr (%)	33	27	30	35	5 (−17 to 27)	0.46
ECMO (%)	0	0	0	4		0.37
PaO_2:FIO_2 on arrival in ICU (mm Hg)						0.51
Median	420	423	422	372		
Range	85–518	86–538	85–538	49–591		
Mechanical ventilation after transplantation (days)						0.15
Median	2	2	2	2		
Range	1–27	1–101	1–101	1–43		
ICU stay after transplantation (days)						0.68
Median	4	5	4	4		
Range	1–34	1–101	1–101	1–103		
Hospital stay after transplantation (days)						0.39
Median	19	34	23	27		
Range	7–54	11–101	7–101	9–156		
Airway complications (%)¶	11	0	5	4	−1 (−10 to 10)	1.0
Mortality at 30 days (%)	22	0	10	5	−5 (−19 to 9)	0.33

N Engl J Med 2011; 364: 1431-40

Continuous distribution of organs

In 2018, the Board of Directors approved a "continuous distribution" model as a framework for future policy development of organ allocation

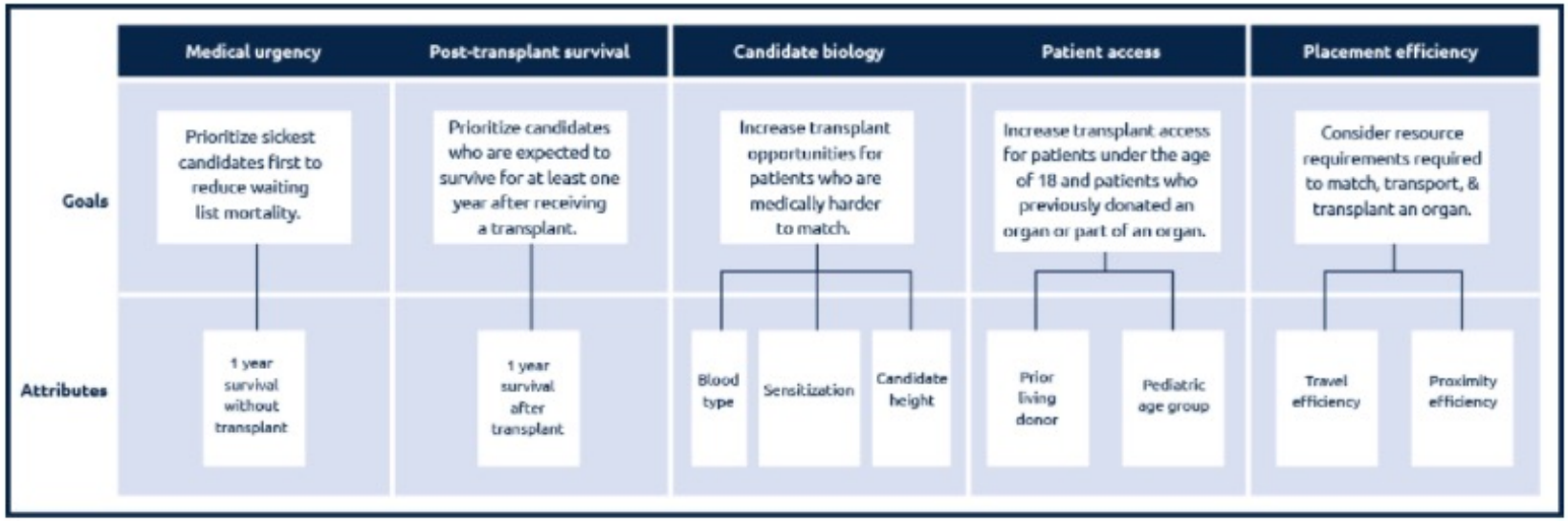
- **Current system**: places candidates into rank-ordered classifications reviewed in sequence
- **New framework**: ranks all candidates using a composite allocation score, without categorizing into classifications
  - The composite score is determined by multiple factors, called "attributes," that are weighted against each other during the calculation

Continuous distribution of organs

Medical urgency + Post-transplant survival + Candidate biology + Patient access + Placement efficiency = Patient's Composite Allocation Score

A higher score puts a patient closer to the top of the waitlist and more likely to receive an organ transplant.

ATTRIBUTES AND THE GOALS THEY SUPPORT



Protocol development: transplantation using hepatitis C positive donors

- Open-label, pilot, safety and efficacy trial for adults on heart or lung transplant wait list eligible for an organ from an increased risk donor with:
  - Active HCV infection → NAT[1] positive
    - or –
  - Prior HCV infection → Ab[2] positive and NAT negative

Study Arm	Donor HCV Status	Timing of Anti-viral Initiation	Treatment Regimen
Arm A	NAT+	Day of transplant	sofosbuvir/velpatasvir 4 weeks
Arm B	Ab+ / NAT–	Evidence of HCV viremia	sofosbuvir/velpatasvir 6 weeks

ORIGINAL ARTICLE

Heart and Lung Transplants from HCV-Infected Donors to Uninfected Recipients

Ann E. Woolley, M.D., Steve K. Singh, M.D., Hilary J. Goldberg, M.D., Hari R. Mallidi, M.D., Michael M. Givertz, M.D., Mandeep R. Mehra, M.D., Antonio Coppolino, M.D., Amanda E. Kusztos, B.S., Megan E. Johnson, B.A., Kaiwen Chen, B.S., Esther A. Haddad, M.D., John Fanikos, R.Ph., David P. Harrington, Ph.D., Phillip C. Camp, M.D., and Lindsey R. Baden, M.D., for the DONATE HCV Trial Team*

