2022 Banff Lung Summary

Elizabeth N. Pavlisko, MD
Associate Professor of Pathology
Duke University Medical Center
Overview of Lung Program

• Section 1: “Non-rejection” pathology in the lung allograft

• Section 2: New technologies - molecular and AI

• Section 3: Project updates and discussion
“Non-rejection” Pathology: Acute and Organizing Lung Injury

Elizabeth N. Pavlisko, MD
Acute and organizing lung injury

• Well-established to be associated with allograft loss

• Some associated with restrictive allograft syndrome as well as DSAs
Acute and organizing lung injury

• Determine the **frequency** of ALI and OP events in a multicenter, prospective, observational study

• Examine **occurrence, timing and impact on long-term graft outcomes**

• Identify **donor or recipient factors** most strongly associated with ALI or OP development
CTOT-20: Clinical factors and biological mechanisms behind CLAD after transplantation

• Adult lung transplant recipients
• 5 North American centers
• Transplantation: December 2015-August 2018
• Patients were managed according to site-specific practices
• Enrollment: 803 patients
• Biopsies: 4786
Prognostic implications of and clinical risk factors for acute lung injury and organizing pneumonia after lung transplantation: Data from a multicenter prospective cohort study

Elizabeth N. Pavlisko | Megan L. Neely | Heather Kopetskie | David M. Hwang | Carol F. Farver | W. Dean Wallace | Andrea Arrossi | Peter Illei | Michelle L. Sever | Jerry Kirchner | Courtney W. Frankel | Laurie D. Snyder | Tereza Martinu | Michael Y. Shino | Lorenzo Zaffiri | Nikki Williams | Mark A. Robien | Lianne G. Singer | Marie Budev | Wayne Tsuang | Pali D. Shah | John M. Reynolds | S. Sam Weigt | John A. Belperio | Scott M. Palmer | Jamie L. Todd
Summary: acute and organizing lung injury

• Frequency: 41% of patients; 5-6% of biopsies

• Timing: Late ALI/OP was associated with two-threefold elevated risk of CLAD and allograft loss

• Donor/recipient factors for late ALI/OP:
  • Grade 3 primary graft dysfunction
  • Higher degree of donor/recipient human leukocyte antigen mismatch
  • Bacterial or viral respiratory infection
  • DSA detection
  • Early ALI/OP event
Multiple “insults”

- Fungal
- Viral
- Respiratory Infections & colonizations
- Bacterial

ACR → AMR

PGD

Autoimmune Reactivity

Air Pollution

GERD

CLAD
CXCL9 and CXCL10 are increased in BAL fluid during non-AR lung allograft injury

**TABLE 6  Univariable Models for CXCR3 Chemokine MFIs**

<table>
<thead>
<tr>
<th></th>
<th>CXCL9</th>
<th></th>
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<th>CXCL10</th>
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<tbody>
<tr>
<td></td>
<td>Fold</td>
<td>95%CI Lower</td>
<td>95%CI Upper</td>
<td>p-value</td>
<td>Fold</td>
<td>95%CI Lower</td>
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<td>p-value</td>
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<td>Any Injury b</td>
<td>1.6</td>
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<td>2.0</td>
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<td>1.1</td>
<td>1.8</td>
<td>.0018</td>
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<tr>
<td>AR</td>
<td>1.7</td>
<td>1.4</td>
<td>2.2</td>
<td>.00001</td>
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<td>1.3</td>
<td>2.1</td>
<td>.00002</td>
</tr>
<tr>
<td>LB</td>
<td>2.4</td>
<td>1.4</td>
<td>4.0</td>
<td>.0012</td>
<td>1.5</td>
<td>0.9</td>
<td>2.7</td>
<td>.1558</td>
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<tr>
<td>OP</td>
<td>1.0</td>
<td>0.6</td>
<td>1.2</td>
<td>.4196</td>
<td>0.7</td>
<td>0.5</td>
<td>1.1</td>
<td>.1719</td>
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<td>ALI</td>
<td>2.0</td>
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<td>.0013</td>
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<td>Pathogen c</td>
<td>1.7</td>
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</table>

a p-values are from mixed effects model comparing each allograft injury with "normal" biopsies. Fold-changes represent mean chemokine changes compared with "normal" biopsies.

b Any injury includes: AR, LB, OP or ALI.

cPathogen is defined as the detection of a pathogenic organism.

