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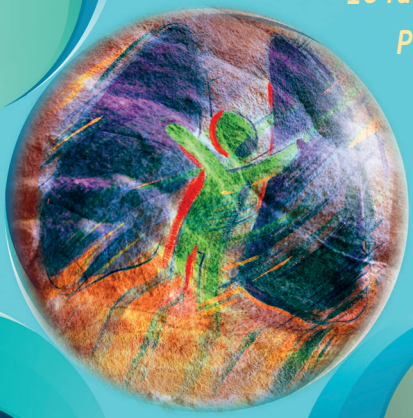

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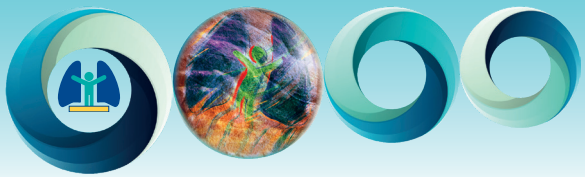

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EFFECT OF DONOR AGE ON SURVIVAL IN LUNG TRANSPLANTATION: RETROSPECTIVE STUDY FROM A MULTICENTRIC COHORT

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Background. Shortage of organ requires to consider older donors of lung transplants but the impact of donor age on the outcomes of lung transplant recipients (LTR) is not clearly established.

Methods. We analyzed data from a French multicenter cohort of 1191 LTR. The main outcome was the time from transplantation to death. Multivariate Cox regression associated with G-computation were used to obtain confounder-adjusted results.

Results. Lung transplants from donor over 60 years of age are more frequently allocated to older recipients, female recipients and candidates with chronic obstructive pulmonary disease and cardiovascular comorbidities. The 5-year confounder-adjusted survival of recipients with lung from donor over 60 was lower than that of recipients of transplants from younger donors (62.1% versus 69.3%, respectively, $p < 0.001$). The corresponding HR was 1.28 (95% CI [1.01-1.63]. For such a follow-up at 5 years, the mean life expectancy was 46.4 months (95% CI [44.4-48.3]) in the group receiving a younger graft versus 42.6 months (95% CI [39.6-45.6]) in the older group. It corresponded to significant difference of 3.8 months gain in the 5-year life expectancy ($p = 0.028$).

Conclusion. Donor age over 60 is an independent risk factor for reduced post-transplant survival. The age criterion must be taken into account when accepting a lung graft as a potential impact to the recipient's survival.

DONOR TO RECIPIENT AGE MATCHING IN LUNG TRANSPLANTATION: A EUROPEAN EXPERIENCE

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Background: The age profile of organ donors and patients on lung transplantation (LT) waiting lists have changed over time. In Europe, the donor population has aged much more rapidly than the recipient population, making allocation decisions on lungs from older donors common. In this study we assessed the impact of donor and recipient age discrepancy on LT outcomes in the UK and France.

Methods: A retrospective analysis of all adult single or bilateral LT in France and the UK between 2010 and 2021. Recipients were stratified into 3 age groups: young (≤ 30 years), middle-aged (30 to 60) and older (≥60). Their donors were also stratified into 2 groups <60, ≥ 60. Primary graft dysfunction (PGD) rates and recipient survival was compared between matched and mismatched donor and recipient age groups. Propensity matching was employed to minimize covariate imbalances and to improve the internal validity of our results.

Results: Our study cohort was 4,696 lung transplant recipients (LTRs). In young and older LTRs, there was no significant difference in 1 and 5-years post-transplant survival dependent on the age category of the donor. Young LTRs who received older donor grafts had a higher risk of severe grade 3 PGD.

Conclusion: Our findings show that clinically usable organs from older donors can be utilized safely in LT, even for younger recipients. Further research is needed to assess if the higher rate of PGD3 associated with use of older donors has an effect on long-term outcomes.

OUTCOMES OF LISTING FOR LUNG AND HEART-LUNG TRANSPLANTATION IN PULMONARY HYPERTENSION: COMPARATIVE EXPERIENCE IN FRANCE AND THE UNITED KINGDOM

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Background: Lung or heart-lung transplantation (LT/HLT) for severe pulmonary hypertension (PH) as the primary disease indication carries a high risk of waiting list mortality and post-transplant complications. France and the UK both have coordinated PH patient services, but with different referral pathways for accessing LT services. We conducted a comparative analysis of adult PH patients listed for LT/HLT in the UK and France.

Results: We included 211 PH patients in France (2006-2018) and 170 in the UK (2010-2019). Cumulative incidence of transplant, delisting, and waiting list death within three-years were 81%; 4%; 11% in France versus 58%; 10%; 15% in the UK ($p<0.001$ for transplant and delisting; $p=0.1$ for death). Median non-priority waiting time was 45 days in France versus 165 in UK ($p<0.001$). High priority listing occurred in 54% and 51% of transplanted patients respectively in France and UK ($p=0.8$). Factors associated with achieving transplantation related to recipients' height, male sex, clinical severity and priority listing status. One-year post transplant survival was 78% in France and 72% in the UK ($p= 0.04$).

Conclusion: Access to transplantation for PH patients is better in France than in the UK where more patients were delisted due to clinical deterioration because of longer waiting time. High rates of priority listing occurred in both countries. Survival for those achieving transplantation was slightly better in France. Ensuring optimal outcomes after transplant listing for PH patients is challenging and may involve early listing of higher risk patients, increasing donor lung utilization and improving allocation rules for these specific patients.

BATTLING *ASPERGILLUS* AFTER LUNG TRANSPLANTATION: RISK FACTORS, STATINS, AND THE IMPACT ON CHRONIC LUNG ALLOGRAFT DYSFUNCTION

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Purpose. Invasive aspergillosis (IA) presents substantial challenges for lung transplant (LTx) patients and is associated with increased morbidity and mortality. To effectively address IA, further understanding is needed regarding the risk factors, potential preventive modalities, and the impact on chronic lung allograft dysfunction (CLAD). Our primary objective is to identify and to quantify risk- and protective factors associated with IA in LTx patients. Secondary objectives concern the impact of IA on CLAD, and all-cause mortality during follow-up.

Methods. We collected data through electronic medical records from all LTx patients transplanted between December 2013 and January 2022 at the University Medical Center Groningen, the Netherlands. IA, including definitive, possible and probable IA, was defined according to the European Organization for Research and Treatment of Cancer criteria. Pre-specified risk factors, nebulised Amphotericin B (AmB), and use of statins were compared between patients with and without IA post-LTx by univariable analysis. All parameters were entered into a multivariable logistic regression analysis model (enter selection). A Cox proportional hazards model with time dependency was used for survival analysis.

Results. Aspergillus was cultured in 110 out of 275 (40%) patients after LTx. Of those 89/110 (81%) were classified as having probable IA and there were no patients with proven or possible IA. Aspergillus colonisation was present in 21/110 patients (19 %). Half of the patients (55/110) received nebulised AmB prophylaxis during hospitalization for LTx. MMF use (OR = 6.59; 95% CI [2.69-16.10]), airway stenosis (OR = 6.00; 95% CI [2.08-17.34]), Aspergillus cultured pre-LTx (OR = 2.66; 95% CI [1.21-5.86]), CLAD (OR = 3.10; 95% CI [1.38-6.70]) and acute rejection (OR = 2.44; 95% CI [1.30-4.60]), were significantly associated with an increased risk of IA, while the use of statins (OR = 0.35; 95% CI [0.18-0;.72]), was associated with a decreased risk. Nebulized AmB prophylaxes was not associated with a decreased risk of IA. Among patients with IA, 27/89 (30%) developed CLAD while in patients without IA, 25/1185 (14%) did. Most patients (20/27 (74%)) developed CLAD after IA, whereas 7/27 (26%) developed CLAD before IA, with 4 of them experiencing progressive CLAD. There was no significant difference in all-cause mortality between patients with and without IA (34%vs 29% respectively).

Conclusions. IA remains a common complication after LTx and is associated with CLAD, but not with all-cause mortality. Use of MMF, airway stenosis, Aspergillus cultured pre-LTx, CLAD and acute rejection were the strongest risk factors for IA in our study. Interestingly, the use of statins was associated with a decreased risk of IA, while AmB was not. Prospective trials are urgently needed to address the causal effects of preventive therapies in reducing the burden of IA in LTx patients.

READY FOR PRIME TIME? A SYSTEMATIC REVIEW OF CYTOMEGALOVIRUS IMMUNE MONITORING ASSAYS FOR PREDICTING CMV-RELATED EVENTS IN LUNG TRANSPLANT

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Background. Cytomegalovirus (CMV) continues to pose a significant cause of morbidity after lung transplantation. There has been a growing body of literature utilizing CMV-specific T-cell mediated immunity (CMV-CMI) to predict CMV-related events. However, its application in lung transplant recipients must still be more adequately understood.

Methods. We searched through several biomedical databases including Medline, Embase, Cochrane CENTRAL, and Web of Science platforms in March 2023. We included observational studies and controlled trials that used CMV-CMI to predict the occurrence of CMV events. We excluded studies with less than 10 participants, lacking CMV-related events as outcome, or involving non-lung transplants from our analysis.

Results. We initially identified 7,387 articles and excluded 6,820 and 447 articles with abstract and full text review, respectively. This resulted in 120 studies in solid organ transplant recipients. Finally, we identified 16 studies in lung transplant recipients including 969 participants: 8 studies assessed CMV-CMI at the end of prophylaxis, 2 of which adjusted the duration of prophylaxis according to the result of CMV-CMI; 5 measured CMV-CMI serially; and 3 studies assessed it pre-transplant, post-treatment, and for predicting self-resolving viremia. As CMV-CMI methodology, QuantiFERON was employed in 8 studies, ELISpot in 7, and intracellular cytokine staining in 3. Among the 6 studies assessing CMV-CMI at the end of prophylaxis, heterogeneity was observed in the serologic risk of the included populations, duration of prophylaxis, and measured CMV-events (Table 1). In R+ individuals, CMV-CMI did not predict any CMV DNAemia in any of the 3 studies, but it was associated with predicting high viral load DNAemia and CMV disease. The only study in D+/R- showed an association between CMV-CMI and a lower risk of late-onset infection. None of the studies using CMV-CMI at the end of prophylaxis were able to predict lung allograft infection successfully. Two interventional studies from the same institution tailored the duration of prophylaxis to the result of CMV-CMI at the end of standard prophylaxis (5 months). Both found no difference in the rate of CMV DNAemia between individuals who underwent standard duration prophylaxis and those who followed immuno-guided duration. However, they found a significant reduction in the magnitude of CMV infection of the lung allograft in those following the immuno-guided approach.

Conclusion. There is considerable variability among the populations, prophylaxis regimens, CMV-events, and methodologies utilized in the different studies. The predictive capacity of CMV-CMI for late-onset CMV infection risk is generally low with most studies, except one, showing no significant difference between those with or without a CMV-CMI response. Furthermore, no study successfully predicted the occurrence of lung allograft infection based on CMV-CMI measurement. While employing CMV-CMI to guide the duration of prophylaxis appears promising, further studies utilizing conventional prophylaxis durations (6-12 months) are necessary. The current evidence is insufficient to recommend the routine use of CMI among lung transplant recipients.

RAPID MOLECULAR DETECTION OF MULTIDRUG RESISTANT BACTERIA IN DONOR LUNGS AS A STRATEGY TO OPTIMIZE PERIOPERATIVE PROPHYLACTIC ANTIBIOTICS

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Rationale: In our program, 37% of transplanted donor lungs are positive for multidrug resistant (MDR) and 20% for carbapenem resistant (CR) gram-negative bacteria[1]. Historically, our perioperative antibiotic prophylaxis protocol consisted of IV meropenem, vancomycin and colistin, pending final respiratory cultures. To expedite MDR bacteria detection and reduce exposure to IV colistin, in June 2022 we incorporated the BioFire® FilmArray® Pneumonia Panel as part of our donor evaluation. In tandem, we modified the institutional protocol to include novel beta lactam antibiotics targeting CR genes (Figure). The study aimed to compare pneumonia panel testing to conventional culture methods for detecting sensitive and MDR bacteria and their effects on antibiotic prescriptions.

Methods: This retrospective, observational study reviewed patients who underwent lung-only transplantation from Jun 2022-May 2023. We compared pneumonia panel results of donor bronchoalveolar lavage (BAL) samples to conventional cultures of donor BAL and bronchial swab samples.

Results:

- 54 patients received lungs from donors with available pneumonia panel test results.
- Common bacteria identified by both PCR and conventional cultures included Staphylococcus aureus (n=11, with 7 MRSA), Acinetobacter baumannii (n=7, with 6 CR), Klebsiella pneumoniae (n=4, with 2 CR), Pseudomonas aeruginosa (n=3, with 1 CR), and Serratia marcescens (n=4).
- All carbapenem-resistant enterobacteraciae or Pseudomonas aeruginosa that were detected on conventional respiratory cultures had a corresponding positive resistance gene in the pneumonia panel.
- The pneumonia panel detected additional cases not grown in conventional cultures: 10 donors with Staphylococcus aureus (including 4 MRSA), 9 with Klebsiella pneumoniae, 7 with Acinetobacter baumannii, and 7 with Pseudomonas aeruginosa.
- The panel identified 11 donors positive for gram negative resistance genes; CTX-M (n=8), NDM (n=8), OXA-48 (n=7), and VIM (n=2).
- The panel missed 1 case of MRSA and 3 cases of Acinetobacter baumannii detected by respiratory cultures, including one with carbapenem-resistant Acinetobacter baumannii cultured from both BAL and bronchial swab samples. Haemophilus influenza and Streptococci were positive in 10 donors' pneumonia panels but not detected in any corresponding respiratory cultures.
- IV colistin prophylaxis was reduced by 83%.

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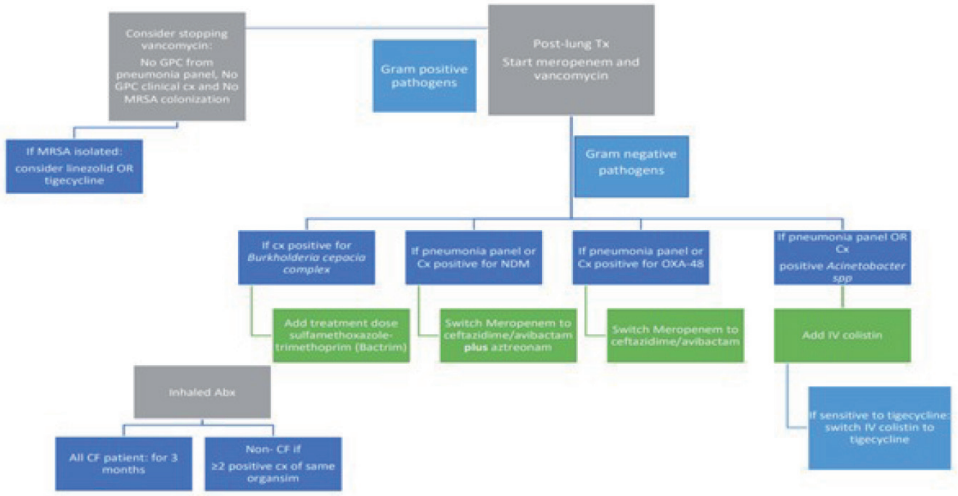
Conclusion: In a setting with a high prevalence of MDR bacteria, the use of a multiplex PCR panel during donor lung evaluation facilitated rapid and accurate identification of MDR bacteria and significantly reduced unnecessary prophylactic IV colistin administration.

1. Abdulqawi R, Saleh RA, Alameer RM, et al. Donor respiratory multidrug-resistant bacteria and lung transplantation outcomes. J Infect. 2024;88(2): 139-148.

Figure: Pneumonia panel based perioperative antibiotics prophylaxis



METABOLOMIC STUDIES REVEAL AN ORGAN-PROTECTIVE HIBERNATION STATE DURING DONOR LUNG PRESERVATION AT 10°C

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Objective: Previous reports showed enhanced graft function in both healthy and injured porcine lungs after preservation at 10°C. The objective of the study is to elucidate the mechanism of lung protection by 10°C and identify potential therapeutic targets to improve organ preservation.

Methods: Metabolomics data was re-evaluated from healthy and injured porcine lungs that underwent extended hypothermic preservation on ice and at 10°C. Tissue sampled before and after preservation were subjected to untargeted metabolic profiling. Significantly changed metabolites between the 2 timepoints were identified and analyzed to determine the underlying metabolic pathways. The level of respiratory activity of lung tissue at 4°C and 10°C was confirmed using high resolution respirometry.

Results: In both healthy and injured lung, principal component analyses (PCA) suggested minimal change in metabolites after 4°C preservation, but significant change of metabolites after 10°C preservation, which was associated with significantly improved lung function as assessed by ex vivo lung perfusion (EVLP) and lung transplantation. For healthy lungs, lipid energy pathway was found primarily active at 10°C. For injured lungs, additional carbohydrate energy pathway and anti-Ferroptosis pathways aiding organ repair were identified.

Conclusion: Untargeted metabolomics revealed a dynamic metabolic gradient for lungs stored at 10°C. Many features identified such as lipid oxidation and antioxidant upregulation are also key features involved in mammal hibernation. Elucidating the underlying mechanisms behind this pathway regulation may lead to strategies that will allow organs "hibernate" for days, potentially making organ banking a reality.

LUNG TRANSPLANT OUTCOMES AFTER IMPLEMENTATION OF A HOSPITAL-BASED 10°C REFRIGERATION FOR COLD ORGAN PRESERVATION

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Background: Recent studies suggest controlled hypothermic storage (CHS) at 10°C for extended periods of time in lung-Tx may offer equivalent or better clinical outcomes and improve operational efficiency. Here we report on our high-volume single center experience successfully implementing a novel protocol and first of its kind hospital-based CHS unit using existing refrigeration resources in the operating room core.

Methods: Consecutive lung-Tx recipients from January 1, 2022 to December 31, 2023 at our center were included. Allografts were procured in usual fashion, triple bagged with preservation solution in each bag and transported to our hospital on ice using an insulated portable cooler. Following, based on operating room (OR) availability and overall service logistics, lungs were transplanted (4°C) or placed in a 10°C temperature monitored hospital refrigerator and transplanted later (10°C). Primary outcomes were primary graft dysfunction (PGD) score at 72hrs and 90-day survival. Statistical analysis was performed by Wilcoxon-rank sum test, Chi-squared tests, and Kaplan Meier for time-to-event analysis.

Results: Patient demographics are shown in the Table. 211 consecutive recipients were included, 120 in the 10°C cohort. Cold ischemic time was longer in 10°C group, greater Lung Allocation Score and more double transplants were observed in 4°C group. No differences were observed in PGD at 72hrs, ventilator days, or 30- and 90-day survival. Overall median follow-up was 316 days. The figure shows equivalent survival.

	Overall	10°C	4°C	
	N = 211[1]	N = 120[1]	N = 91[1]	p-value[2]
Age	62 (54, 67)	61 (54, 66)	63 (54, 67)	0.3
Sex				0.074
Female	103 (49%)	65 (54%)	38 (42%)	
Male	108 (51%)	55 (46%)	53 (58%)	
Lung Allocation Score	41 (32, 55)	38 (31, 46)	45 (37, 72)	<0.001
DCD Donor	24 (11%)	18 (15%)	6 (6.6%)	0.057
Type of Transplant				0.004
Double	91 (43%)	62 (52%)	29 (32%)	
Single	120 (57%)	58 (48%)	62 (68%)	
PGD at 72hrs				>0.9
0	66 (31%)	38 (32%)	28 (31%)	
1	51 (24%)	27 (23%)	24 (26%)	
2	20 (9.5%)	13 (11%)	7 (7.7%)	
3	6 (2.8%)	3 (2.5%)	3 (3.3%)	
ECMO	68 (32%)	39 (33%)	29 (32%)	
Cold Ischemic Time* (Hours)	7.6 (0.96, 20.7)*	9.5 (2.7, 20.7)*	5.2 (0.96, 13.4)*	<0.001[FD1]
Days on Ventilator	3 (2, 8)	3 (2, 9)	3 (1, 6)	0.4
Survival at 30d	205 (97%)	115 (96%)	90 (99%)	0.2
Survival at 90d	191 (94%)	105 (93%)	86 (96%)	0.4

[1]Median (IQR); n (%),*Maximum and Minimum values
[2]Wilcoxon rank sum test; Pearson's Chi-squared test; Fisher's exact test
DCD: Deceased after Cardiac Death, PGD: Primary Graft Dysfunction, ECMO: Extracorporeal Membrane Oxygenation, COPD: Chronic Obstructive Pulmonary Disease

Conclusions: In this consecutive single center lung-Tx experience, we successfully implemented a CHS protocol using existing hospital-based refrigeration resources with excellent short-term outcomes and survival. CHS at 10°C appears to be safe and feasible strategy for optimizing operational efficiency in a high-volume lung-Tx center.

THE IMPACT OF DONOR VENTILATION DURATION ON PULMONARY FUNCTION POST-LUNG TRANSPLANTATION

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Background: Prolonged mechanical ventilation increases the risk of developing ventilator-induced lung injury, but the relationship between duration of donor mechanical ventilation (DDV) and post-lung transplant lung function is not known.