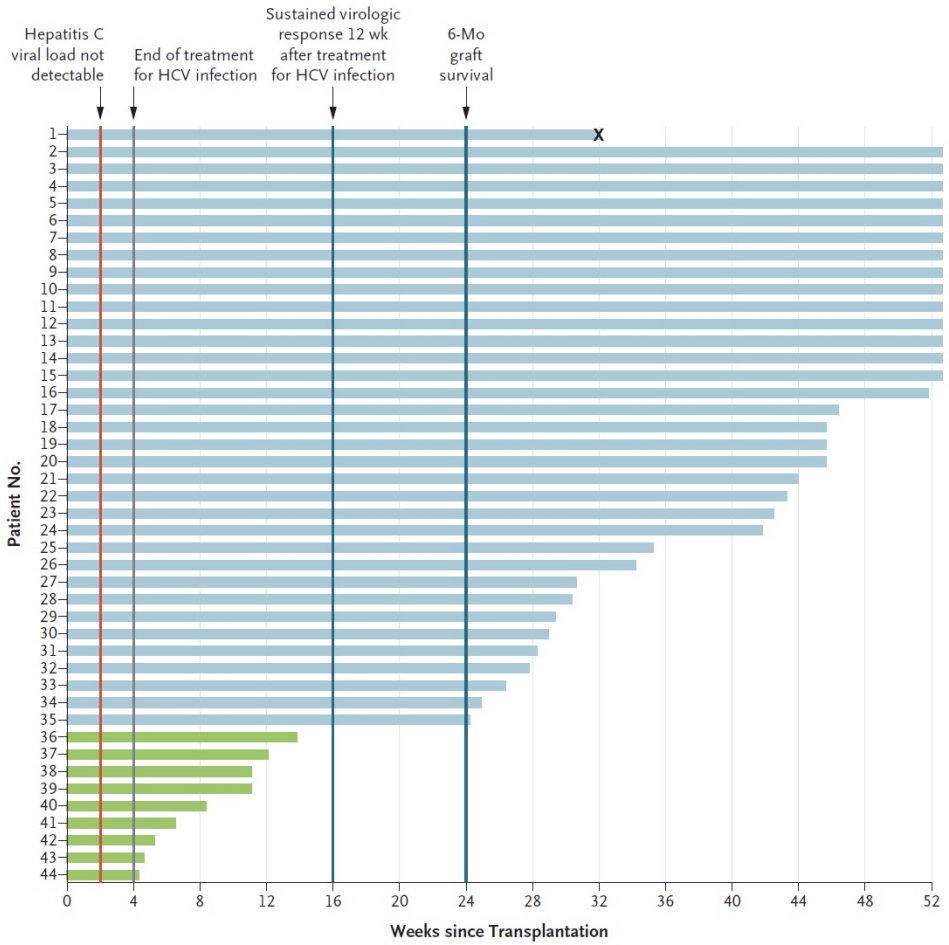


Figure 2. Results of Patient Follow-up after Transplantation.

The black X indicates that Patient 1 died at week 32. The green bars represent patients who had not completed 16 weeks of follow-up by July 31, 2018.

