Methods: Retrospective study including all stable LTx recipients at 6 months post-LTx, during period 2008-2012 at Bichat Hospital, France. Outcomes including CLAD and graft survival were correlated with the presence or absence of persistent Luminex-detected DSA (detected after 6 months post-LTx and persistent at last follow-up in stable patients or persistent within the 3 previous months of the date of CLAD onset), and of transient DSA. Multivariable Cox models were built to assess the relationship between persistent DSA and time to CLAD onset while adjusting for potential confounding factors.
Results: 85 LTx recipients were included and 550 sera analyzed. Mean follow-up was 58 (+ 14) months.
Freedom from CLAD was lower in patients with persistent DSA (n=32) compared to those with transient DSA (n=19) (28 [5-67] versus 45 [14-80] months; HR= 4.015; IC95%[1.39 ;11.6]; Log rank p=0.01), and compared to those without DSA (n=34) (28 [5-67] versus 53 [9-80] months; HR=5.42 [2.53;11.63]; Log-rank test <0.01). In addition, freedom from CLAD was similar in patients with transient DSA versus those without DSA (HR=1.31 [0.44;3.80]; Log-rank p=0.63).
Median graft survival was lower in patients with persistent DSA versus those without DSA (45 versus 60 months; HR=1,81 (IC95%[1.95 ;19.09]) p<0.01), and similar to those with transient DSA (45 versus 51 months; HR=1,59 IC95%[0.64 ; 3.97] Log rank p=0.32).
In a multivariate Cox model, persistent DSAs (and not transient DSAs) was an independent risk factor for CLAD development (HR=3.37, p=0.012).
Conclusion: Persistence of Luminex-detected DSA was an independent predictor of CLAD in this study, which indicates that posttransplant anti-HLA abs monitoring routine could be appropriate for detection of persistent DSA as a biomarker for CLAD occurrence.

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Short Term Safety and Tolerance of Mesenchymal Stem Cells (MSC) Infusion as Cell Therapy for Patients Experiencing Treatment-Refractory Moderate Chronic Lung Allograft Dysfunction (CLAD)

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Purpose: There is no published data regarding safety and tolerance of MSC infusion for cell therapy in lung transplant recipients with CLAD. We recorded clinical and functional variables to assess safety and tolerance of MSC infusion as there is no previously reported data on this population of patients.
Methods: Nine lung transplant recipients with moderate obstructive CLAD received a single infusion of allogeneic bone marrow derived MSC with volumes ranging from 1, 2 and 4 million MSC/Kg as cell therapy for CLAD. We recorded clinical and functional data prior infusion (Day-1), during infusion (Day 0) and at days 1 and 7 post MSC infusion.
Results: Seven males and 2 females (age 69+-5) who were recipients of double lung transplant (5) or single lung transplant (4), diagnosed with moderate obstructive CLAD occurring at 4.8 +- 2 years post transplant were studied. Indications for Single Lung Transplant were COPD (3) and IPF (1), Indications for DLT were IPF (2), COPD (1), Primary Ciliary Dyskinesia (1) and BOS (1 redo transplant). Average decline in FEV1 from peak after transplant was 43+-3%. None of these patients were candidates for re-transplantation and they were refractory to standard medical therapy. Clinical and functional variables before, during and after infusion of MSC are included (see table).
Conclusion: Infusion of MSC on patients with obstructive CLAD was safe and well tolerated and did not produce any acute significant change in clinical and or functional variables during infusion and at 1 and 7 days post infusion.

Functional Variables Before, During and After MSC Infusion

VARIABLE	DAY - 1	DAY 0	DAY + 1	Day + 7
FVC (L)	2.6+-1	2.58+-1	2.54+-1	2.56+-1
FEV1 (L)	1.62+-0.5	1.61+-0.5	1.60+-0.5	1.64+-0.4
$PaCO_2$ (mmHg)	39 +- 4			30 +- 4
PaO_2 (mmHg)	80+-8			81+-10
SaO_2 (%)	95+-1	94+-2	97+-1	95+-1

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Serial Parametric Response Mapping to Diagnose Bronchiolitis Obliterans Syndrome

