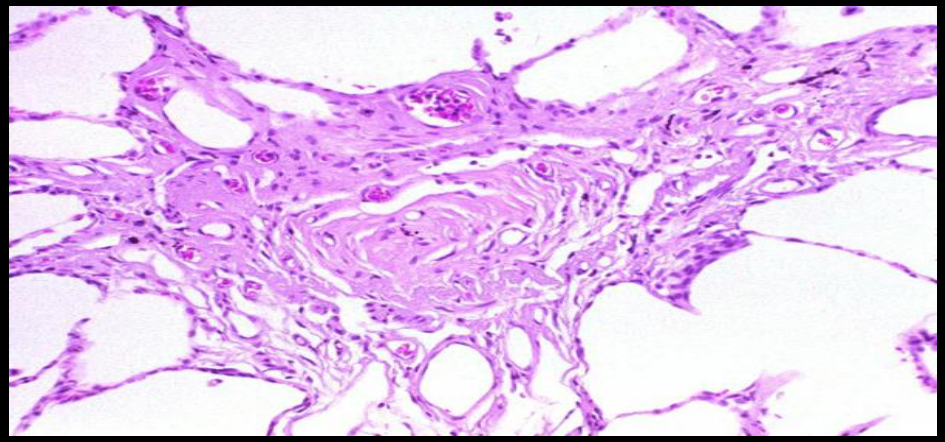
The Role of Photopheresis in the Treatment of Bronchiolitis Obliterans Syndrome



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Terminology/Definitions

- **OB=BO: Obliterative bronchiolitis or bronchiolitis obliterans**
  - **Histopathologic term used to describe the finding of fibrous obliteration of small airways after LTx**
- **BOS: Bronchiolitis obliterans syndrome**
  - **Clinical/physiologic definition of chronic lung allograft dysfunction caused by OB and characterized by progressive airflow limitation**
  - **Term originally proposed in 1993 and revised in 2002**

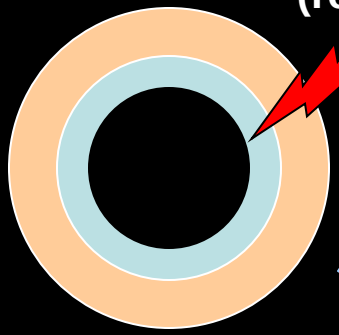
Bronchiolitis Obliterans Syndrome
Clinical Impact

Very common and deadly

- **Cumulative risk of 50-80% between 5 and 10 years after lung transplantation**
- **Leading cause of long-term mortality**
  - **Directly or indirectly accounts for at least 30 to 50% of deaths after third post-operative year**
  - **Less than 40% survival at 5 years after its onset**

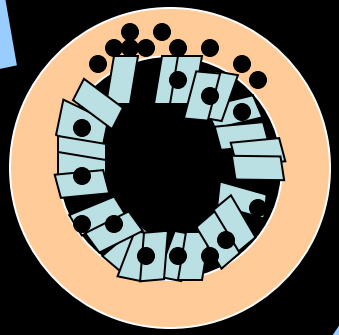
Pathogenesis of OB

Normal



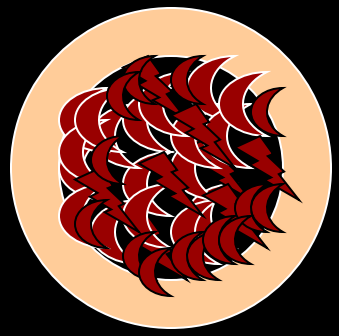
Injury to airway epithelium
Alloimmune or non-alloimmune
(rejection, infection, aspiration, ischemia)

Innate and adaptive immune response
(PMN, macrophage, DC, T- and B-lymphocytes)
IL-1, IL-2, IL-6, IL-8, IL-12, TNF-α, MCP-1, complement, IFN-γ, RANTES, ROS, NO, peroxides, leukotrienes