New Engl J Med 2019; 380: 1606

The NEW ENGLAND JOURNAL of MEDICINE

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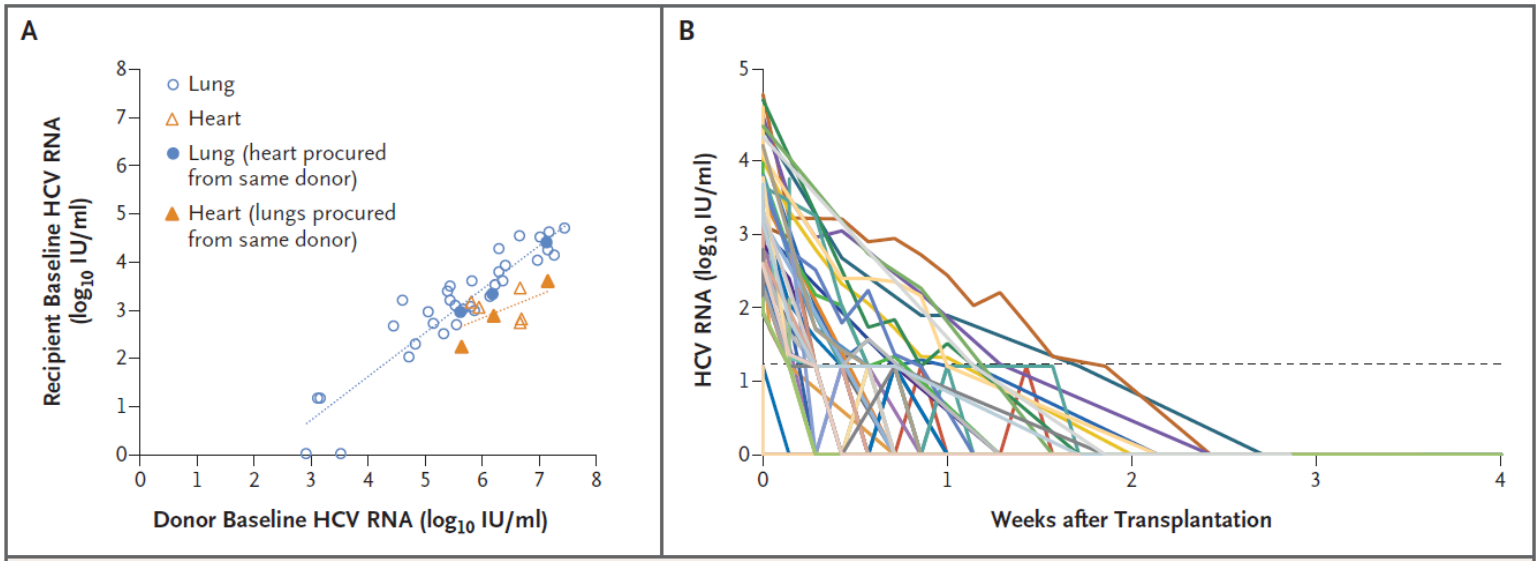
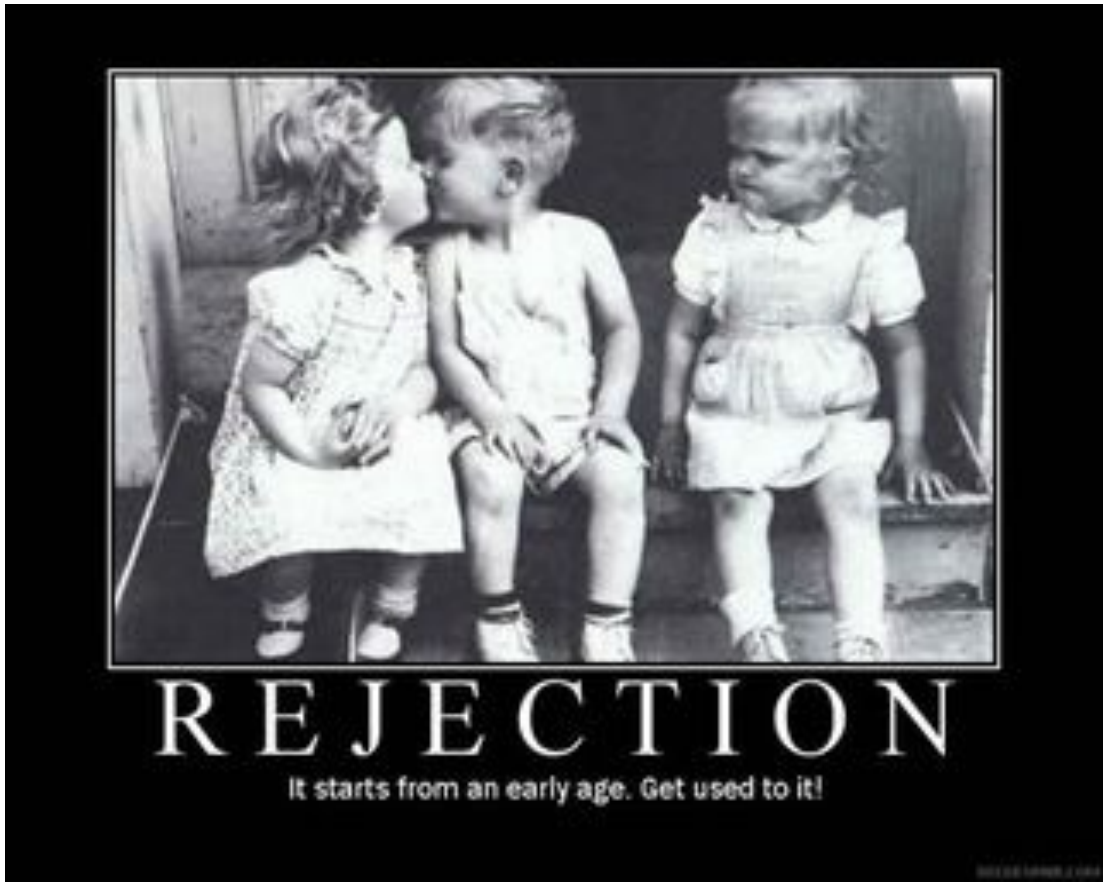
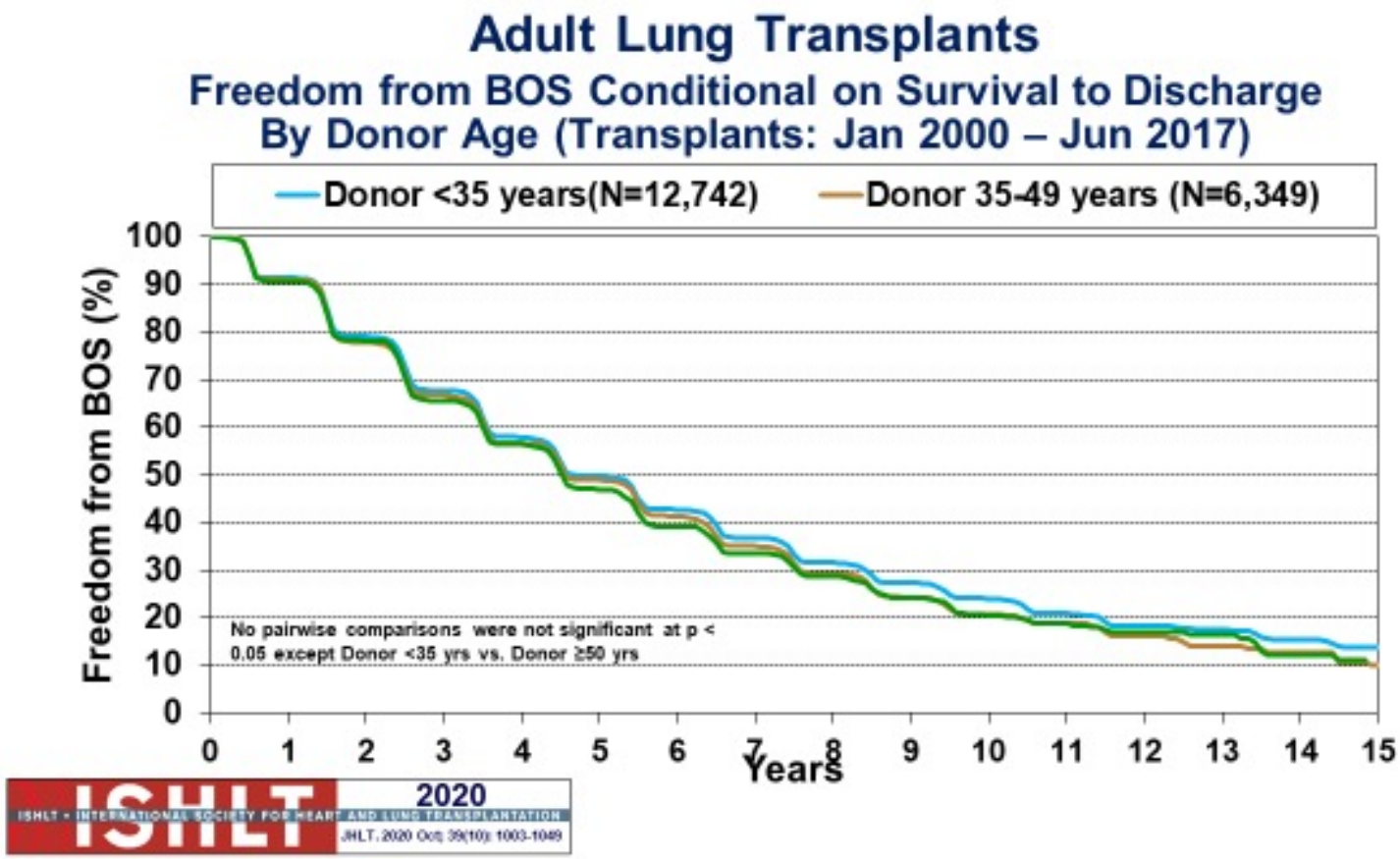


