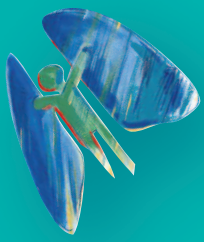
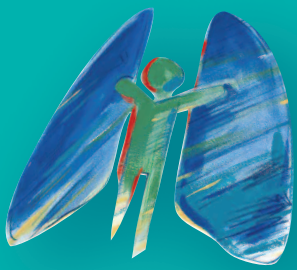


10th International Congress on LUNG TRANSPLANTATION

Paris, september 20-21, 2012



Union Internationale des Chemins de Fer
16, rue Jean Rey, PARIS 15e

Program

10th International Congress on LUNG TRANSPLANTATION

Paris, september 20-21, 2012

under the Patronage of

Fondation Franco-Américaine
du Maréchal Foch

Contents

Welcome Address

Dear Colleagues,

The 10th edition of the International Congress on Lung Transplantation will be headed by our two presidents : Edward GARRITY from Chicago and Alexander PATTERSON from Washington, eminent leaders of two bestknown teams in the field of lung transplantation.

The scientific program will include new subjects in addition to classic topics. Our hope is that the numerous lectures and debates will be fruitful and have a positive impact for the future activity of each participant.

Best regards

Dr. Marc STERN

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✱ If you are a chairperson

You must be in your session room 10 minutes prior the beginning of the session.
Make sure that all speakers observe timing.
Participants should not speak without permission.
They should first clearly state their name, institution and country.

✱ If you are a speaker

Locate your session room in due time.
Speakers must go to the preview room and turn in their slide or computer assisted presentations that will be handed out to the session room. **Laptops will not be allowed in the meeting room**.
In the session room, strictly follow instructions from the chairperson, in particular those regarding the timing of your presentation.

General Information

✱ Administrative Secretariat

Office hours:
Thursday, September 20 7:30 a.m. - 6:30 p.m.
Friday, September 21 7:30 a.m. - 4:30 p.m.

After the Congress:

VBCE - Lung Transplantation
43, rue de l'Abbé Groult
75015 Paris
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✱ Badges

For security and regulation reasons, all participants will be required to wear their badge at all time throughout the Congress.

✱ Certificate of attendance

A certificate of attendance for pre-registered participants is included in the documentation issued upon arrival. Participants who register on site should apply directly to the registration desk.

✱ Technical Exhibition

The technical exhibition is located close to the conference rooms. Please plan to visit the exhibits regularly, and especially during the breaks.

✱ Thursday, September 20

DINNER at the restaurant "Le Bouillon Racine"
3 rue Racine
75006 Paris

7:30 p.m.

Price per person: 100 €
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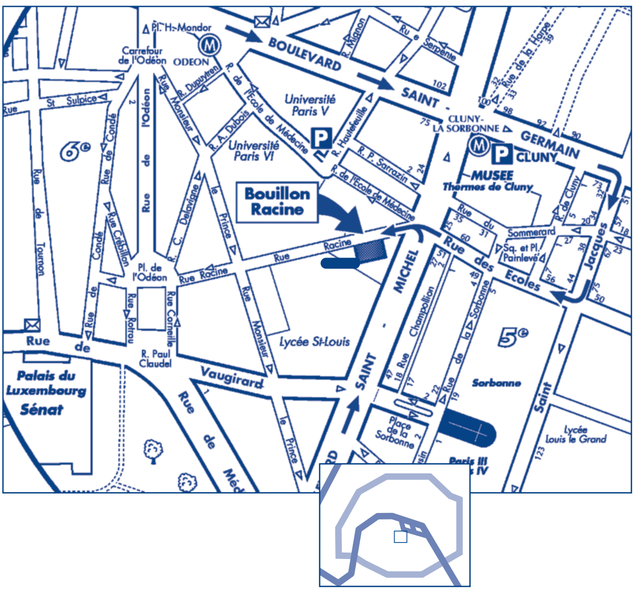

Ⓜ Métro Station: Cluny - La Sorbonne (line 10)

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The Organizing Committee wishes to extend its thanks and appreciation to the following sponsors for their contribution:

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Notes

Scientific Program

Notes

Scientific Program — Thursday 20

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8:45	ECMO p 15	
10:00	Break	
10:20	Antibody-mediated rejection p 16	Free communications p 17
12:30	Lunch	Lunch
14:00	Immunosuppression: present and future p 19	Free communications p 20
16:00		Break
16:20		Post operative management p 22
18:00		
18:30		

Scientific Program — Friday 21

	Room Louis Armand	Room 203
8:00	Ex vivo lung perfusion p 23	
10:00	Break	
10:20	Biomarkers of chronic lung dysfunction p 24	Special issues and combined lung transplantation p 25
12:30	Lunch	
13:00	Rising science in lung transplantation Symposium Sponsored by Astellas p 26	
14:30	Lung transplantation for cystic fibrosis patients p 27	
17:10		

8:30 → 8:45 **Room Louis Armand**

Opening

M. STERN (France)
President of the Organizing Committee

E. GARRITY (USA) **& A. PATTERSON** (USA)
Presidents of the Congress

8:45 → 10:00 **Room Louis Armand**

ECMO

Chairpersons: **E. Garrity** (Chicago, USA),
A. Patterson (St Louis, USA)

8:45 **ECMO as bridge to transplant: Lessons from a large experience**
G. Lang (Vienna, Austria)

9:10 **Ambulatory ECMO as bridge to transplant**
M. Cypel (Toronto, Canada)

9:35 **Veno-venous ECMO or Novalung**
M. Struber (Leipzig, Germany)

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10:20 → 12:30 **Room Louis Armand**

Antibody-mediated rejection

Chairpersons: S. Bhorade (Chicago, USA),
D. Glotz (Paris, France)

10:20 **Anti HLA antibodies: today and tomorrow techniques**
C. Suberbielle (Paris, France)

10:45 **Impact of Luminex detected pre-transplant donor specific HLA antibodies on outcome of lung transplantation** **01**
J.D Smith, H Newell, M.W Ibrahim, M Carby (Harefield, UK)

10:57 **Clinical relevance of pretransplant virtual crossmatching for donor specific anti-HLA in lung transplantation** **02**
C. Gautreau, C. Suberbielle, M. Colombat, M. Carmagnat, D. Charron, M. Stern (Paris, France)

11:10 **Pre transplantation HLA Ab desensitization: the renal experience**
C. Lefaucheur (Paris, France)

11:35 **Diagnostic markers of humoral rejection**
S. Bohrade (Chicago, USA)

12:00 **Post transplantation anti HLA antibodies monitoring**
L. Singer (Toronto, Canada)

10:20 → 12:30 **Room 203**

Free communications

Chairpersons: P. Jaksch (Vienna, Austria),
C. Picard (Suresnes, France)

10:20 **Assessment of pain in patients awaiting lung transplantation** **03**
M. Michel-Cherqui, L. Ley, B. Szekely, J.F. Dreyfus, M. Fischler
(Suresnes, France)

10:35 **The impact of smoking relapse on the outcome after lung transplantation** **04**
D. Ruttens, S.E. Verleden, R. Vos, A. Vaneylen, E. Vandermeulen, D.E. Van Raemdonck, B.M. Vanaudenaerde, G.M. Verleden
(Leuven, Belgium)

10:50 **Histologic characterization of renal lesions after thoracic transplantation** **05**
P. Housset, R. Guillemain, M. Roland , C. Amrein, A. Karras, V. Boussaud, D. Nochy, V. Pezzela, E. Thervet (Paris, France)

11:05 **Proteinuria and chronic kidney disease in lung transplant recipients** **06**
N. Partovi, S.Huang, N. Zalunardo, G. Espino, J. Swiston, J. Yee, R.D. Levy (Vancouver, Canada)

11:20 **Oral human serum immunoglobulin for Norovirus diarrhea in pulmonary transplant patients** **07**
A.C. Gairard-Dory, T. Dégot, A. Saula, S. Hirschi, A. Schuller, M. Canuet, A.C. Gerout, B. Gourieux, R. Kessler (Strasbourg, France)

11:35 **Alterations in esophageal motility post-lung transplantation** **08**
Y. Nasser, M.V. Thakrar, D. Helmersen, M. Storr, C.N. Andrews
(Calgary, Canada)

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11:50 **Determinants of quality of life after lung transplantation: Assessing the ideal candidate** **09**
F. Ihle, W. von Wulffen, N. Kneidinger, T. Meis, C. Baezner, V. Arias Herrera, G. Zimmermann, C. Schild, R. Hatz, S. Czerner, L. Frey, P. Ueberfuhr, B. Meiser, J. Behr, C. Neurohr (Munich, Germany)

12:05 **From the annoucement to the transplant** **010**
S. Odie, R. Pauthe (Suresnes, France)

12:20 **An interdisciplinary lung transplant center: a collaboration between a university hospital and a transregional center for pulmonology** **011**
C. Baum, T. Deuse, S. Meyer, C. Oelschner, M. Oldigs, C. Kugler, S. Meierling, K. Rabe, A. Costard-Jäckle, H. Reichenspurner (Hamburg, Germany)

Thursday 20

14:00 → 18:00 **Room Louis Armand**

Immunosuppression : present and future

Chairpersons: P. Corris (Nexcastle, UK),
H. Reichenspurner (Hamburg, Germany)

14:00 **Alemtuzumab induction in lung transplantation**
J. Jaksch (Vienna, Austria)

14:25 **Belatacept: the near future in lung transplantation**
S. Bohrade (Chicago, USA)

14:50 **Everolimus in lung transplant recipients**
M. Struber (Leipzig, Germany)

15:15 **Minimization of immunosuppression therapy**
E. Garrity (Chicago, USA)

15:40 **Photopheresis : role in BOS care**
R. Hachem (Saint-Louis, USA)

16:05 Break

16:20 **Evidence for excellent adherence with immunosuppressive medications in lung transplant recipients utilizing a centralized dispensing strategy** **012**
N. Partovi, E.D. Greanya, D. Strong, J. Swiston, J. Yee, R.D. Levy (Vancouver, Canada)

16:35 **Azithromycin: a crucial role in lung transplantation**
G.M. Verleden (Leuven, Belgium)