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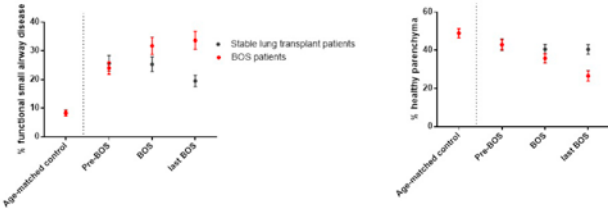
Purpose: Bronchiolitis Obliterans Syndrome (BOS) remains a major complication after lung transplantation impairing allograft function and ultimately resulting in increased morbidity and mortality. Imaging aids in diagnosing BOS with mosaic attenuation and air trapping being the major hallmarks. However quantitative analysis of CT scans is seldom performed.
Methods: We analyzed whole-lung computed tomography (CT) scans acquired at inspiration and expiration of 20 individuals with BOS, according to ISHLT guidelines. The last CT before BOS development (pre-BOS), the CT at BOS diagnosis and the last available CT were used for analysis. Parametric response mapping (PRM) identifies the percentage of voxels with normal parenchyma, functional small airway disease (fSAD), emphysema and parenchymal alterations. As control, 20 post-operative day, age, gender and native disease matched patients were used with stable pulmonary function. We compared our data with 23 age-matched non-transplant patients (Galban et al. Biol Blood Marrow Transplant. 2014;20(10):1592-8.).
Results: The pre-BOS PRM (normal pulmonary function) showed an increased % of fSAD in transplant patients compared to controls, however there was no difference between stable transplant patients and future BOS patients (p=0.43). At the moment of BOS diagnosis the % of fSAD increased compared to preBOS (p=0.05), however this increase was not different compared to post-operative day matched stable lung transplant patients (p=0.10). At the last available CT, there was a significant increase in fSAD in BOS patients compared to stable (p=0.0008). The % of healthy parenchyma, was lower in transplant recipients compared to age-matched controls. This percentage remained constant in stable lung transplant patients, while it decreased in BOS patients.
Conclusion: Functional small airway disease takes up about 25% of the transplanted lung and this increased to >30 in patients with BOS. PRM might be a useful tool to aid in the diagnosis of BOS.



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Bronchial & Alveolar Lipidomic Profile as a Marker of the Immunological and Functional Status of the Lung Allograft

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Purpose: Lung transplantation is the last option for end stage lung disease. Long term outcomes are halted by rejection and chronic lung allograft dysfunction (CLAD). To date no biological markers have been identified to investigate the immunological and functional status of the allograft. The lipidomic profiles in bronchial washing (BW) and bronchoalveolar lavage (BAL) were studied in association with the histological and functional status of the lung allograft.
Methods: Post transplantation, 597 bronchial washings (20 ml NS in proximal airways) and 190 bronchoalveolar lavages (100 ml NS in distal airways) were prospectively collected from 287 pts at surveillance bronchoscopies, and in 273 pts 546 transbronchial biopsies. BW and BAL were assayed by Liquid chromatography-mass spectrometry for 250 lipids of 25 lipid families.
Results: CLAD was diagnosed in 134/287 pts. BAL collected after CLAD onset (52/190) had reduced dipalmitoylphosphatidylcholine and

acylphosphatidylglycerol ($p<0.05$), while BW (113/597) had greater cholesteryl ester (CE), sphingomyelin (SM), dihydrosphingomyelin (dhSM), lactosylceramide (LacCer), phosphatidylcholine ether (PCe), phosphatidylethanolamine-p (PEp), phosphatidylserine, lysophosphatidylethanolamine (LPE) and lysophosphatidylethanolamine-p (LPEp) and lower ceramide (Cer) ($p<0.05$). Acute rejection was found in 51 biopsies (38 A1, 13 A2), A0 in 445 and Ax in 50. Airway inflammation was found in 59 biopsies (57 B1, 2 B2), B0 in 333 and Bx in 154. BW collected at time of acute rejection differed ($p<0.05$) for diacylglycerol (DAG), triacylglycerol, LacCer, LPE and LPEp. BAL collected at time of airway inflammation differed ($p<0.05$) for DAG, LacCer, N-Acylphosphatidylserine, SM, dhSM, monosialodihexosylganglioside, PCe, Phosphatidylinositol, Pep, whereas BW differed ($p<0.05$) for CE, Cer, LacCer, PCe, PEp.

Conclusion: The bronchial and alveolar lipidomic profile offers different signatures of the functional and immunological status of the lung allograft and varies between BW and BAL. In lungs with acute rejection, differences are found in BW lipidome. Airway inflammation shows changes in BW and BAL. CLAD had an altered profile of the lipids, in particular surfactant phospholipids in BW and BAL. A clinical use of bronchial and alveolar lipidome as a marker of the allograft's pathophysiology is speculated.

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Association of Prolonged Hospital Stay during Transplant Surgery with Long Term Outcomes among Patients with Lung Transplantation

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Purpose: Long term outcomes after lung transplantation remain lower than those after other solid organ transplantation. Whereas primary graft dysfunction at 72 hours is known to be associated with early bronchiolitis obliterans syndrome, association of other variables during the index hospitalization for transplantation with long term outcome has not been evaluated. We sought to identify potentially modifiable predictors of 5 year survival among patients undergoing transplantation in the post lung allocation score (LAS) era.

Methods: We interrogated the United Network of Organ Sharing (UNOS) database for adult patients (≥ 18 years of age) undergoing LTx between 2005 and 2011 (n=7781). Five year survival was the primary outcome measures. We sought to identify variables during the hospital admission for transplantation that were associated with 5 year survival. Variables significant on univariate analysis along with demographics, indication for lung transplant and LAS were selected as covariates for multivariate logistic regression analysis (MVLR) to determine independent predictors of 5 year survival.