New Engl J Med 2019; 380: 1606

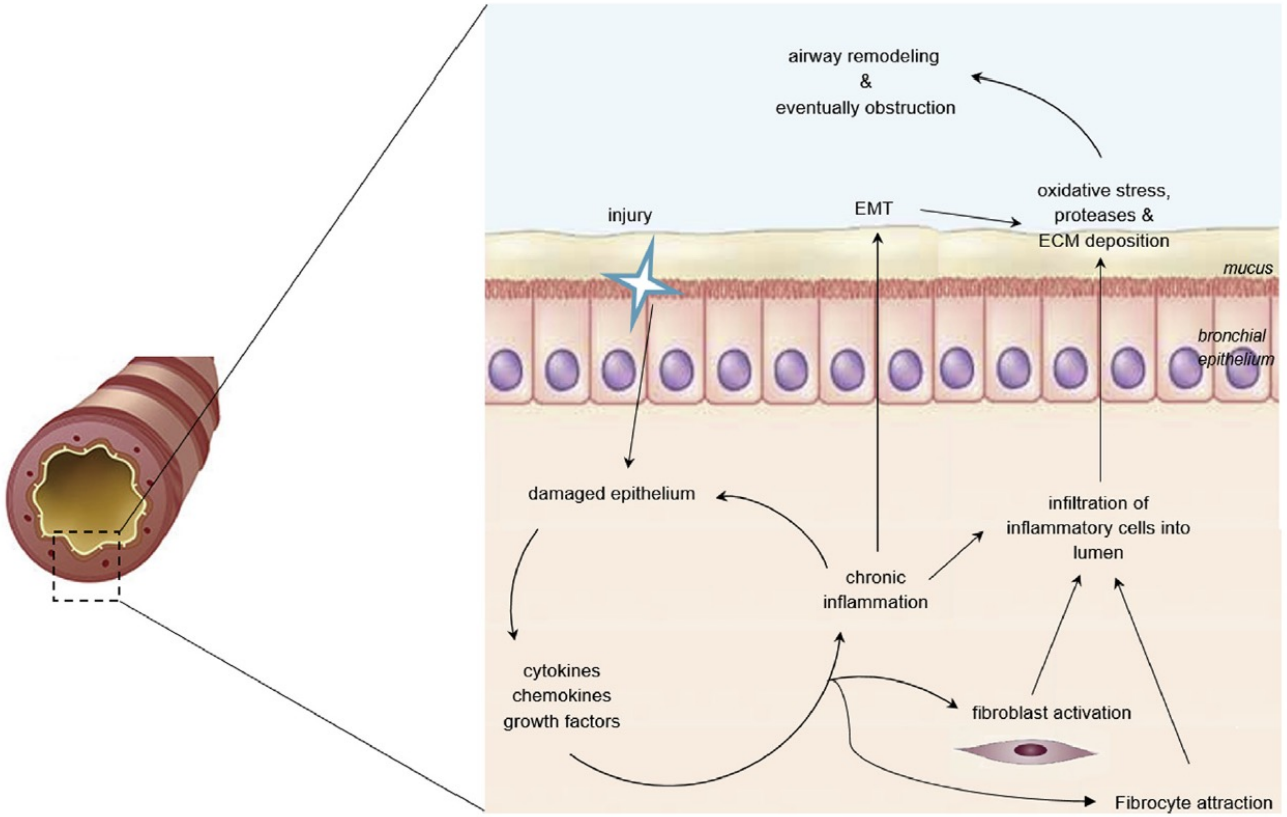
Post-transplant



Available registry data focuses on BOS

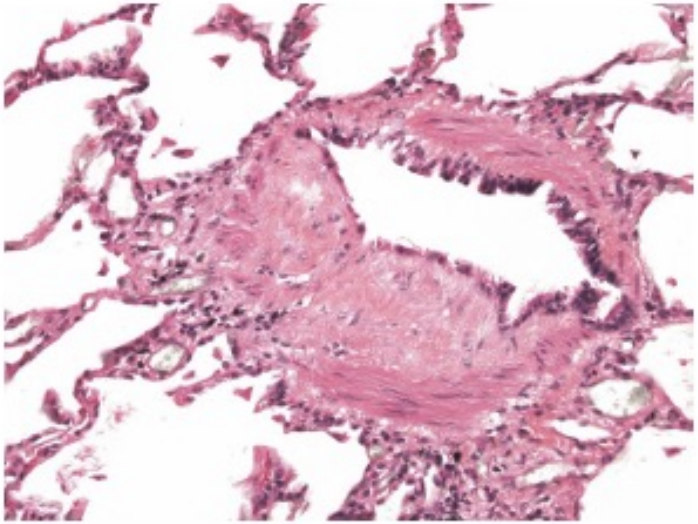


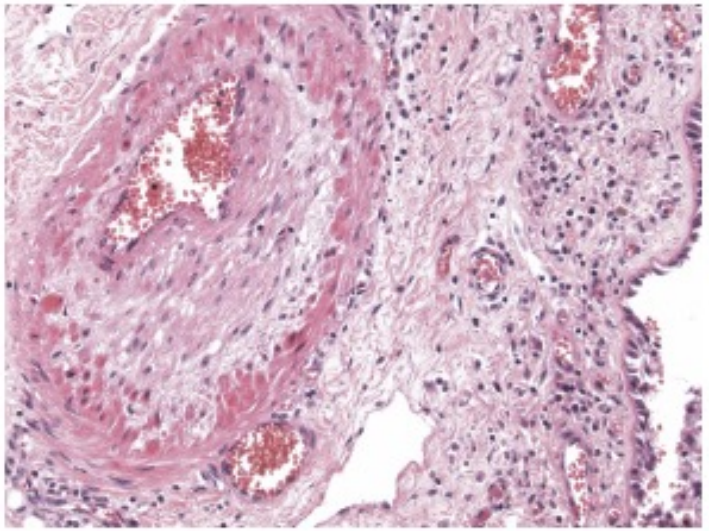
Pathophysiology of rejection



Chest 2016; 150: 219

“Chronic Rejection”





J Heart Lung Transplant 2007; 26: 1229

Bronchiolitis obliterans syndrome (BOS)

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} ≤ 75% of baseline
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.