17:00 **Azithromycin: a place in BOS management**
P. Corris (Newcastle, UK)

14:00 → 16:00 **Room 203**

Free communications

Chairpersons: **A. Roux** (Paris, France),
L. Singer (Toronto, Canada)

14:00 **CMV-specific CD8+ T-cell immunity is a co-factor for acute rejection in lung transplantation** **O13**
A. Roux, G. Mourin, S. Fastenackels, J.R. Almeida, M.Candela Iglesias, E. Gostick, M. Larsen, D.A. Price, K. Sacre, D.C. Douek, B.Autran, S. de Miranda, C. Picard, D. Sauce, M. Stern, V. Appay (Paris, France)

14:15 **Association of the polymorphism of the PDCD1 gene to lung and kidney graft survival, and the implication of the CMV serological status of the donors and recipients** **O14**
C. Forconi, M. Stern, P. Gatault, R. Guillemain, A. Magnan, R. Guibon, J.M. Halimi, F. Velge-Roussel, Y. Lebranchu, C. Baron (Tours, France)

14:30 **Triple co-culture model mimicking the epithelial mesenchymal transition of bronchiolitis obliterans during lung transplantation** **O15**
Ph. Lacoste, M. Pain, Ph. Aubert, K. Botturi, A. Magnan (Nantes, France)

14:45 **Circulating NK T-like cells are increased but are functionally impaired following lung transplantation** **O16**
M.Gieschen-Krische, W.R.Critchley, A.Rowan, M.Al-Aloul, N.Yonan, J.E.Fildes (Manchester, UK)

15:00 **Role of immune repertoire in potential lung transplantation patients** **O17**
E. Lambright, H. Hoy, S. Levy, J. Loyd (Nashville, USA)

15:15 **Hepatocyte growth factor induces the polarisation of monocyte derived dendritic cells to a regulatory DC10 phenotype: Implications following lung transplantation** **O18**
M.A. Hussain, W.R. Critchley, M. Gieschen-Krische, N. O'Neill, N. Yonan, J.E. Fildes (Manchester, UK)

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15:30 **Hepatocyte growth factor levels are independent of CMV and EBV infection following lung transplantation** **O19**
D.M. Perry, M. Gieschen-Krische, A. Rowan, M. Al-Aloul, N. Yonan, J.E. Fildes (Manchester, UK)

15:45 **Prevention of ischemia-reperfusion lung injury by supplementation of the preservation solution with an oxygen carrier in porcine lung transplant model** **O20**
M. Glorion, E.Sage, F. Zal, E. Fadel, A. Chapelier (Suresnes, France)

16:20 → 18:30 **Room 203**

Post operative management

Chairpersons: A. Chapelier (Suresnes, France),
A. Patterson (St Louis, USA)

16:20 **Primary graft dysfunction: a protective effect of ex vivo lung reperfusion?**
M. Cypel (Toronto, Canada)

16:45 **Long term impact of primary graft dysfunction**
R.R. Hachem (St Louis, USA)

17:10 **Airway complications and surgical anastomotic techniques**
A. Patterson (St Louis, USA)

17:35 **Bronchoscopic management of bronchial healing complications**
F. Gonin (Suresnes, France)

18:00 **Microbleeds and posterior reversible encephalopathy promoted by tacrolimus after lung transplantation** **021**
L. Mechtouff, F. Piegay, J. Traclet, F. Philit, M. Hermier, I. Durieu, N. Nighoghossian, J.F. Mornex (Lyon, France)

8:00 → 10:00 **Room Louis Armand**

Ex vivo lung perfusion

Chairpersons: S. Keshavjee (Toronto, Canada),
D. Van Raemdonck (Leuwen, Belgium)

8:00 **Animal models and lung viability criteria**
D. Van Raemdonck (Leuwen, Belgium)

8:20 **Toronto clinical experience**
S. Keshavjee (Toronto, Canada)

8:40 **Where are we yet ? The Foch experience**
E. Sage (Suresnes, France)

9:00 **OCS lung perfusion: a clinical experience**
G. Warnecke (Hannover, Germany)

9:20 **Donor smoking is associated with increased pulmonary edema and lower rates of alveolar fluid clearance in the ex vivo donor lung** **O22**
L.B. Ware, J.W. Lee, M. Landeck, M.A. Matthay, C.S. Calfee and the California Transplant Donor Network (Nashville & San Francisco, USA)

9:35 **Ex vivo perfusion: the next horizon**
S. Keshavjee (Toronto, Canada)

10:20 → 12:30 **Room Louis Armand**

Biomarkers of chronic lung dysfunction

Chairpersons: D. Israel-Biet (Paris, France),
G. Verleden (Leuwen, Belgium)

10:20 **Lymphocytic airways inflammation: a good marker for future chronic rejection?**
G.M. Verleden (Leuwen, Belgium)

10:40 **Phenotypes of BOS: what's new**
P. Corris (Newcastle, UK)

11:00 **Role of alloimmunity-induced autoimmunity**
R. Hachem (St Louis, USA)

11:20 **Hepatocyte growth factor is not elevated in chronic rejection following lung transplantation** **O23**
D.M. Perry, M. Gieschen-Krische, C. Cowan, N. Yonan, J.E. Fildes (Manchester, UK)

11:45 **Anti HLA alloimmunisation and chronic lung dysfunction**
O. Brugière (Paris, France)

12:05 **De novo donor HLA-specific antibodies after lung transplantation are associated with development of BOS and poor patient survival** **O24**
S. Safavi, J.D. Smith, M. Carby, A. Simon (London,UK)

12:20 **First insights from the COLT study: French COhort in Lung Transplantation** **O25**
A. Tissot, K. Botturi, M. Stern, M. Reynaud-Gaubert, R. Kessler, O. Brugière, S. Mussot, F. Mornex, C. Pison, C. Dromer, R. Guillemain, M. Dahan, A. Magnan. (Nantes, France)

10:20 → 12:30 **Room 203**

Special issues and combined lung transplantation

Chairpersons: E. Sage (Suresnes, France),
G. Snell (Sydney, Australia)

10:20 **Heart-lung transplantation: it's place in 2012**
E. Fadel (Le Plessis-Robinson, France)

10:45 **Liver-lung transplantation**
V. Boussaud, O. Scatton (Paris, France)

11:15 **Langerhans pancreatic islets and lung transplantation**
L. Kessler (Strasbourg, France)

11:40 **Lung retransplantation**
A. Patterson (St Louis, USA)

12:05 **An update on DCD donor in lung transplantation**
G. Snell (Sydney, Australia)

13:00 → 14:30 **Room Louis Armand**

Rising science in lung transplantation

Symposium Sponsored by Astellas

Chairpersons: P. Corris (Newcastle, UK),
M. Stern (Suresnes, France)

Induction therapy and lung transplantation
P. Jaksch (Vienna, Austria)

Entering a new era in phenotyping chronic rejection after lung transplantation
S. Verleden (Leuven, Belgium)

Overview on BOS a disease of injury and dysregulated repair
L. Borthwick (NewCastle, UK)

Plasmapheresis: practical aspects and difficulties during lung transplantation
F. Parquin (Suresnes, France)

14:30 → 17:10 **Room Louis Armand**

Lung transplantation for cystic fibrosis patients

Chairpersons: **E. Garrity** (Chicago, USA),
L. Singer (Toronto, Canada)

14:30 **Lobar lung transplantation**
D. Mitilian (Suresnes, France)

14:50 **Size does matter: Lobar lung transplants for patients with small chest cavities**
T. Deuse (Germany)

15:10 **Cystic fibrosis, lung transplantation and waiting list in Latin America: Single centre experience** **026**
A.M. Bertolotti, R.R. Favaloro, R. Ahumada, G. Wagner, J.O. Caneva, J.M. Osses (Buenos Aires, Argentina)

15:25 **Liver disease in CF: old aspects and new findings**
S. Hillaire (Suresnes, France)

15:45 **Interest of urine crystals screening in cystic fibrosis lung transplanted patients** **027**
L. Tricot, M. Le Quintrec, M. Daudon, S. De Miranda, C. Picard, M. Delahousse, M. Stern, D. Grenet (Suresnes, France)

16:00 **Multiresistant bacterial colonisation: a challenge for lung transplantation**
E. Garrity (Chicago, USA)

16:20 **Fungal and mycobacterial pathogens: what limit to lung transplantation?**
L. Singer (Toronto, Canada)

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16:40 **Lung transplantation of cystic fibrosis patients with nontuberculous mycobacterial disease results in a rapid fall in specific immunoglobulin G antibodies** **O28**
T. Qvist, T. Pressler, L. Mared, M. Iversen, T.L. Katzenstein, N. Høiby (Copenhagen, Danemark)

16:55 **Outbreak of pulmonary tuberculosis among lung transplant recipients** **O29**
A. Sénéchal, F. Philit, G. Carret, J. Grando, J.F. Mornex (Lyon, France)

Abstracts

IMPACT OF LUMINEX DETECTED PRE-TRANSPLANT DONOR SPECIFIC HLA ANTIBODIES ON OUTCOME OF LUNG TRANSPLANTATION

J.D. Smith, H. Newell, M.W. Ibrahim, M. Carby
Tissue Typing Laboratory, Harefield Hospital, UK

Transplantation against pre-formed donor HLA specific antibodies (DSA) is associated with poor outcome. Following the introduction of sensitive Luminex based assays, numbers of sensitised patients awaiting cardiothoracic transplantation has increased. The clinical impact of Luminex detected HLA antibodies on lung transplantation is unclear. The purpose of this study was to analyse pre-transplant Luminex detected HLA antibodies, their complement-fixing ability and potential effect on lung allograft survival.

Pre-transplant serum from 425 adult lung transplant recipients performed between 1991 and 2003 were selected for analysis. All patients underwent CDC-based HLA antibody screening prior to transplantation. Retrospective screening was performed using Luminex based assays. Complement deposition on HLA coated Luminex beads was measured using a modified Luminex assay. For each DSA+ve patient, the cumulative median fluorescence intensity values (cMFI) were calculated as a measure of 'levels' of DSA.
Twenty-seven patients were transplanted against DSA and 35 patients with non-donor specific HLA antibodies (NDSA). These were matched for age, underlying disease, type and era of transplant, with 110 patients as controls for univariable and multivariable analysis of pre-transplant clinical determinants. Controls had no Luminex detectable HLA antibodies prior to transplant.