Both injury and high CXCL9 (or CXCL10) are required to cause CLAD

<table>
<thead>
<tr>
<th>TABLE 7 Risk of chronic lung allograft dysfunction by histopathologic findings and CXCL9 and CXCL10 interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Plasma CXCL9</strong></td>
</tr>
<tr>
<td>Allograft injury only</td>
</tr>
<tr>
<td>High CXCL9 only</td>
</tr>
<tr>
<td>Allograft injury with CXCL9</td>
</tr>
<tr>
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<td>Allograft injury with CXCL9</td>
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| **Plasma CXCL10** | n | HR | 95% CI  | p-value |
| Allograft injury only | 94 | 1.7 | 0.7-4.4 | .2424 |
| High CXCL10 only | 155 | 1.5 | 0.7-3.2 | .2563 |
| Allograft injury with CXCL10 | 94 | 4.4 | 2.2-9.1 | .0001 |
| **BAL CXCL10** | n | HR | 95% CI  | p-value |
| Allograft injury only | 124 | 2.2 | 1.0-5.2 | .0637 |
| High CXCL10 only | 154 | 1.9 | 1.0-3.7 | .0656 |
| Allograft injury with CXCL10 | 125 | 2.9 | 1.4-6.2 | .0052 |

Both injury and high CXCL9 (or CXCL10) are required to cause CLAD

<table>
<thead>
<tr>
<th>Injury/High Plasma/BAL CXCL9</th>
<th>n</th>
<th>HR^a</th>
<th>95% CI</th>
<th>p-value^a</th>
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<tbody>
<tr>
<td>Allograft injury only</td>
<td>94</td>
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<tr>
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<td>0.4-2.0</td>
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Injury with high plasma or BAL CXCL10 identifies risk of CLAD.

Summary and Future Directions

• Non-rejection injury patterns can be accompanied by elevated injury markers in BAL fluid (CXCL9 and CXCL10)

• CXCL9 and CXCL10 are associated with elevated risk of CLAD and can be used to help stratify risk
BALT in the lung allograft

Daniel Kreisel, MD PhD
Professor of Thoracic Surgery
Washington University in St. Louis
Lung Allograft Acceptance is Associated with Lymphoid Neogenesis

Accepted Lung Graft

Native Lung

Mucosal Immunology, 2012
Foxp3+ cells accumulate in iBALT
Selective depletion of graft-resident Foxp3+ cells

Balb/c → B6 – Foxp3 DTR

≥30 d

Secondary recipient

Harvest

JCI, 2019
Depletion of recipient B cells
Depletion of recipient B cells
- Depletion of graft-resident Foxp3 cells -> antibody mediated rejection (mouse model)
- AMR is dependent on recipient B cells and CXCL13 mediated chemotaxis, occurs in the lung graft itself, possibly setting it apart from other solid organ transplants.
Conclusions

• Rejection and tolerance are regulated at level of lung allograft

• Tertiary lymphoid organs maintain tolerant state
Section 2: New Technologies – Molecular and AI
Machine Learning in Lung Transplantation

Carolyn Glass MD PhD
Duke University School of Medicine/Duke University Health Systems
Associate Professor, Department of Pathology
Co-Director, Division of Artificial Intelligence
and Computational Pathology
Artificial Intelligence (AI) Machine Learning Diagnoses Lung Transplant Rejection

- Acute cellular rejection (ACR) is an important cause of morbidity and mortality.

- The reproducibility of the histologic diagnosis of ACR is quite variable, with published kappa values of interobserver agreement at 0.183 and 0.24-0.62.