Methods: We conducted a retrospective analysis of patients undergoing lung transplantation in our program between January 2007 and December 2020. The risk factor of interest was DDV in days prior to organ retrieval. The primary outcome was FEV1% predicted at 1-year post-transplant (1yrFEV1%). We used multiple linear regression to test the association between DDV and 1yrFEV1%, adjusting for known confounders. Secondary outcomes included lung function at 3 months, incidence of primary graft dysfunction, ICU and hospital length of stay, development of baseline and chronic lung allograft dysfunction, and 3-month and 1-year mortality.

Results: 714 patients were eligible for study, 588 of whom had available DDV data. Median DDV was 3 days (range 0-37 days). 336 donors (59%) had bronchial wash cultures positive for clinically relevant organisms. In the multivariate analysis, longer DDV was not associated with a lower 1yrFEV1% (p=0.725) or with other identified secondary outcomes. DDV was however associated with donor bronchial wash culture positivity for clinically relevant organisms (odds ratio [OR] 1.11 per day of ventilation, 95% CI 1.02 – 1.21, p=0.02).

Conclusion: Duration of donor ventilation prior to procurement was not associated with FEV1% predicted at 1-year post-transplant, but we noted an increased likelihood of donor bronchial wash culture positivity. This suggests acceptable donors with extended ventilation duration prior to offer can be safely considered for lung transplantation.

ANALYSING THE UTILITY OF SINGLE LUNG TRANSPLANTATION IN INTERSTITIAL LUNG DISEASE USING DISCRETE EVENT SIMULATION OF DONOR ORGAN ALLOCATION

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Purpose: Single lung transplantation (SLT) for interstitial lung disease (ILD) has dramatically declined globally due to reported inferior long-term outcomes compared to bilateral lung transplantation. However, the impact of this approach on overall population-level waiting list mortality and net transplant benefit is unknown. This study aimed to model potential UK allocation policies with and without prioritising SLT for ILD using a discrete event simulation engine to compare impacts of this approach.

Methods: Five policies were simulated, varying in how pre- and post-transplant outcomes were weighted in decision making. The weighting varied from waiting list survival (WL) only to post-transplant survival (PTX) only, with also 2:1, 1:1 and 1:2 ratios of WL:PTX. For each policy, the impact of preferentially allocating single lungs to ILD patients was assessed. Candidates were prioritised according to the predicted additional life gained from transplant (i.e., net benefit). The SLT policies identified scenarios where transplanting two ILD patients with SLT resulted in higher overall net benefit than transplanting one patient (of any diagnosis) with a lung pair. Each policy was simulated repeatedly to calculate average survival metrics: annual waiting list deaths, mean net benefit, and post-transplant survival at 1- and 5-years.

Results: The SLT policy with a 1:2 WL:PTX ratio resulted in the fewest waiting list deaths (average 31/year vs 51/year without SLT), an average net benefit per patient of 2165 days compared to 2459 days without SLT, and post-transplant survival rates of 79.3% at 1 year and 52.1% at 5 years (compared to 81.8% and 56.4% without SLT). Increasing the use of SLT in ILD dramatically reduces waiting list deaths by 39%, whilst causing a modest reduction in net benefit (294 days / 12% reduction) and non-clinically meaningful drop in post-transplant survival (2.5% at 1-year and 4.3% at 5-years).

Conclusion: Lung allocation policies differentially weighted for competing benefits can be simulated to assess their impact on both waiting list and post-transplant outcomes. Our modelling suggests a policy that prioritises use of SLT for ILD patients may offer increased access to lung transplantation for this patient group without significant negative effects on outcomes after transplantation for the total transplant population.

RESULTS OF UNCONTROLLED DONATION AFTER CARDIO-CIRCULATORY DEATH PROGRAM

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Purpose of the study. Lung transplantations performed from uncontrolled donation after cardio-circulatory death (uDCD) donors registered an increasing incidence in the recent years, enabling to decrease the shortage of suitable lungs for transplant. The issues characterizing this type of graft procurement are well known: the logistical difficulties and the long warm ischemic times. We report our experience with uDCD donors and the main causes for which it is necessary to discontinue graft recovery.

Statements of the methods. We analysed the process of referrals, recovery and lung transplantation from uncontrolled DCD donors; recipients outcome were also reviewed. Our protocol consists of an in-situ open and ventilated normothermic lung preservation (i.e., recruitment manoeuvres and cPAP, without chest tubes placement, nor topical cooling). Grafts are then preserved ex-vivo through a custom-made circuit to perform Ex Vivo Lung Perfusion (EVLP).

Summary of the results presenting sufficient details to support the conclusion. From 2014 to 2024, fifty-two referrals of potential donors were registered but only fourteen of the recovered grafts were considered suitable for transplantation. Main causes of graft recovery suspension are reported in Figure 1. Eight donors were ruled out due to severe smoking habits, four families declined consent to donation and three subjects were rejected as a result of long ischemic times. Seven grafts were considered inadequate due to worsening of graft function during EVLP, two were rejected because of the donor's bronchoalveolar lavage (BAL) positivity to COVID-19 and one was discarded after the diagnosis of lung cancer. Furthermore, we encountered logistical issues four times.
Patients receiving lung from a uDCD donor, according to our protocol, reached a satisfactory outcome (Table 1); we registered one case of primary graft dysfunction grade 3 (PGD3). No bronchial anastomotic dehiscence occurred, while two bronchial stenosis were treated with pneumatic dilatation. Two recipients developed chronic lung allograft dysfunction (CLAD).

Statement of the conclusion reached. Despite the high rate of cessation in the procurement or the evaluation of lungs from uDCD donors, they constitute a valuable resource to implement the donors pool and meet the demand for organs. In particular, uDCD donors represent almost 20% of the transplants carried out in 2023; in general, they account for 5% of lung transplants performed in the last ten years in our centre. Difficulties encountered during uncontrolled DCD graft procurement can still be managed through close cooperation between the hospitals involved and within the same centre.

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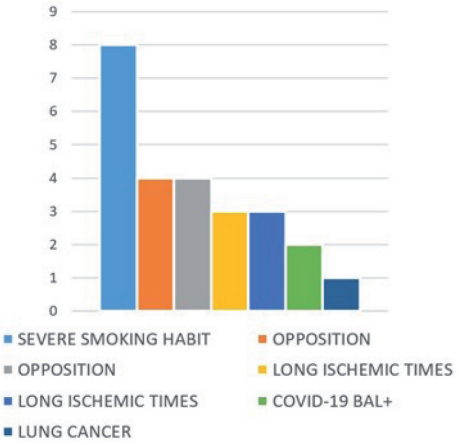

Figure 1: Main causes of graft rejection in uncontrolled DCD. (BAL: bronchoalveolar lavage)

	uDCD (n = 14)
Donor	
Sex: M (n, %)	13 (92,85%)
Age, mean (years)	53,7 (11,62)
Smoking history, median	0 (0)
Bronchoscopy, median	0 (0,75)
Chest X-Ray, median	0 (0,75)
$paO_2/pFiO_2$, mean	NA
Procurement	
Cardiac arrest – cold flush, mean (min)	246 (44)
Cardiac arrest – reperfusion first lung/second lung, mean (min)	1128 (198) / 1332 (223)
Total ischemic time first lung/second lung, mean (min)	684 (92) / 889 (115)
Recipient	
Sex: M (n, %)	11 (78,57%)
Age, mean (years)	50,1 (12,9)
Disease: CF (n, %)	4 (28,57%)
COPD (n, %)	3 (21,42%)
ILD (n, %)	7 (50%)
PGD3 within 72h (n, %)	1 (7,14%)
Airway anastomotic complications (n, %)	2 (14,28%)
CLAD (n, %)	2 (14,28%)
Retransplant (n, %)	0 (0%)
Best FEV1%, mean	2,55% (0,93)
Follow up, mean (days)	1113 (983)
Alive at follow-up (n, %)	10 (71,42%)

Table 1: Donors, procurement and recipients characteristics. (CF: cystic fibrosis; COPD: chronic obstructive pulmonary disease; ILD: interstitial lung disease; PGD: primary graft dysfunction; CLAD: chronic lung allograft dysfunction; FEV1: forced expiratory volume in the first second).

EFFECT OF TIME FROM BRAIN STEM DEATH (BSD) ON POST LUNG TRANSPLANT OUTCOME: PROLONGING TIME TO RETRIEVAL COULD BE OF BENEFIT

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Purpose of the Study. Brain stem death (BSD) is associated with changes that damage organs, particularly the lung. Heart and kidney utilisation rates, and function, improve with time, optimal at 36 hours post BSD. Previously, no such improvement been seen for the lung. With the development of lung-protective ventilation strategies we hypothesise that, in the modern era, a longer time between BSD to organ retrieval could be beneficial.

Methods. Data prospectively collected in the UK Transplant Registry (UKTR) for all adult first lung-transplants from DBD donors between 1 January 2010 and 31 December 2019 were reviewed, with analysis of retrospective data collected for the diagnosis and grading grade 3 Primary Graft Dysfunction occurring within the first 72-hours post-transplant (PGD3). Lungs treated with Ex Vivo Lung Perfusion were excluded. Time from BSD was defined as the time from fixed-dilated pupils to the start of organ retrieval. BSD duration was categorised by interquartile range (IQR). Unadjusted 90-day and 1-year survival by BSD duration was assessed using regression models, with logistic regression analysis of the of PGD3 by BSD duration. Likelihood ratios tests were used to assess significance.

Summary of Results. Complete BSD data were available for 1,042 patients (85%). The median BSD duration increased from 33.0 hours in 2010 (IQR 26.3 to 45.9) to 52.0 hours in 2019 (IQR: 41.9 to 73.0).
There was no significant difference in survival at 90-days (p value 0.24) or 1-year (p value 0.13) by BSD duration IQR group. Similarly, there was no evidence of a linear effect (p=0.99, p=0.52 respectively).
There was a significant difference in the odds of PGD3 by BSD duration IQR group (p=0.05) and also when examining BSD duration as a continuous variable (p=0.02). The odds of PGD3 for BSD durations shorter than 29.6 hours were higher than for longer BSD durations; the odds were 36% lower for durations between 29.6 and 40.5 hours, 22% lower for durations between 40.5 and 54.5 hours and 44% lower for durations 54.5 hours or longer.

Conclusions. BSD duration in the UK has increased over the period of study, with no evidence of an impact on 90-day or 1-year survival. Our data suggests that implementation of lung protective ventilation strategies are beneficial. The association between BSD duration and PGD3 appears to be statistically significant, however requires further investigation to understand the relationship.

THE IMPACT OF THORACO-ABDOMINAL NORMOTHERMIC REGIONAL PERFUSION ON LUNG GRAFTS EVALUATED BY EX-VIVO LUNG PERFUSION

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Goal: Pre-clinical evaluation of the impact of thoraco-abdominal normothermic regional perfusion (TA-NRP) on lung grafts.

Introduction: TA-NRP is a new strategy for cardiac resuscitation after death by cardiocirculatory arrest (DCD). Its impact on lung grafts is unknown.

Hypothesis: TA-NRP could affect lung function compared to direct procurement (DP), which is the current standard.

Methods: A DCD porcine model developed in our lab was used. After a 30-minutes period of functional warm ischemia, 8 pigs were divided in 2 groups: one TA-NRP group (n=4) with 60 minutes of in-situ reperfusion with extracorporeal circulation divided in 2 groups: one TA-NRP group (n=4) with 60 minutes of in-situ reperfusion with extracorporeal circulation followed by a 30-minutes evaluation and one DP group (n=4). The lungs were then perfused with EVLP (Lund protocol) for 4 hours to evaluate their function and to validate their qualification for transplantation.

Results: The lungs of both groups were qualified for transplantation. Exchange capacity (PaO2/FiO2), lactate and glucose levels evaluated in the perfusate after 4 hours of EVLP were similar in the 2 groups (549 ± 68 vs. 551 ± 64 mmol/L, p = 0.69),(8.2 ± 2.7 vs. 7.8 ± 2.9 mmol/L, p = 0.89) and (8.7 ± 2.0 vs. 8.0 ± 0.5 mmol/L, p = 0.69). However, lung weight gain (TA-PRN: 7.2 ± 5.9 vs. DP: -2.0 ± 4.2%, p = 0.03) and pulmonary vascular resistance (p = 0.04) were higher in the TA-NRP group while static pulmonary compliance (p = 0.049) was lower in TA-NRP group.

Conclusion: TA-NRP does not have a significant effect on transplantability of lung grafts in a DCD porcine model. In our experimental conditions, this method appears to be safe and may help increase number of organs harvested from DCD donors.
However, some differences on lung physiological parameters were observed and should be investigated further.

UK EXPERIENCE OF DIRECT PROCUREMENT OF LUNGS WITH ONGOING ABDOMINAL NORMOTHERMIC REGIONAL PERFUSION FROM CONTROLLED DCD DONORS

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Purpose: To describe the UK experience of direct procurement (DRP) of lungs for transplantation alongside abdominal normothermic regional perfusion (A-NRP), with an analysis of early outcomes for lungs transplanted with this method compared to standard retrieval after circulatory death (DCD).

Methods: Lung utilisation and 90-data survival data from DCD lung transplants between 1 January 2015 and 31 December 2022 were obtained from the NHSBT registry. Case notes from all DCD lung recipients in this cohort were analysed to define primary graft dysfunction (PGD) grade using ISHLT criteria. 90-day survival rates were compared for standard DCD retrieval and DRP with A-NRP using the log-rank test. Grade 3 PGD rates at 72 hours after transplant were compared using Fisher's exact test.

Results

Lung utilisation: There were 307 DCD lung donors in this cohort; 3 underwent thoraco-abdominal normothermic regional perfusion (TA-NRP), 18 DRP with A-NRP and 289 standard DCD retrieval. 13 (72%) A-NRP donors and 236 (82%) standard DCD resulted in transplants. There was no significant difference in utilisation between the two methods (p=0.50).

Lung Outcomes: 90-day survival rate for standard DCD lung transplant recipients was 87.3% (95% CI: 82.3-91.0%). 90-day survival rate for lung transplant recipients who received DCD lungs procured with concomitant A-NRP was 92.3% (95% CI: 56.6-98.9%, log rank p-value = 0.59).

After the exclusion of transplants with key data missing and retransplants, 238 transplants were included in the PGD analysis (12 A-NRP with DRP, 223 standard DCD). The rate of Grade 3 PGD at 72 hours after transplant for standard DCD lungs without A-NRP was 24.2% (95% CI: 18.7-30.4%) versus 25.0% (95% CI: 5.5-57.2%) with concomitant A-NRP (Fisher's exact test p-value >0.99).

Conclusions: Direct procurement of lungs with A-NRP is feasible and has comparable organ utilisation, 90-day mortality and severe PGD rates, whilst improving outcomes for abdominal organ recipients from DCD donors.

BILE ACID ASPIRATION INDUCES FIBROSIS AND DERANGES SURFACTANT HOMEOSTASIS IN HUMAN LUNGS

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Purpose: Lung transplantation remains the only treatment for end-stage lung disease. However, survival remains limited by chronic lung allograft dysfunction (CLAD) characterized by progressive distal airway fibrosis. Multiple risk factors have been associated with CLAD, including gastroesophageal reflux aspiration. Previous studies have established Bile Acids (BA), detected in the airways, as markers of reflux aspiration and predictors of CLAD. The action of BA on human broncho-alveolar cell and tissue components is poorly explored, although its understanding could contribute to defining mechanisms for CLAD. We hypothesize that BA acting as inflammatory molecules in the lungs, may trigger a pro-fibrotic cell phenotype and affect lung innate defenses leading to CLAD.

Methods: Three normal human lung models were studied: In vitro, epithelial cells (H441) and 3D primary organoid culture model (epithelial cells and co-culture with fibroblasts); and ex vivo, precision cut lung slices (PCLS). We tested the most clinically relevant unconjugated (CA, CDCA) and conjugated (GCA, TCDCA) BA. Cell viability and toxicity were studied with WST1 and LDH assay respectively. Expression of markers of fibrosis, inflammation, extracellular matrix remodeling, and surfactant proteins, was measured with qRT-PCR and by confocal microscopy. Adherens junctions' expression was tested by western blot.

Results: BA induce an EMT-driven fibrotic lung phenotype. BA affect viability of lung epithelium and PCLS and increased marker of fibrosis (TGFb1, CTGF), inflammation (IL8, IL10), and extracellular matrix proteins (MMP2, MMP9). BA also decreased E-cadherin in epithelial cells and increased α-SMA and FN level in PCLS. Moreover, in all three lung models BA reduced the expression of all surfactant proteins (A1, A2, D, B and C). No difference noted between BA unconjugated and conjugated BA.

Conclusions: Here we show that bile acids, markers of aspiration and adverse lung allograft outcomes, induce lung fibrosis, EMT and decrease the surfactant proteins, damaging the protective role of the lung innate immune system. Moreover, we demonstrate that bile acids affect lung epithelium homeostasis in cells, in organoid co-culture and in PCLS. These translational findings using in vitro, and ex vivo human lung models provide insights into the pro-fibrotic mechanism of BA aspiration in lung injury and CLAD pathophysiology.

INSIGHTS INTO THE LUNG MICROENVIRONMENT DURING REJECTION IN LUNG TRANSPLANTED PATIENTS

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Purpose of the study: Little is known about the pathomolecular signaling in the lung microenvironment that precedes and drives chronic graft rejection (CLAD), the major cause of graft failure and patients' death. We investigated the immunological messages delivered by BAL-extracellular vesicles (BAL-EVs) from patients with stable (CTRL), or chronic (CLAD) rejection, in recipient human primary bronchial cells (HBECs) and we analyzed the transcriptome and proteome of HBECs cocultured with BAL-EVs focusing on inflammatory molecules. Further we characterized the origin of BAL-EV and integrated proteomic and transcriptomic data of HBEC exposed to BAL-EV to preliminary chart the lung microenvironment during early onset of CLAD.

Methods: BAL-EVs were isolated from patients with stable (CTRL), or chronic (CLAD) rejection and co-cultured with HBECs cells for 48h. BAL-EV origin was phenotyped using the ExoView platform and antibodies against CD45, EpCam and CD68. Then, cytokine arrays with bronchial cell culture extracts and supernatants were performed. A transcriptomic analysis using the Banff Human Organ Transplant panel on a nCounter Flex instrument was also performed on cell extracts. Raw data were normalized against controls and expressed as log2. Ingenuity Pathway analysis (IPA) was used to analyse proteins and genes panels.

Results: The majority of BAL-EVs express the CD45 antigen on their surface (65%), supporting their leukocytic origin. CLAD-EVs induced in recipient cells both secretion and transcription of cytokines belonging to the IL-17 (such as TNF, CCL2, IL4 and IL5), wound healing and pathogen-induced cytokine storm signaling (Canonical Pathway analysis in IPA; z-score p val<0.05). At the transcriptional level, HBECs cocultured with BAL-EVs from patients with CLAD show consistent upregulation the Aryl Hydrocarbon Receptor gene (AHR), a transcription factor involved in Th17 differentiation of T-cells.

Conclusions: BAL-EVs vehiculate functional signals into recipient bronchial cells with a role in the onset and perpetuation of inflammatory processes. These data together with previous evidence preliminary chart the lung microenvironment during the early phases of chronic dysfunction, showing that leukocytes-derived EVs can activate in respiratory cell the IL17 pathway both at the transcription and protein level, through the upregulation of AHR gene and the upregulation of intra-and extra-cellular IL17-related cytokines. This is accompanied by activation of wound repair factors, potentially responsible of tissue fibrosis. This novel knowledge sheds light on the lung microenvironment during the early onset of CLAD, contributing in the understanding the pathomolecular mechanisms behind chronic rejection.

GENOME-WIDE ASSOCIATION STUDY OF CHRONIC LUNG ALLOGRAFT DYSFUNCTION

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Background: Chronic respiratory diseases are among the leading causes of morbidity and mortality worldwide with 3.3 million deaths each year. For patients with end-stage lung disease, the only viable option is lung transplantation (LT), but graft survival remains limited with only 63% survival at 5 years post-transplantation. The greatest limitation to long-term survival is the development of chronic lung allograft dysfunction (CLAD) which affects arounds 50% of recipients after 5 years. There is an essential need for better understanding the molecular mechanisms involved in the CLAD phenotype's pathophysiology.

Methods: We performed the first genome-wide association study GWAS investigating genetic factors associated with CLAD. CLAD is defined by a >=20% decline in measured forced expiratory volume from the baseline level (3 months after transplant in the absence of infection or another identifiable cause). We genotyped a subset of 392 LT donor-recipient pairs from the COLT multicentric cohort (Cohort in Lung Transplantation) using the Affymetrix Axiom PRMA microarray (900,000 SNPs). Our genetic cohort represents an accurate snapshot of the entire COLT cohort as no variable (e.g. age, sex, initial respiratory disease, survival rate) significantly diverged from the global cohort (p>0.05). After quality controls and SNP imputation, we tested 7 million SNPs for association with CLAD using multivariate logistic regression models corrected for age, sex and genetic ancestry.

Results: We did not observe any significant association between the donors' genotypes and the CLAD development. However, we tested 54 CLAD (BOS=34, RAS=9 and mixte=11) against 160 stable recipients and we identified four SNPs significantly associated with CLAD in European recipients ($p<5x10-8$). Interestingly, we found a signal in a gene encoding a protein previously associated with the risk for bronchopulmonary dysplasia. Recipients with CLAD exhibited a lower allelic frequency (34%) for this genetic locus than recipients without CLAD (66%), suggesting a protective role for this allele against the development of CLAD.