Patients transplanted with DSA had a 1 year survival of 51.9% compared to 77.8% for NDSA (n=35) and 71.8% for negative patients (n=363), p=0.029. The one year survival of patients with complement-fixing DSA was 12.5% compared to 62.5% for non-complement-fixing DSA (n=16), 75.8% for non complement-fixing NDSA (n=33) and 71.8% for negative patients (n=363), p<0.0001.
There was a significant association between antibody levels (cMFI) and survival. DSA patients with cMFI >5000 had a one year survival of 33.3% compared to 71.4% for cMFI 2-5000 and 62.5% for cMFI <2000, p=0.0046. In the 13 DSA patients who had not survived 1 year, the mean cMFI was 18935 (range 1360-66836) compared to 4037 (range 988-10443), for DSA patients surviving more than 1 year, p=0.048.
Other clinical factors found to have a significant association with survival were reason for transplant: emphysema being associated with improved survival (p=0.0086) and increasing bilirubin levels >35 being associated with poor survival (p=0.0317).

Multivariable analysis models revealed DSA to be an independent predictor of poor patient survival within 1 year (p=0.0010, HR = 3.569) as well as complement-fixing DSA (p<0.0001, HR = 11.083) and DSA with cMFI>5000 (p=0.0001, HR = 5.512).

In conclusion, pre-formed DSA are associated with poor survival within the first year after lung transplantation. Not all Luminex detected DSA should be considered a contraindication to transplantation. Risk stratification according to complement fixation or cMFI levels may increase transplantation of sensitised patients.

CLINICAL RELEVANCE OF PRETRANSPLANT VIRTUAL CROSSMATCHING FOR DONOR SPECIFIC ANTI-HLA IN LUNG TRANSPLANTATION

C. Gautreau[1], C. Suberbielle[2], M. Colombat[1], M. Carmagnat[1], D. Charron[3], M. Stern[1]
1- Service d'Immunologie et d'Histocompatibilité, AP-HP, Hôpital Saint Louis, Paris, France ;
2- Service d'Anatomopathologie Hôpital Foch, Suresnes, France ;
3 Service de Pneumologie et transplantation pulmonaire, Hôpital Foch, Suresnes, France

Purpose of the study. Acute rejection is a major risk factor for the development of chronic airflow obstruction thus limiting long-term transplant survival. The detection of donor specific anti-HLA antibodies (DSA)directed to the graft in conjunction with tissue immunostaining for Complement fixation (C4d) have provided clinical evidence that antibody-mediated rejection occurs in lung transplantation. Due to the short ischemia time allowed between organ harvest and transplantation, it is difficult to do a prospective Complement dependent cytotoxic crossmatch.and a ''virtual crossmatch''is thus performed to determine the compatibility between the donor HLA antigens and the recipient antibodies. This retrospective study aimed to assess the relevance on occurrence of acute humoral rejection (AHR) of donor specific antibodies (DSA) detected by luminex single antigen "virtual crossmatching"(VC) in pre-transplant serum samples from lung transplanted patients.

Methods. Thirty seven patients were consecutively lung transplanted between February 2008 and April 2009 in Hôpital Foch transplant unit. For each patient one serum drawn within one year before transplantation was retrospectively tested by Luminex single antigen assay (One Lambda). The mean fluorescence intensity threshold is>500. DSA anti-HLA class I and class II were identified. "Virtual crossmatch" is considered negative when no DSA is identified. Diagnosis of AHR was supported by C4d staining of lung biopsy and circulating DSA at time rejection.

Results. Pretransplant virtual crossmatch (class I and/or class II). was found positive in 16 patients (43%). An AHR episode occurred in 10 patients (27%) during the first year. 70% of AHR occurred within the first month post-transplant and one AHR at 2 months and the other AHR at 9 month post-transplant. C4d staining was performed for 8 patients exhibiting AHR and 75% of the C4d were found positive. Circulating DSA class I and/or class II were found in post-transplant in 90% of AHR. Five patients were treated by plasma exchange and IVIG. Two patients deceased from chronic rejection (CR) at 2 years post-transplant without exhibiting any previous AHR. Positive VC has a positive predictive value of 44% on AHR ($p<0.05$) and of 60% on AHR and CR ($p<0.01$). A negative VC predicts no AHR in 86% of patients.

Conclusion. This study suggests that in our clinical and laboratory experience, a positive VC predicts the occurrence of AHR. Treatment (as plasma exchange) to lower anti-HLA in pretransplant should be performed in the purpose of avoiding acute humoral rejection in presensitized patients.

ASSESSMENT OF PAIN IN PATIENTS AWAITING LUNG TRANSPLANTATION

Mireille Michel-Cherqui, MD, Léa Ley, MD, Barbara Szekely, MD, Jean-François Dreyfus, MD PhD, and Marc Fischler MD.
Department of Anesthesiology, Hôpital Foch, 40 rue Worth, 92150 Suresnes, France.mireille.cherqui.38@gmail.com

Objectives: Chronic pain is a common feature in western population and a prevalence of 19% for moderate to severe pain i.e., affecting quality of life has been recently reported in a European study. This prevalence may be higher in patients on a lung transplant waiting list due to specific medications, physical limitations and possible involvement of other organs. Moreover low preoperative levels of quality of life, pain and anxiety have been associated with decreased post transplant quality of life and survival. The goal of the study was to investigate prospectively the prevalence and characteristics of pain in patients at the time of their registration on the waiting list of lung transplantation. Consequences on quality of life and administered treatment were also studied.

Methods: From June 2008 to May 2011, when registering on the transplantation list in our institution, 143 patients underwent a 45-min interview and physical examination by a pain-qualified anesthesiologist and filled several questionnaires: 3 numeric pain scales, a french adaptation of the McGill Pain Questionnaire, the Hospital Anxiety and Depression Scale, the DN4 test and a quality of life test.

Results: One hundred and forty three presenting patients were enrolled in the study. Lung diseases included cystic fibrosis (n=73), emphysema (n=38), fibrosis (n=19) and other diseases (n=13).
Prevalence of pain was 59%. The commoner pain symptoms reported were backache, headache, joint pain and chest pain, each quoted by more than 30% of patients in the pain group. Compared to pain free patients, patients with pain were more frequently women (75% vs 25%), cystic fibrosis patients (71% vs 28%), diabetics 80% vs 20%), presenting a moderate to severe anxiety (78% vs 19%), and depression (86% vs 14%). Their quality of life, especially ability to walk and daily life activities were more altered (58% vs 8% an 68% vs 7%). Among patients with pain 39% took analgesic drugs daily, while non pharmacological approaches concerned 13% of all our patients. Among all the patients, 19% underwent regular physical therapy and reconditioning.

Conclusion: prevalence of pain in this group of patients makes it an issue of major concern. Appropriate assessment and treatment of pain and anxiety must be considered an essential component of the managment of these patients.

THE IMPACT OF SMOKING RELAPSE ON THE OUTCOME AFTER LUNG TRANSPLANTATION

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Lung transplantation (LTx) is a life saving treatment for end-stage lung diseases. A smoking free period of at least 6 months is obliged before listing for LTx. We previously reported that 17% of former smokers resume smoking after lung transplantation. The current aim is to re-evaluate the prevalence of post transplant smoking resumption and the impact on outcome after LTx with as main parameters chronic rejection and the development of (solid tissue) cancer.
All 353 LTx recipients currently in follow-up in the University Hospital Gasthuisberg Leuven, Belgium were included and evaluated for past and current smoking habits by a questionnaire and an eCO measurement with an electrochemical (Bedfont EC50-piCO-V Smokerlyzer, Bedfont Scientific, Kent, UK) sensor. An eCO >10 ppm was considered positive. The association between post-LTx smoking and (solid) tissue cancer was tested using a contingency table (GraphPad prism 4.0).

Before transplantation 229 patients (65.1%) smoked, of whom 167 had COPD (47%); 39 patients (11%) reported smoking post-LTx, of whom 35 were transplanted for COPD. There were 15 (4.2%) current smokers. eCO was increased in 30 patients of whom only 11 patients admitted active smoking.
Second-hand smoking was reported in 33% of the total population and in 87% of the active smokers (80% had a first generation family member who smoked).
In the 39 patients admitting smoking post-transplant, 13 patients suffered from chronic rejection (33% compared with 37% of the total population, p=0.78) and cancer was reported in 10 patients (27% compared with 12.5% of the total population, p=0.02), median follow-up in the group with the smokers is comparable. More specifically, solid tissue cancer was found in 8 patients (21% compared with 7% of the total population, p=0.009). The types of cancer diagnosed: lung cancer (n=4), gynaecological cancer (n=2), digestive cancer (n=2), adenocarcinoma of spinal marrow (n=1) and haematological cancer (n=1)

After LTx, 11% of the patients admit to have resumed smoking, especially the COPD patients are at increased risk. There was an increased risk for de development of solid tissue cancer but not for chronic rejection. There is a discrepancy between the eCO and the questionnaire, therefore additional measurement of urinary cotinine seems to be necessary.

HISTOLOGIC CHARACTERIZATION OF RENAL LESIONS AFTER THORACIC TRANSPLANTATION

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background/Purpose: Chronic kidney disease (CKD) is a frequent complication after thoracic (lung and/or heart) transplantation and is associated with significant morbidity and mortality. The aim of this study was to assess the clinical and histological features, and the renal outcomes in ThT recipients (ThTR).

Methods: We included retrospectively all ThTR between 2000 and 2010 who underwent renal biopsy (RB) in our institution (n=36, 78 % males). The clinical, biological and histological characteristics were analyzed.