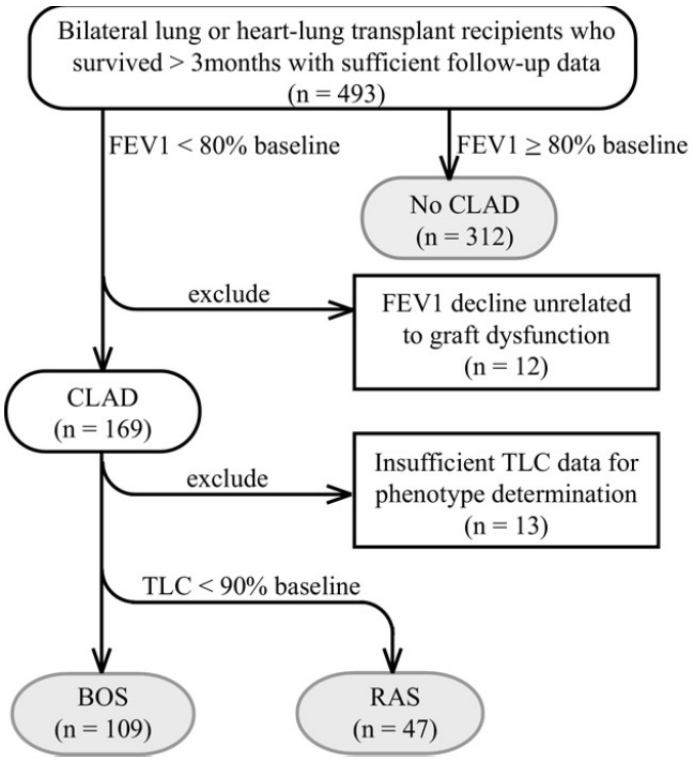
Table 2 CLAD Staging

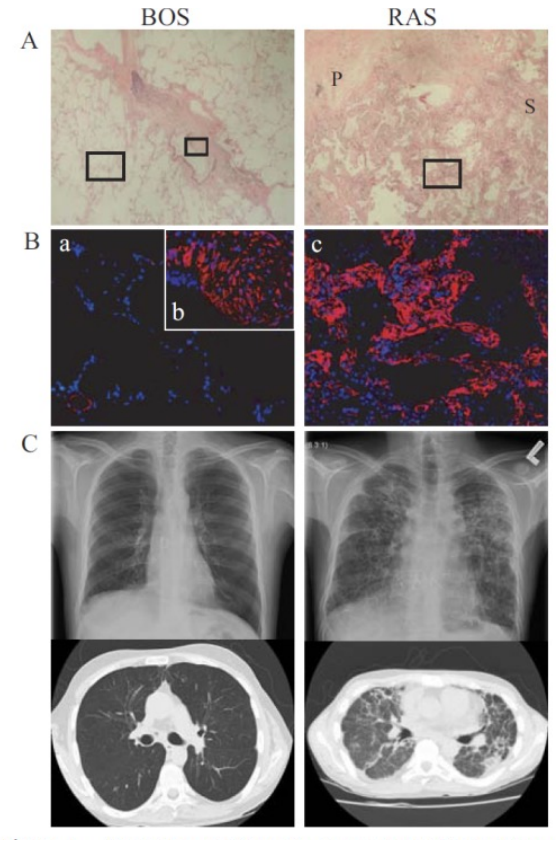
Stage	Spirometry
CLAD 0	Current FEV_1 >80% FEV_1 baseline
CLAD 1	Current FEV_1 >65–80% FEV_1 baseline
CLAD 2	Current FEV_1 >50–65% FEV_1 baseline
CLAD 3	Current FEV_1 >35–50% FEV_1 baseline
CLAD 4	Current FEV_1 ≤35% FEV_1 baseline

CLAD, chronic lung allograft dysfunction; FEV_1, forced expiratory volume in 1 second. Once CLAD is diagnosed, staging is performed according to the decline in FEV_1, compared with baseline. The date of onset of CLAD is defined as the date at which the first value of FEV_1 ≤80% of baseline was recorded when subsequent values taken at least 3 weeks (and for definite CLAD up to 3 months) apart also fell below the threshold. The same principle holds for each stage.

J Heart Lung Transplant 2002; 21: 297
J Heart Lung Transplant 2019; 38: 493

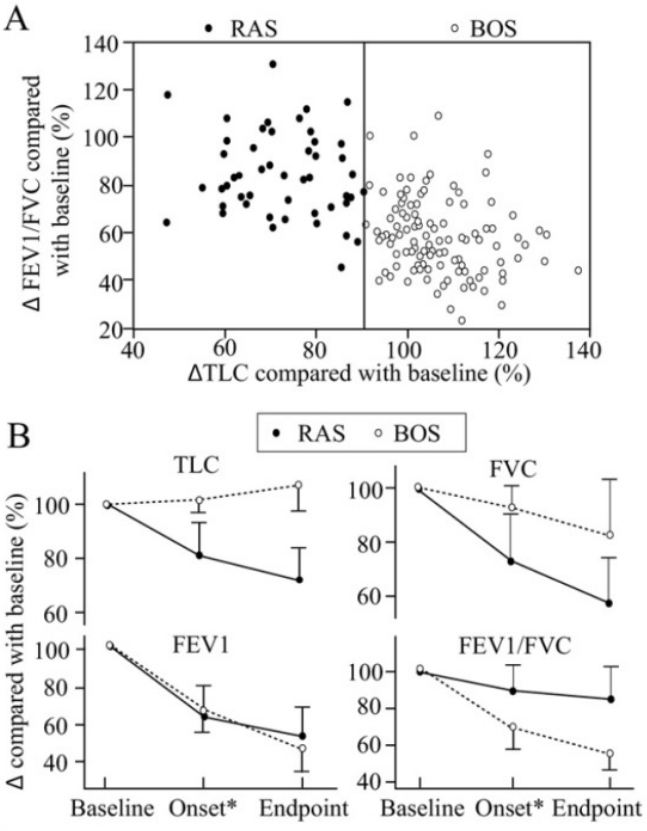
Restrictive allograft syndrome (RAS)