Conclusions: Here, we unveiled the first GWAS conducted in lung transplantation, displaying biologically relevant results from the recipient's genome. We will next jointly investigate the donor and recipient's genomes to assess HLA and non-HLA mismatches that might contribute to CLAD. Further investigations into the functional implications of these genetic variants could provide valuable insights into pathogenesis and potential therapeutic targets for CLAD.

Keywords: Genome-wide association study, Lung transplantation, Chronic lung allograft dysfunction, immunogenetics

INVARIANT NATURAL KILLER T CELLS IN LUNG TRANSPLANT ALLOGRAFTS: A PILOT STUDY ON SURVEILLANCE BRONCHOALVEOLAR LAVAGE CELLS.

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Background: Acute cellular rejection (ACR) in lung transplant recipients (LTRs) is predominantly a T cell-mediated response and risk factor for chronic lung allograft dysfunction. Rare unconventional T cells react to lipid antigens and a subset, the invariant Natural Killer T cells (iNKT), seems to play a detrimental role in acute lung injury models. The airway lipidome of LTRs is altered by post-transplant noxious events as bile acids aspiration, a known risk factor for allograft dysfunction. We sought to investigate the presence of iNKT cells in the airways of LTRs and study their relationship with ACR.

Methods: 24 cryopreserved bronchoalveolar lavage (BAL) cell samples collected at surveillance bronchoscopies were arbitrarily selected from our lung transplant biorepository for: concomitant ACR in 12 recipients and negative (A0B0) ACR in 12 recipients. BAL were selected from LTRs without diagnosis of connective tissue diseases, autoimmune disorders or cystic fibrosis and further that samples were negative for microbiology. The cryopreserved BAL cell pellets were stained with antibodies for CD45, CD3, iNKT T cell receptor, CD4, CD8 and with a viability dye. Flow cytometry was performed, and a stringent gating strategy applied. The following exclusion criteria were applied: any samples with fewer than 3 total iNKT cells were excluded from the analysis of iNKT and iNKT CD4/CD8 expression. Non-parametrical statistical analysis was performed.

Results: iNKT cells were found in 91% of samples and their median percentage over total T cells was 0.36%, (IQR 0.06%-1.47%). No difference was noted for presence or absence of ACR, median 0.13% vs 0.43%. In 17 samples (8 with ACR and 9 A0B0) the number of iNKT cells was sufficient to subdivide them by CD4/CD8 expression. iNKT were predominantly CD4-/CD8-. In LTRs with ACR, the percentages of CD4-/CD8- iNKT over total iNKT were decreased (median % in ACR 36.82 vs 72.73 in A0B0, p=0.01), while CD4-/CD8+ iNKT were increased (median % in ACR 15.99 vs 0 in A0B0, p=0.03). CD4+/CD8- iNKT showed an increased trend. The percentages of CD4-/CD8- iNKT over total T cells were decreased in acute rejection (median % 0.03 in ACR vs 0.4 in A0B0, p=0.04). The median number of T cells was 2668 (940-3320). Moreover, the percentages of CD4-/CD8+ T cells over total T cells were increased (p=0.02) in ACR, while CD4+/CD8- T cells showed a decreased trend.

Conclusions: iNKT cells are present in LTRs allografts irrespective of ACR. Although, in allografts with ACR the proportion of double negative (CD4-/CD8-) iNKT seems to be decreased with a consequent higher percentage of CD4+/CD8- and CD4-/CD8+ variants. iNKT cells are a rare population, therefore studying them in a small cohort is challenging. These preliminary results stimulate and warrant a large cohort investigation to further explore their role in lung transplantation.

NK CELL-MEDIATED ALLORECOGNITION IN LUNG TRANSPLANTATION: A DOUBLE-EDGED SWORD

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Background: Two pathways of allorecognition lead to the production of donor specific antibodies (DSA) after transplantation: the canonical indirect pathway (involving recipient CD4+ T and B cells), and the recently described by our team "inverted direct pathway", in which passenger donor CD4+ T cells from the graft provide an unconventional help to recipient B cells.

Given the absence of the characteristic early and transient DSA surge in certain recipients of T cell-rich grafts, like those in lung and intestine transplants, we posit that the inverted direct pathway might be regulated by immune mechanisms warranting further investigation.

Methods and results: Emulating the clinical inter-individual heterogeneity, a cardiac graft from CBA (H-2k) mice induces an early DSA response in a CD3εKO C57BL/6 (H-2b) recipient mouse through the inverted direct pathway, whereas a Balb/c (H-2d) heart graft does not.

Using adoptive transfer of T cells, we observed that CD4+ T cells from Balb/c donor survive shorter than their CBA counterparts in recipient mice. This difference was explained by the fact that, in contrast with CBA T cells, T cells from Balb/c are promptly eliminated by recipient's NK cells, thus preventing their interaction with recipient's B cells. In line with this hypothesis, depletion of NK cells in CD3εKO C57BL/6 recipient mice prolonged the survival of transferred allogeneic Balb/c CD4+ T cells, thereby restoring DSA production through the inverted direct pathway.

The clinical validity of these experimental findings is currently being investigated in a large (n>500) multicentric cohort of lung transplant recipients.

Conclusions: Although NK cell-mediated allorecognition has been demonstrated to trigger DSA-independent microvascular lesions and subsequent graft rejection, it's noteworthy that in the specific scenario of lung transplantation, this very mechanism may paradoxically confer protection against microvascular lesions arising from the de novo generation of DSA via the inverted direct pathway.

THE NATURE OF CHRONIC REJECTION AFTER LUNG TRANSPLANTATION: A MURINE ORTHOTOPIC LUNG TRANSPLANT STUDY

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Chronic rejection is a major complication post-transplantation. Within lung transplantation, chronic rejection was considered as airway centred. Chronic Lung Allograft Dysfunction (CLAD), defined to cover all late chronic complications, makes chronic rejection from an immunological perspective enigmatic. This study investigated the true nature, timing and location of chronic rejection as a whole, within mouse lung transplantation. 40 mice underwent an orthotopic left lung transplantation, were sacrificed at day 70 and evaluated by histology and in vivo µCT. For timing and location of rejection, extra grafts were sacrificed at day 7, 35, 56 and investigated by ex vivo µCT or single cell RNA (scRNA) profiling. Chronic rejection originated as innate inflammation around small arteries evolving toward adaptive organization with subsequent end-arterial fibrosis and obliterans. Subsequently, venous and pleural infiltration appeared, followed by airway related bronchiolar folding and rarely bronchiolitis obliterans was observed. Ex vivo µCT and scRNA profiling validated the time, location and sequence of events with endothelial destruction and activation as primary onset. Against the current belief, chronic rejection in lung transplantation may start as arterial response, followed by venules, pleura and only in a late stage in bronchioles as may be seen in some but not all patients with CLAD.

EFFECTIVE AND IMMEDIATE DELIVERY OF FUNCTIONAL REPORTER ENZYMES TO THE LUNG USING VIRUS-LIKE PARTICLES: A FIRST PROOF-OF-CONCEPT STUDY IN THE RAT EX-VIVO LUNG PERFUSION MODEL

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Purpose: Ex-vivo lung perfusion (EVLP) allows isolated modulation of donor lungs. Future techniques of allograft treatment and modulation will enable both donor pool expansion and alteration of the innate and adaptive immune response after lung transplantation (LTx). Our goal was to explore the potential of donor lung modulation during EVLP, mediated by virus-like particles (VLPs). These VLPs transiently deliver functional enzymes to lung parenchymal cells. Delivery with other vectors like adenovirus and adeno-associated virus is known to be slower and/or associated with inflammation. VLP-mediated delivery could allow safe and swift genetic CRISPR/Cas9 modulation of lung grafts in the early post-LTx phase. We explored for the first time in a model of rat EVLP the potential of VLPs for immediate delivery of functional enzymes to the lung.

Methods: The heart-lung block of Sprague-Dawley rats was cold-flushed, followed by immediate EVLP with 75mL of Steen solution. Steady state and normothermia were reached after 1h. VLPs loaded with firefly luciferase (VLP-fLuc) were next added to the perfusate and circulated for 3h (n=8) or 6h (n=9). Culture medium without VLPs served as sham for 3h (n=5) and 6h (n=6). Ten minutes before end of EVLP, D-luciferin (50mg/L) was circulated. After EVLP, fLuc delivery was quantified with bioluminescence imaging (BLI). VLPs with beta-galactosidase (VLP-betaGal) were circulated for 3h (n=3) or 6h (n=3) and delivery was visualized with histochemical X-gal staining. Lungs were weighed before and after EVLP to measure edema formation.

Results: (A) BLI signal was 2.68e2-fold higher after VLP-fLuc EVLP delivery compared to sham for 3h circulation (8.89e6 vs. 3.32e4 photons(p)/second(s); p=.0002) and 2.25e2-fold higher for 6h circulation (1.25e7 vs. 5.55e4 p/s; p<.0001). No difference in BLI signal was measured between 3h and 6h of VLP-fLuc circulation (p=.0999). (B) VLP-betaGal delivery was confirmed with blue histochemical staining of cells in the alveolar walls. (C) Extent of pulmonary edema was not different for sham (culture medium) vs. VLPs after 3h (0.4860 vs. 0.5688 grams; p=.8448) and 6h (4.653 vs. 3.364 grams; p=.4943) of EVLP circulation.

Conclusion: We provide the first evidence and proof-of-concept for immediate and safe VLP-mediated protein delivery and activity in the lung during EVLP. VLPs efficiently target the lung during rat EVLP, displaying enzyme activity after only 3 hours. VLP-mediated delivery of CRISPR/Cas can be a new and promising avenue in the future toolbox of genetic allograft modulation in LTx.

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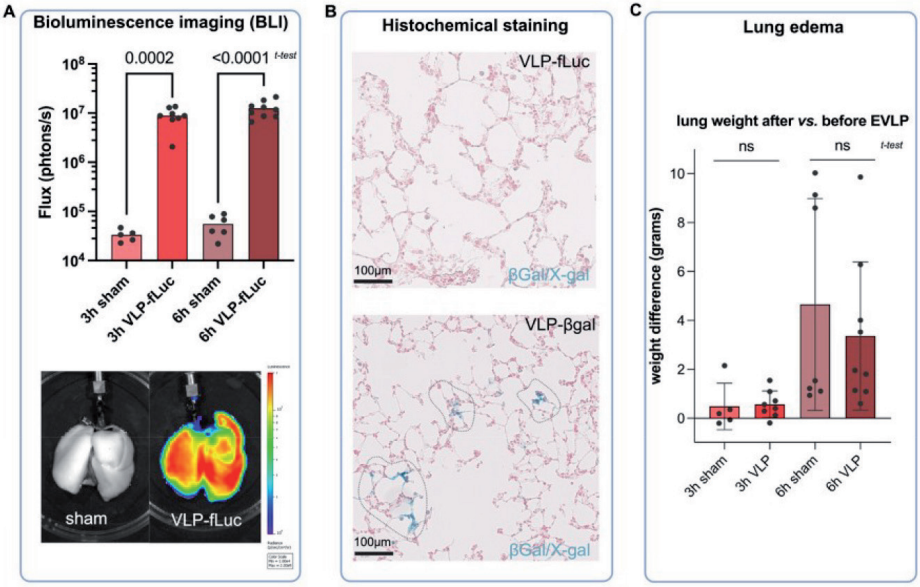
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weight difference (grams)
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3h VLP
6h sham
6h VLP

LUNGS FROM DONORS WITH CHEST TRAUMA CAN SAFELY BE PERFUSED ON EVLP - AND USED FOR TRANSPLANTATION

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Purpose: Moderate traumatic injuries and lung contusions are considered a clear exclusion criterion for ex-vivo lung perfusion (EVLP) by most transplant centers. This is due to the presumed poor performance during perfusion, which is caused by increased capillary leak and resulting pulmonary edema.

The aim of this study was to evaluate the performance of trauma lungs on EVLP and their consecutive suitability for transplantation.

Methods: A retrospective, single-center analysis was performed, including all donor lungs that were evaluated on EVLP between March 2010 and May 2024. Donor characteristics were assessed based on donor report data and clinical findings during procurement. Acellular normothermic EVLP was performed for a maximum of 6 hours. For all lungs accepted after EVLP, lung transplant recipient outcome was evaluated with PGD at 72 hours, perioperative outcome, as well as post-transplant survival at 1, 3 and 12 months.

Results: EVLP was performed for a total of 117 marginal donor lungs with an overall conversion rate of 58.1% (n=68). 17 donors died from trauma including the chest (13 brain dead donors and 4 uncontrolled DCDs), mostly in traffic accidents or due to high altitude falls. Trauma donors were significantly younger (median 49 vs. 27 years; p=0.002), but there were no other donor specific differences between the groups in terms of BMI (26 vs. 25; p=0.893), length of mechanical ventilation (86 vs. 95 hours; p=0.249), or arterial blood gas values. Median P/F ratio was 343 in the non-trauma lung group compared to 313 in trauma lungs (p=0.739).

10 (58.8%) trauma lungs were ultimately accepted for transplantation after EVLP. Recipient outcomes were comparable between the groups in terms of length of mechanical ventilation (2 vs. 2 days; p=0.636), ICU stay (6 vs. 6 days; p=0.609), and hospital admission (22 vs. 22 days; p=0.825). There were 2 cases of PGD3 after 72 hours, both in the non-trauma donor lung group. There was no significant difference in survival at 30 days (survival probability 98.1 vs. 90.0%; p=0.165), 90 days (94.4 vs. 80.0%; p=0.110) or 12 months (87 vs. 70%; p=0.174) after lung transplantation.

Conclusion: Donor lungs with significant chest trauma can safely be evaluated on EVLP and show an acceptable conversion rate, similar to non-trauma lungs, and satisfactory mid-term outcome of recipients.

BANFF HUMAN ORGAN TRANSPLANT PANEL FOR DETECTING ACUTE CELLULAR REJECTION IN LUNG TRANSPLANT BIOPSIES

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Purpose: Diagnosing the grade of acute cellular rejection (ACR) in lung transplant patients remains challenging, yet crucial, given its association with long-term adverse graft outcomes. To gain insight in the pathophysiological mechanisms involved, we aim to identify the molecular profile and capture the functional pathways among different severity grades of ACR using the Banff Human Organ Transplant (B-HOT) panel.

Methods: We analysed 212 routine transbronchial biopsies from 174 deeply-phenotyped lung allograft recipients transplanted between 2010 and 2019 at Foch Hospital, Paris, and classified them as per ISHLT guidelines in the following clinical scenarios: subclinical biopsy-proven A1 ACR (n=42), biopsy-proven A1 with graft dysfunction or A2 ACR (n=46), antibody-mediated rejection (n=52), and non-rejection phenotypes (n=72). We sequenced all biopsies using the B-HOT panel, and performed differential gene expression analysis comparing different severity grades of ACR vs. all non-ACR biopsies. Significant differentially expressed genes (false discovery rate <0.05) were used as input for pathway analysis with ReactomePA.

Results: Subclinical biopsy-proven A1 ACR cases demonstrated no differentially expressed genes when compared to non-ACR cases. However, for biopsy-proven A1 with graft dysfunction and A2 ACR, we identified a molecular signature with top significant upregulated transcripts associated with a T-cell mediated immune response, including T-cell activation and antigen recognition (CD3E, CD28, CTLA4, CD7, CD5, CD27, CD247, JAK3, IKZF1, ICOS, CD2, IL2RA, LILRB2), chemokine signalling (CXCL9, CXCL10), innate immunity responses (PTX3, CALHM6, GBP5, CASP4, CD209) with macrophage activation (CD163, IRF8, C1qB) as well as cell-related injury and repair (SOD2). Pathway analysis showed that the top significant clinical ACR-associated pathways included: TCR signalling (with phosphorylation of CD3 and TCR zeta chains), lymphocyte interactions (specifically co-stimulation by CD28), interferon and interleukin (in particular interleukin-4 and 13) signalling.

Conclusion: Using the B-HOT panel, we identified a molecular signature and key functional pathways involved in clinical pulmonary ACR. We also show that subclinical minimal ACR cases do not demonstrate an immune-related molecular profile, aligning with prior evidence suggesting subclinical minimal ACR cases can be monitored, and may not require treatment.

MULTICENTER VALIDATION OF LARGE AIRWAY BRONCHIAL WASH (LABW) BILE ACID SIGNATURE FOR THE DIAGNOSIS OF ASPIRATION AND PREDICTION OF CHRONIC LUNG ALLOGRAFT DYSFUNCTION

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Purpose - Microaspiration of gastrointestinal contents into the tracheobronchial tree has been previously identified to be a risk factor for chronic lung allograft dysfunction (CLAD) in lung transplant recipients (LTRs). Bile acids (BA) measured in airways of LTRs has been independently validated as a marker of aspiration and linked to an increased risk of CLAD. Indeed, BA in LABW at 3 months are predictive of CLAD and correlate with increased levels of cytokines and lipids in the airway. We sought to confirm that a LABW BA-based aspiration signature will predict CLAD in a large multi-center cohort and that this signature will be associated with early allograft dysfunction, inflammation, and damage.

Methods - We created two-center retrospective derivation (n=313) and prospective validation cohorts (n=242) including consecutive adult LTRs with LABW available at 3-months post-transplant. Fifteen BA and 48 inflammatory mediators were measured in LABW by tandem mass spectrometry and by 48-multiplex assay, respectively. Student's t-test, Mann-Whitney, chi-squared, and Fisher's exact tests will be used to compare groups. Analysis of the area under the receiver operating characteristic (AUROC) curve for BA cutoff determination will be employed. Multivariable Cox proportional hazard model will be used for time-to-event analysis for CLAD and mortality (defined as either death or re-transplantation). Logistic regression will be applied to evaluate association with concurrent clinical factors.

Results - In the retrospective cohort, 61% were male, 80% received double lung transplant, and 44% were CMV-serostatus-mismatched. The primary diagnosis was ILD in 52%, COPD in 24%, and CF in 13%. The median concentration of LABW total BA was 4.25 (interquartile range 1.87-14.34). Primary conjugated BA, GCA and GCDCA, were the most abundant species. 8.6nM and 86% were the upper tertile cutoffs and used to define high total BA concentration and percent conjugated BA, respectively. Having both high total BA levels and high percentage of conjugated BA in the LABW independently predicted CLAD (HR 1.88, 95% CI 1.21-2.91, p-value 0.005) and mortality (HR 2.61, 95% CI 1.72-3.96, p-value < 0.001), when adjusted for clinically-relevant covariates selected a priori. Primary unconjugated and conjugated BAs had strong correlations with most pro-inflammatory cytokines tested.

In the prospective validation cohort the median LABW total BA concentration was 5.122 (interquartile range 2.27-16.32). Primary conjugated BA, GCA and GCDCA, were the most abundant species. The upper tertile cutoff for high total BA is 9.5 nM and 84% for high percentage of conjugated BA. The long-term outcomes of interest, CLAD and mortality are being prospectively monitored in this cohort for further analysis.

Conclusion – Elevated bile acids in the LABW at three months after transplant, particularly conjugated BAs, are predictors of mortality and chronic lung allograft dysfunction (CLAD). Additionally, increased levels of primary bile acids correlate with high cytokines, highlighting their pro-inflammatory role. These findings in a large multi-center cohort support our previous observations and emphasize that a LABW bile acid-based signature can serve as a diagnostic tool for aspiration and as a predictor of poor long-term outcomes. The analysis of the prospective cohort will enable further validation.

SECRETORY PHOSPHOLIPASE A2-IIA IN THE AIRWAYS OF LUNG TRANSPLANT RECIPIENTS IS ASSOCIATED WITH BILE ACID ASPIRATION, AIRWAY INFECTIONS AND INFLAMMATORY MEDIATORS: FIRST INSIGHT ON ITS ROLE IN LUNG ALLOGRAFTS

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Purpose: Inflammation is a driving force in the process leading to chronic lung allograft dysfunction (CLAD). Several inflammatory lung diseases are associated with increased airway levels of secretory phospholipase A2 type IIA (sPLA2-IIA), an enzyme that hydrolyzes membrane and surfactant phospholipids releasing arachidonic acid metabolites. Bile acid (BA) aspiration in lung transplant recipients predicts CLAD. Moreover, in experimental lung models, BA increased sPLA2-IIA expression.Wesought to study the role of sPLA2-IIA in airways of lung transplant recipients and its relationship with aspirated BA, bacterial infections and inflammatory mediators.

Methods: Bronchoalveolar lavage (BAL) and large airway bronchial wash (LABW) were prospectively collected from 137 recipients at the 3-monthpost-transplant surveillance bronchoscopy and assayed for sPLA2-IIA by ELISA. The LABW were assayed for conjugated and unconjugated BA by tandem mass spectrometry and for inflammatory mediators by 48-multiplex. BAL microbiology was monitored. Non-parametric statistical analysis was performed.