Results: The population comprised heart (n=16), lung (n=19) and heart and lung (n=1) recipients. Mean recipient age at transplantation was 42.9±15.6 (range 14-66). Main indications for lung transplantation were mucovicidosis (n=12), bronchiectasis (n=4) and pulmonary fibrosis (3). For heart tranplant, there were congestive cardiomyopathy (n=9), congenital (n=2), valvular (n=3) and ischemic cardiopathy (n=3, including the recipient of combined heart lung). At transplantation, 6 and 7 patients were hypertensive and diabetic respectively. Mean serum creatinine (SeCr) and estimated glomerular filtration rate (eGFR) were respectively 94,5±61,9 µmol/l (25-321) and 113.2±93.4 ml/min (17-44.7) Of note, 8 presented CKD (eGFR ≤ 60 ml/min) and 6 patients a proteinuria-creatininuria ratio (PCR) ≥ 1 g/g. After transplantation, 18 patients (50 %) experienced acute renal failure, requiring dialysis in 11. During the follow up, 5 patients (14 %) experienced a progression to end-stage renal disease (ESRD), after a mean delay of 3.4±2.8 years. Patient survival was 88 %, with a mean delay of 3.2±2.7 years after transplantation (0.5-8.3).
RB was performed 3.2±2.7 years after ThT (0.19-9.4). At RB, hypertension and diabetes mellitus were present in 86 % and 39 % respectively; 29 patients were receiving calcineurine inhibitors (mostly tacrolimus, n=25) and 18 received mTOR inhibitor. Mean SeCr was 231±128 µmol/l, mean eGFR was 32.2±15.8 ml/min and 11 patients had a PCR > 1 g/g. The main histopathological finding was advanced renal fibrosis in 33 patients (35,89±20,37 % of the biopsy surface, range 10-80). The described lesions included nephrosclerosis (n=23), diabetic glomerulopathy (n=9), and focal segmental glomerulosclerosis (n=7). CNI toxicity was present in 28 patients (arteriolar hyalinosis in 20, arteriolar thrombotic microangiopathy in 20 and arteriolar C3 staining in 12). Finally, 5 patients had oxalate crystals deposits.

Conclusions: These preliminary results demonstrated that CKD is frequent before ThT and may worsen during the follow-up. Precise histological diagnosis should be made as soon as possible since fibrosis present on RB could be avoided with specific treatment of the underlying condition. In summary, we propose a better monitoring of renal biological signs (repeated measured GFR and frequent PCR assessment) to screen the ThTR who could benefit from a RB.

PROTEINURIA AND CHRONIC KIDNEY DISEASE IN LUNG TRANSPLANT RECIPIENTS

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Purpose: Lung transplant (LT) recipients are at risk for chronic kidney disease (CKD). Proteinuria is a risk factor for CKD and mortality in the general population but has not been studied in LT recipients. The purpose of this study was to determine the prevalence of, and risk factors for, CKD and proteinuria in LT recipients in British Columbia, Canada.

Methods: Retrospective study of LT recipients followed at Vancouver General Hospital as of August 1, 2011. Logistic regression to determine factors associated with CKD (estimated GFR < 60 mL/min/1.73 m2) and proteinuria (urine albumin to creatinine ratio (ACR) ≥ 3.0 mg/mmol). Those on dialysis (N=1) or with a kidney transplant (N=3) excluded. Patients were treated with a calcineurin inhibitor (cyclosporine (N=4) or tacrolimus), mycophenolate or azathioprine, and prednisone. All received sulfamethoxazole prophylaxis.

Results: There were 71 (of 91) patients with urine protein assessments. Reasons for LT included chronic obstructive lung disease (38%), pulmonary fibrosis (32%), and cystic fibrosis (20%). Median time from LT was 5.4 (2.4-10.3) years; 56% were male; mean age at LT was 50 (+/-13) years. 2 (3%) subjects had diabetes pre-transplant; 5 (7%) developed diabetes post-transplant. At most recent follow-up, CKD was present in 39 subjects (55%) (5 (13%) stage 3; 34 (87%) stage 4 CKD). 19 patients (27%) had proteinruia, with median urine ACR 4.95 (3.70-11.95) mg/mmol. Female sex (OR=6.33; CI:1.76-22.82), cardiovascular complications (OR=9.88; CI:1.94-50.48), and CMV disease (OR=3.79; CI:1.13-12.74), but not proteinuria (OR=0.80; CI:0.21-3.04), were associated with CKD. Higher systolic blood pressure (OR=1.04; CI:1.00-1.07) was associated with proteinuria, but there was no significant association with CKD (OR=1.59; CI:0.52-4.85).

Conclusions: CKD was common among LT recipients and associated with cardiovascular and CMV disease. Proteinuria was present in 27% of patients, most of which was mild (microalbuminuria). Proteinuria was associated with higher systolic blood pressure but not CKD.

ORAL HUMAN SERUM IMMUNOGLOBULIN FOR NOROVIRUS DIARRHEA IN PULMONARY TRANSPLANT PATIENTS

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Norovirus-induced diarrhea is generally a selt-limiting disease but can become prolonged and severe in transplant patients. No effective therapeutic agents arecurrently available. Oral human serum immunoglobulin (OHIG) have been previously used in patients with viral diarrhea with clinical improvement.

We performed a retrospective study to evaluate the efficacy of OHIG for Norovirus enteritisin our pulmonary transplant patients. Clinical data (age, number, duration and severity of diarrhea, others infections) and biological data (viral identification, tacrolimus level) and treatments (immunosuppressive regimen, antiinfectious drugs and oral human serum immunoglobulin) of patients who developed Norovirus related diarrhea were recorded between 2009 and 2012.

The Norovirus enteritis prevalence was 4.3% (6/140) with 6 pulmonary transplant patients who developed 8 episodes of gastroenteritis. Diarrhea developed between 18 month and 4 years after transplantation. Mean age was 58.6 years.. Norovirus ELISA test was positive in stools after first to fifth examination. One patient developed a co infection with Enterocytozoon bieneusi. Diarrhea frequency was 5 to 10 per day and duration was at least 1 week. 4 patients developed acute renal failure and 2 patients showed hyperkaliemia induced by deshydratation. Diarrhea were not modified by immunosuppression reduction. OHIG was administered at 25 mg/kg every 6 or 8 hour for 2 consecutive days. Diarrhea resolved after 2 to 3 days after treatment initiation. We observed no side effects during oral human serum immunoglobulin treatment. Diarrhea were not associated with high tacrolimus levels in our patients in contrast with a study in pediatric intestinal transplant patients. Late occurrence of viral enteritis did not seem to be related with increased immunosuppression.

This study is the first description of Norovirus diarrhea in pulmonary transplantation. OHIG shortened the resolution of diarrhea similar to results published in case reports.

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ALTERATIONS IN ESOPHAGEAL MOTILITY POST-LUNG TRANSPLANTATION

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Background/Aims: Gastroesophageal reflux (GER) and subsequent aspiration events are hypothesized to be important contributors to allograft rejection post-lung transplantation. Limited data exist on changes in GER, esophageal motility and pH-impedance after transplantation. We hypothesized that patients who had undergone lung transplantation would be predisposed to increased GER, secondary to changes in esophageal motility.

Methods: Retrospective comparative series of 31 pre-transplant patients (55% female) and 22 post-transplant patients (23% female) being evaluated for GER. Cause of lung disease was similar (Interstitial lung disease: 42% pre-transplant, 45% post-transplant. Chronic obstructive pulmonary disease: 39% pre-transplant, 23% post-transplant). 36 patients, who had no lung disease and no motility disorders (67% female), were evaluated as controls. All groups underwent esophageal manometry and 24hour pH monitoring with impedance. Data was analyzed using a 1-way ANOVA with a Dunnett's post-test.

Results: Mean age was similar between groups (Control: 47.9 years, 95% CI: 42.7-53.1; Pre: 52.7 years, 95% CI: 48.6-56.8; Post: 55.2 years, 95% CI: 50.7-59.7; p= 0.09). No difference in baseline lower esophageal pressure or residual pressure was noted between groups. There was a trend towards weaker mean distal esophageal contractions post-transplantation as well as a trend towards a decrease in the percent of peristaltic waves in patients pre-transplantation (Table). No difference in the DeMeester score or in the number of acid and non-acid reflux events were noted among groups on proton pump inhibitor (PPI) therapy. Proximal reflux events were significantly increased in patients post-lung transplantation, despite PPI therapy (Table).

	Mean distal contraction amplitude	% Peristaltic waves	Proximal reflux events
Control	90.5mmHg (95% CI: 79.1- 102.0)	93.2% (95% CI: 90.2-96.3)	21.7 (95% CI: 9.9-33.6)
Pre-transplantation	76.4mmHg (95%CI: 61.1-91.8)	78.0% (95% CI: 65.5 – 90.5)	NA
Post-transplantation	64.2mmHg (95% CI: 42.7-85.7)	81.7% (95% CI: 68.5-94.8)	47.6 (95% CI: 27.1-68.0)
P value	0.063	0.056	0.03

Conclusion: Patients post-lung transplantation have a trend towards weaker distal esophageal contractions, and increased proximal reflux events, which may predispose them to aspiration and subsequent allograft rejection. The cause of these changes is unknown, but alterations in thoracic physiology or medication effects could be hypothesized to play a role.

DETERMINANTS OF QUALITY OF LIFE AFTER LUNG TRANSPLANTATION: ASSESSING THE IDEAL CANDIDATE

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Background: Health-related quality of life (HRQOL) has increasingly been accepted as an important outcome measure for patients after lung transplantation (LTx). However, clinical and non-clinical predictors of HRQOL are still controversial. Therefore we examined clinical-, individual-, social- and physical determinants of HRQOL in lung transplant recipients (LTR).

Methods: HRQOL was measured cross-sectional in 152 consecutive LTR of our LTx follow-up program (4.5±3.2 years after LTx; 95 [63%] double LTx; 80 [53%] female; age 50±11.9 years; 28 [18%] bronchiolitis obliterans syndrome (BOS) stage ≥ 1) using the standardized global SF-36 questionnaire, the "St. Georges` Respiratory Questionnaire" (SGRQ) as well as the "Quality of Life Profile for Chronic Diseases Questionnaire" (PLC). The following variables were tested for their predictive value by non-parametric significance tests along with ANOVA and ANCOVA: gender, age, body-mass-index (BMI), time after LTx, procedure type, underlying disease, marital- and professional status and exercise capacity (6-minute walk test).