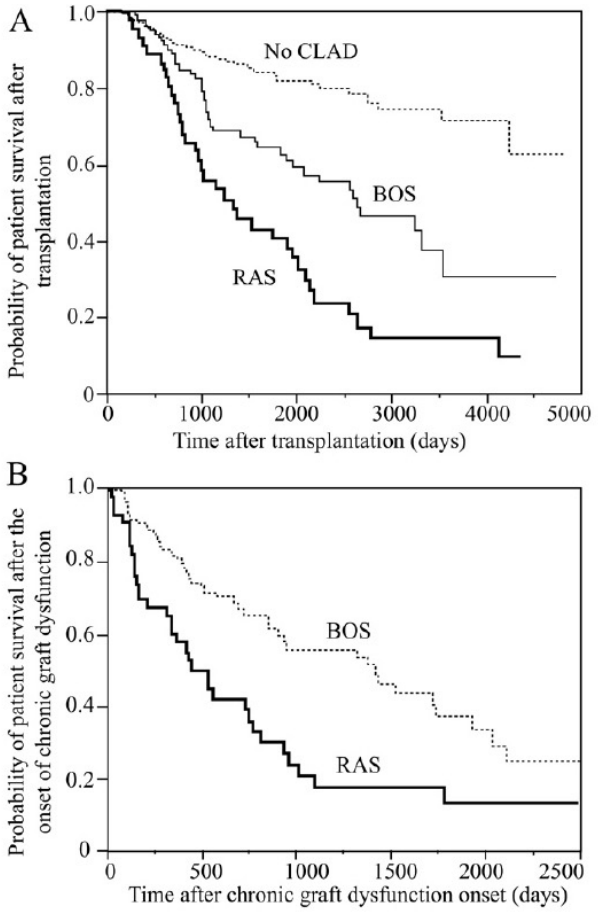




J Heart Lung Trans 2011; 30: 735

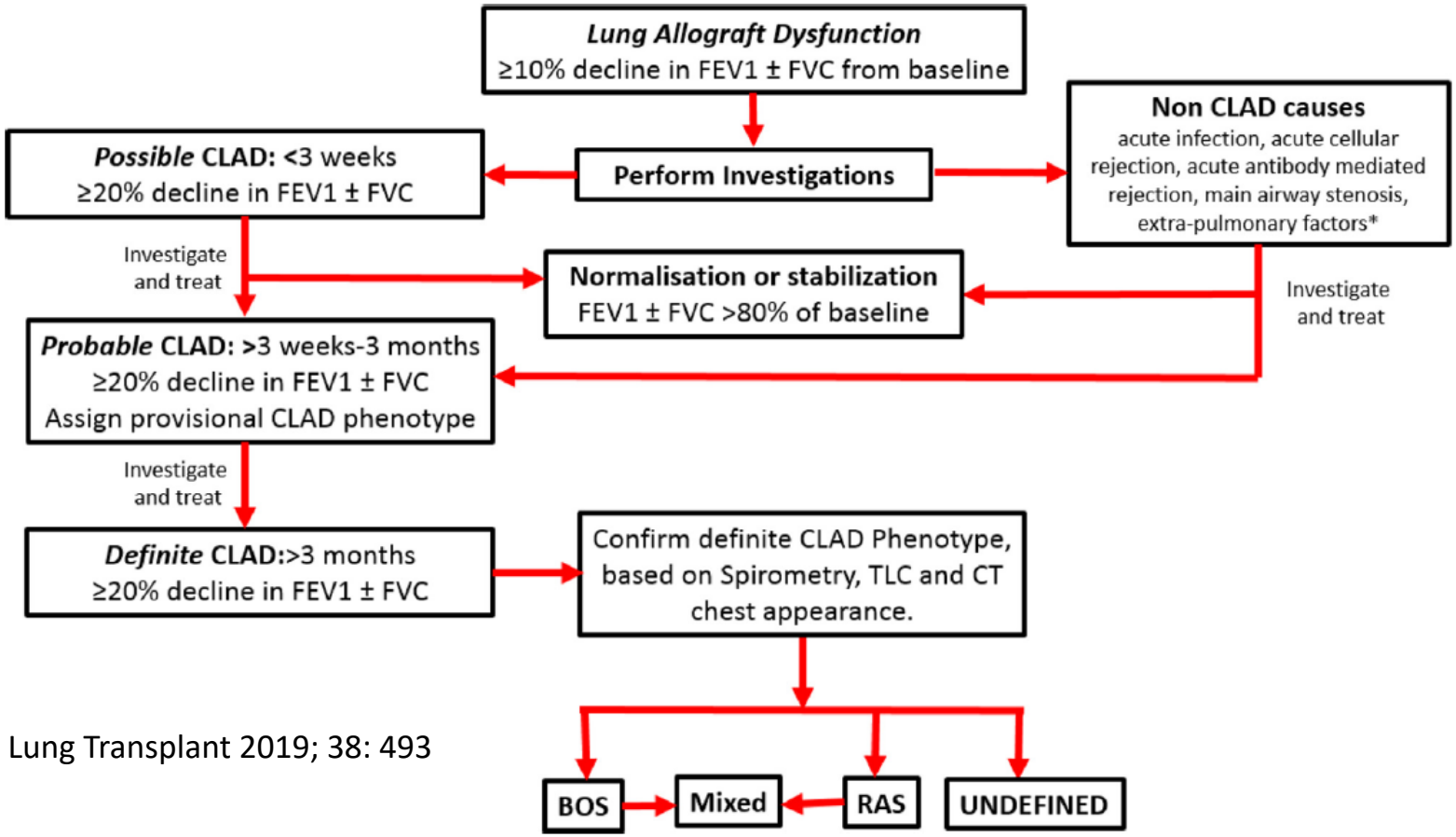
Restrictive allograft syndrome





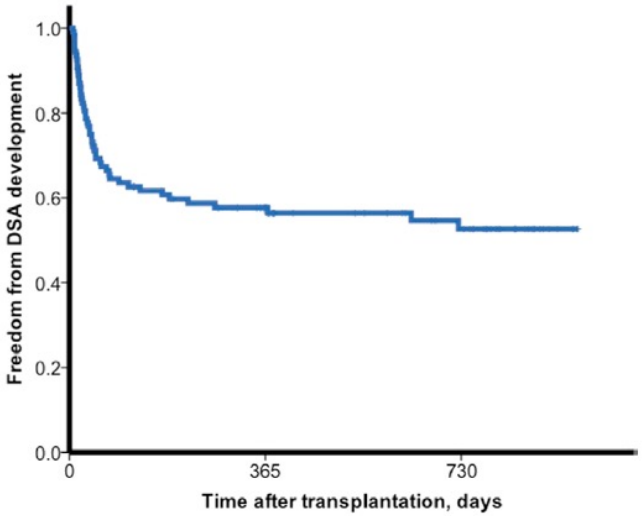
J Heart Lung Trans 2011; 30: 735

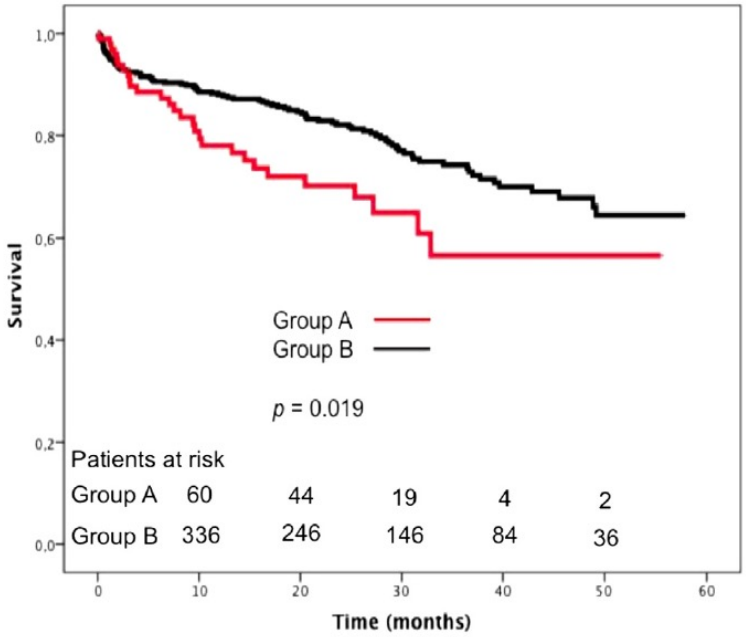
Chronic lung allograft dysfunction (CLAD)