Results: sPLA2-IIA was quantifiable in 76% of BAL samples (median 376.6 pg/ml; IQR range: 37.69-1760), and in 93%of LABW (1797 pg/ml (350-3998)). The BAL and LABW sPLA2-IIA concentrations directly correlated (Spearman r=0.66, p<0.0001). sPLA2-IIA correlated with total BA levels in LABW (r=0.32 p=0.0002). Samples with high BA (upper tertile) showed greater sPLA2-IIA levels: 3160pg/ml(1319-5051) vs 1440 pg/ml (236-3573) (Mann-Whitney p=0.0027). Correlation was stronger with conjugated versus unconjugated BA (r=0.31 p=0.0003 vs r=0.25 p=0.0036). BAL sPLA2-IIA levels were higher in samples positive for bacteria (642.6 pg/ml; 130-3227) compared to negative samples (223.5 pg/ml; 15.65-1151) (p=0.0036). sPLA2-IIA and BA correlation persisted in absence of bacteria (r=0.32, p=0.0025). sPLA2-IIA correlated with 85% of inflammatory mediators in LABW: strongest correlations were found with EGF (r=0.73), IL-1RA (r=0.70), IL-1α (r=0.63) and PDGF-AA (r=0.64), p<0.0001.

Conclusions: sPLA2-IIA levels in the airways of lung transplant recipients were comparable to other inflammatory lung disorders, and markedly greater than in healthy controls (median 28 pg/ml, Long et al. Am J Med Sci 2012). sPLA2-IIA independently correlated with aspirated bile acids, particularly with the conjugated species. sPLA2-IIA also correlated with several inflammatory mediators, including cytokines implied in fibroblast proliferation, inflammation and inflammatory response regulation. sPLA2-IIA was also associated with presence of bacteria. This study explores for the first time the role of sPLA2-IIA in lung allograft airways and suggests it may serve as a marker of noxious events, such as aspiration and infection. These original findings support a larger longitudinal investigation of the role of sPLA2-IIA in chronic lung allograft dysfunction.

SOLUBLE IMMUNE CHECK POINT RECEPTORS AS POSSIBLE MARKERS OF REJECTION IN LUNG TRANSPLANTED PATIENTS

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Purpose: Chronic rejection (CR) is the leading cause of late morbidity and mortality in lung transplantation (LuTx), and there is still a gap of knowledge about immune-mediated rejection mechanism. Easily accessible markers of CR need to be identified, leaving transbronchial biopsies (TBB) to be the gold standard of diagnosis. Activation of the immune response or tolerance to foreign antigen is driven by complex mechanisms among which different costimulatory molecules play a fundamental role; immune check point receptor (ICR), in particular, are regulators of the immune system and are crucial for tolerance. We have recently shown that ICR expression in TBB is different in LuTx patients who do or do not undergo CR. ICR are also secreted and can be quantified in peripheral blood.

Methods: A pilot clinical trial enrolled 20 CF LuTx patients who underwent standard immunosuppressive therapy. Plasma samples were collected 72 h, 3 months, 6 months, 12 months and 18 months post LuTx. Soluble ICRs (Galectin9, TIM3, PD1 and PDL1) were evaluated in plasma by ELISA at each time points; surveillance TBB were performed at 3, 6, 12 months for diagnosis of rejection. Clinical parameters, including respiratory volumes (e.g. FEV1), rejection episodes and infections, were recorded as well.

Results: Soluble Galectin9 (sGAL9) plasma concentration was greatly reduced in patients undergoing acute rejection (AR) as early as the month 3, compared to no-rejection LuTx subjects. Such difference was maintained throughout all the timepoints, reaching statistical significance at month 18 ($p<0.05$). In patients with CR a similar trend was observed from month 6. Considering all the rejection events together (AR+CR), a significantly reduced sGAL9 plasma concentration was detected through month 18 ($p<0.05$) compared to no-rejection. Trends that did not reach statistical significance, could be observed in plasma concentrations of the other analyzed sICRs. In tissue the same ICR were analyzed, and PD1 were significantly higher in AR.

Conclusions: Results of this pilot study suggests that measurement of sICRs in plasma could be a useful and non-traumatic way to ameliorate the diagnosis of rejection in LuTx patients. Identification of soluble markers of CR would be of great importance in supporting the clinical management of LuTx patients.

A BLOOD GENE SIGNATURE TO PROGNOSE CHRONIC LUNG ALLOGRAFT DYSFUNCTION

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Purpose of this study: Chronic lung allograft dysfunction (CLAD) is the main limitation to long-term survival after lung transplantation. We previously identified three genes whose expression levels in the blood were associated with CLAD, namely, BLK, POU2AF1 and TCL1A. The purpose of this study was to validate this signature using new samples from lung transplant recipients.

Methods: The expression levels of the 3 genes were measured by quantitative PCR in blood samples from 154 lung transplantation patients of the multicenter COLT cohort at three time points: 12, 18 and 24 months posttransplantation. These patients included 85 patients with good graft function at least 3 years after transplantation (STA) and 45 patients with BOS diagnosis at least 3 months after sampling.

Results: At 24 months posttransplantation, we validated the decreases in the expression levels of the three genes in blood from patients who developed BOS 3 to 24 months after testing compared to patients with maintained graft function (p=0.041, 0.029 and 0.038 for BLK, POU2AF1 and TCL1A, respectively). We built a risk score composed of the expression of the three genes and one clinical parameter, the experience of previous acute rejection episodes. This prognosis score reaches a global c-index of 0.829 and has a better prognosis capacity than the measure of pulmonary function.

Conclusions: This score would allow the identification of patients at risk of CLAD to prevent lung allograft damage. The 3 genes defining this prognosis score are associated with B-cell functions and support the growing evidence of B-cell involvement in CLAD pathogenesis.

DYNAMIC ^{19}F MRI OF PULMONARY VENTILATION IN LUNG TRANSPLANT RECIPIENTS WITH AND WITHOUT CHRONIC LUNG ALLOGRAFT DYSFUNCTION: A FEASIBILITY STUDY

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Background: Pulmonary function tests remain the standard way to monitor allograft health after lung transplantation. However, by the time there is a detectable drop in pulmonary function, significant and irreversible damage to the lung allograft may already have occurred. Dynamic ^{19}F MRI of inhaled perfluoropropane (PFP) may detect subtle changes in regional lung ventilation which is a feature of chronic lung allograft dysfunction (CLAD) and its two main phenotypes, bronchiolitis obliterans syndrome (BOS) and restrictive allograft syndrome (RAS). We performed a feasibility study to assess use of quantitative ventilation imaging in lung recipients to determine its applicability in this patient group.

Methods: Multi breath-hold dynamic ^{19}F MRI using a 79% PFP/21% O2 gas mixture was performed in ten lung transplant recipients, four with stable allograft function and six with CLAD (5 BOS, 1 RAS). Gas wash-in and washout dynamics were assessed and a regional lung clearance index (RLCI) was used to quantify regional lung ventilation.

Results: Compared to stable patients, BOS patients had substantially more variation in regional ventilation with more regions of reduced ventilation, especially in the periphery. Washout was homogeneous and rapid in stable patients, but highly heterogeneous in CLAD. CLAD patients exhibited significant difference in RLCI between central and peripheral lung regions ($p=0.0016$) and a wider interquartile range of RLCI for wash-in compared with stable patients (no CLAD 4.1, BOS 10.5, $p=0.036$). FEV1 (% of baseline) negatively correlated with ventilation during wash-in, most strongly for the periphery.

Conclusions: Dynamic ^{19}F MRI identified quantifiable differences in regional ventilation in lung transplant recipients with and without CLAD and was well tolerated. Larger longitudinal studies using this approach will determine if early detection of changes in regional ventilation in lung transplant patients allows earlier detection of CLAD.

CONFIRMATION OF THE MULTI-PARAMETRIC CFDNA ALGORITHM FOR EARLY ALLOGRAFT INJURY EVENTS IN LUNG TRANSPLANTATION

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Our team previously published (1) results at one month after lung transplantation (LTx) that donor-derived cfDNA (dd-cfDNA) alone is not specific for discriminating acute rejection (AR) from other early events such as infection (INF). We demonstrated the importance of a multi-parametric cfDNA study by an algorithm that considers the %dd-cfDNA to differentiate stable from non-stable patients, and the fragmentome study of cfDNA size to discriminate the injury type (INF,AR). The aims of the study are to confirm these results and adjust the diagnosis threshold of the algorithm previously published, using a larger cohort. This was a prospective study involving 92 patients (62 first patients and 30 additional patients) from the Marseille Hospital. %dd-cfDNA was determined by NGS (AlloSeq cfDNA assay, CareDx) and size profile was assessed by BIABooster (Adelis). A biopsy at day 30 (D30) established the following groups among patients: stable and non-stable (AR, INF and AR+INF). The results of this new analysis are consistent with our previous results. % dd-cfDNA was significantly higher in non-stable patients at D30 (p=0.001). The threshold previously identified as 1.72%was adjusted to 2.19%, yielding satisfactory analytical performance (sensitivity=72.7%, specificity=87.2%, PPV=76.2%), and notably, an NPV=85.0% for discriminating stable patients. Among the "non-stable" group, the results confirmed that patients with INF had significantly higher percentages of small cfDNA fragments (80-120bp) compared to AR patients (p=0.028) and stable patients (p=0.044). The initial threshold of 3.7%, adjusted to 3.4%, facilitated the identification of INF patients among non-stable patients (PPV=88.9%). The combination of the two analyses effectively differentiates the type of allograft injury. This study, conducted on a larger cohort confirms the previous results and adjust the previously established cut-off values to increase the test reliability.

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BASELINE LUNG ALLOGRAFT DYSFUNCTION IS ASSOCIATED WITH DIFFERENTIAL KINETICS FOR TOTAL AND DONOR-DERIVED CELL-FREE DNA AFTER LUNG TRANSPLANTATION.

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Purpose: Baseline Lung Allograft Dysfunction (BLAD) represents a failure to achieve normal lung function (FVC and FEV1>80%) after lung transplant (LT).1 BLAD may result from severe primary graft dysfunction (PGD Grade 3) and contribute to worsened mortality after bilateral LT.2 We assessed Total cell-free DNA (TcfDNA) and the donor-derived cfDNA (dd-cfDNA), a marker of graft injury, at serial timepoints post-LT.

Methods: This prospective, two-center TIBURON-Lung Study collected samples and data over a one-year period between 2021-2022. Specifically, presence of BLAD (B) vs Non-BLAD (NB) was determined from serial spirometry data, and correlated with trends in prospectively collected samples analyzed for TcfDNA and ddcfDNA (the Prospera™ test; Natera, Austin, TX). Log transformed data were corrected for repeated measures, exclusion of intercurrent infection events (within 14 days of test) and compared by Generalized Estimating Equation (GEE) with repeated measure and BLAD binary (y/n) as the outcome at 3-, 6-, 9-, 12-, and >12-months post-LT (Median / 25-75% IQR / $p<0.05$).

Summary Results: A total of 354 TcfDNA and dd-cfDNA tests obtained from N=66 LT recipients (B=30, NB=36) were analyzed (TABLE). Median time post-LT for the >12-month study period was 1481.5 (424-1765) and 1252 (651-1584) days for the B and LB groups, respectively ($p=0.27$). TcfDNA levels were not significantly different for all timepoints during the initial 1-year; however, they were statistically higher for the BLAD cohort in the later epoch >12-months. DdcfDNA fractions were not statistically different however "trended" higher for BLAD across all timepoints.

Conclusions:

1. TcfDNA levels were not different for B vs NB at timepoints until the epoch after the initial 12-months post-LT, however ddcfDNA fraction "trended" higher for the BLAD cohort across at all timepoints.
2. We speculate that severe PGD or an abnormal pathobiology with BLAD may contribute to a perpetuated inflammatory response manifested by sustained elevation in TcfDNA after the initial 12-months and associated molecular injury of the allograft as reflected in an attenuated decline in ddcfDNA kinetics.
3. Further study of this BLAD phenotype in a larger cohort with longer-term outcomes should prove valuable in understanding the complex pathobiology and relation to CLAD development.

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Table

		3	6	9	12	>12-months
TcfDNA (cp/mL)	BLAD	1280.6 (773.9-3001.2)	1391.7 (792.8-2616.4)	1362.0 (810.0-2332.3)	1357.7 (860.9-2308.1)	**1232.09** (795.9-2988.4)
	Non-BLAD	1448.3 (543.9-2869.4)	1346.3 (911.0-2105.3)	1346.3 (950.9-2105.3)	1229.3 (812.8-1879.9)	**692.8** (468.7-1112.9)
	p-value	0.50	0.75	0.55	0.29	**0.02**
ddcfDNA (%)	BLAD	2.10 (1.23-3.81)	0.99 (0.27-2.15)	0.85 (0.30-1.85)	0.81 (0.31-1.78)	0.86 (0.39-2.36)
	Non-BLAD	1.98 (0.97-4.66)	0.69 (0.35-1.96)	0.69 (0.29-1.42)	0.66 (0.23-1.51)	0.75 (0.43-1.85)
	p-value	0.78	0.58	0.42	0.62	0.34

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SPATIALLY RESOLVED IMMUNE CELL INFILTRATION AT THE VASCULAR-BRONCHIAL INTERFACE IN PRIMARY GRAFT DYSFUNCTION: LESSONS FROM A 72H PORCINE TRANSPLANT MODEL

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Several advanced therapy medicinal products (ATMP's) as for example mesenchymal stroma cells (MSC) are being explored within the context of lung transplantation as a means to rescue marginal donor lungs and increase end transplant numbers. But, what happens to marginal lungs that are transplanted without therapy, and what exactly are these therapies mitigating in the pulmonary immuno-inflammatory landscape?

To try and answer this question our group has developed a porcine lung transplant model, with a 72h follow up, a critical time window when considering the development of primary graft dysfunction (PGD). To mimic the presentation of a marginal donor lung, all donors undergo aspiration injury. Lungs then either receive MSC therapy or no treatment, and while treated grafts function well and are well tolerated by the recipient, the untreated lungs develop grade 2-3 PGD.

To better understand the cellular and sub-cellular pathophysiological cascades at play in these untreated and treated lungs we have developed an advanced imaging pipeline using a new lung tissue processing technique, coupled to scanning electron microscopy, high resolution volumetric laser scanning confocal microscopy, and ultrahigh content fluorescence imaging. The evident diverse immune cell invasion and neutrophil extracellular trap deposition in these lungs leads to specific patterns of extracellular matrix degradation, which is most prominent at the vessels, bronchioles and their interface. 16-plex ultrahigh content imaging of these regions at sub-cellular resolution permitted the analysis of over 750, 000 cells in a spatially-resolved manner and revealed a pattern of immune cell infiltration and expansion, including CD3+, CD4+, PCNA+ and Ki67+ populations.

The spatially-conserved localisation of these cells at the vascular-bronchial interface may represent the early cellular correlates of acute and chronic lung allograft dysfunction. Thus, deeper proteomic and transcriptomic profiling of these regions would be valuable in better understanding this heterogenous pathophysiology, as well as lend insights into what the MSC therapy is alleviating at a cellular level.

PROTEOMIC PROFILING OF PRIMARY GRAFT DYSFUNCTION IN A PORCINE MODEL OF LUNG TRANSPLANTATION

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Purpose of the study: Despite the challenges that primary graft dysfunction (PGD) presents to the post-operative lung transplant recipient, the underlying pathophysiology of PGD is not entirely elucidated. One hurdle in understanding the molecular mechanisms of this post-operative complication is the difficulty of obtaining representative samples from patients. A large animal model of lung transplantation with a high fidelity to clinical practice could prove to be invaluable in providing insights into PGD.

Methods: A large animal model was developed to undergo an orthotopic left lung transplantation into porcine recipients. In total, 21 recipients were transplanted and kept under surveillance and maintenance per clinical guidelines. Recipients were then followed for three days post-transplantation and assessed for PGD according to the International Society of Heart and Lung Transplantation (ISHLT) guidelines. Lung tissue samples were acquired at the end of the experiment from the transplanted lungs and were then evaluated through liquid chromatography-mass spectrometry to characterize the proteome.

Results: 9 recipients developed PGD grade 2-3 while 12 did not develop PGD by the conclusion of the observational period. In comparing samples from recipients with PGD to those without, significant differences were observed across the proteomic profiling of the tissue samples. 302 proteins were significantly overexpressed in the PGD group while 55 were underexpressed. Using gene set enrichment analysis, distinct patterns in immune activation, responses to inflammation, wound healing, and regulatory pathways of coagulation were found to be enriched within the PGD group.

Conclusion: Due to a lack of available tissue for analysis, a complete proteomic profiling of PGD has yet to be achieved and reported in the literature. This study represents the successful characterization of biological pathways and differentially expressed proteins in a cohort of recipients with PGD using a large animal model. This characterization of the proteome is needed to better understand the pathophysiology of PGD and could be leveraged for novel therapeutic targets.

ANTI-HLA ANTIBODIES, DONOR-SPECIFIC ANTIBODIES AND AMR IN RESTRICTIVE ALLOGRAFT SYNDROME: A NESTED CASE-CONTROL STUDY

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Purpose: Donor-specific antibodies (DSAs) against human leukocyte antigen (HLA) are associated with antibody-mediated rejection (AMR), chronic lung allograft dysfunction (CLAD) and mortality after lung transplantation (LTx). We aimed to further evaluate the role of anti-HLA antibodiesand AMR forrestrictive allograft syndrome (RAS) development post-LTx.

Methods: All LTxrecipients transplanted from 2010 to 2021 (n=789) were evaluated, and we included 69 patients with CLAD-RAS and 69 CLAD-free matched controls. Occurrenceof anti-HLA antibodies, DSAs, and AMR regarding RAS onset was assessed using (time-dependent) Cox regression.Anti-HLA antibodies were detected using Luminex technology and classified as positive (MFI≥500) or negative (MFI<500). Measurements were performedon the day of transplant, 1, 3, 6, 9, 12, 18, and 24 months post-LTx, and yearly thereafter, or when clinically indicated, as part of routine clinical practice. Persistent anti-HLA antibodies (both DSAs and non-DSAs) were defined as the presence of anti-HLA antibodies targeting the same donor HLA locus in at least two separate measurements, at least three weeks apart.All other were classified as transient. AMR was diagnosed according to the 2016 ISHLT consensus, including possible, probable, and definite clinical AMR.

Results: Any anti-HLA antibodies (non-DSAs and DSAs, both transient and persistent) were significantly associated with RAS in univariate analysis (Figure 1).

Non-DSAs: Inthe RAS group, 26 patients (38%) developed transient non-DSA antibodies, compared to 9 controls (13%) (p=0.0015). RAS patients had transient non-DSA antibodies against a median of 3 loci versus 1 locus in controls (p=0.0215). Persistent non-DSA antibodies were found in 25 RAS patients (36%) versus 16 controls (23%) (p=0.1357), with a median of 2 loci in both groups.

DSAs: Transient DSAs were observed in 11 RAS patients (16%) and 3 controls (4%) (p=0.0452). Persistent DSAs were found in 13 RAS patients (19%) versus 7 controls (10%) (p=0.2261). Controls typically had DSAs targeting one locus, while RAS patients had DSAs against 1 to 3 loci (p=0.0368). Transient DSAs in RAS patients were often directed against DR, DQ, and A loci (29%, 24%, and 24%, respectively). Persistent DSAs in RAS patients targeted DQ (67%) and DR (30%).

AMR: AMR occurred only in the RAS group (n=12, 17%), significantly increasing the hazard of RAS (HR 4.7043, p<0.0001). Persistent DSAs and AMR remained significant in multivariable analysis (p<0.0001 and p<0.0001, respectively)(Figure 1). Time to first DSA was shorter in RAS compared to control, and median time to RAS (including all patients with DSA) after occurrence of first DSA was 16.3 months (Figure 2).

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Conclusion: We demonstrated an association of anti-HLA antibodies with RAS, with greater risk in persistent versus transient antibodies, class II versus class I anti-HLA antibodies, and an especially high hazard for DQ-DSA. Clinical AMR strongly predicted RAS development.

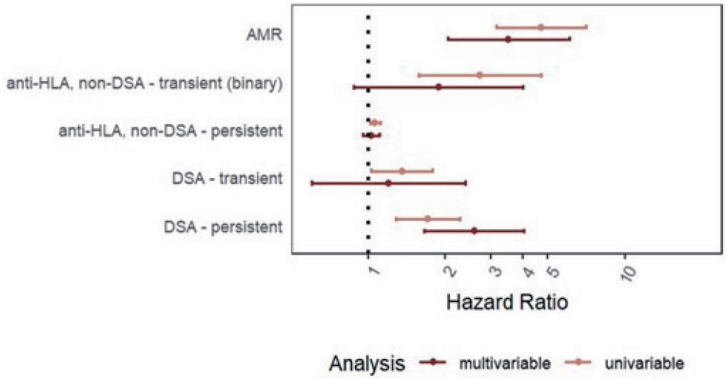

Figure 1: univariate and multivariate hazard ratio's. Each bar represents a specific variable, with the dot indicating the estimated HR value and error bars the 95% confidence intervals for each HR estimate.