- Can a convolutional neural network (CNN) distinguish acute cellular rejection from normal lung tissue?
Detecting Acute Cellular Rejection in Lung Transplant Biopsies by Artificial Intelligence: A Novel Deep Learning Approach

- ML algorithm distinguished ACR from normal alveolated lung tissue with 95% validation accuracy.
- First study to provide evidence that a supervised ML can reach acceptable, and possibly surpass, performance of current diagnostic standards of identifying ACR in lung transplant patients.
- Ongoing studies include multi-institutional validation testing.

Can a CNN distinguish acute cellular rejection from infection in lung tissue?
Transplanting thoracic COVID-19 positive donor

- Lungs were eligible if the donor first tested PCR positive on nasopharyngeal swab (NPS) for COVID-19 > 20 days prior to procurement and had a negative lower respiratory tract specimen.

- 14 thoracic organs including 12 hearts and 2 sets of lungs from COVID-19 positive donors were transplanted in 13 recipients between January 1, 2021 and February 2, 2022.

- None of the recipients developed signs or symptoms of COVID-19 infection with median duration of follow up 215 days. Patient survival is 92% to date, and graft is survival 93%.

- Limitation: sample size small with only 2 lung recipients.

- Kaul DR et al. (2021) have reported prior transmission to recipients.

*J Heart Lung Transplant.* 2022 Jun 30:S1053-2498(22)01997-0.
Representative H&Es from macaque lungs challenges with SARS-CoV-2 virus and two different doses of vaccination after 7 days of infection (perivascular mononuclear infiltrate with mixed macrophages). Guebre-Xabier et al. NVX-CoV2373 vaccine protects cynomolgus macaque upper and lower airways against SARS-CoV-2 challenge. Vaccine. 2020 Nov 25;38(50):7892-7896.
Future Considerations

• As COVID+ donor lung transplants increase, improved surveillance methods for distinguishing viral infection versus acute cellular rejection in asymptomatic/early transplant recipients that are timely are important.

• Can we use ML to distinguish infection from acute cellular rejection for transplant surveillance patients using WSIs? Not yet...

• Lung Tx machine learning development (pathology) is still in the very early stages, with a focus on diagnostics, rather than predictive outcomes.
CT scan: diagnostic and prognostic value

Stijn E Verleden, PhD
ASTARC, Antwerp University
Pneumology and thoracic- and vascular surgery (UZA)
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 (1993)

**Pulmonary Function Testing = “gold standard”**
<table>
<thead>
<tr>
<th>Subtype</th>
<th>Spirometric Findings</th>
<th>CT Findings</th>
<th>Pathologic Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Obstructive</td>
<td>$\text{FEV}_1 \leq 80%$ of the baseline value after 3 posttransplant months in the absence of infection or other identifiable cause when two separate measures 3 wk apart meet the threshold (i.e., irreversible) (3)</td>
<td>Airtrapping, mosaic attenuation, bronchial wall thickening, bronchiectasis, centrilobular nodules</td>
<td>BO</td>
</tr>
<tr>
<td>Restrictive</td>
<td>Persistent $\geq 20%$ decline in $\text{FEV}_1$ compared with the posttransplant baseline value, computed as the mean of the best two postoperative $\text{FEV}_1$ measurements taken $\geq 3$ wk apart (64); concomitant $\geq 10%$ decline in TLC compared with posttransplant baseline value, computed as the mean of the two TLC measurements taken at the time of, or very near to the time of, the best two postoperative $\text{FEV}_1$ measurements (64)</td>
<td>Persistent parenchymal with or without pleural-based opacities on chest imaging (64): Apically predominant pleural or subpleural fibrosis; pleural thickening; subpleural and peribronchovascular reticulation; interlobular septal thickening; perilymphatic nodules, perilobular consolidation, or OP reaction pattern; nonresolving subpleural consolidation on serial studies; persistent peripheral or less frequently central ground-glass opacities; traction bronchiectasis</td>
<td>PPFE, DAD, OP, AFO, BO, ACR, NSIP, eosinophilic interstitial infiltrate</td>
</tr>
<tr>
<td>Mixed</td>
<td>Obstruction: $\text{FEV}_1 / \text{FVC} &lt; 0.7$; restriction: TLC decline $\geq 10%$ from baseline (3)</td>
<td>Combination of imaging findings in detailed obstructive and restrictive phenotypes, apical predominance (60)</td>
<td>Combination of pathologic conditions in obstructive and restrictive phenotypes</td>
</tr>
</tbody>
</table>
Diagnostic value of HRCT with quantitative image analysis at CLAD onset
Prognostic value of CT