Results: There was a significant association with higher physical HRQOL scores for age < 48 years ($p<0.05$), BMI in the range of 21.0 and 25.2 kg/m2 ($p<0.05$), 6-minute walk distance × 430m ($p<0.001$), for patients with cystic fibrosis ($p<0.05$) and who go to work ($p=0.018$). Female gender played a role for superior social health ($p=0.04$) ans less respiratory symptoms ($p=0.023$), whereas double LTx was a significant predictor for both, mental and physical health ($p<0.05$). Subsequent analysis of covariance revealed only BMI ($p=0.024$), underlying disease ($p=0.01$) and exercise capacity according to 6-minute walking distance ($p<0.001$) as significant predictors for HRQOL independent of age.

Conclusion: The study results suggest that returning to or maintaining normal BMI and improving exercise capacity seem to be important therapeutic approaches to further enhance HRQOL after LTx. Follow-up data and intervention-studies are necessary to promote the sustainability of these findings.

FROM THE ANNOUCEMENT TO THE TRANSPLANT

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Depuis l'annonce de la nécessité prochaine d'une greffe pulmonaire, jusqu'à l'opération elle-même, les patients passent par des bouleversements psychiques et émotionnels importants (sidération, dépression, renoncement, acceptation, espoir...).
Ces bouleversements demandent du temps pour être élaborés, et pour permettre aux patients de prendre une décision dans un contexte émotionnel plus favorable.
Ce temps peut être le temps du bilan pré-greffe, ou le temps de l'attente.
Au travers de cas cliniques, nous présenterons le vécu de certains de ces patients, pendant ces moments difficiles. Nous évoquerons les processus de décision, l'attente (avant et après l'inscription sur liste), et ce selon la durée d'attente sur liste.

From the announcement of the necessity of a lung transplant, to the surgery itself, patients come go through psychological and emotional upheavals important (astonishment, depression, denial, acceptance, hope ...).
These changes require time to be worked out, and to allow patients to make a decision in an emotional context more favorable.
This time may be the time for assessment pre-transplant, or the period on waiting list.
Through clinical cases, we will present some of the experiences of patients during this specific moment. We will discuss the decision process, the wait (before and after registration on the waiting list), and depending on the length on waiting list.

Key words: lung transplant, psychological upheavals, waiting list.

AN INTERDISCIPLINARY LUNG TRANSPLANT CENTER: A COLLABORATION BETWEEN A UNIVERSITY HOSPITAL AND A TRANSREGIONAL CENTER FOR PULMONOLOGY

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Objectives. The aim of our study was to prove the effectiveness of the collaboration between a university transplant center and a center for pulmonology. While lung transplantations can only be performed in a university hospital, a pulmonology center can provide the resources for pre- and post-transplant care.

Methods. We performed a retrospective chart review of all 39 patients who underwent a lung or combined heart-lung transplantation from 2003 to 2011. Organ recipients were 23 men (59%) and 16 women (41%) ranging in age from 24 to 62 (46.3±10.4) years. Reasons for transplantation were restrictive (n=16) and obliterative (n=13) lung disease, cystic fibrosis (n=3), pulmonary hypertension (n=3) and congenital cardiac defects (VSD with Eisenmenger disease, TGA, or total anomalous pulmonary venous connection; n=4).

Results. Lung transplantation was performed as single lung (n=1), double lung (n=27), lobar transplantation (n=5), or combined heart-lung transplantation (n=6). The median 30-day, 90-day, 180-day, 1-year, and 2-year survival of all lung recipients was 92.3%, 81.6%, 79.4%, 71.4% and 61.9%, respectively. Of the 10 patients (25.6%), who died, 30% died within the first 30 days, 70% within the first 3 months, and 80% within the first two years. Causes of death were septic multi organ failure (61.5%), pneumonia (15.4%), acute transplant failure (15.4%), and subdural hematoma (7.7%). Bronchiolitis obliterans syndrome (BOS) occurred in 8 patients (20.5%; BOS 1 in 5 patients [62.5%], BOS 2 in 2 patients [25%], BOS 3 in 1 patient [12.5%]). No acute rejection episodes were observed.

Conclusions. The interdisciplinary management of lung transplant patients between a university hospital and a transregional pulmonology is an important precondition for a successful lung transplant program.

EVIDENCE FOR EXCELLENT ADHERENCE WITH IMMUNOSUPPRESSIVE MEDICATIONS IN LUNG TRANSPLANT RECIPIENTS UTILIZING A CENTRALIZED DISPENSING STRATEGY

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Purpose: Non-adherence (NA) to immunosuppression (IMS) regimens following organ transplantation is associated with poor allograft and patient outcomes. The goal of this study was to determine the prevalence of NA in a lung transplant population where consequences of NA may be severe.

Methods and Materials: This cross-sectional retrospective cohort study evaluated prescribed dosing and central IMS prescription records of all living lung transplant recipients followed in our outpatient clinic between September 2008 and August 2010. Medication Possession Ratio (MPR), as defined as the number of days of medication supplied to the patient over the two-year study period, was used as a surrogate marker for adherence based on methods described in a large renal transplant population (Pinsky, AJT 2009). A gap in IMS prescription fills was defined as a >30 day lapse between expected depletion of supply and next medication refill.

Results: The charts of seventy-five single (n=44) or double (n=31) lung transplant recipients with mean±SD age 55±13 years, who were 6±4 years post-transplant, were reviewed. Mean MPR for IMS use was 95±8% (range 65-100%). An MPR > 95% was present in 72% of patients, with only 6 patients MPR < 90% and only 2 collecting < 70% of the prescribed medication. Twenty patients (27%) had at least one gap in filling prescriptions during the two-year follow-up.

Conclusions: Lung transplant recipients at our centre demonstrated excellent adherence as measured by MPR > 95%. This finding is reassuring in view of results reported for a large group of recipients early post renal transplant where only 50% of patients achieved a similar MPR. A number of explanations could account for this difference including the use of a centralized dispensing strategy, and possible variability in adherence between organ recipients. Determination of the variables contributing to NA within and between organ recipients will be helpful in developing educational and other strategies to optimize adherence.

CMV-SPECIFIC CD8+ T-CELL IMMUNITY IS A CO-FACTOR FOR ACUTE REJECTION IN LUNG TRANSPLANTATION

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Purpose: Lung transplantation is the definitive treatment for terminal respiratory disease, but the associated mortality rate is high. Acute rejection of the transplanted lung is a key determinant of adverse prognosis. An epidemiological relationship has been established between acute lung rejection and CMV. However, the reasons for this association remain unclear.

Methods: We performed a longitudinal study of CMV-specific T-cell responses and immune activation status, in PBMC and bronchoalveolar lavage fluid of lung transplant patients.
Four groups were designated according to donor/recipient CMV serostatus: D-/R-, D+/R-, D-/R+ and D+/R+.

Results: 44 patients were included in this study. In D+ and D-/R- patients, in PBMC and in BAL, acute rejection was associated with higher levels of cellular activation (respectively p=0,0280 and p=0,0143). In D+/R- patients, CD38 expression on total memory CD8+ T-cells was strongly correlated with those on CMV-specific CD8+ T-cells (r=0,78; p<0,0001), and with the frequency of CMV tetramer+ CD8+ T-cells (r=0,63; p<0,0001).
CD38 levels on memory CD8+ T-cells, frequency of CMV tetramer+ were strongly correlated in blood and BAL from D+/R- patients (r=0,63; p=0,012 and r=0,73; p<0,0001), in contrast to D-/R- patients (r=0,08; p=0,6 and r=0,1; p=0,7).
We observed the same dominant clonotypes in CMV-specific CD8+ T-cell populations from lung and blood, suggesting migration from periphery to CMV infected graft.

Conclusion: These findings provides further support that CMV-specific CD8+ T-cell immunity links the observed relationship between CMV infection and the occurrence of acute lung rejection.

ASSOCIATION OF THE POLYMORPHISM OF THE PDCD1 GENE TO LUNG AND KIDNEY GRAFT SURVIVAL, AND THE IMPLICATION OF THE CMV SEROLOGICAL STATUS OF THE DONORS AND RECIPIENTS

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Context and objectives: In transplant patients, the Cytomegalovirus (CMV) is associated with an increased risk of chronic graft dysfunction especially in lung transplant patients. However, the factors of those deleterious effects remain poorly understood. Programmed cell Death-1 (PD-1) is involved in T-cell clonal exhaustion allowing an increase of the viral burden in human. A polymorphism in the PDCD1 gene (G->A, SNP G7809) has been associated with a variation of PD-1 expression, which might modify the ability of the immune system to control the viral replication within the graft and thus affect organ allograft survival. In this study, we analyzed the association of this PDCD1 SNP with allograft survival in 2 cohorts of lung (n=193) and kidney transplant patients (n=1120).

Patients and methods: The SNP was characterized by the OLA (Oligonucleotide Ligation Assay) technique in 1120 renal graft recipients, transplanted between 1985 and 2008 in Tours, and in a validation cohort of 193 lung transplant patients from the HEGP, FOCH and Nantes CHRU hospitals. The graft survival was assessed by the Kaplan-Meier method according to the SNP genotype (patients carrying the variant allele AA/GA versus those homozygous for the wild type GG). Then, the association between the SNP and graft survival was assessed in two groups of patients: firstly those who received an organ from a CMV-infected donor (D+) and secondly the group of patients for which both donors and recipients were CMV-negative (D-/R-).

Results: The frequency of the A allele was similarly in renal and lung transplant patients (13.8%) and close to that reported in Caucasians. The renal graft survival of the A variant allele carriers was significantly better (p=0.004; death censored). This association remained significant in multivariate analysis after adjustment on donor age, graft rank, acute rejection (HR=1.685 [1.018-2.408]; p<0.05). Interestingly, this association was highly significant in the D+ patients (n=486; p=0.001), while it was not in D-/R- patients (n=305; p=0.522). Importantly, in the lung transplant patients, the survival of the A allele carriers was also significantly better (n=193; p<0.05). Similarly to renal patients, the association was significant in D+ lung transplant patient group (n=83; p<0.05) but not in the D-/R- patients (n=60; p>0.05).

Conclusion: These results indicate that the polymorphism of the PD-1 gene was significantly associated with graft survival in both lung and renal transplant patients receiving a graft from a CMV-infected donor. Interestingly, this association suggests that the PD-1 polymorphism would impact the recipient's ability to control the viral replication in the graft particularly in the lung which is a major site of virus latency. This study is the first to identify a genetic risk factor of graft survival in two different types of transplant organs. These results may lead to future prospective clinical studies.