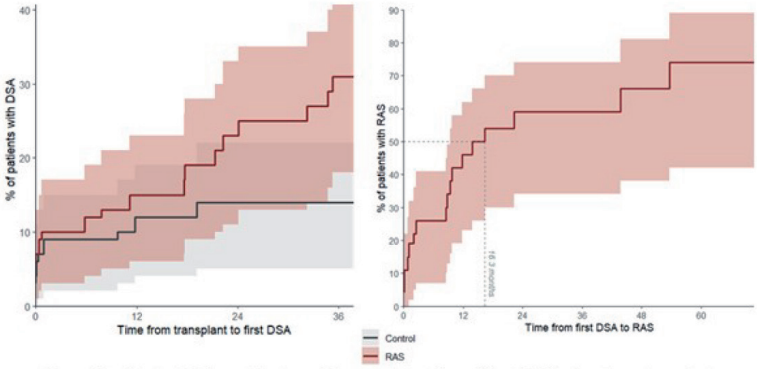

Figure 2: Kaplan Meier estimates of time to detection of first DSA after lung transplant in RAS vs. non-CLAD control (left) and time to RAS after first measurement of DSA (right).

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ALTERED PIGR/IGA MUCOSAL IMMUNITY IN BRONCHIOLITIS OBLITERANS SYNDROME (BOS): A NEW PLAYER IN THE TRIGGERING OF BOS?

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Rationale. Long-term survival after lung transplantation (LTx) is hampered by the occurrence of chronic lung allograft dysfunction (CLAD), which manifests most often as bronchiolitis obliterans syndrome (BOS). CLAD may be triggered by several factors, including recurrent post-LTx infections. As immunoglobulin (Ig) A is crucial for ensuring mucosal immunity and reducing airway microbial burden, we explored whether IgA and its epithelial receptor, the polymeric Ig receptor (pIgR), were impaired in BOS.

Methods. In a first part of this study, bronchoalveolar lavage fluids (BALF, n=120) and sera (n=120) from LT recipients from the Cohort for Lung Transplantation (COLT) were collected at pre-defined timepoints, prior to the diagnosis of persistent functional stability (BOS-free, n=30) or BOS (pre-BOS, n=30). BALF were assessed for secretory (S)-IgA, while sera were assessed for IgA, S-IgA and secretory component. In a second part, a cross-sectional immunehistological study was performed in 66 patients from Foch Hospital, to compared pIgR expression in bronchiolar epithelium from BOS-free (n=20), pre-BOS (n=19) and BOS LT recipients (n=12), and in end-stage BOS explants (n=15).

Results. In the COLT cohort, S-IgA levels were reduced in BALF from pre-BOS versus BOS-free LTx recipients ($p<0.01$). Serum IgA levels were similar across the groups, whereas SC levels were increased in serum at M6 and M12 from pre-BOS versus stable patients ($p<0.01$, and $p<0.01$, respectively). Freedom from BOS at 3 years post-LTx was higher for the high S-IgA versus low S-IgA BALF group using a 12.59 cut-off level at M12 defined according to the maximum Youden index (Log-rank test, $p<0.001$).

In Foch Cohort, immunohistological study showed that pIgR bronchiolar expression was significantly reduced in BOS and end-stage BOS patients as compared to stable patients ($p<0.01$ and $p<0.01$).

Conclusions. Our findings suggest an early impairment of the pIgR/IgA pathway in BOS patients, which occurs before the date of functional diagnosis of CLAD. This alteration of pIgR/IgA mucosal immunity after LTx could promote both recurrence of infections and a defective immune exclusion of auto/alloantigens in airways, with subsequent triggering of CLAD process.

CD38 ANTIBODY DARATUMUMAB AS AN ADD-ON RESCUE THERAPY FOR AMR – FIRST REPORT IN CLINICAL LUNG TRANSPLANTATION

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Purpose of the Study: Antibody-mediated rejection (AMR) following lung transplantation (LTx) poses a major threat to allograft function. Current treatments focus on depleting circulating antibodies and suppressing B-cell activity, but these treatments often fail to reduce donor-specific antibodies (DSAs) adequately. Daratumumab is a monoclonal antibody targeting CD38 and depletes plasma cells and NK cells. Thus, it could potentially improve the outcomes of AMR. Herein, we report the first use of daratumumab in the setting of lung transplantation.

Methods: We conducted a retrospective single-center analysis, including all lung transplant recipients who received daratumumab as an add-on rescue therapy for AMR or as part of desensitization therapy pre-/post-transplant in our institution. Baseline demographics, immunological characteristics with a particular focus on DSAs as well as long-term transplant outcomes were analyzed. DSAs were detected by Luminex bead assay.

Results: 17 patients received subcutaneous doses of 1800mg of daratumumab due to the following indications: 14 patients with de novo DSAs and AMR and 3 patients with pre-transplant DSAs without clinical AMR. Daratumumab was safely administered in all cases. The most frequently observed complications associated with daratumumab treatment were infections (52.9%) and neutropenia (58.8%). Among the AMR group, daratumumab especially led to a significant reduction in DSA against HLA class I in all patients with median mean fluorescence intensity (MFI) values dropping to < 25- 50% of the baseline within 12 weeks after the first dose of daratumumab. DSA against HLA class II were reduced in 35.7%. 11 patients (78.6%) who received daratumumab as an add-on rescue therapy survived acute AMR. Despite this, five of these patients developed chronic allograft dysfunction (CLAD), three of which required retransplantation. Among the desensitization group, mean MFI values of all three patients decreased to 50.6%, 48.0% and 29.7% of the baseline and none of these patients developed AMR.

Conclusion: Targeting CD38 can be successful in decreasing DSA – especially against HLA class I – in patients with AMR and thus might present an effective rescue therapy in patients without clinical response to other treatments. Our findings encourage the conduction of future prospective studies to further elucidate the therapeutic potential of this novel treatment approach in LTx.

EXTRACORPOREAL PHOTOPHERESIS IN LUNG TRANSPLANTATION, REAL-LIFE INDICATION NOT LIMITED TO BOS

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Purpose of the study : Chronic lung allograft dysfunction (CLAD) affects almost half of lung transplant recipients at 5 years and is the main limitation for long term survival. Previous studies have suggested extracorporeal photopheresis (ECP) to be able to prevent and stabilize CLAD by modulation of the immune system. We describe here, real-life use of ECP in lung transplantation over a twelve-year period.

Methods : This is a retrospective multicentric descriptive study based on the COLT (Cohort Lung Transplantation) database. All recipients who had undergone ECP were included. CLAD phenotypes were determined at the time of ECP initiation by adjudication committee. We also defined a preCLAD phenotype by persistent decline of more than 10% but less than 20% from baseline FEV1.

Results : From 2009 to 2021, 128 recipients were found to have benefited from ECP. Mean age at transplant was 42.8 + 14 years, there were 55 women (43%) and 73 men (57%). The most common underlying disease was cystic fibrosis (40 patients, 31%), followed by chronic obstructive pulmonary disease (38 patients, 30%), interstitial lung disease (18 patients, 14%), group I pulmonary hypertension (18 patients, 14%) and other aetiologies (14 patients, 11%). CLAD was found in 97 patients (76%) of whom phenotype at the start of ECP was bronchiolitis obliterans syndrome (BOS) in 70 patients (55%), restrictive allograft syndrome (RAS) in 6 patients (5%), mixed in 7 patients (5%) and undefined in 22 patients (17%). We identified 14 preCLAD patients and 9 recipients were neither CLAD nor pre-CLAD. Median FEV1 at the start of ECP was 1.45 l IQR[1.03 -1.92] (Q1 - Q3 : 1.03 - 1.92) in the CLAD group and 1.86 l IQR[1.49 – 2.79] in the pre-CLAD group. The median duration of ECP was 9.5 months IQR[3 -23], with a mean survival time of 4.7 + 2.8 years for the whole cohort. Analysis of the FEV1 evolution show after ECP start, a trend to stabilization of lung function in CLAD recipients and a moderate increase in the preCLAD group.

Conclusion : The main indication of ECP was BOS but more than 40% of ECP-treated recipients were of other phenotype including preCLAD recipients who seem to have a stronger lung function benefit from treatment.

THE IMPACT OF PREFORMED DONOR-SPECIFIC ANTIBODIES ON OUTCOME AFTER LUNG TRANSPLANTATION: A RETROSPECTIVE SINGLE-CENTER EXPERIENCE

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Purpose of the study: Patients with pre-existing antibodies against donor human leukocyte antigens (HLA) represent a unique immunological challenge for most lung transplant centers. Despite screening techniques now being routine clinical practice, the management of these patients significantly varies across centers. This study aimed to analyze the long-term outcomes of pre-sensitized patients in our institution.

Methods: This is a retrospective analysis including lung transplant recipients with preformed donor-specific antigens (DSAs) and post-transplant de novo DSAs (dnDSAs), transplanted in our institution between 2016 and 2021. Patients who underwent re-transplantation or multi-organ transplantation were not included. Presence of pre-existing antibodies was first screened with complement-dependent lymphoma assay at the time of listing. In case of positivity, single antigen bead assay was used and unacceptable antigens (UAGs) were defined. On the day of transplantation, all patients underwent a single antigen bead assay. Outcomes were overall survival, freedom from chronic lung allograft dysfunction (CLAD), incidence of acute cellular rejection (ACR) and antibody mediated rejection (AMR).

Results: Within the study period, 572 patients have been transplanted at our institution. 205 patients developed dnDSAs during post-transplant follow-up. 5.9% of these patients (n=11) had UAGs, all of which received an organ from an HLA-matched donor. Incidence of AMR (p=0.818) and ACR (p=0.492) was not increased, and overall survival and freedom from CLAD were similar compared to the non-presensitized cohort (p= 0.070 and p=0.623, respectively).

Notably, 28 patients (13.6%), initially screened as negative, displayed preformed DSAs on their day of transplantation and were not matched. However, post-transplant crossmatch in all these patients was negative. ACR and AMR showed no significantly higher incidence compared to non-presensitized patients (p=0.341 and p=0.580, respectively). Although no differences in overall survival could be observed (p=0.636), freedom from CLAD was significantly lower in these patients (p=0.018).

Conclusion: Based on our findings, matching of patients with UAGs is possible and leads to excellent results. Unmatched patients showed shorter freedom from CLAD and should be considered for post-transplant desensitization protocols.

INDUCTION THERAPY IN THE LIGHT OF THE NOVEL BIOMARKER: TORQUE TENO VIRUS

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Purpose: Due to encouraging studies of the monoclonal antibody targeting CD52, alemtuzumab belongs to the most commonly applied induction therapies after solid organ transplantation. However, its superiority in regard to acute cellular rejections is not well understood.

Methods: A retrospective review of medical records was performed on all patients (n=498) who underwent lung transplantation in our institution between 01/2018-12/2022. Patients were followed up until 04/2024. Of these patients those with and without induction tehrapy with alemtuzumab were compared with respect to overall survival (OS), acute rejection (ACR), antibody-mediated rejection (AMR), chronic lung allograft dysfuction (CLAD), infections, re-transplantation and other relevant events. Routinely Torque Teno Virus (TTV) levels were monitored on average 2-3 times per month. During the folllow up period TTV levels did not enter therapeutic decision-making in these patients.

Results: From overall 498 patients, 105 received no induction therapy, while 334 received alemtuzumab induction. During an average follow up of 28 months, 126 deaths occurred in patients with and w/o induciton. Alemtuzumab led to a 27%survival benefit (hazard ration (HR=0.63 95% CI:0.43-0.91). Risk of ACR was singificantly lower in those receiving alemtuzumab (HR: 0.60 95% CI: 0.37-0.97) other events showed no statistically signficiant differences. TTV levels during the first year after the first month post-transplant were significantly lower in patients without induciton (4.6x108 vs. 1.4x109) and fluctuation of TTV levels were less in patients receiving induction during this time interval (3.8 vs. 4.4 undulations per year). However, neither baseline TTV levels nor increase of TTV levels during the first month was significantly different between groups.

Conclusion:TTV load is a promising biomarker for monitoring immunosuppression after SOT. In this observational study, we confirmed the lower incidence of ACR followed by alemtuzumab induction. The stability of the immunosuppression highlighted by the low-density TTV level oscillation, seem to be key features of induction therapy to avoid acute cellular rejection and to improve survival.

TTV GUIDED BELATACEPT CONVERSION AFTER LUNG TRANSPLANTATION: A REPORT OF 22 CASES

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Purpose of the Study: Calcineurin inhibitor (CNI)-based protocols remain the standard immunosuppressive regimen (IS) after lung transplantation (LTx), despite the potential for CNI-related toxic effects. Belatacept, a novel immunosuppressant that blocks a T-cell co-stimulation pathway, is a non-nephrotoxic drug indicated as an alternative to CNIs in kidney transplantation. However, in most published reports on the use of belatacept after LTx in combination with CNI-sparing protocols, the incidence of acute rejection episodes and early CLAD was unacceptably high. This study investigated the use of Torque Teno Virus (TTV)-guided belatacept dosing to overcome this issue.

Methods: We reviewed a series of 22 LuTx recipients who were converted to a CNI-sparing belatacept IS regimen within the first 5 years post-LTx (n = 22) (minimum follow-up of 6 months after initiation of belatacept). Belatacept dosing was initially based on the protocol for kidney transplantation and subsequently adapted using TTV PCR levels (therapeutic range log7 -log9 TTV-PCR copies).

Results: The use of belatacept was prompted by severe renal failure in all patients. The time to belatacept administration after LTx was 636±487 days (range 67-1994 days). The mean estimated glomerular filtration rate (eGFR) significantly improved 6 months after starting belatacept (eGFR before initiation: 34.0±9.8 mL/min/1.73m2; eGFR after 6 months: 42.9±9.3 mL/min/1.73m2, p=0.003). Tacrolimus was reduced but not discontinued (target level reduced to 1.5-2.5 ng/mL). There were no episodes of acute cellular rejection (ACR) or antibody-mediated rejection (AMR) and none of the paients developed CLAD. One pat died due to pulmonary embolism 101 days after starting belatacept. In 10 patients, the belatacept dose had to be increased according to TTV levels (10mg/kg every 3-4 weeks).

Conclusion: Conversion to a CNI-reduced belatacept-based IS regimen with TTV-guided belatacept dosing improved renal function without increasing the risk of ACR, AMR or CLAD. Further studies are required to confirm the safety and efficacy of this therapeutic regimen.

THE VIENNA EXPERIENCE: CHARACTERIZING ACUTE LUNG ALLOGRAFT DYSFUNCTION IN LUNG TRANSPLANT RECIPIENTS

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Purpose of the study: The term "acute lung allograft dysfunction" (ALAD) is becoming increasingly recognized, however, its definition continues to be debated. A clear definition will enhance both management and research of early onset lung allograft dysfunction among lung transplant recipients. The aim of this study was to describe the characteristics of ALAD patients in our cohort, thereby providing a deeper insight into this as-yet-undefined type of graft dysfunction.

Methods: The study included patients undergoing lung transplantation from January 2017 to December 2023. Patients with fewer than four pulmonary function tests (PFTs) or less than 24 weeks of follow-up post-transplantation were excluded. ALAD was identified by a decrease in FEV1 of at least 10%, occurring within a three-month period (12 weeks). This change had to return to the previous level of graft function, or it could indicate the onset of chronic lung allograft dysfunction (CLAD). CLAD was defined according to the International Society for Heart and Lung Transplantation (ISHLT) consensus statement.

Results: Between 2017 and 2023, a total of 647 patients were transplanted at our center. Of these, 33 did not have adequate follow-up data (at least 6 months) or sufficient PFTs, and had to be excluded. 137 (21%) patients had at least one episode of FEV1 drop and return to baseline in the follow-up period. Of the 137 FEV1 drops, 94 were attributed to infections, histologically proven rejections, or other factors (eg. pleural effusion, chest pain) causing the decline in lung function. Forty-three patients (34%) met the criteria for ALAD, with no other identifiable causes for the decline in lung function and recovery to baseline within three months. The median onset of ALAD was 184 days (IQR 105-324) after transplantation. Although not statistically significant, there was a trend suggesting that patients with ALAD were more likely to develop CLAD (p=0.07).

Conclusion: The findings of this study highlight the complexity of ALAD within the lung transplant population and show a potential correlation between ALAD and the subsequent development of CLAD. This illustrates the need for a standardized definition of ALAD, which would facilitate more precise clinical and research methodologies and potentially improve patient outcomes. Additionally, it is important to consider the natural variability in FEV1, as even minor factors such as postoperative chest pain can cause fluctuations in lung function testing.

SYSTEMATIC ASSESSMENT OF BRONCHIAL ISCHEMIA AND ASSOCIATED PROGNOSIS IN A TEN YEARS COHORT OF CONSECUTIVE BILATERAL LUNG TRANSPLANT RECIPIENTS

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Purpose: Bronchial ischemia is common after lung transplantation (LT) and may lead to airway complications such as dehiscence and bronchial stenosis with detrimental outcomes on survival or respiratory function. However, few studies assess its incidence using MDS and/or ISHLT classifications.

Methods: We performed a retrospective analysis of consecutive bilateral LT between 2011 and 2021 in Foch Hospital. Patients had at least weekly bronchoscopies during the first month. All bronchoscopy reports, photos and videos were reviewed in order to grade airway status using ISHLT and MDS classifications for mucosal ischemia. Further outcomes such as the occurrence of airway dehiscence, the risk of further bronchial stent for stenosis, the maximal FEV1 acquired and survival were also reported according to initial mucosal ischemia status.

Results: A total of 560 patients were included, accounting for 1120 anastomosis. Bronchial mucosal ischemia occurred in 79% of anastomoses, preferentially at the right side (85.5% right versus 71.7% left). Mucosal ischemia involved more than half of the circumference in 44.8% of anastomoses. Lobar or segmental bronchi (MDS M3C ischemia grade) were involved in 15% of anastomoses. Necrotic mucosa was present in 14.3% of anastomoses.

Dehiscence occurred in 14.6% of anastomoses, of less than 25% of its circumference in 60% of cases. Dehiscence was only seen on ischemic anastomosis and its risk was significantly associated with the extent of ischemia in all dimensions (Chi 2; $p<0,001$) especially in cases of M3C ischemia.

After Kaplan-Meier analysis the presence of mucosal ischemia was not associated with mortality (log rank p=0.3), in contrast with the longitudinal extent of M3C ischemia, which was found to be associated with increased mortality (log rank p=0.012 vs other stages). The circumferential extent of mucosal ischemia or the presence of necrosis according to ISHLT grade is not associated with mortality (log rank p= 0,28).

Further stent for stenosis was required in 20% of all patients. In patients with M3C ischemia and ISHLT stage d (circumferential necrosis), a stent was required in 50% of cases (log rank $p<0.001$ versus other ischemia stages).

The mean maximal FEV1 was lower in patients with M3C ischemia : 83% of predicted values (SD 22) versus 90% in others (SD 22), Mann Whitney; p=0.01. Similar results were obtained when comparing ISHLT grade c/d vs others (p=0.011).

Conclusions: This work underlines the high incidence of bronchial ischemia after LT. Natural history of mucosal ischemia associated with the risk of airway dehiscence, stenosis and lower lung function is described. Assessment of severity of ischemia identifies lobar or segmental bronchial ischemia (MDS stage 3C) as the parameter most strongly associated with those issues and with overall mortality.

THE NATURAL HISTORY OF PULMONARY FUNCTION BEFORE AND AFTER DEVELOPMENT OF CHRONIC LUNG ALLOGRAFT DYSFUNCTION IN BILATERAL AND SINGLE LUNG TRANSPLANT RECIPIENTS

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Purpose: Chronic lung allograft dysfunction (CLAD) remains a major cause of morbidity and reduced survival following lung transplant. Our understanding of factors that affect the course of pulmonary function tests (PFTs) before and after CLAD onset are limited.

Methods: In our single-center retrospective cohort study, we reviewed the PFT data of 923 lung transplant recipients between January 2000 and January 2020. We examined the course of forced expiratory volume in 1 second (FEV1) in the 12 months before and after CLAD onset using joint models. We looked at the association of transplant type on course of FEV1 before and after CLAD.

Results: 315 (34%) patients developed CLAD at a median of 817 (101-6318) days post-transplant, including 170 (54%) bilateral (BLT) and 145 (46%) single lung transplants (SLT). The median age of patients was 62 (18-79) years, and 183 (58%) were male. During the 1-year prior to CLAD, the mean FEV1% predicted was lower for SLTs as compared to BLTs (75% vs. 84%, p<0.001), but the rate of decline in FEV1% predicted was similar for SLTs and BLTs (-0.25%/mo. vs. -0.18%/mo,). The change in mean FEV1% predicted between pre-CLAD and post-CLAD was greater in BLTs (p<0.05), as shown in Fig.1. However, the rate of decline in FEV1% predicted in the year after CLAD onset was essentially flat and similar for SLTs and BLTs (-0.02%/mo. vs -0.01%/mo,).

Conclusion: At CLAD onset, there is a more dramatic loss of FEV1 for BLT's as compared to SLTs, but the rates of change in the year prior and after CLAD are similar. This higher loss of lung function in BLTs is likely due to the double the size of the allograft for bilateral compared to SLTs.

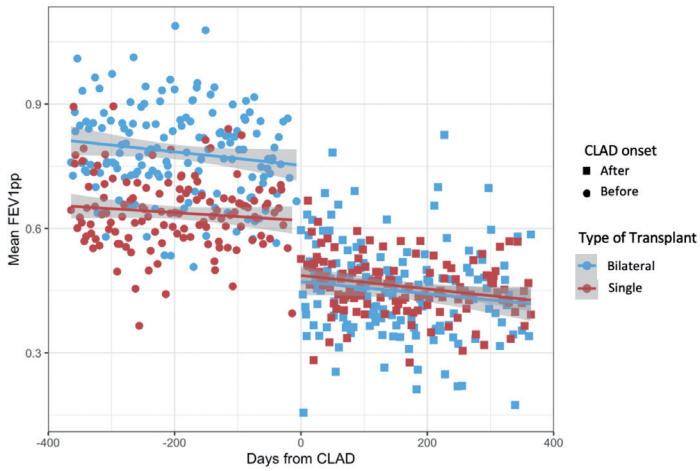

Fig.1. The FEV1% predicted trajectory in single and bilateral lung transplants.