Slow progressor

Fast progressor

Prognostic value of CT

A

- Basal (n=15)
- Diffuse (n=10)
- Apical (n=28)

B
C
D

Chest CT and AI: summary and future

- Software packages are increasingly being used to phenotype CLAD (BOS vs RAS)

- Within a given phenotype, CT can be used for additional prognostic stratification

- CT might be more important than physiology in the future
Molecular analysis of lung transplant samples
Molecular T-cell–mediated rejection in transbronchial and mucosal lung transplant biopsies is associated with future risk of graft loss

Kieran Halloran, MD, MSc, Michael D. Parkes, MSc, Irina Timofte, MD, Gregory Snell, MD, Glen Westall, MD, PhD, Jan Havlin, MD, PhD, Robert Lischke, MD, PhD, Ramsey Hachem, MD, Daniel Kreisel, MD, PhD, Deborah Levine, MD, Bartosz Kubisa, MD, PhD, Maria Piotrowska, MD, Stephen Juvet, MD, PhD, Shaf Keshavjee, MD, MSc, Peter Jakusch, MD, Walter Klepetko, MD, Alim Hirji, MD, MSc, Justin Weinkauf, MD, and Philip F. Halloran, MD, PhD

- 457 TBB + 314 MB
- TBB-TCMR scores correlate with A>0
- MB-TCMR scores correlate with B>0
- Molecular TCMR (but not histology or DSA) associated with graft loss
Transcripts associated with chronic lung allograft dysfunction in transbronchial biopsies of lung transplants

Michael D. Parkes\textsuperscript{1} | Kieran Halloran\textsuperscript{1} | Alim Hirji\textsuperscript{1} | Shane Pon\textsuperscript{1} | Justin Weinauf\textsuperscript{1} | Irina L. Timofte\textsuperscript{2} | Greg I. Snell\textsuperscript{3} | Glen P. Westall\textsuperscript{3} | Jan Havlin\textsuperscript{4} | Robert Lischke\textsuperscript{4} | Andrea Zajacová\textsuperscript{4} | Ramsey Hachem\textsuperscript{5} | Daniel Kreisel\textsuperscript{5} | Deborah Levine\textsuperscript{6} | Bartosz Kubisa\textsuperscript{7} | Maria Piotrowska\textsuperscript{7} | Stephen Juvet\textsuperscript{8} | Shaf Keshavjee\textsuperscript{8} | Peter Jaksch\textsuperscript{9} | Walter Klepetko\textsuperscript{9} | Philip F. Halloran\textsuperscript{1}

- 498 TBB (90 CLAD)
- Time assoc. with inflammation genes
- After correcting for time, CLAD assoc. with parenchymal response to wounding genes
- Molecular classifiers predicted CLAD with AUC 0.70 (no time-correction) and 0.87 (time-corrected)
Chronic Antibody-Mediated Rejection in Nonhuman Primate Renal Allografts: Validation of Human Histological and Molecular Phenotypes

B. A. Adam1,*, R. N. Smith2, I. A. Rosales2, M. Matsunami1, B. Afzali1, T. Oura3, A. B. Cosimi2, T. Kawai2, R. B. Colvin2 and M. Mengel1