TRIPLE CO-CULTURE MODEL MIMICKING THE EPITHELIAL MESENCHYMAL TRANSITION OF BRONCHIOLITIS OBLITERANS DURING LUNG TRANSPLANTATION

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Purpose of the study. Bronchiolitis Obliterans (BO) is the manifestation of chronic lung allograft rejection. There is a key role of bronchial epithelial cells (BEC), allogenic target of Dendritic Cells and T Lymphocytes (TL), in this condition. Recent evidence suggests the implication of epithelial mesenchymal transition (EMT) characterized by loss of tight junctions and accumulation of mesenchymal markers, in the development of BO.

Statements of the methods. We developed a triple co-culture model in allogenic conditions melting BEC (16HBE14O- cell line), blood monocyte-derived dendritic cells (moDC) and TL sorted with anti-CD3 and anti-CD14 magnetic beads. BEC are cultured on a pore membrane (Transwell®). Monocytes are derived into dendritic cells with IL-4 and GMCSF during 5 days, while TL are stimulated by anti-CD3. TL and moDC are then coated at the basal pole of the Transwell® for 4 days. Control conditions are represented by moDC co-cultured with TL only. RNA and Western blot analyses are performed on BEC in order to study mesenchymal markers expression (vimentin, α-SMA) and BEC junctions (E-Cadherin, ZO-1). TL are analyzed by flow cytometry to detect memory T-cell (CD45RO) and activated T-cell (ICOS, CD28).

Summary of the results. An increase in vimentin expression is observed in BEC after 4 days of triple co-culture. E-Cadherin and ZO-1 expression levels are unchanged. A significant drop of ICOS and CD45RO expression is observed at the surface of co-cultured T cells.

Statements of the conclusion. The triple co-culture induces an increased expression of Vimentin, suggesting a mesenchymal differenciation of BEC upon allogenic stimulation. A kinetic of this process must be established and a loss of E-Cadherin and ZO-1 explored in longer cultures. The mRNA analysis will further decipher this process. A shift of the CD4 low T cells towards a regulatory phenotype must be explored further as well.
This triple co-culture model will be applied to donor-derived primary bronchial epithelial cell cultures from transplanted patients in the frame of the COLT study to establish whether the EMT process is modified in patients at risk of BO.

Thanks to "fond de dotation recherche en santé respiratoire", "Vaincre la mucoviscidose" and "Agence de la Biomédecine" for their support.

CIRCULATING NK T-LIKE CELLS ARE INCREASED BUT ARE FUNCTIONALLY IMPAIRED FOLLOWING LUNG TRANSPLANTATION

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Introduction: NK T-like cells share phenotypic and functional characteristics of both NK and T cells. NK T-like cells have the capacity to secrete inflammatory and regulatory cytokines in response to alloantigen, and may therefore orchestrate immune responses following lung transplantation. On these grounds, this study was designed to characterise NK T-like cells in terms of population and functionality following lung transplantation.

Methods: Peripheral blood of sixty lung transplant recipients was analysed by flow cytometry and compared to healthy volunteers. Populations of NK T-like cells were identified according to their phenotype: CD3+CD16+, CD3+CD56+ and CD3+CD16+CD56+. Cellular granulation, cytotoxicity and activation was characterised according to cell surface expression of CD107a, CD161 and NKG2D respectively.

Results: There was a significant increase in circulating CD107a+ and CD161+ NK T-like cells ($p<0.05$ and $p<0.05$) in the transplant cohort compared to healthy controls. Interestingly, the mean cell surface expression of CD107a, CD161 and NKG2D was significantly lower to that of healthy volunteers ($p=0.05$, 0.021 and 0.01, respectively).

Conclusion: Following lung transplantation there is a mobilisation of NK T-like cells in the circulation, with a concommitant loss of responsiveness, characterised by down-regulation of CD107a, CD161 and NKG2D. This combined with our previous data demonstrating rapid diapedesis of NK T-like cells from the vascular bed to the alveolar space provides further evidence that this cell could contribute to the immune response following lung transplantation.

ROLE OF IMMUNE REPERTOIRE IN POTENTIAL LUNG TRANSPLANTATION PATIENTS

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The purpose of our study is to pilot the role of an immune repertoire in clinical diagnosis and therapeutic monitoring in transplantation. An immune repertoire is the sum total of functionally diverse B and T cells in ones circulation at any given moment. Using high-performance sequencing and innovative sample preparation methods, clinicians can efficiently and cost-effectively monitor changes in the adaptive immune system and relate those changes to a specific disease or therapeutic goal. T cell receptor diversity is a dynamic and quantitative biomarker for phenotypic changes in humans.

Each individualized immune repertoire will be determined by three key factors: 1) genetic polymorphism at the MHC loci, 2) antigen exposure and history 3) constant regulation and modulation of the immune system. Loss of T cell diversity or clonal expansion of a small subset of T cells has been observed in colon cancer, breast cancer, and autoimmune conditions. By measuring the diversity of the adaptive immune system or immune cell receptor repertoire using high-performance sequencing provides the ability for both clinical diagnosis as well as therapeutic monitoring. High-performance sequencing will be used with existing frozen isolated lymphocytes from more than 100 IPF patients- serum and plasma, and RNA if applicable to create an immune repertoire for potential use in clinical diagnosis and transplantation therapeutic monitoring.

Results are pending at the time of abstract submission. However, Tcell homogeneity or heterogeneity will both provide useful information for bench scientists and affect applicability for clinicians. Thus, directions in either direction will be a worthwhile result to report.

Future applicability in transplantation includes pre-transplantation eligibility for transplantation and post-transplantation changes during various levels of immunosuppression and during rejection. Initial potential uses include clinical diagnosis and transplantation therapeutic monitoring. Results and analysis of results will be completed by July 2012.

HEPATOCYTE GROWTH FACTOR INDUCES THE POLARISATION OF MONOCYTE DERIVED DENDRITIC CELLS TO A REGULATORY DC10 PHENOTYPE: IMPLICATIONS FOLLOWING LUNG TRANSPLANTATION

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Introduction: Hepatocyte growth factor (HGF) is a sensitive predictor of acute rejection following lung transplantation, with well reported anti-apoptotic and anti-fibrotic effects. However, its role in recipient immunity is unclear. In this study, we aimed to define the effects of HGF on dendritic cell (DC) generation, as this represents the central nexus of allorecognition.

Methods: Peripheral blood monocytes were isolated from (n=5) lung transplant recipients and cultured for 7 days in the presence or absence of HGF. Lipopolysaccharide was added to cultures on day 6 to induce DC maturation. Resulting cells were phenotyped for specific DC markers via flow cytometry.

Results: There was a significant polarisation to DC following exposure to HGF (mean cell number 44319.6 vs. 75883.2 in control and HGF respectively, $p=0.037$). Within the DC population, there was a significant increase in intracellular IL-10 and cell surface expression of CD83+ in the presence of HGF ($p<0.05$).

Conclusion: HGF promotes the generation of a DC-10 phenotype from monocytes. The upregulation of the costimulatory molecule CD83 suggests HGF conditioned DC induce CD4+ and CD8+ T cell activation. Further functional analysis is necessary to clarify the effect of HGF on DC in the presence of naïve T cells. Potentially HGF may represent a novel therapeutic molecule for the prevention of acute rejection via the generation of regulatory T cells and the induction of tolerance.

HEPATOCYTE GROWTH FACTOR LEVELS ARE INDEPENDENT OF CMV AND EBV INFECTION FOLLOWING LUNG TRANSPLANTATION

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Background: Hepatocyte growth factor (HGF) may represent a non-invasive diagnostic tool for acute rejection following lung transplantation. Prior to clinical use, associations between HGF and other clinical complications need to be assessed. For this purpose our aim was to investigate if any relationship could be reported between serum HGF concentration and CMV and EBV, which are highly prevalent in this population.

Methods: HGF concentration was quantified by ELISA in 60 lung transplant recipients who were acute rejection negative at the time of analysis. EBV and CMV copy numbers were measured by PCR. Patients were categorised according to viral infection and comparisons with HGF were statistically determined.

Results: HGF concentration was not significantly different among all viral infection groups or controls (p=0.991); CMV positive group (137.07 ng/ml ± 51.92, n=6), EBV positive group (169.56 ng/ml, ± 142.20, n=27), and CMV/EBV negative group (181.82 ng/ml ± 188.95, n=27). There was no significant difference in HGF levels between CMV seropositive and negative patients (p=0.384) as well as the EBV seropositive and negative patients (p=0.906). There were no significant associations between HGF concentrations and CMV vs EBV seropositive patients (p=0.930 and =0.630, respectively).

Conclusion: Our findings demonstrate that CMV and EBV infection do not affect serum HGF concentration following lung transplantation. This deta further validates HGF as a prognostic indicator of acute rejection following lung transplantation, as CMV and EBV will not cause false positive results.

PREVENTION OF ISCHEMIA-REPERFUSION LUNG INJURY BY SUPPLEMENTATION OF THE PRESERVATION SOLUTION WITH AN OXYGEN CARRIER IN PORCINE LUNG TRANSPLANT MODEL

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Background: M101 is a new oxygen carrier extracted from arenicola marina with high-oxygen affinity and the ability to function at low temperature. This study assessed the effect of M101 in adjonction to static preservation solution on primary graft dysfonction after lung transplantation.

Methods: A porcine single left lung allotransplantation was performed in 2 experimental groups after 24 hours of cold storage. Donor Lungs were flushed and preserved with low-potassium dextran (LPD) in group 1 whereas M101 (2g/l) was added to LPD in group 2. Control animals underwent a sham operation. The HIF-1 protein level was evaluated during cold storage on sequential right lung parenchymal samples. After left lung transplantation, the right pulmonary artery was clamped to evaluate graft function. During 5 hours of reperfusion, hemodynamics, oxygenation and dynamic compliance were monitored and compared with controls. HMG-B1, TNF alpha, LDH, and IL-8 were measured in serum. After 5 hours of reperfusion, TNF-alpha and LDH were measured in bronchoalveolar lavage.