A QUANTITATIVE APPRAISAL OF AIRWAY OBLITERATION AND BRONCHO-ALVEOLAR COLLATERAL VENTILATION IN BOS-EXPLANT LUNGS

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Purpose: In lungs with Bronchiolitis Obliterans Syndrome (BOS), about 50-70% of the small airways are obliterated. Collateral ventilation likely plays a vital role in preventing retro-obstructive alveolar collapse and the preservation of gas exchange. While an increase in the number of alveolar-alveolar connections (pores of Kohn) was already reported, other forms of collateral ventilation such as bronchoalveolar connections (Lambert's channels) may also be involved and have not been investigated thus far.

Methods: We scanned an entire human explant lung obtained at redo transplantation for end-stage BOS using Hierarchical Phase Contrast Tomography (HiP-CT) at 20µm resolution. In addition, non-destructive zoom scans (total volume = 78.8ml) were obtained at 4µm resolution, allowing three-dimensional quantitative assessment at microscopic level of the number of airway lesions and Lambert's channels within BOS lungs. Our observations were validated in 5 other lung explants with BOS post-lung transplant using micro-CT of excised lung specimens.

Results: In 1 zoom scan of 78.8ml lung tissue, we assessed 322 entire airways. A total of 26 airway lesions were found (58% complete luminal obliteration vs 38% subtotal luminal obliteration vs 4% complete airway collapse) affecting 1 or multiple generations. These lesions were not located at the level of the terminal bronchioles (0/159 airways, 0%), but rather in more proximal airways, specifically 1 (10/63 airways, 16%), 2 (14/35 airways, 40%), 3 (15/26 airways, 58%), 4 (8/15 airways, 53%), 5 (6/8 airways, 75%), 6 (3/5 airways, 60%), 7 (2/4 airways, 50%) and 8 (2/2 airways, 100%) generations proximal of the terminal bronchioles. In generation 9 (0/1 airway, 0%), 10 (0/1 airway, 0%), 11 (0/1 airway, 0%), 12 (0/1 airway, 0%) and 13 (0/1 airway, 0%) proximal of the terminal bronchioles, no lesions were observed. Strikingly, 37 Lambert's channels were observed in this scan, which were all located more distal to the airway obstruction. Such channels were not observed in any of our control lungs. Furthermore, Lambert's channels were also found in 5 other investigated BOS lungs using a micro-CT based approach.

Conclusion: This is the first quantitative estimation of both the number of airway lesions within BOS affected lungs as well as the presence and number of Lambert's channels. This may be an important step to further investigate and emphasize the clinical relevance of collateral ventilation in BOS.

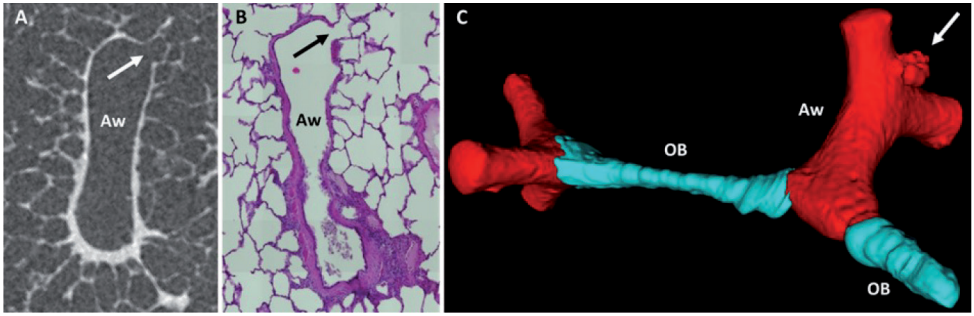

Figure 1. Comparison micro-CT image (A) with hematoxylin and eosin (H&E) stained histological section (B) of a bronchiole (Aw) in lung tissue of a patient with BOS. Arrow indicating Lambert's channel. (C) Segmentation airways BOS patient. Red indicating healthy airways, blue indicating obstructed airways (OB) and arrow indicating Lambert's channel.

IMPROVEMENT IN QUALITY OF LIFE AFTER LUNG TRANSPLANTATION AMONG PATIENTS WITH AND WITHOUT BASELINE LUNG ALLOGRAFT DYSFUNCTION

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Background: One of the key aims of lung transplantation is to improve quality of life in patients with debilitating respiratory illness. Patients with Baseline Lung Allograft Dysfunction (BLAD) fail to achieve a "normal" post-transplant lung function and have shorter survival, and may also fail to receive a significant benefit in health-related quality of life (HRQOL).

Aims: To compare the pre-and post-transplant HRQOL scores between BLAD and non-BLAD patients.

Methods: This retrospective analysis included adult patients undergoing lung transplantation at Foch Hospital between 1994 and 2022, who survived at least 1 year post-transplant and completed a HRQOL questionnaire before and after transplantation. HRQOL was measured using the Nottingham Health Profile (NHP) and the Perceived Quality of Life Scale (PQOL). The NHP poses a series of yes/no questions across 6 "packages" (pain, emotion, mobility, sleep, energy and social isolation), with higher scores indicating increased distress. The PQOL asks the patient to rate their satisfaction with 11 different aspects of their life from 0 to 100. The average of these responses is the overall PQOL score, with higher scores indicating better QOL. Pre-transplant scores for each patient were taken from the last questionnaire completed before transplant. Post-transplant scores were taken from the questionnaire completed closest to the 18-month timepoint, within a maximum window of 6-24 months post-transplant.

Patients were classified as BLAD if the maximum post-transplant FEV1 did not exceed 80% predicted.

The scores for each NHP package, and the PQOL score, were compared before and after transplant using a paired Wilcoxon-signed rank test across the entire cohort. The absolute change in each score following transplantation was then compared between the BLAD and non-BLAD group using the Mann-Witney test.

Results: The cohort included 296 patients, of whom 91 (31%) had BLAD.

For the cohort as a whole, the median PQOL score improved from 65.45 to 80.00 ($p<0.0001$). Median scores for pain, emotion, mobility, energy and social functioning all fell to zero from 11.4, 10.57, 34.95, 65.52 and 18.59 respectively ($p < 0.0001$ for all comparisons), and the score for sleep fell from 20.36 to 16.5 ($p=0.018$).

Pre-transplant, the BLAD group had higher median scores for emotion, mobility, sleep and energy, and a lower PQOL score, but none of the differences were statistically significant. Post-transplant, the median scores for all NHP packages except sleep fell to zero in both groups. The mean post-transplant score for mobility was significantly higher in the BLAD group (14.21±19.72 vs 7.06±15.03, $p=0.001$). The median absolute improvement post-transplant did not differ between the BLAD and non-BLAD group for any of the NHP packages or the PQOL score.

Conclusion: Quality of life improves after transplantation across all tested domains, regardless of whether patients achieve an "optimal" lung function outcome.

COMPARISON BETWEEN STANDARD-RELEASE AND EXTENDED-RELEASE FORMULATIONS OF TACROLIMUS IN LUNG TRANSPLANTATION

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Purpose of the study:Tacrolimus is considered the cornerstone of immunosuppression in solid organ transplantation. Two oral formulations of tacrolimus are available in Switzerland: a twice-daily administered immediate-release (IR-TAC) and a once-daily extended-release (XL-TAC). The safety and efficacy of these formulations has not been adequately compared in lung transplantation (LT).

Methods: We retrospectively assessed adult LT recipients (2008-2022, Lausanne University Hospital), who underwent conversion from IR-TAC to XL-TAC. Treatment safety and efficacy were evaluated by analysing the changes over time, following conversion from IR-TAC to XL-TAC, in the slope of the forced expiratory volume in 1 second (FEV1) and estimated glomerular filtration rate (eGFR). Tacrolimus trough level stability was assessed by comparing the percentage of on-target concentrations before and after conversion, using a random effects logistic regression model.

Results: Sixty-two patients (females n=31, 50%) were included in the study. The conversion took place 759 (SD 812) days after LT. We observed a statistically significant decrease in the slope of FEV1 (p=0.0061) following conversion. However, this decrease in FEV1 cannot be directly attributed to the conversion, as it is consistent with the usual course of lung function after LT (initial peak during the first year followed by a gradual decline, often due to chronic lung allograft dysfunction). The introduction of XL-TAC was associated with a decrease of the rate of decline of eGFR (p=0.0105). Tacrolimus trough levels were on-target in 38% of patients while on IR-TAC and 40% on XL-TAC (p=0.392).

Conclusion: The conversion of IR-TAC to XL-TAC was associated with a decrease of nephrotoxicity but did not result in an increase of on-target tacrolimus trough levels. The observed decline in lung function, albeit significant, likely corresponds to the natural course of graft function after LT. Further prospective studies are required in order to investigate the impact of XL-TAC on lung function and graft survival.

HISTOLOGICAL RECLASSIFICATION AFTER TRANSBRONCHIAL CRYOBIOPSY IN LUNG TRANSPLANTATION: ANALYSIS OF 18 CONSECUTIVE PROCEDURES

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Introduction: After lung transplantation, transbronchial biopsy (TBB) is currently the standard method for obtaining a histological sample during bronchoscopy. Several studies have shown that transbronchial cryobiopsy (TBC) provide higher-quality histology, with a similar safety profile. However, these studies are scarce, and the clinical impact of using TBC remains poorly defined. This study aims to specify the diagnostic contribution and clinical impact of TBC compared to TBB.

Methods: TBB and TBC were performed concurrently during bronchoscopies conducted between June 2023 and April 2024 as part of assessments carried out during the first-year post-lung transplan-tation rehabilitation. Biopsies were assessed according to ISHLT criteria.

Histological characteristics of specimens obtained using both techniques were compared, includ-ing counts of alveoli and bronchioles. Diagnostic reclassification resulting from TCB examina-tions, reclassifications leading to therapeutic modifications, bleeding, its severity, and pneumo-thorax and need for drainage were recorded.

Quantitative data are presented as means ± standard deviation (SD). Categorical variables are expressed as frequencies (n) and percentages (%). Mean comparisons are conducted using a Wilcoxon-Mann-Whitney test.

Results: A total of 18 patients were included, with 18 TBC and 18 TBB performed during 18 procedures.

Despite a lower mean number of biopsies per procedure for TCB (3.89 +/- 0.32) compared to TBB (4.99 +/- 1.21) ($p<0.05$), the mean number of alveoli ($p<0.05$) and bronchioles ($p<0.05$) was higher (248 +/- 116 and 1.83 +/- 1.79) in TCB specimens compared to TBB specimens (79 (SD +/- 70) and 0.44 (SD +/- 0.70)).

Among the 13 (72.2%) cases with identical histopathology in both TBB and TBC, 11 (61.1%) cases exhibited normal histology, one (5.6%) case displayed organizing pneumonia (OP), and one (5.6%) case displayed acute bronchiolitis.

TBC resulted in the reclassification of 5 (27.8%) diagnoses: one case of grade 1 acute cellular rejection (ACR) was identified in 1 (5.6%) TBB case, reclassified as ACR2 on TBC; one non-contributory biopsy was detected in 1 (5.6%) TBB case, reclassified as normal histology on TBC; one case (5.6%) of normal histology on TBB was reclassified as OP on TBC, and 2 cases of normal histology (11%) were reclassified as granulomas on TBC.

In total, 3 (17%) cases underwent modification of therapeutic management based on TBC re-sults. Among the side effects, 6 (33%) cases of bleeding were observed in both groups, without severe bleeding, and 4 (22%) cases of pneumothorax without the need for drainage.

Conclusions: With superior histological quality compared to TBB and an acceptable profile of side effects, TBC led to reclassification in 27.8% of cases, resulting in a modification of management in 17% of cases. Large prospective studies should better define the role of TBC after lung trans-plantation.

TEMPERATURE DYNAMICS OF DONOR LUNGS FROM PROCUREMENT TO REPERFUSION: STATIC ICE VERSUS CONTROLLED HYPOTHERMIC STORAGE

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Background: Ischemia-reperfusion injury (IRI) remains an important challenge in lung transplantation (LTx). The ischemic period can be divided into three phases: lungs are cooled during procurement re-ducing metabolic demand, cold-preserved, and rewarmed during implantation. During each phase, temperature fluctuations influence metabolic processes and cellular damage, exacerbating IRI. Despite its crucial impact on severity of IRI in LTx, actual organ temperature dynamics have not been studied. Therefore, we aim to characterize donor lung temperature dynamics in clinical LTx for both static ice storage (SIS) and controlled hypothermic storage (CHS).

Methodology: From December 2022 to January 2024, we included 35 SIS and 19 CHS double-LTx cases at a single-center. Lungs were split at the donor center and preserved individually, resulting in 70 SIS lungs on ice and 38 CHS lungs in LUNGguard.

Surface temperature (surfaceT°) was measured with a thermography camera before pulmople-gia, after pneumonectomy, before packing, after unpacking, and at 10-minute intervals during implantation. Preservation temperature (preservationT°) was measured for 6 SIS and 6 CHS lungs using a Bluetooth thermometer (Tempodisc) positioned along the left lung. Core tempera-ture (coreT°) was measured using a flexible probe positioned in the lower lobe bronchus imme-diately after unpacking and at 10-minute intervals during implantation. LUNGguard provided continuous device-monitored preservationT° in CHS cases.

A Spearman matrix correlation was performed on 36 CHS lungs to investigate associations be-tween average and end-preservationT° measured by the LUNGguard versus surfaceT° and co-reT° after unpacking. Data are reported as median (Q1-Q3).

Results: Regarding SIS (Figure 1A), median (Q1-Q3) surfaceT° was 30(29-33)°C before pulmoplegia, 18(15-19)°C after pneumonectomy, 8.4(6.9-10)°C before packing. After 3hrs SIS, preserva-tionT° was 0.4(0-1)°C. After unpacking, surfaceT° was 1.3(0.3-2.7)°C, coreT° was 1.45(0.7-2.1)°C. Thirty mins after implantation, surfaceT° was 25(23-28)°C, coreT° was 21(19-25)°C. Sixty mins after implantation, surfaceT° reached 27(26-29)°C, coreT° was 29(26-30)°C. Medi-an pulmoplegia-pneumonectomy and pneumonectomy-packing durations were 26 and 35mins. SIS duration was 264mins.

Regarding CHS (Figure 1B), surfaceT° was 31(28-33)°C before pulmoplegia, 18(15-19)°C af-ter pneumonectomy, 9.3(8.2-13)°C before packing. PreservationT° after 3hrs CHS was 7.6(6.4-8.8)°C using Tempodisc, 7.1(5.8-9.2)°C using LUNGguard. After unpacking, surfaceT° was 7.7(6.3-9.3)°C, coreT° was 7.2(6.5-7.7)°C. Thirty mins after implantation, surfaceT° was 26(25-28)°C, coreT° was 23(21-27)°C. Sixty mins after implantation, surfaceT° was 27(26-

28)°C, coreT° was 29(27-30)°C. Median pulmoplegia-pneumonectomy and pneumonectomy-packing durations were 28 and 44mins. CHS duration was 750mins.

The Spearman correlation analysis revealed the highest positive correlation between average LUNGguard device preservationT° and measured lung coreT° after preservation (r=0.70, P<0.0001).

Conclusion: We characterized temperature dynamics of lungs in clinical LTx from procurement to reperfu-sion. We observed rapid temperature decrease with pulmoplegia, a potential risk of freezing in-jury with SIS, and good correlation between average LUNGguard preservationT° and coreT°. After SIS and CHS conditions, lungs quickly rewarm during implantation. Our clinical observa-tions advocate the importance of measuring actual organ temperature in the new era of CHS.

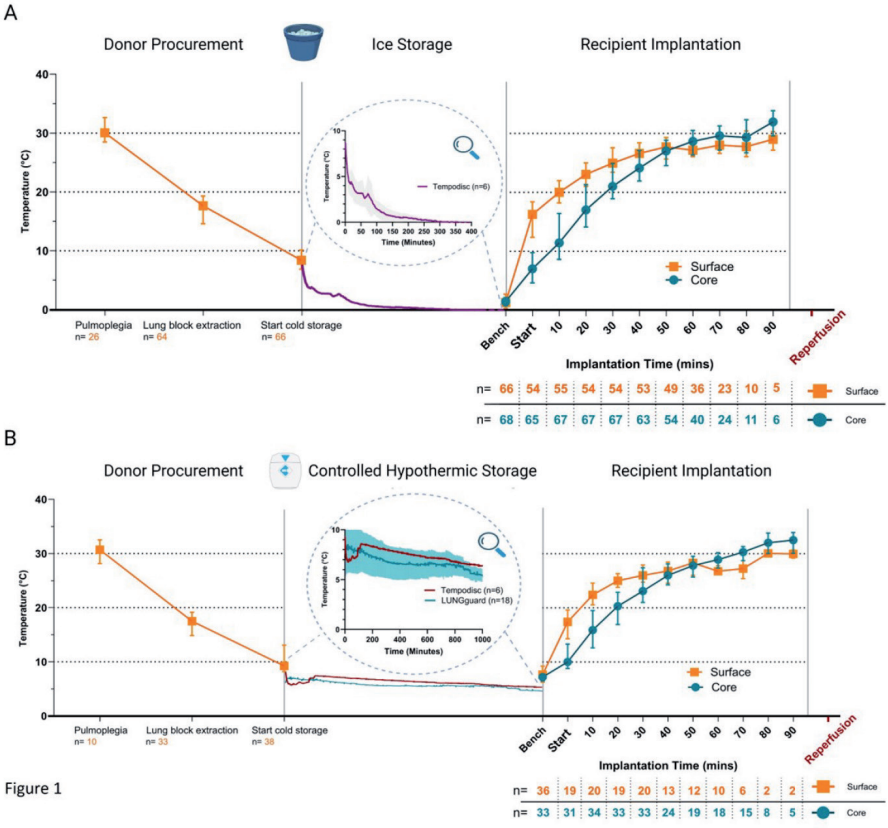

Figure 1

TACROLIMUS INTOXICATION IN LUNG TRANSPLANT RECIPIENTS

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Purpose of the Study: The aim of this retrospective study was to assess the impact of tacrolimus overdose episodes on renal function and other medical complications in lung transplant recipients.

Methods: A retrospective analysis of lung transplant recipients at a medium volume lung transplant center from January 2022 to January 2024. Patient data were reviewed included monitoring renal function parameters such as creatinine levels and estimated glomerular filtration rate (eGFR), assessing the occurrence of acute kidney injury (AKI) and chronic kidney disease (CKD), and potassium and C-reactive protein levels. Additionally, symptoms indicative of tacrolimus toxici-ty, including neurological and gastrointestinal manifestations and medication were documented. Measured drug levels of >15 µmol/L were considered to be caused by tacrolimus overdosing, drug levels >25 were considered as intoxications.

Results: 61 lung transplant recipients with documented overdosing were included in the analysis, more males (39; 63.9%) than females (22), mean age 58 years (22-73). In the study period 70 trans-plantations were performed and additionally 220 patients were in follow-up.

Tacrolimus overdose occurred at a mean of 81 days post-transplantation (1-459) with a mean tacrolimus level of 22 ng/ml (10-39). It took on average 11 days to normalize post-overdose (0-87).The mean creatinine level was 102 µmol/L (47-417). The eGFR at maximal tacrolimus lev-els had a mean of 72 ml/min/1.73m^2, (29-126). Chronic kidney disease was observed in 3 (4.9%) of patients. Among them, 1 patient was classified as stage KDIGO G3 and 2 as stage KDIGO G4, none in stage KDIGO G5.

AKI diagnosed in 22 (36.1%) patients. Maximal potassium levels had a mean of 4.4 mmol/L (3.1-5.6). The mean C-reactive protein level was 39 mg/L (0.6-209).

Regarding the frequency of tacrolimus overdose episodes, mild episodes occurred on average 1.9 times (0-6). Moderate episodes occurred on average 0.5 times (0-2) and severe 0.4 times, (0-4).

Posterior reversible encephalopathy syndrome (PRES) was observed in 1 patient (2%), while neurological symptoms (excluding PRES) were observed in 9.8% of patients and gastrointestinal symptoms at presentation were noted in 11.5% of patients.

Comedications included itraconazole, prescribed to 98.4% of patients, macrolide maintenance therapy for 11.5% of patients, and proton pump inhibitors for 98.4% of patients.

Conclusion: Approximately 1/5 of lung transplant recipients had an overdosed tacrolimus in the study peri-od. The impact on renal function and other complications are relevant. The findings underscore the importance of vigilant monitoring and timely intervention in managing tacrolimus therapy post-transplantation. Further research is warranted to optimize tacrolimus dosing regimens and minimize the risk of overdose-related complications in this vulnerable patient population.