Molecular Assessment of Microcirculation Injury in Formalin-Fixed Human Cardiac Allograft Biopsies With Antibody-Mediated Rejection

B. Afzali1,2, E. Chapman1, M. Racape3, B. Adam1, P. Bruneval3, F. Gil4, D. Kim4, L. Hidalgo1, P. Campbell1, B. Sis1, J. P. Duong Van Huyen3 and M. Mengel1,*


Afzali et al. AJT. 2017;17(2):496-505.
Microarray-based gene expression in FFPE TBBx: Identification of novel gene sets for ACR, AMR and infection (pending validation)

Conclusions

- Gene transcripts utilized for kidney and heart do not perform well in the lung and further work is needed.
Infection and aspiration drive airway inflammation

Gene expression in lymphocytic bronchitis

Lung transplant recipients undergoing large airway brush (2013-2014, N=61)

Airway brushes during E-grade rejection (LB), N=6

Next-generation RNA sequencing of all RNA transcripts

Control airway brushes, N=18

Comparison of Rejection Pathologies


- No pathology control biopsies
- A-grade rejection transbronchial bx

- No pathology control biopsies
- B-grade rejection transbronchial bx

- No pathology control biopsies
- E-grade rejection (LB) Endobronchial bx

Digital RNA counting of 800 select targets (nanoString) N=48

Common allograft rejection signatures

Lymphocytic Bronchitis
Common Rejection Module
Broad Hallmark Allograft Rejection
Renal Antibody Mediated Rejection (ABMR)
Renal T cell Mediated Rejection (TCMR)

Metagene score (standard deviation)
Validating in small airway brushes

442 Lung transplant recipients
• Approached between 4/2013 and 6/2016

38 (9%) Declined to participate

404 Subjects prospectively followed

252 (63%) No brush collected during study period

152 subjects with airway brushes

113 (74%) Stable FEV₁

39 subjects with CLAD
• Brush after or ≥3 months prior to CLAD onset

6 Alternative cause of FEV₁ decline
  3 Pleural disease
  2 Airway stenosis
  1 Malignancy
  7 Diagnostic uncertainty
  4 Poor quality RNA (by PCA)

22 CLAD cases

27 Controls matched on post-transplant time and infection status

Dugger D. et. al. Am. J. Transplant 2020
CLAD gene expression changes greater on brushes than biopsies

Dugger D. et. al. Am. J. Transplant 2020
Conclusions

- Gene signatures of allograft rejection can be identified early in CLAD.
  - Even when transbronchial biopsy pathology is normal
  - Predict time to retransplant or death

- Multicenter validation studies are underway
Graft function after lung transplantation: Time to re-think our monitoring strategy.

*How does dd-cfDNA fit in?*

Deborah Jo Levine MD FAST FCCP
Stanford University
Challenges with early identification and recognition of risks...

Transplant

Infection
Viral, Bacterial, Fungal

Immune injury
ACR, AMR,

Non-immune injury
PGD, Non-adherence, Reflux

CLAD

Graft function
dd-cfDNA and CLAD, Rejection, and Infection

Figure 1A. Donor derived cell-free DNA Results by Cohort

<table>
<thead>
<tr>
<th></th>
<th>Normal</th>
<th>CLAD</th>
<th>ACR</th>
<th>Infection</th>
<th>Total AMR</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>148</td>
<td>48</td>
<td>7</td>
<td>50</td>
<td>34</td>
</tr>
<tr>
<td>Median</td>
<td>0.32%</td>
<td>0.88%</td>
<td>1.80%</td>
<td>1.34%</td>
<td>1.41%</td>
</tr>
<tr>
<td>IQR</td>
<td>0.21, 0.58</td>
<td>0.59, 1.72</td>
<td>0.41, 2.55</td>
<td>0.70, 1.98</td>
<td>0.50, 2.11</td>
</tr>
</tbody>
</table>

All p-values between each cohort versus normal were <0.0001

dd-cfDNA samples retrospectively adjudicated to event cohort (normal, CLAD, ACR, AMR, infection)
dd-cfDNA