Results: During the cold ischemia the HIF-1 protein level remains unchanged. After 5 hours of reperfusion, group 2 led to a significant reduction of graft vascular resistance (1217 +/- 104 vs 1627 +/- 211 dynes/s/cm^5, $p < 0.05$), graft oxygenation ratio was significantly higher (436 +/-10 vs 324 +/- 32 mm Hg, $p<0.05$) and alveolo arterial gradient values tended to be lower (221 vs 321 mmHg, $p = 0.06$). Expression of HMG B1 in serum tended to be lower (2.1+/- 0.8 vs 4.6+/-1.5 p = 0,07) compared with group 1. The TNF alpha, LDH and IL-8 serum levels remained unchanged during reperfusion. However TNF-alpha and IL-8 in bronchoalveolar lavage were significantly higher in the 2 experimental groups compared to control (group 1: 164 +/-18 pg/ml, group 2: 151 +/- 20 pg/ml vs sham 69 +/-18 pg/ml, $p<0.05$ and group 1: 1.14 +/- 0.21 pg/ml, group 2: 1.12 +/-0.26 pg/ml vs sham 0.5 +/- 0.2 pg/ml, $p<0.05$ respectively).

Conclusions: In this preliminary study, adjunction of a new oxygen carrier M101 in lung preservation solution improves early graft function after prolonged cold ischemia.

MICROBLEEDS AND POSTERIOR REVERSIBLE ENCEPHALOPATHY PROMOTED BY TACROLIMUS AFTER LUNG TRANSPLANTATION

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Posterior reversible encephalopathy syndrome has been widely described as a neurologic complication of tacrolimus. Classical MRI pattern is subcortical white matter changes. A 19 year-old man and a 26 year-old woman with cystic fibrosis underwent double lung transplantation. Immunosuppression regimen included tacrolimus. The first patient was admitted 4 months after surgery for generalised seizures, the second 3 months after surgery for generalised seizures and altered mental status followed by transitory visual impairment in the setting of a septic shock caused by klebsiella pneumoniae. Brain MRI had similarities and showed (1) supratentorial cortico-subcortical hyperintensities on FLAIR with high apparent diffusion coefficient (ADC) and (2) multiple hypointense signal changes on T2* in the cortico-subcortical junction of the two cerebral hemispheres, suggesting microbleeds. No arterial abnormality was associated. In these two patients, cerebral spinal fluid was unremarkable.. Blood pressure was below 160/105 mmHg. The tacrolimus concentrations were within the therapeutic range. There was concomitant corticotherapy. In this context, the final diagnosis was posterior reversible encephalopathy syndrome. The dose of tacrolimus was decreased and everolimus initiated. The patients did not experience further seizures. Control MRI performed one month later showed complete regression of hypersignal on FLAIR images and the persistance of microbleeds on T2*. Cerebral microbleeds has rarely been reported after lung transplantation in patients treated with tacrolimus. This can be explained by damage of the microcirculation. Control MRI including T2* could be considered in the follow-up of transplant patients treated with tacrolimus.

DONOR SMOKING IS ASSOCIATED WITH INCREASED PULMONARY EDEMA AND LOWER RATES OF ALVEOLAR FLUID CLEARANCE IN THE EX VIVO DONOR LUNG

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Purpose of the Study: Cigarette smoking is very common in organ donors, but the effects of smoking on the formation and clearance of pulmonary edema in the donor lung are unknown. The objective of this study was to test the association between donor smoking history and the degree of pulmonary edema (measured by total lung weight) and the rate of net alveolar fluid clearance in the *ex vivo* donor lung.

Methods: Data were derived from the recently completed Beta-agonists for Oxygenation in Lung Donors (BOLD) study (NCT00310401) of inhaled albuterol vs. placebo in organ donors. Among the 591 donors evaluated for enrollment, 229 had lungs resected for physiologic studies, and these 229 donors comprise the study population. Smoking history and clinical data were obtained from the donor medical records. Lungs that were not utilized for transplantation were resected without perfusion and transported to our laboratory at 4C. Upon receipt, lungs were weighed, then rewarmed to 37C. The rate of alveolar fluid clearance (AFC) was measured by intra-alveolar instillation of a 5% albumin solution.

Results: Among 229 donors, 95 (42%) were current smokers (mean 24 ± 22 pack years) and 29 (13%) were former smokers. Females were less likely to be ever or current smokers than males but tended to have more pack years of smoking. Pulmonary edema as assessed by lung weight was 8% higher in current smokers (891 vs. 827g, p = 0.046) compared to former or non-smokers. Likewise, current smokers had poorer oxygenation at study enrollment compared to former or non-smokers (PaO_2/FiO_2 295 ± 150 vs. 328 ± 148, p = 0.015). Although rates of AFC in the *ex vivo* lung did not differ based on smoking status, among ever smokers there was an inverse association between pack years of smoking and the rate of AFC (r = -0.38, p = 0.02) in female but not male donors. Results were not different when analyzed by treatment group (albuterol vs. placebo).

Conclusions: Among organ donors evaluated for enrollment in a clinical trial of albuterol vs. placebo for donor oxygenation, donor smoking history was significantly associated with more pulmonary edema in the resected lung and poorer donor oxygenation. In addition, increasing doses of smoke exposure as measured by pack years of smoking were associated with slower rates of alveolar fluid clearance in female donors. These findings suggest that chronic exposure to cigarette smoke has important effects on lung fluid balance in the organ donor that could potentially influence lung function in the lung transplant recipient.

HEPATOCYTE GROWTH FACTOR IS NOT ELEVATED IN CHRONIC REJECTION FOLLOWING LUNG TRANSPLANTATION

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Background: Acute rejection is a major cause of morbidity and mortality following lung transplantation. Current diagnostic methods are invasive and high risk, and the lack of a rapid, safe and non-invasive diagnostic tool results in rejection episodes often being missed. Hepatocyte growth factor (HGF) represents a novel prognostic biomarker of acute rejection, with clinically viable specificity and sensitivity. To further validate HGF, any association with chronic rejection needs to be determined. Our aim was to investigate if any relationship could be shown between HGF levels and chronic rejection.

Methods: HGF concentration in the serum of 79 lung transplant recipients which were categorised according to their BOS grade were quantified by ELISA. BOS grading was determined using ISHLT guidelines. Differences in mean HGF levels among BOS grades were determined using Independent T Test and partial correlation coefficient analysis. The latter test controls for time post transplantation, as BOS and organ age are intrinsically linked.

Results: All patients included in the study were negative for acute rejection, determined either histologically or symptomatically. The mean HGF concentration in the entire population was 183.61 ng/mL (+/- 167.08). The mean HGF levels for BOS grades 0, 1, 2 and 3 were 149.93 (+/-86.97), 213.41 (+/-213.87), 152.16 (+/-94.07) and 243.38 (+/-242.05) respectively.

Conclusion: The findings of this study further validate the use of HGF as a prognostic indicator for acute rejection following lung transplantation. The fact that chronic rejection has no effect on circulating HGF concentration rules out this variable in false positive reporting.

DE NOVO DONOR HLA-SPECIFIC ANTIBODIES AFTER LUNG TRANSPLANTATION ARE ASSOCIATED WITH DEVELOPMENT OF BOS AND POOR PATIENT SURVIVAL

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Lung transplantation is the definitive treatment for end-stage lung disease. However, despite advances in surgical technique and immunosuppressant therapy, median survival after transplantation remains at 5 years. Development of bronchiolitis obliterans syndrome (BOS) has a significant negative impact on graft survival. BOS is multifactorial in aetiology with a number of factors suggested to pre-dispose to development. The objective of this study was to determine if the *de novo* development of donor specific HLA antibodies (DSA) are an independent predictor of development of BOS or graft failure.

This was a retrospective observational study, analysing 93 consecutive lung transplant recipients, with a follow up period range of 2-5 years. All patients were transplanted in the absence of DSA and all had a negative crossmatch. HLA antibodies were measured at regular intervals after transplantation using Luminex based assays (Labscreen, One Lambda, USA). In addition to *de novo* DSA a number of clinical parameters including rejection, infection, immunosuppression and ischaemia time were analysed. Cox proportional hazards models were used in univariable analysis of survival and time to development of BOS.

Univariable analysis of time to development of BOS suggested that ischaemia time, rejection episodes, HLA mismatch, recipient/donor age and immunosuppressant change had no significant impact. However, patients with pre-transplant non-donor specific HLA antibodies, as well as those with *de novo* DSA, developed BOS at a significantly shorter time, with hazard ratio (HR) of 2.84 and 2.51(p value= 0.0078 and 0.037), respectively. Repeated infections showed a trend for shorter time to BOS (HR=2.24, p=0.058) which did not quite reach statistical significance.

Univariable analysis for graft survival showed significant evidence of shorter survival times after initial *de novo* DSA (HR= 4.00, p value= 0.0075) and even shorter survival times after persistent *de novo* DSA (HR= 5.32, p value= 0.013). There was also significant evidence of shorter survival times for patients who have rejection (HR= 2.57, p value= 0.031). Patients having infection also had shorter survival times (HR= 2.91, p value= 0.035) with even shorter survival times after multiple infections (HR= 6.29, p value= 0.0006).

These results suggest that the development of *de novo* DSA is a major risk factor for progression to BOS, as well as shorter graft survival. Treatment options to limit antibody mediated damage and antibody removal therapies should be considered when DSA are first detected.

FIRST INSIGHTS FROM THE COLT STUDY : FRENCH COHORT IN LUNG TRANSPLANTATION

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Purpose of the study: To analyze epidemiologic data from the COhort of Lung Tranplantation (COLT).

Statements of the methods: The Cohort of Lung Transplantation is a French multicentric longitudinal cohort, started in 2009. Its objectives were to create a database associated to a biocollection in order to identify and validate predictive markers for chronic lung rejection. Data were extracted from the COLT database via the IDBC interface. We looked up for recipient age, indication of transplantation, type of procedure and donor age distribution. Kaplan-Meier survival was analyzed globally and specifically related to these parameters.