RECOVERY OF RIGHT VENTRICULAR FUNCTION ASSESSED BY MRI IN LUNG TRANSPLANTATION FOR PULMONARY HYPERTENSION: ROLE OF PULMONARY HYPERTENSION ETIOLOGIES AND IMPACT ON POST-TRANSPLANTATION OUTCOME

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Objective: Double lung transplantation is a validated option in the management of severe pul-monary hypertension (PH). This option provides good outcome even at the stage of advanced right heart failure, mainly due to the potential for recovery and reverse remodeling of the right ventricle. However, different etiologies of PH may impact the right ventricle recovery capacity. In this study, we compared the recovery of the right ventricle evaluated by cardiac magnetic resonance imaging (MRI) and the clinical evolution post-transplantation of five groups of pa-tients, respectively affected by idiopathic pulmonary arterial hypertension (IPAH), heritable PAH, PAH associated with systemic sclerosis, group 3 PH, and group 5 PH.

Materials and Methods: We conducted a comparative, monocentric, retrospective study, in-cluding n = 38 patients who underwent double lung transplantation between 09/19/2018 and 10/08/2022 : 12 patients with IPAH, 11 patients with heritable PAH, 7 patients with PAH asso-ciated with systemic sclerosis, 4 patients with group 3 PH, and 4 patients with group 5 PH. The primary outcome measure was the change in indexed right ventricular end-systolic volume (RVESVi) between pre- and post-transplantation MRI. The results are described by their median and interquartile range (IQR).

Results: The mean time to post-transplantation MRI was 9.7 months. The median change in RVESVi for the entire population was 56 % [IQR 42 ; 74], and was 49 % [IQR 40 ; 58] in the IPAH group, 61 % [IQR 46 ; 77] in the heritable PAH group, 81 % [IQR 50 ; 82] in the sys-temic sclerosis group, 55 % in the group 3 PH, and 40 % [IQR 11 ; 68] in the group 5 PH. The difference between groups was not significant (p = 0.66). The occurrence of primary graft dys-function of grade III at 72 hours was associated with a less significant decrease in RVESVi (p = 0,03). One-year survival for the entire population was 79 %, and was respectively 83 %, 73 %, 57 % in the IPAH, heritable, systemic sclerosis groups, and 100 % in the remaining 2 groups, and was not impacted by the degree of decrease in RVESVi (p = 0,91).

Conclusion: Right ventricular recovery after double lung transplantation was remarkable, with RVESVi halved. The etiology of PH did not have a significant impact on the extent of RVESVi decrease, nor on the evolution of other MRI and echocardiographic parameters, nor on survival. We hypothesize that the group of patients with systemic sclerosis may exhibit greater RVESVi recovery, contrasting with a poorer one-year survival, although these results were not statistical-ly significant. Further studies with larger sample sizes will be necessary to verify this hypothesis.

COMPARING PATIENT AND CLINICIAN PERSPECTIVES ON GOALS OF DIFFERENT DONOR LUNG ALLOCATION POLICIES

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Background: Lung allocation policies must adhere to a range of ethical principles and aim to achieve multiple (often conflicting) goals. The lung allocation score (LAS) allows lung transplant candidates to be prioritised according to a weighted allocation score, with greater scores corresponding to candidates most likely to benefit from transplant (i.e., survive longer compared to remaining on the waiting list, also referred to as "net benefit"). The score weighting strongly influences the demographics of candidates prioritised for transplant. The original implementation of the LAS used a 2:1 ratio of waiting list survival (WL) to post-transplant survival (PTX), therefore allocating according to net benefit, but trading off some of that net benefit to give greater priority to those candidates at highest risk of waiting list death.

A custom lung allocation simulation engine was developed to evaluate the impact of different allocation score weights on waiting list mortality, post-transplant survival, and net benefit on the UK lung transplant population. The goal of this research was to identify which of the simulated policies best aligned with the goals and values of stakeholders in the lung transplant clinical and patient communities.

Methods: A survey was circulated to two groups of stakeholders: transplant clinicians (surgeons, physicians, nurses etc.) and patients (actively listed candidates, lung recipients, carers etc.) Four different allocation goals were compared in a pairwise manner: reducing waiting list deaths, increasing post-transplant survival rates, increasing net benefit per recipient, and reducing waiting times. For each pair of goals, the participant had to decide which (if any) were more important, and the degree to which their selected goal was more important (moderate, strong, very strong, or extreme) than the comparator. The survey responses were then analysed using the analytic hierarchy process to determine the relative weight (i.e., importance) of each goal according to each survey participant. From these weights, it was possible to identify which simulated policies aligned most closely with each survey participant's opinion.

Results: 62 clinicians and 100 patients responded to the surveys. There was a wide spread of opinion within each group. Overall, patients gave slightly higher priority to the policy that maximises post-transplant survival (PTX): 38% of patients and 22.6% of clinicians. Clinicians assigned more weight to net benefit, resulting in the 1:2 WL:PTX policy aligning with 46.8% of clinicians and 31% of patients. Overall, the 1:2 WL:PTX aligned with the greatest number of both clinician and patient survey participants (37%).

Conclusion: The combination of simulated policy outcomes and survey results identified that for the UK lung transplant population, an allocation score that is weighted in favour of prioritising post-transplant survival would align with the greatest number of stakeholders, with either a 1:2 WL:PTX ratio or prioritising only PTX.

Acknowledgements: We would like to thank Dr Jasvir Parmar (Cardiothoracic Advisory Group Lungs Chair), Robert Burns (Cardiothoracic Advisory Group Patient Group Chair), and Rachel Johnson (NHS Blood and Transplant, Assistant Director) for their support in designing and circulating the surveys used for this research.

GENDER IN LUNG TRANSPLANTATION: DOES IT MATTER?

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Background: Gender differences has been increasingly recognized as one of the most important factors for graft health after solid organ transplantation, yet only limited data is available in the field of lung transplantation.

Methods: A retrospective review of medical records was performed on all patients (n=498) undergoing lung transplantation at our institution between 01/2018-01/2023. The impact of gender on main epidemiological and immunopathological factors were determined.

Results: One-hundred and ninety-three (38.8%) female and 305 (61.2%) male patients were transplanted in our center within the study period. There was a male dominance regarding the native lung disease in ILD (33.1% vs 20.7%) and ARDS (9.2% vs 3.6%), however we did not find any difference in COPD, CF and PAH. Retransplantation for CLAD was more frequently performed in females than in males (9.3% vs 4.6%). The mean age at the transplantation was 51.9 ± 16.7 in the female cohort, five years less than in males (56.0 ± 13.3 years).

We did not observe any difference in type of lung transplant. (double lung transplantation 93.3% vs. 93.8% or single left 4.7% vs. 2% right 2.1% vs. 4.3%). Similarly, the rate of postoperative complications including bacterial, fungal, viral infections and the need for negative pressure wound therapy (16.6% vs 18.7% p=0.55) were similar between the two study groups. There was no difference in early survival (p=0.284).

Females were presenzitised significant more often (9.3% vs 1.3%; p=0.0002), and had a positive cross match more frequently (3.6% vs. 1.0%; r=0.051). Consequently, ATG was more often part of their early immunosuppressive regime (4.7% vs. 1.3%). Despite this, no differences were noticed in the development of persistent donor specific antibodies, acute or early chronic rejections (AMR 9.8% vs 5.6%, p=0,073; ACR 16.1% vs 12.8%, p=0.306; non-HLA 3.1% vs. 2.6%p=0.749; early CLAD 18.1% vs.18.4% p=0.949). Male patients more frequent developed RAS (1.6% vs. 4.9% p=0.05), No difference was found in the TTV load (8.19 vs. 8.22 log10 c/mL) .

Conclusions: We noticed significant differences between males and females in this retrospective single-center analysis of a high-volume lung transplant center. Despite this variability, outcome was similar between the two groups.

PRIMARY GRAFT DYSFUNCTION IN LUNG TRANSPLANTATION: INFLUENCE OF INTRAOPERATIVE CIRCULATORY SUPPORT MODE AND CONSEQUENCES FOR THE RECIPIENT

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Introduction: In 2023, lung transplantation remains the only curative treatment for end-stage chronic respiratory failure. Over the past 60 years, survival rates have improved steadily. Despite this progress, they remain inferior to those of other organ transplants. In addition to chronic graft dysfunction, primary graft dysfunction (PGD) also worsens the post-transplant prognosis. Over the past 20 years, intraoperative circulatory support techniques have evolved considerably. The aim of this study was to assess the impact of the use of circulatory assistance in the event of PGD.

Method: Monocentric retrospective study of 197 bi-pulmonary transplant patients between 2012 and 2020. Patients were divided into 2 groups according to the occurrence (47 patients) or not (150 patients) of a grade 3 DPG according to the ISHLT definition.

Results: On multivariate analysis, the mode of intraoperative circulatory support did not influence the risk of DPG. Significant risk factors for the occurrence of DPG were donor smoking, donor CPT and P/F ratio, pulmonary fibrosis and intraoperative transfusion. DPG 3 increases post-operative morbidity (acute dialysis, ventilatory weaning tracheostomy, surgical site infections), in-hospital mortality and length of hospital stay. Survival curves showed a decrease in long-term survival in the DPG 3 group. The DPG 3 group also showed impaired graft function, with a drop in median FEV1 during the first 2 years post-transplant and from the 6th year post-transplant.

Conclusion: Intraoperative circulatory support does not appear to significantly influence the risk of DPG 3. In both the short and long term, DPG 3 has a negative impact on recipient morbidity and mortality and graft function.

RESULTS FROM THE FRENCH COMPASSIONATE PROGRAM OF MARIBAVIR USE FOR REFRACTORY CMV INFECTION/DISEASE.

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Background: Maribavir, a benzimidazole riboside, inhibits Cytomegalovirus (CMV) replication by inhibiting the UL97 protein kinase. Its indication is "treatment of CMV infection and/or disease that are refractory to one or more prior therapies in patients who had a hematopoietic stem cell transplant (HSCT) or solid organ transplant (SOT)". In France, patients were treated with maribavir, through a compassionate use program (CUP), from November 2021 to April 2023, prior to the granting of European marketing authorization.

Methods: The main objectives of the CUP were to describe patient characteristics, maribavir use, effectiveness, and safety data. Effectiveness was assessed by viral clearance (i.e., CMV DNA concentration below the lower limit of quantification, ie, <137 IU/mL for plasma or <411 IU/ml for whole blood). These analyses were conducted using an intention-to-treat (ITT) approach (including all treated patients), and a sensitivity analysis approach, excluding lost to follow-up and deceased patients.

Results: In total, 82 patients were treated with maribavir. Most patients had a SOT (n=71, 84.5%; mainly kidney transplants n=55, 77.5%) and 15.5% of them had a HSCT (n=13). Twenty-four (29.0%) patients with cytopenia (N=17, neutrophil <1000/mm3 or hemoglobin <8 g/dl) and/or severe renal failure (n=13, creatinine clearance ≤30 mL/min/1.73 m^2) and were included in the CUP (such patients were excluded from the SOLSTICE trial). CMV disease was observed in 31 patients (36.9%), with 67.9% of them having involvement of the gastrointestinal tract. Resistance testing was performed for 80 (95.2%) patients, of which 59 (78.7%) had identified mutations in UL97 (55.9%) and in UL54 (32.2%) gene. Median treatment duration was 8.4 weeks. Viremia clearance at week 8 was observed in 42,0% of SOT patients (N=69) and 38.5% of HSCT patients (N=13) using the ITT approach. Using the sensitivity analysis approach, viremia clearance at week 8 was achieved in 46.0% of SOT patients (N=63) and 62.5% of HSCT patients (N=8). There were no new safety signals.

Conclusions: This was the first analyses of maribavir outside the SOLSTICE pivotal trial (NCT02931539), in France. The population analyzed differed from the SOLSTICE population in that it had a higher proportion of SOT recipients, with CMV disease, more severe biological criteria and with identified antiviral resistance. Despite the more severe CUP patient profiles, the results showed coherent efficacy and safety findings with the pivotal study.

LATE NON-CATHETER-RELATED VENOUS THROMBOTIC EVENTS IN LUNG TRANSPLANT RECIPIENTS

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Background: Deep venous thrombosis (DVT) is a common complication in Lung Transplant Recipients (LTRs) despite prophylactic anticoagulation (1) and was demonstrated as being associated with lower 1-year mortality rates (2). Within our population of LTRs we found that the majority of thrombotic events occurred shortly after surgery so we suspected them to be related to the use of central venous catheter (CVC) or extracorporeal membrane oxygenation (ECMO) during ICU stay. This is the reason why with this study we are focusing on thrombotic events that occurred at least 60 days after surgery and in sites that weren't used for CVC or ECMO application.

Methods: This study is a retrospective analysis from a tertiary-care, university-affiliated referral centre based in Milan, Italy. Clinical records of all lung transplant recipients between January 2014 to August 2022 were reviewed for thrombotic events. Demographic information and preoperative patient characteristics including age, sex, indication for transplantation, use of ECMO as a bridge to transplantation or intraoperatively, immunosuppressive therapy at the time of the event and risk factors for thrombophilia (see Table) were reported. Follow-up was obtained until January 15, 2023. Thrombotic events in sites of CVC or ECMO, or occurring within 60 days from transplant were excluded.

Results: The study comprised 13 patients (see Image 1), 9 of which were men (69%). Median age was 56 (24, 67). 3 patients (23%) had a history of venous thrombosis and 2 patients (15%) had a history of pulmonary embolism, these same 2 patients were also the only ones to have risk factors for thrombophilia/coagulopathy (one of them had hyperomocysteinemia and the other had factor V Leiden). ECMO as bridge to transplantation or during surgery was necessary for 6 patients (48%). See Image 1 for other risk factors. Median time of first-time thrombotic event occurrence from transplantation was 134 days (34, 1757). Of all events in this group of patients, 7 of them (54%) were DVTs of lower extremities. We also recorded 3 cases of pulmonary embolism, 2 of them were concomitant with DVTs.

Conclusion: Lung transplantation is a pro-thrombotic condition and DVT is a relevant problem not only in the postoperative period. Approximatively 18% of LTRs of our patients with a diagnosis of thrombosis had a late event, so in a period of time in which surveillance for thrombosis is usually low, as the majority of lung transplant centers are only screening for thrombosis shortly after ICU discharge. Early detection of events occurring later in the follow-up of LTRs can be difficult. We believe is necessary to implement screening programs for the long term.

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Image 1

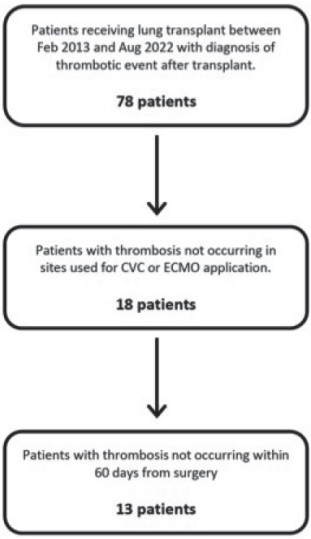

Table 1 – Risk factors for VTE

Risk factors	
EVEROLIMUS as part of maintenance immunosuppressive regimen	2 (15%)
Major orthopaedic surgery	0
Lower-extremity paralysis due to spinal cord injury	0
Fracture of the pelvis, hip or long bones	0
Multiple trauma	0
Cancer	1
Previous history of VTE/PE	2 (15%)
Age > 40 yrs	11 (85%)
Obesity	2 (15%)
Immobility	0
Oral Contraceptives or estrogen treatment	1 (8%)
Family history of VTE	2 (15%)
Physical inactivity	1 (8%)
Genetic blood conditions that affect clotting	2 (15%)

USE OF DUPILUMAB IN ASTHMA RELAPSE AFTER LUNG TRANSPLANT

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Background: Dupilumab is a fully human monoclonal antibody against the IL4 receptor alpha subunit and blocks the action of both IL4 and IL13. It has shown great potential in the treatment of severe eosinophilic asthma1, as well as in other conditions such as nasal polyposis. However, its use in lung transplantation (LuTx) has not been described yet. We present the use of dupilumab in a LuTx recipient, who suffered an asthma relapse shortly after surgery.

Case Report: A 37-year-old man underwent bilateral LuTx in April 2023 for sarcoidosis.

His past medical history included obesity/overweight and severe asthma being successfully treated with dupilumab; this biological drug was discontinued after transplant surgery.

After discharge, in May 2023, he started complaining of progressive dyspnoea on exertion, which then complicated with cough, sputum and a significant FEV1 decrease; no fever was reported. After an initial course of oral antibiotics and steroid taper on, with subsequent temporary benefit, on May 29th he was hospitalized because of acute respiratory failure; he was diagnosed with massive embolism with right upper pulmonary vein obstruction and anticoagulant therapy was promptly initiated.

However, despite initial improvement, his gas exchange suddenly started deteriorating again, with severe wheezing occurring: steroid dosage was increased and he was adapted to non-invasive ventilation. Several investigations were performed and after excluding other underlying clinical conditions (especially rejectionand/or infection), we concluded for high suspicion of asthma flare-up. Therefore, based on the benefit-risk assessment, we restarted the subcutaneous administration of dupilumab (300 mg once every two weeks after an initial loading dose of 600 mg) in June 2023.

After discharge, we noticed a progressive functional recovery, with normal gas exchange on roomair both at rest and on exertion; therapy was well-tolerated and no side effects or other respiratory exacerbations were reported.

Conclusions: Although dupilumab is considered to be both safe and non-immunosuppressive, given its immunomodulatory nature, there might be concerns when it is used for immunosuppressed patients. To our knowledge, our case is the first to report the use of dupilumab in the treatment of an asthma relapse in a LuTx recipient. Further studies are needed to assess the efficacy and the safety of biological treatments in these patients.

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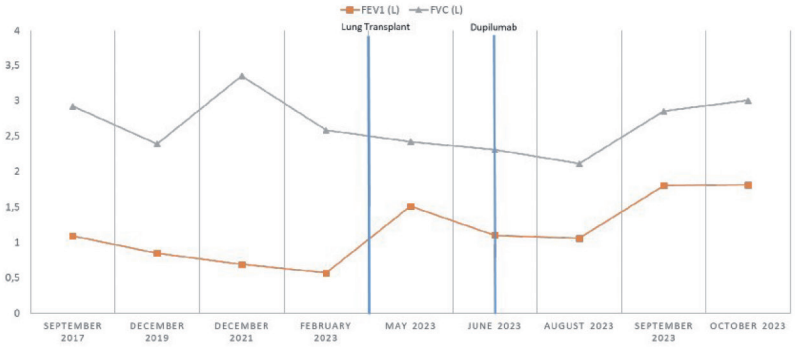
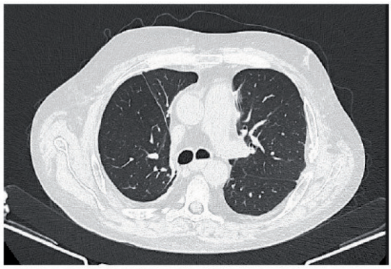
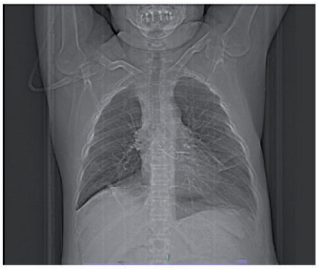


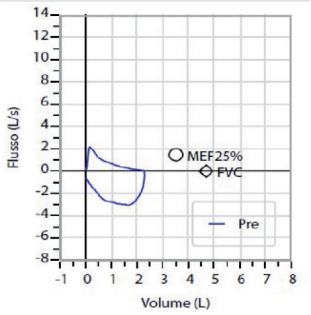
Graphic: forced expiratory volume in one second (FEV1) and forced vital capacity (FVC) at pre- and post-transplant standard follow-up visits, and during hospital admissions



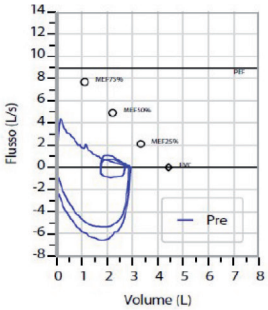


CT scans during hospital admission

PFR- June 2023



PFR – October 2023



SYSTEMATIC REVIEW & META-ANALYSIS: PRE-LUNG TRANSPLANTATION BODY COMPOSITION AND POST-LUNG TRANSPLANTATION OUTCOMES

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Purpose: Lung transplantation (LTx) is a life-saving intervention for patients with end-stage pulmonary disease. Patients referred for LTx undergo evaluation of their medical and physical suitability. The impact of pre-transplantation body composition on post-transplant outcomes is increasingly recognized. Current guidelines for recipient selection only consider abnormal BMI and low serum albumin as increased risk. Guidance regarding other body composition measures is lacking.

Studies have indicated that not just the quantity, but also body fat distribution and proportion of lean muscle mass can influence short and long-term outcomes in different solid organ transplantation. Therefore, this study aimed to systematically assess the relationships of various body composition parameters before LTx with outcomes post-lung transplantation, including hospital and ICU length of stay, duration of mechanical ventilation, and short-term and long-term mortality.

Method: A systematic literature search was performed in PubMed, Embase, MEDLINE, Web of Science, Cochrane Library, and Google Scholar for articles until the 22nd of April 2024. We included studies on LTx recipients (age > 18 years) providing an association between pre-transplant body composition parameters and post-transplant outcomes. A meta-analysis was performed on the articles assessing the relationship between BMI classification and all-cause mortality.