- dd-cfDNA is a marker of injury
- Statistically significant increase in dd-cfDNA between each event type compared to a normal cohort, but no statistical differences between groups
- May be a great monitoring biomarker…
Banff Project Updates

• Banff Lung AMR Molecular Signature Project
• LASA template
Banff Lung AMR Molecular Signature Project

Benjamin A. Adam, MD, FRCPC
Associate Professor, Department of Laboratory Medicine and Pathology, University of Alberta
Site Chief of Laboratory Medicine & Divisional Director of Anatomic Pathology, University of Alberta Hospital

September 20, 2022
Banff Lung AMR Molecular Signature Project

Transplant lung (n=160 transbronchial biopsies)

DSA/C4d pos

Definite clinical AMR (n=30)
Clinical, histo, C4d & DSA positive

Early ALI (n=20)
d10-d21 post-Tx

DSA and C4d negative (throughout pre/post-transplant period)

Post-transplant time matched to AMR group (n=110)

ACR (n=30)
Pure A1-A3 (10 each)

Infection (n=60)
20 x viral, 20 x fungal, 20 x bacterial

Normal (n=20)
Clinical, histo, C4d & DSA negative

Normal from tumor resection (n=20)

ALI (n=20)

Final discovery cohort (n=200): collate clinical, DSA and histology data; confirm 2 mm² remaining tissue in block

Cut 5 x 20 µm curls from each FFPE block (RNase-free technique, stored in microfuge tubes) → send to University of Alberta

Gene expression testing: deparaffinization, RNA extraction, NanoString® analysis (University of Alberta)

Analysis: normalization, differential expression, clinical/histology correlation, gene set/classifier derivation, etc.

Or

Send entire FFPE block to University of Alberta for cutting

Sequential biopsy analysis: biopsies preceding diagnosis of definite clinical AMR (n=20-40)

Independent validation cohort: same groups as discovery cohort plus probable/possible AMR, A4, B1R/B2R, CLAD, etc.
Original clinical science

Lung allograft standardized histological analysis (LASHA) template: A research consensus proposal

Fiorella Calabrese MD, Anja C. Roden MD, Elizabeth Pavlisko MD, Francesca Lunardi MD, ScD, PhD, Desley Neil MD, Benjamin Adam MD, David Hwang MD, Martin Goddard MD, Gerald J. Berry MD, Marina Ivanovic MD, Jan von der Thüsen MD, PhD, Laure Gibault MD, Chieh-Yu Lin MD, Katharina Wassilew MD, MHBA, Carolyn Glass MD, Glen Westall MD, Adriana Zeevi MD, Deborah Jo Levine MD, Antoine Roux MD.
LUNG ALLOGRAFT STANDARDIZED HISTOLOGICAL ANALYSIS (LASHA)

**Type of sample:** Transbronchial biopsy □ Transbronchial cryobiopsy □ Wedge biopsy □ Other (__________) □

**Stainings/techniques:** H&E □ Connective tissue staining □ Silver stains □ Other special stains (__________) □

Other ancillary tools (____________________) □

**C4d evaluation:** Immunohistochemistry (IP) □ Immunofluorescence (IF) □

IP: Distribution: <10% □ 10-50% □ >50% □ IF: Intensity (score): 0 □ 1 □ 2 □ 3 □

**Biopsy***: adequate □ insufficient □ inadequate □

Bronchi: YES □ NO □
Bronchioles: YES □ NO □
Artery: YES □ NO □

**Lesions suggestive of acute cellular rejection:**
- Perivascular mononuclear infiltrates: YES □ NO □
- Lymphocytic bronchiolitis: YES □ NO □