J Heart Lung Transplant 2019; 38: 493

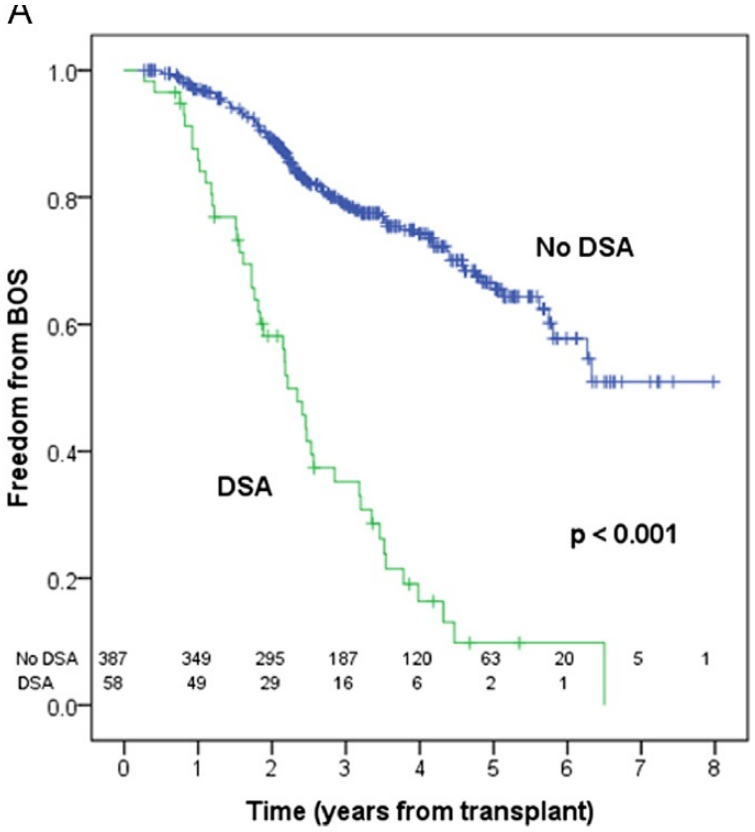
Post-transplant donor specific antibodies

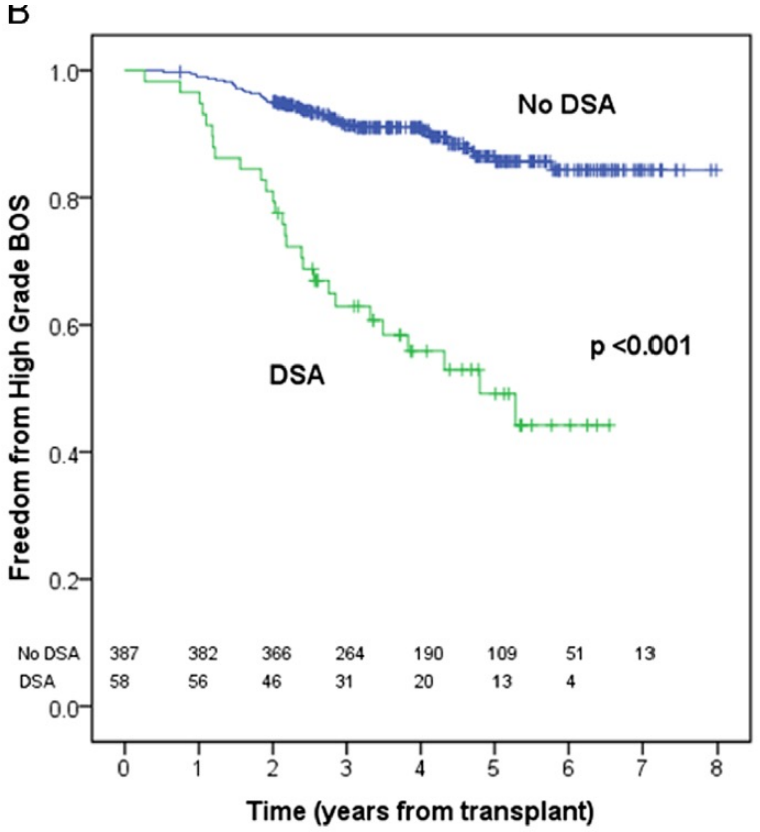




JHLT 2014; 33: 1255

Post-transplant donor specific antibodies





J Heart Lung Trans 2014; 33: 1288

Antibody mediated lung allograft rejection (AMR)

Table 1 Stages of Antibody-Mediated Rejection of the Pulmonary Allograft[a]

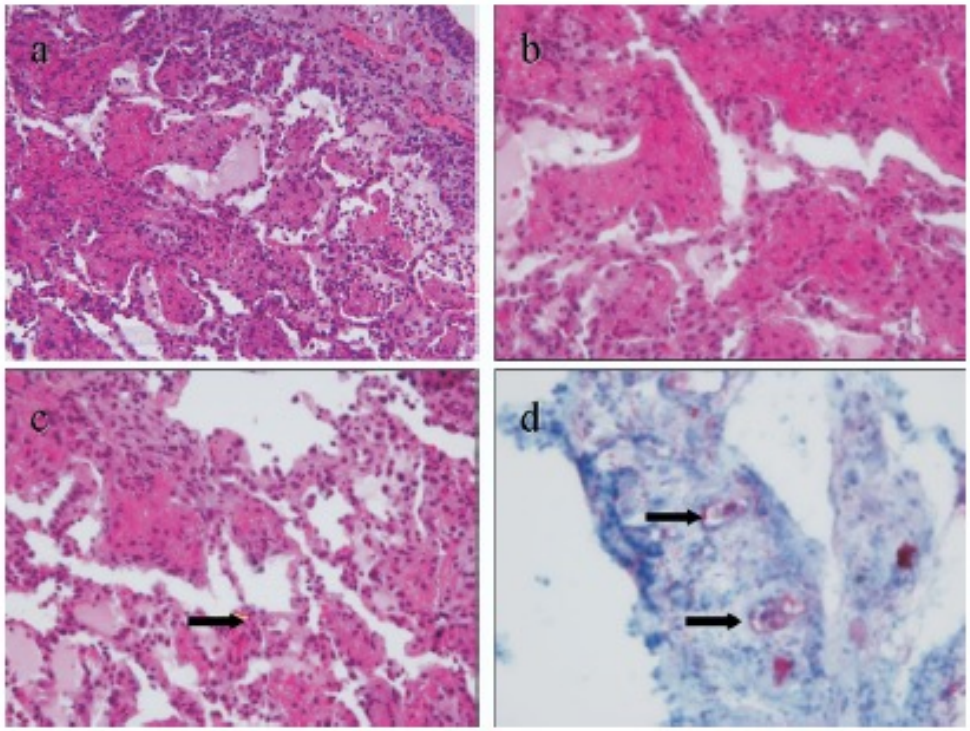
Stage of humoral rejection	Circulating antibody[b]	Lung biopsy specimen	Graft dysfunction
I: Latent	Yes	Normal	No
II: Silent	Yes	C4d	No
III: Subclinical	Yes	C4d + tissue pathology	No
IV: Clinical	Yes	C4d + tissue pathology	Yes

[a]After Takemoto et al.[2]

[b]Presence of circulating antibody to human leukocyte antigen or other donor antigens.