Results: 40 articles met the inclusion criteria, of which six articles were included in the meta-analyses. In the multivariate analysis, being underweight was significantly associated with increased all-cause mortality (pooled HR of 1.35 (95% CI, 1.10-1.66, I2=0%, p-value < 0.001). Overweight and obesity were not significantly associated with mortality (pooled HR of 1.06 (95% CI, 0.94-1.19, I2=0.01%, 1.09 (95% CI, 0.63-1.88, I2=70.1%), respectively). Other studies reported that a favorable change in BMI, for example from obesity to overweight, or underweight to normal weight, was more predictive for mortality than baseline BMI. Low albumin was associated with post-operative parameters and was stated as a more sensitive marker of malnutrition because BMI changes more slowly.

Muscle quality and quantity were assessed via CT imaging, where muscle quality was measured by average muscle attenuation or density, and muscle quantity by cross-sectional area. Multiple studies showed that quality and quantity of muscle were associated with short-term post-transplant outcomes and survival.

Conclusion: Various body composition parameters are associated with post-transplant outcomes. Due to the considerable heterogeneity among the studies and the absence of comparative analyses across different body composition metrics, no conclusions can be drawn regarding which measures provide the best yield. Body composition measured by cross-sectional area and density on CT scans is a promising objective measurement. For future studies, we recommend focusing on mutual comparison between body composition parameters and outcomes to support clinical recommendations in future guideline development.

PLASMAPHERESIS BEFORE LUNG TRANSPLANTATION IS ASSOCIATED WITH AN INCREASE IN TISSUE FACTOR ACTIVITY

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Background: Plasma exchange (PE) can be performed prior to organ transplantation in order to reduce anti-HLA antibodies. PE is usually associated with a depletion in fibrinogen, coagulation factors, and platelets, particularly if albumin is used as a fluid replacement leading to bleeding complications. The use of plasma instead of albumin enables compensation for the loss of coagulation factors. Previous studies have revealed that the amount of thrombin generated is not significantly affected in plasma from patients after PE replaced with a mixture of plasma and albumin, suggesting that the hemostatic balance is relatively preserved.

Aims: To assess the impact of PE replaced with fresh frozen plasma (FFP) just before lung transplantation (LT) on hemostasis by measuring tissue factor activity (TFA), procoagulant phospholipids (PPL) and thrombin generation.

Methods: This is a retrospective study conducted between January 2020 and December 2021, in which 49 lung transplanted patients were enrolled. PE replaced with FFP was performed in 23 (47%) patients prior to transplantation. Blood samples were collected at several time points (pre-transplantation after PE, post-transplantation, day 1 and day 2). We measured TF-dependent procoagulant activity of the microparticles using the CY-QUANT MV-TF activity kit (BioCytex from Diagnostica Stago France). PPL were also measured using the STA-Procoag-PPL kit (Diagnostica Stago). Thrombin generation (TG) was performed on CAT analyzer (Diagnostica Stago).

Results: TFA was significantly increased preoperatively in patients with PE (11.5 [3.5-15.5] fM vs 3.7 [2.5-9.5] fM, p=0.009) whereas procoagulant PPL tend to increase in patients with PE (39.4 [34.6-42.2] sec vs 51.3 [36.7-58.2] sec, p=0.094) compared to those without PE. Fibrinogen was slightly lower in patients with PE than those without PE (3.39 [2.84-3.93] g/L vs 3.84 [3.45-4.87] g/L, p=0.013) but remained within the normal range, whereas prothrombin time and platelet counts were similar in both groups. The day after transplantation, TFA was significantly higher in all patients compared to preoperatively (21 [13-38] fM vs 9 [3-14] fM, p=0.0007) without a difference between the PE and non-PE groups. These results are associated with a shortened lag time in TG in patients with PE compared to those without PE (3.5 [3.0-4.1] min vs 4.1 [3.7-4.8] min, p=0.027). These results are consistent with a procoagulant phenotype. Clinically, number of patients who received more than 3 blood products was similar in PE and non-PE patients (Fisher's exact test, p=0.08 and p=0.76 for red blood cells and FFP, respectively). There was no difference in the occurrence of deep vein thrombosis within 15 days post-surgery between both groups (p=0.75).

Conclusion: Preoperative PE in LT is associated with an unusual procoagulant profile, but it is not associated with an elevated risk of thrombosis or a decrease need for blood products. Further investigation should be conducted to confirm these preliminary data.

ANALYTICAL AND CLINICAL VALIDATION OF THE ONE LAMBDA™ DEVYSER ACCEPT cfDNA KIT

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Our team has published (1) that %dd-cfDNA can identify patients free of early lung transplantation (LTx) events (acute rejection (AR), infection), 30 days after LTx. Our biopsy decision algorithm for suspected AR is based on a pre-analytical and analytical process defined by our laboratory. However, it is known that different pre-analytical (extraction) or analytical processes, have a major influence on the dd-cfDNA interpretation. The aim of this study is to check the performance of the One Lambda™ Devyser Accept cfDNA kit, and to compare the results with our gold-standard (AlloSeq cfDNA-CareDX®). 6 dd-cfDNA control, 5 artificial dd-cfDNA (0.5% to 10%) and 3 LTx patients (at day 0, 15, 30, 90 and 180 of LTx) were tested. Use of the One Lambda™ Devyser Accept cfDNA kit requires manual steps lasting 2:10, such as preparation for two PCR reactions and purification on beads (equipment/incubation time of 3:40). Two libraries are prepared, one for screening and the other for monitoring, then loaded onto the sequencer (Miseq, micro 300 v2, sequencing time ~16h). The artificial panel higlighted the good analytical performance of the Accept cfDNA kit. All patients points were comparable to our reference and consistent with our clinical algorithm (stable, AR or infection). The One Lambda™ Advyser Solid Organs software is user-friendly, with the option of selecting markers for %dd-cfDNA calculations. Many steps were performed manually, but few functions automate the process of importing fastq into the correct timepoint, for example. Concerning the need for pre-LTx DNA, whereas the laboratory has not systematically donor pre-LTx DNA, his availability reduced background noise. Our experience with the One Lambda™ Devyser Accept cfDNA kit validated its analytical performance and comparability with our reference (AlloSeq cfDNA-CareDX®). Patients are classified identically in our algorithm. This method is promising, and we're going to test it on the entire cohort of LTx patients.

1. Pedini P, Coiffard B, Cherouat N, Casas S, Fina F, Boutonnet A, Baudey JB, Aho P, Basire A, Simon S, et al. Clinical relevance of cell-free DNA quantification and qualification during the first month after lung transplantation. Front Immunol (2023) 14:1183949. doi: 10.3389/fimmu.2023.1183949

COLORECTAL CANCER AFTER LUNG TRANSPLANTATION FOR CYSTIC FIBROSIS : INCIDENCE AND RESULTS OF COLONOSCOPY SCREENING IN A SINGLE CENTER

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Purpose : Cystic fibrosis (CF) and lung transplantation (LT) are associated with an increased risk of colorectal cancer (CRC). A taskforce CF fundation recommended 5 years screening colonoscopy in CF LT recipients (CFLTR) after the age of 30 years old. We report the results of that protocol in our program.

Methods: Two step retrospective analysis of any CFLTR followed in Foch hospital since 1990. In the first analysis, incidence of CRC was analysed in the whole cohort since 1990. In the second analysis, the results of screening incidence of CRC was analysed in the whole cohort since 1990. In the second analysis, the results of screening colonoscopy since 2018 in patients currently under follow-up are reported.

Results : Since 1990, CRC occured in 7 patients out of 509 CFLTR . Prevalence is 1.4% of the CFLTR and incidence is 1.87 per 1000 patients-years) ; 3 patients were<40 years old at diagnosis and 3 patients died due to CRC. Since 2018, among 362 CFLTR under follow up, screening colonoscopy was indicated in 237 and performed in 131. Boston scale was >6 in 73/101 (72%) of patients. Polypectomy was performed in 38 patients (29%). The most frequent histology was tubulous adenoma with low grade dysplasia. Polyps were located in right colon in 51%, transverse in 14% and left colon in 35%. The reason for absence of colonoscopy in the 106 remaining CFLTR was : screening not prescibed in 29, patient refusal in 3, patient accepted without proceeding in 80 cases.

Conclusion : The high incidence of CRC in young patients and the high incidence of polypectomy during procedure justifies screening colonoscopy as recommended. We believe that those results could help to persuade patients and physicians to adhere this recommendation. The predominant location of the lesions in the right colon and the higher risk of inadequate colonoscopy preparation is also confirmed. As a consequence, a particular attention should be paid to an intensive preparation in the context of CF.

THE ISCHEMIA REPERFUSION INJURY AND THE LUNG METABOLISM: DEVELOPMENT OF AN EXTRA CORPOREAL LUNG PERFUSION RAT MODEL

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Purpose: Ex-vivo lung perfusion (EVLP) is a tool to evaluate and recover marginal grafts in lung transplant (LuTx). Nevertheless, EVLP is still not a reconditioning so that the ischemic damage worsens over time during perfusion. Steen solution is the gold standard in this setting, and its composition is not known precisely due to patent's protection, but high hormones concentrations in this solution may afflict negatively lung function. The lung metabolism is influenced by triiodothyronine (T3), that acts on mitochondrial function and energy production, as documented in studies on animal cardiac-ischemia models. The aim of this study was to identify, in a DCD lung rat model, the effects of Steen solution and T3 titration on IRI and mitochondrial DNA (mtDNA), release during 180 minutes of EVLP as a marker of mitochondrial damage.

Methods: 8 groups of five rats were scheduled, the harvesting and EVLP were conducted as previously described by our group. DNA was extracted and mtDNA levels were measured in frozen parenchima, plasma and in perfusate at 30, 60, 120 e 180 min. Functional parameters (EGA, vascular resistance, compliance), biomolecular markers (ATP, ROS, freeT3) and gene expression were evaluated at the same time points.

Results: As expected, mtDNA tissue levels were similar in all the groups analyzed. The free mtDNA detected in perfusate increased in a time dependent manner in ischemic group and EVLP T3 groups, as NADH and ATP (in tissue), confirming the mitochondrial dysfunction and cell damage induced by too much stress. However, this increase is more pronounced in T3 groups. This is confirmed also by functional results, as vascular resistances increase in T3 groups.

Conclusions: Our results showed the metabolic effect of Steen solution and T3 on IRI during EVLP. Time-dependent increase of mtDNA suggests that EVLP does not improve IRI and too high T3 concentration increases mitochondrial dysfunction and likely promotes inflammation, as mtDNA can act as a proinflammatory molecule. Finding the best T3 concentration should allow a better metabolic effect on mitochondria and the best reconditioning during EVLP.

SINGLE CENTER EXPERIENCE OF LUNG PRESERVATION, RECONDITIONING AND ASSESSMENT WITH THE ORGAN CARE SYSTEM

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Objectives: Ex-vivo lung perfusion has been used for more than ten years for the reconditioning and evaluation of initially rejected lungs. The technique is also validated for extending the preservation of initially accepted organs. Besides, its use is extended as a mandatory step in France for assessment of lungs retrieved from Maastricht category 3 donors. According to published series, the EVLP techniques may alleviate organ availability up to 20 % in centers used to the technique. The OCS lung system has been used in our center for more than 10 years (program starting in 2011) for all three conditions preservation, reconditioning and assessment of M3 donor lungs. In this study we aimed at presenting the outcome of patients receiving lungs following perfusion and ventilation on OCS.

Methods: Starting Jan 1st, 2011, we conducted a retrospective study of all patients at our institution receiving lungs following normothermic perfusion and ventilation on OCS whatever the initial indication for choosing the technique. From our lung transplantation database, we recorded recipients and donors' demographic characteristics, the peri-operative period of lung transplantation and clinical outcome. Occurrence of primary graft dysfunction (PGD), in-hospital clinical complications of lung transplantation, duration of mechanical ventilation and delay to ICU and in hospital discharge, 30 days and 90 days mortality were recorded as well. For long-term follow-up, overall survival as well as Chronic Lung Allograft Dysfunction (CLAD) free survival were calculated using a Kaplan-Meier curve.

Results: During the study period we performed 495 lung transplantation at our institution. Among them, a total of 30 (6%) patients received lungs following normothermic perfusion and ventilation on OCS lung. Median age of recipients was 61 years (min 27 years-max 70 years). Donors had a mean mechanical ventilation duration of 10.3 days (DS = 22.4 days) and high PaO2/FiO2 (mean 442, DS = 89) at acceptance. Two donors (6%) were allocated from reconditioning (with PaO2/FiO2 < 200). The other donors represented M3s for 43% and preservation OCSs for 50% of cases.

The PGD grade 3 rate over the first 72 hours was 23% (7 patients). Post-operative follow-up showed mortality at D30 %(n=1) to D90 %(n=4). Only one patient had an extracorporeal membrane oxygenation after surgery. The median length of stay in intensive care unit was 7.5 days (min max), and 37 (min max) days for the overall in-hospital stay. Median survival was 6.13 years, and median CLAD-free survival was 4.16 years.

Conclusion: In our study, we make the demonstration the OCS lung system is versatile and easily adaptable for all three conditions preservation, reconditioning, and M3 donors' assessment. The outcome for our patients was consistent with published data on EVLP techniques available to date. In future analysis, we will compare OCS lung recipients to all other recipients transplanted during the same time period at our institution.

TNFALPHA-PNEUMOCYTES II UNDER HYPOXIA-HYPOTHERMIA CONDITIONS: IMPACT ON SURFACTANT SECRETION

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Purpose of the study: Post-transplant prognosis is correlated to the onset of primary graft dysfunction (PGD), resulting from ischemia-reperfusion injury. TNFalpha-activated pneumocyte II undergoes a stress-induced inflammatory, oxidative and immunological cascade, leading to pulmonary edema and subsequent PGD. The pulmonary surfactant plays a protective role in the context of lesional edema.

We are investigating whether pneumocyte II plays a role in the response to ischemia-reperfusion, independent of TNFalpha-mediated macrophage activation, in hypoxia-hypothermia.

Statements of the methods: Establishment of a TNFalpha-mediated macrophagic stimulation model in pneumocyte II. Creation of an in vitro hypoxia-hypothermia model using a bypass purge system. Stimulated and unstimulated cells were studied at 3 points in time (before/after hypoxia-hypothermia, and reoxygenation). Surfactant protein B assay by ELISA at each step.

Results: A TNFalpha concentration of 20ng/mL for 32h of incubation produces a large quantity of Surfactant protein B without altering the viability of pneumocytes II. The hypoxia-hypothermia model is validated by a difference in the partial pressure of oxygen in the medium, and the fraction of oxygen in air, before and after hypoxia. ROS production confirms molecular hypoxia. No significant difference was observed in surfactant protein B production.

Conclusion: Pneumocyte II produce TNFalpha-independent Surfactant protein B under stress, with no reduction in cell viability. If pneumocyte II does indeed exhibit autonomous protective activity, blocking the macrophage-initiated lesion pathway could be an idea of therapy for the prevention of primary graft dysfunction. Surfactant protein B could have a negative feedback effect on the macrophage, making the use of exogenous surfactant interesting.

IMPACT OF REMDESIVIR TREATMENT ON CLINICAL PROGRESSION AND LUNG FUNCTION IN LUNG TRANSPLANT RECIPIENTS WITH COVID-19

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Background: COVID-19 has emerged as a prevalent infection among lung transplant recipients (LTR) posing significant risks for adverse outcomes. While initial outcomes during the pandemic were concerning, the impact of COVID-19 therapies is still unclear. Our study aims to assess how the treatment by Remdesivir in COVID-19 LTR influences the clinical progression and lung function in a cohort of COVID-19 -LTR from France.

Methods: We conducted a retrospective cohort study, including 130 lung transplant recipients diagnosed with confirmed COVID-19 and hospitalised at Marie Lannelongue Hospital from Paris, France in the period from January 2020 to December 2023. We compared clinical outcomes, details regarding hospitalisation (duration, oxygen requirement, admission in intensive care unit), severity and and spirometry results before and 3 months after infection in patients treated with remdesivir (n=50, R group) versus control group, LTR-COVID19 infected without remdesivir treatment, (n=50, NR group).

Results: The two groups were homogenous in terms of vaccinations, and both groups presented similar rates of severe COVID19 disease. There was no significative difference in the hospitalisation length, oxygen requirement and rate of ICU admission between the two groups. There was not observed a significative decline in forced expiratory volume in 1 second of expiration (FEV1) at 3 months after infection in those treated with R versus those NR, but a significative decline in FEF25-75% was observed in NR group ($p<0.05$).

Conclusion: In our COVID-19 infection in LTR treated with R or NR results a clinically significant decline in lung function (FEF25-75%) at 3 months in those without remdesivir treatment.

THE INCREASING CONTRIBUTION OF ORGAN DONATION AFTER EUTHANASIA TO THE LUNG TRANSPLANTATION DONOR POOL IN THE NETHERLANDS

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Background: The number of organ donation after euthanasia (ODE) procedures performed in the Netherlands has grown substantially over recent years. The extent to which ODE contributes to the total pool of lung-donors, the quality, and utilization of donor lungs remains unclear. Furthermore, there is no clinical consensus on how lungs of these potential ODE donors should be assessed prior to donation. Therefore, we aimed to 1) describe the total contribution of ODE to the lung-donor pool in the Netherlands and 2) describe the assessment of potential ODE lung-donors, to gain insight and provide guidance for future clinical practice.

Methods: We collected details from all ODE procedures performed between 2012 and 2023 in the Netherlands. We assessed the number of ODE-lungs offered, accepted and transplanted. Reasons for declining lungs are described. Characteristics of declined and transplanted donor lungs were compared. In addition, assessment of donors prior to the ODE procedures and reasons for decline or acceptance was investigated.

Results: In total 1041 lung donors were offered of which 471 (45%) were from DCD donors. Within the group of DCD donors 122 (26%) were ODE lung donors. Between 2012 and 2023 the ODE lung donors comprised 12% of all lung donors and 26% of all DCD lung donors in the Netherlands. The numbers of DCD-ODE have risen from 3% in 2012, to 40% in 2023 of all DCD lung donors. The vast majority of ODE was performed after MAiD for psychiatric causes (N=40, 33%), neuro-muscular disorders (N=26, 21%) and neuro-degenerative diseases (N=22, 18%). The total proportion of donor lungs acceptable to offer for lung transplantation across all ODE donors was 88 (72%). From those lungs offered, the majority (94%) was accepted for retrieval and 89% of all offered ODE lungs were transplanted. Reasons for not accepting the offered donor lungs were most frequently smoking history and prior thoracic surgery.

Evaluation prior to donation was highly variable, with medical history and chest CT most affecting acceptance decisions.

Conclusion: In conclusion, we found that ODE lung donors make up an increasing part of the donor lung pool in the Netherlands, with high donor acceptance rates, despite highly variable lung evaluations performed prior to the ODE-lung offer. The evaluation of potential lung donors prior to ODE can be further standardized based on the current clinical experience to further increase acceptance of donor lungs. Based on the current experience with ODE lung donation a limited evaluation including at least medical history, virological evaluation and chest CT may suffice in most cases to make appropriate decisions.

HEPATITIS E AFTER LUNG TRANSPLANTATION: E FOR ENIGMA?

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Introduction: Hepatitis E (HEV) is a potentially lethal infectious complication of lung transplant recipients (LTRs) with risk of both acute fulminant liver failure and chronicity. Chronic infection is defined as a persistence of HEV RNA in serum or stool for longer than 6 months. In Europe, genotype 4 is the most prevalent. In LTRs, reduction of immunosuppression is recommended as a first step, followed by off-label ribavirin therapy. There are currently no clear guidelines on how to approach the reduction of immunosuppression, determine the dosage, and establish the length of ribavirin therapy in LTRs, especially in immunologically sensitized patients. We present a case series of 6 patients affected by HEV at our center.

Case series: 6 LTRs were tested positive at our center for HEV between 2023 and 2024.

Patient 1 was diagnosed with HEV at a critical condition while on ECMO support following alemtuzumab administration for severe rejection and passed away shortly after HEV diagnosis.

Patient 2 failed to clear HEV twice despite receiving 30 days of ribavirin with a concurrent reduction of immunosuppression. As HEV RNA remained persistently positive in serum, the patient fulfilled the diagnostic criteria for chronic HEV and currently receives ribavirin therapy without a reduction in immunosuppressive regimen.

Patients 3-5 received at least 3 months of ribavirin alongside a concurrent reduction of maintenance immunosuppression. They remain clinically stable, showing no signs of liver failure or rejection, and have achieved long-term negative HEV RNA levels in serum. Patient 3 developed grade 3 anemia following ribavirin treatment, requiring transfusions and erythropoietin therapy. Patient 4's disease course was uneventful. Patient 5 presented a rare complication, HEV encephalitis, which responded well to therapy with no long term consequences.

Patient 6 was recently diagnosed and currently receiving ribavirin therapy without a reduction in immunosuppressive regimen.

Conclusion: This case series aimed to identify current gaps in managing HEV in LTRs. In the Czech Republic, genetic typing is unavailable, which is a limiting factor for diagnosis as certain genotypes are more likely to result in chronicity. There are no clear guidelines on how to handle calcineurin-inhibitors, antimetabolites and corticosteroids in affected LTRs. Similarly, no precise guidelines exist for ribavirin indication, dosage and duration of therapy. Randomized controlled trials are required to determine an optimal therapeutic approach for HEV in LTRs.

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