**Lesions suggestive of chronic rejection:**
- Obliterative bronchiolitis: YES □ NO □
- Vascular rejection: YES □ NO □
Alveolar septal injury pattern:
- Neutrophils in alveolar septa (score):
- Neutrophilic/cellular debris in alveolar septa (score):
- Platelet-fibrin thrombi in alveolar capillaries (score):
- Alveolar capillary dilatation (score):
- Septal wall oedema/widening (score):
- Mononuclear cells in alveolar septa (score):
- Septal fibrous thickening (score):
Intra-alveolar Injury pattern:
- Neutrophils in alveolar spaces (score):
- Hyaline membranes (score):
- Pneumocyte hypertrophy/reactive changes (score):
- Granulation tissue plugs in alveolar spaces/OP (score):
- Fibrin balls in alveolar spaces (suggestive of AFOP) (score):
- Alveolar proteinosis (score):
- Macrophages (score):
  Specify subtypes: normal □ hemosiderophages □ foamy □ cholesterol clefts □ giant cells □
  Foreign body in alveolar spaces: YES □ NO □

Injury pattern in other sites (e.g. subpleural, interlobular septa, large airways)
- Suspected pleuroparenchymal/intralveolar fibroelastosis
- Inflammation of subpleural/interlobular areas (specify the type)
- Injury of the large airways (specify the type)
Other:
- Arteritis/endotheliitis:
- Thrombus:
- Ischemic necrosis:
- Viral inclusions:
- Fungal organisms:
- Other infectious organisms:
- Granuloma:
- Suspected PTLD
- Suspected recurrent disease
- Eosinophilia (interst/alv):
- BALT***:
- Previous biopsy site
- Other (specify) ____________________________
SUMMARY

**Acute cellular rejection: A & B Grades**
(A Grade): 0 □ 1 □ 2 □ 3 □ 4 □ X □
(B Grade): 0 □ 1R □ 2R □ X □

**Infection:** yes/no (specify the type)

**Lesions suggestive of AMR:** yes/no (specify the lesions and C4d staining)

**Lesions suggestive of chronic rejection:** yes/no (specify if OB, RAS-like or vascular, reporting the C a.

**Lesions suggestive of I/R injury:** yes/no (specify the lesions)

**Lesions suggestive of other diagnosis:** yes/no (specify the diagnosis)
2022 Banff Lung Paper Proposal

Dr. Elizabeth Pavlisko
Pr. Antoine Roux
NON-rejection lung allograft pathology
OR « beyond classical rejection definition (A lesion) »

Need for classification?
Based on lesion associated with graft outcome
Proven based on publication
Start with LASHA template

REJECTION or PAGO (Pathology Associated with Graft Outcome)

- Step 1: Identification of pathology
- Step 2: Exclude differential etiology*
- Step 3: Humoral component? Complement dependent component?

No gold standard for rejection >>> association with graft outcome reveals the clinically relevant parameters “A lesion” first described in lung allograft early 90’s, because unseen in other lung disease before. Then was called rejection, but there are likely other lesions that are related to graft outcome, and this could also be rejection.
Pathology Associated with Graft Outcome

- ISHLT Grade A Lesions
- Arteritis
- Acute Lung Injury
- Interstitial changes
- C4d staining
- ISHLT Grade B Lesions
- BAL Eosinophilia

Other causes:
Methodology

• Delphi with pathologists from US, Canada and Europe (n=18)
• For each lesion of the LASHA template: grade your answer [-5; 5]

➢ This lesion is associated with graft outcome?

➢ This lesion should be considered as rejection after exclusion of concurrent diagnosis as the sole cause of graft dysfunction. *

➢ This lesion should be considered a Pathology Associated with Graft Outcome

*Other causes: other diagnoses or etiology that could lead to this histological pattern. If after therapy for this diagnosis, the histological changes continue, it reinforces the diagnosis of rejection.
<table>
<thead>
<tr>
<th>Lesion (LASHA)</th>
<th>Exclusion diagnosis (Banff 2017 Report)</th>
<th>Association with DSA/AMR</th>
<th>Association with graft outcome (Delphi)</th>
<th>Association with graft outcome (References)</th>
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