JHLT 2010; 29: 395

Antibody mediated rejection



JHLT 2009; 28: 96

Pathology of antibody mediated rejection

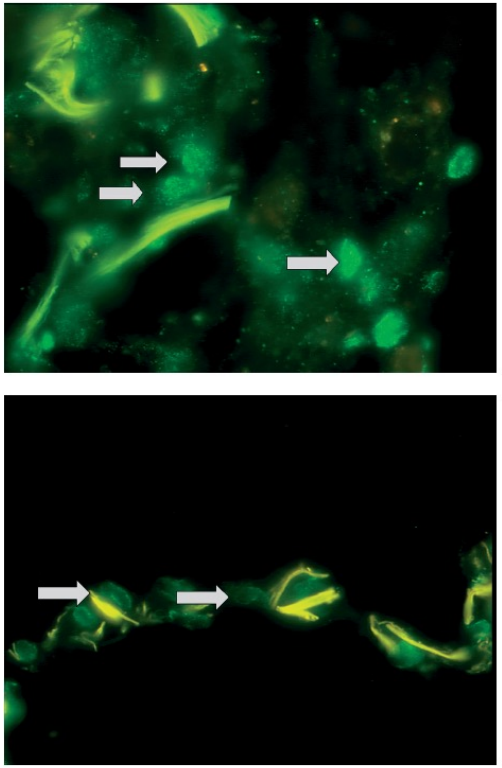
Table 2 Histopathologic Indications for Immunopathologic Evaluation

1. Neutrophilic capillaritis
2. Neutrophilic septal margination
3. High-grade acute cellular rejection ($\geq$A3)
4. Persistent/recurrent acute cellular rejection (any A Grade)
5. Acute lung injury pattern/diffuse alveolar damage
6. High-grade lymphocytic bronchiolitis (Grade B2R)
7. Persistent low-grade lymphocytic bronchiolitis (Grade B1R)
8. Obliterative bronchiolitis (Grade C1)
9. Arteritis in the absence of infection or cellular rejection
10. Graft dysfunction without morphologic explanation
11. Any histologic findings in setting of de novo DSA positivity

DSA, donor-specific antibodies.

JHLT 2013; 32: 14

Pathology of antibody mediated rejection



- C4d Background antibody staining not clearly defined
- Positive staining is variable, non-specific pattern
- Cannot be used alone to detect AMR

JHLT 2003; 3: 1143 JHLT 2010; 29: 395

Diagnostic challenges

Table 1 Definition and Diagnostic Certainty of Clinical Pulmonary Antibody-mediated Rejection

	Allograft dysfunction	Other causes excluded	Lung histology	Lung biopsy C4d	DSA
Definite	+	+	+	+	+
Probable[a]	+	+	+	–	+
Probable	+	+	+	+	–
Probable	+	+	–	+	+
Probable	+	–	+	+	+
Possible	+	+	+	–	–
Possible	+	+	–	–	+
Possible	+	+	–	+	–
Possible	+	–	+	+	–
Possible	+	–	+	–	+
Possible	+	–	–	+	+

DSA, donor-specific antibodies; +, item present; –, item absent or missing.

[a]There is building evidence that antibody-mediated rejection can be diagnosed confidently in the absence of positive C4d staining, hence this group is recognized separately.

Table 2 Definition and Diagnostic Certainty of Sub-clinical Pulmonary Antibody-mediated Rejection

	Lung histology	Lung biopsy C4d	DSA
Definite	+	+	+
Probable	+	–	+
Probable	–	+	+
Probable	+	+	–
Possible	+	–	–
Possible	–	+	–
Possible	–	–	+

DSA, donor-specific antibodies; +, item present; –, item absent or missing.

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The evolving face of rejection in lung transplantation

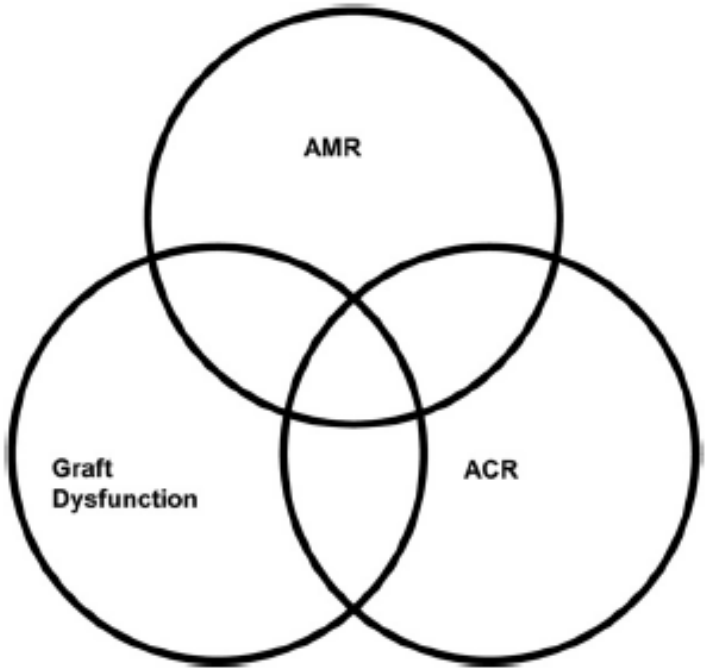

Figure 1 A Venn diagram shows the potential relationships between antibody-mediated rejection (AMR), acute cellular rejection (ACR), and pulmonary allograft dysfunction.

Key Points

- Lung allocation prioritizes survival benefits, which leads to higher acuity and complexity of candidates
- Lung transplant candidates often require mechanical support in the pretransplant period to allow for successful bridge to transplant
- The recovery from the transplant procedure is therefore often longer and more complex

Key Points

- Rejection remains the main impediment to long term survival benefits after lung transplantation
- Rejection presents with a variety of phenotypes, and requires a comprehensive evaluation platform for diagnosis
- Further study to create a more personalized approach to treatment of rejection is still needed.

Question

- A 40 year old woman with cystic fibrosis is 2 years post bilateral lung transplant. She presents with new onset dyspnea with exercise. Saturations are stable. CXR shows no infiltrates or effusions. Spirometry shows a 15% decline in FEV1. A bronchoscopy is performed. This shows no inflammatory infiltrate but a paucity of obvious terminal airways is noted.

Question

- The most likely diagnosis is:
  1) Sampling error
  2) Obstructive CLAD
  3) Restrictive CLAD
  4) AMR

Thank you