Results: Mean duration of survival after transplantation was 45.6 months. On univariate analysis, age, ethnicity, body mass index, underlying diagnosis, functional status, total bilirubin, need of ventilator support, LAS at the time of transplantation and duration of hospital stay after transplantation were associated with 5 year survival. On MVLR, younger age [adjusted odds ratio (AOR), 95% confidence interval (CI): 0.993, 0.989-0.997; $p<0.001$), LAS <45 (AOR, 95% CI: 1.38, 1.22-1.55; $p<0.001$) and hospital stay < 15 days (AOR, 95% CI: 1.37, 1.23-1.52; $p<0.001$) were independent predictors of 5 year post-transplant survival.

Conclusion: Five year outcomes after lung transplantation remain low. Among the variables at time of transplantation, a prolonged hospital stay (> 2 weeks) is independently associated with worse 5 year survival. Whereas the premise of transplant urgency among patients with high LAS score is based upon an expectation of higher 'transplant benefit', an LAS score >45 at the time of transplantation is independently associated with worse 5 year survival.

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Serum miRNAs as Potential Biomarkers for the Bronchiolitis Obliterans Syndrome after Lung Transplantation

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Purpose: Lung transplantation (LTx) is the last treatment for patients suffering from end-stage lung diseases. Survival post-LTx is hampered by the development of the bronchiolitis obliterans syndrome (BOS), hallmarked by fibrotic complications, of which the clinical diagnosis is based on a surrogate marker, FEV1 decline, and is often late. Therefore, there is clinical need for novel biomarkers for BOS development at an earlier stage.

Methods: We hypothesized that selected miRNAs could serve as stratification markers for patients who do or do not develop BOS post-LTx. We analyzed serum levels of selected pro-fibrotic (miR-21, miR-155), anti-fibrotic (miR-29a) and fibrosis-unrelated (miR-103, miR-191) miRNAs in end-stage lung disease patients and during follow-up in a cohort of LTx patients.

Results: When stratified per lung disease, we observed significant elevated circulatory miRNA serum levels for all investigated miRNAs in both chronic obstructive pulmonary disease and interstitial lung disease patients compared to healthy controls. Only miR-103 was increased for cystic fibrosis patients. Levels of all miRNAs analyzed were significantly increased in the serum of BOS+ vs. BOS- patients. Additionally, levels of miR-21 and miR-103 were significantly higher in BOS+ patients prior to the clinical diagnosis of BOS. Similar observations were made for miR-155 and miR-191.

Conclusion: We demonstrate that a selected group of miRNAs is elevated in end-stage lung disease and in BOS+ patients compared to BOS- patients. This difference is present prior to the clinical diagnosis of BOS. However, further research is justified on the prognostic value of circulating miRNAs in BOS and lung conditions in general.

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Influence of Non-Donor Specific Antibodies on Chronic Lung Allograft Dysfunction -A New Risk Factor in Lung Transplantation?

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Purpose: Chronic Lung Allograft Dysfunction (CLAD) following lung transplantation (LTX) is associated with worse outcomes particularly long-term survival. The role of de novo donor human leukocyte antigen (HLA) specific antibodies (DSA) as a significant risk factor for CLAD is well known. However, it is still unclear as to whether non-specific antibodies (non-DSA) should be considered a risk factor for CLAD. We present our single-centre experience analyzing the impact of non-DSA HLA on development of graft dysfunction after LTX.

Methods: The study design was a retrospective review of the prospectively collected data. All consecutive patients developing non-DSA HLA positive antibodies after LTX performed from January 1998 till October 2015 were included in the present analysis.

Results: A total of 21 patients developed non-DSA HLA positive antibodies during the study period. Though 57% had positive HLA ranging from 1% to 90% prior to LTX, a negative donor cross-match was confirmed prior to LTX. The mean freedom from non-DSA HLA after LTX was 546±1116 days. The mean difference between the best achieved FEV1 and FEV1 at the time of detecting non-DSA HLA was 0.509±0.384 whereas lung function significantly worsened at the time of detecting non-DSA HLA ($p=0.001$, 95% CI 0.324-0.694). Nine patients (43 %) of the patient cohort developed bronchiolitis obliterans syndrome (BOS). Of them 2 patients (9.5%) had grade 3, 4 patients (19%) had grade 2 and 3 patients (14.5%) had grade 1 BOS.

Conclusion: This is the first study presenting the incidence of CLAD in non-DSA HLA positive patients after LTX. Non-DSA HLA antibodies might be associated with significantly increased risk of BOS. Further studies are warranted to support our preliminary findings and evaluate the impact of non-DSA antibodies on long-term mortality and morbidity.

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A National Survey of Practice and Perceptions Regarding Anti-Fibrotic Medication in Lung Transplant Recipients

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