Summary of the results: All of the eleven French centers for lung transplantation participated to this study. In May 2012, 770 patients are included and 538 patients have undergone lung transplantation. Medium age of the recipients is 42,7 years. The two most represented age categories are the 18-34 and 50-59 years old. The major diagnosis for lung transplantation is cystic fibrosis (35,7%), followed by COPD/emphysema (30,6%) and fibrosis (15%). There are marked differences on this point between centers. Medium donor age is 40,83 years. Bilateral lung transplantation procedure represents 72% of all transplantations, whereas single lung procedure represents 19%. Global survival at 2 years is 73%. Cystic fibrosis patients have the best survival which is 85%, fibrosis survival is the worst at 55% at two years. Bilateral lung procedure has a better survival compared to single lung and cardio-pulmonary procedure. With two and half years of distance from the first transplantations, 18% of proved or suspected chronic rejections are documented in the database.

Statement of the conclusion: Within two and a half year, the initial objective of 500 lung transplanted patients has been reached and exceeded. The COLT cohort gives an exhaustive view of lung transplantation in France where cystic fibrosis is the main diagnosis and the medium age recipients is slightly younger than the ISHLT datas. A longer time follow-up is needed for chronic lung rejection analysis.

The COLT study was granted by Vaincre La Mucoviscidose and Grégory Lemarchal associations.

CYSTIC FIBROSIS, LUNG TRANSPLANTATION AND WAITING LIST IN LATIN AMERICA: SINGLE CENTRE EXPERIENCE

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Background: Lung transplant is the standard of care in end stage lung disease due to Cystic Fibrosis (CF). The mortality rate on Waiting List (WL) for these patients (pts) is influenced by the scarce number of donors and the severity of the disease at referral time; and differs also between countries and regions. There is little information regarding this issue in Latin America Objective: To analyze the outcome of end stage CF pts on the Lung Transplant Waiting List at a single centre in Argentina.

Methods: A retrospective analysis of the incidence of transplant and death in a cohort of 77 end stage CF pts referred to our centre between Jan 1990 and May 2012 was performed. Pts eligible for the WL were included in the present study. Four different periods were considered: 1990-1999 (n=15 pts); 2000-2004 (n=20 pts); 2005-2009 (n=23 pts) and 2010-2012 (n=19 pts). Clinical variables at referral time and mortality predictors of end stage CF pts were considered to investigate its relationship with the WL outcome at the 4 different periods. One way ANOVA and Chi square test were used for this purpose.

Results: The incidence of mortality on WL among the different correlative periods was: 60% (9/15); 70% (14/20); 27% (6/23) and 16% (3/19) (p<0.001). The percentage of transplanted pts was: 40% (6/15); 30% (6/20); 60% (14/23) and 26% (5/19) respectively (p=NS). The following table shows some of the variables at referral time for the different periods.

Variables (mean±SD)	*1990-1999*	*2000-2004*	*2005-2009*	*2010-2012*	*P value (<0.05)*
Age (years)	24±7	27±12	27±7	23±5	NS
Weight (Kg)	42±9	46±12	51±9	52±11	NS
BMI	16±2	18±3	18±3	19±1	NS
FEV_1 (% pred)	23±6	18±4	22±7	26±11	NS
pCO_2 (mmHg; room air)	47±12	61±23	47±8	44±10	NS
mPAP (mmHg)	21±3	27±4	23±8	23±6	NS
Days on WL	559±362	264±359	838±556	234±189	NS

Conclusions: The mortality incidence on WL in end stage CF pts has decreased significatively over more than 20 years at our centre. The clinical variables included in this study failed to explain this improvement. The WL mortality is influenced by multiple factors; and some of them were not analyzed. We believe that there is a trend to earlier referral of pts by their physicians through the four periods, thus the pts showed better clinical status. This demonstrates an increased confidence on the transplantation therapy, team management and results. A new policy to allocate donor lungs has been implemented in Argentina since 2010, increasing the opportunities for CF and IPF pts too.

INTEREST OF URINE CRYSTALS SCREENING IN CYSTIC FIBROSIS LUNG TRANSPLANTED PATIENTS

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Chronic kidney disease is of major concern in lung transplanted patients. Half of the patients have a 50% reduction in Glomerular Filtration Rate at 2 years post-transplantation. Loss of renal function occurs in the first 6 months after transplantation. Beside classical risk factors for kidney disease, CF patients are at increased risk of hyperoxaluria due to exocrine pancreatic insufficiency and lack of Oxalobacter formigenes, an enteric oxalate degrading bacteria. Enteric hyperoxaluria can be complicated by calcium oxalate crystals aggregation and kidney deposits leading to accelerated renal function loss and end stage renal disease. Crystal precipitation is enhanced by acute tubular necrosis, hypovolemia and drug toxicity, all contributing factors which may be present after lung transplantation.

We reported an incidence of 30% (11/32) positive crystalluria in CF patients followed in Pulmonology Center, Hôpital Foch, over a period of 8 months in a previous study (abstract 245, ECFS, 2012). The main crystal species identified was calcium oxalate, in accordance with the role of enteric hyperoxaluria. Based on this high incidence of crystalluria in CF patients, we examined the incidence of crystalluria in lung transplant recipients to examine whether the presence of crystalluria could contribute to rapid renal function decline in lung transplanted patients.

In this study, we report crystalluria screening in 12 lung transplant CF patients over a period of 12 months. Mean time between transplantation and crystalluria screening was 4.8 +/- 4.4 yr. Mean age was 40.6 +/- 9.8 yr at time of screening. Crystalluria was positive in 41% of patients (5/12). Calcium oxalate was the main species found (3/5). On CT-scan screening, 2/5 patients with positive crystalluria and one out of seven patients without crystalluria had nephrolithiasis. Mean e-GFR was 47.5 +/- 25 ml/min/1.73 m2. Renal function was not correlated with crystalluria presence.

We conclude that crystalluria made of calcium oxalate is frequent in CF with lung transplantation. Crystalluria could be a useful screening test in these patients to predict the risk of nephrolithiasis and chronic kidney disease. Next step will be to confirm these data in more patients, early after lung transplantation — when risk factors of crystalluria are more prominent — and to compare renal function decline according to the presence or absence of crystalluria.

LUNG TRANSPLANTATION OF CYSTIC FIBROSIS PATIENTS WITH NONTUBERCULOUS MYCOBACTERIAL DISEASE RESULTS IN A RAPID FALL IN SPECIFIC IMMUNOGLOBULIN G ANTIBODIES

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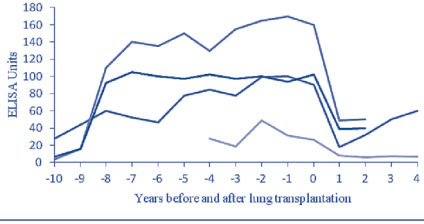
Purpose: Monitoring infection with nontuberculous mycobacteria (NTM) after lung transplantation (LTX) can be notoriously difficult. In order to better understand specific immunoglobulin G (IgG) kinetics following transplantation, we present a novel method for studying the antibody response to nontuberculous mycobacteria, which could potentially prove useful as a diagnostic and prognostic marker.

Methods: Antimycobacterial antibody levels were determined by enzyme-linked immunosorbent assay (ELISA). A mycobacterial antigen was produced by X-pressing and sonication of a *Mycobacterium abscessus* obtained from an infected cystic fibrosis (CF) patient. Micro-titer wells were coated with diluted antigen and thawed serum samples from LTX patients from the Copenhagen Cystic Fibrosis Centre Biobank were then applied. Rabbit anti-human IgG conjugate was added, followed by substrate. The reaction was measured, using an ELISA reader.

Results: 131 serum samples taken from 8 CF patients with NTM disease who had undergone LTX, and from 12 healthy non-CF controls, were studied. 6 patients were infected with *Mycobacterium abscessus* and two with *Mycobacterium avium*. The median observation time was 17 years (IQR 12 – 20) and covered both the pre- and post-transplant periods. During infection with NTM, the median IgG level was 105 ELISA units (IQR 62 – 193) compared to 7 ELISA units (IQR 2 – 15) in the healthy controls. 4 patients developed high antibody responses upon infection and were later lung transplanted, while still actively infected. All 4 were treated with antimycobacterial drugs leading up to and following LTX, cleared the infection, and demonstrated rapid drops in NTM-specific IgG levels as seen in Fig. 1. All 4 patients had normal concentrations of total IgG in serum before and after LTX.

Fig. 1. Nontuberculous Mycobacterial Specific IgG in Four Cystic Fibrosis Patients with Active Infection Before and After Lung Transplantation



Conclusion: Infection with nontuberculous mycobacteria results in an increase in NTM-specific IgG. Clearing infection, either due to antimycobacterial treatment, lung transplantation or both is associated with a rapid fall in IgG. Further investigation will reveal the diagnostic and prognostic utility of the method.

OUTBREAK OF PULMONARY TUBERCULOSIS AMONG LUNG TRANSPLANT RECIPIENTS

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Tuberculosis infection is a rare infectious complication after solid organ transplantation (prevalence ranging from 1.2 to 6.4 percent). We report three cases of pulmonary tuberculosis occurring in lung transplant recipients between February and December 2010 in the same pulmonary medicine ward (Louis Pradel hospital, Lyon, France). Three women, aged 24, 37 and 40 years, had double lung transplantation for cystic fibrosis (2 patients) and idiopathic pulmonary fibrosis (1 patient) in october 2009, february 2010 and july 2009 respectively. In all three patients, the diagnosis of pulmonary tuberculosis was made on the basis of positive culture of the bronchoalveolar lavage (direct examination was negative). For two patients, this diagnosis was unexpected, obtained on systematic bronchoscopy in the first year after transplantation, only one patient presented with fever and cough. CT scans of the three patients showed micronodular opacities; one patient had pleural involvement. Each strain of *Mycobacterium tuberculosis* was genetically characterized by spoligotyping and MIRU-VNTR. The three strains were different from each other, but each strain was paired to another strain isolated from three distinct hospitalized patients within the same hospital. A thorough epidemiological and sanitary investigation suggests that each transplant recipients had a very brief contact with one of the three associated case. These data suggest that the hospital can be a risky place for lung transplant recipients regarding tuberculosis. Preventive measures such as wearing FFP1 mask outside the room in the hospital should be implemented.

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