Inflammatory response
Vascular changes

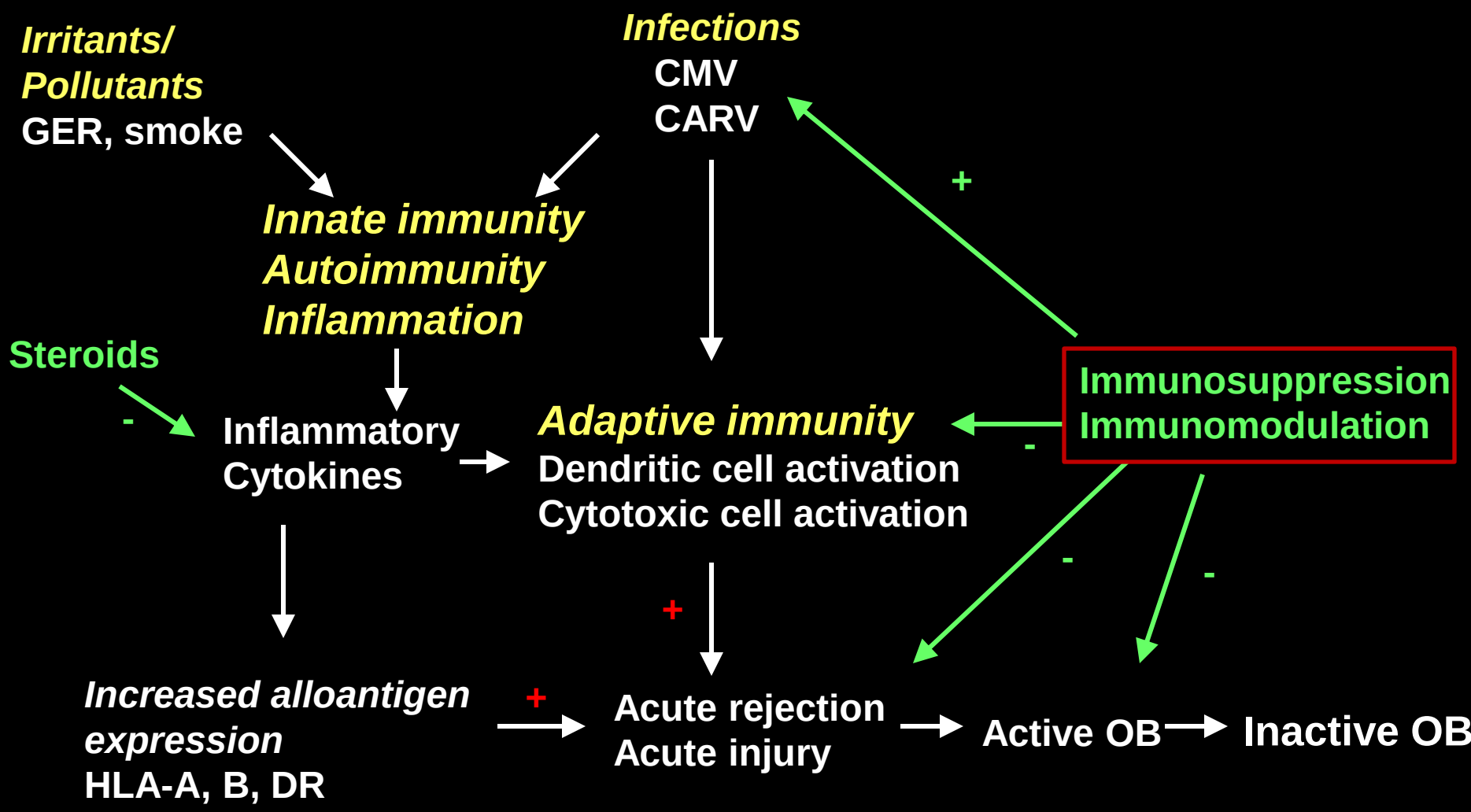
TGF-ß,PDGF,
IGF, FGF, ET-1



Final common pathway
Repair response
Fibroblast proliferation
EC matrix deposition

Mechanisms and Therapy of OB After Lung Tx

Adapted from *Nicod. Proc Am Thorac Soc 2006;3:444*



Prevention and Treatment of BOS

Potential Therapies

- Induction therapy
- Tacrolimus
- Mycophenolate mofetil
- Everolimus
- Aerosol Cyclosporine
- Azithromycin
- Antireflux procedures for GER
- Statins
- Extracorporeal photopheresis
- Lympholytic therapy
- Total lymphoid irradiation
- Donor bone marrow tx
- Cyclophosphamide
- Methotrexate
- Preservation of airway microcirculation

Potential Mechanisms of ECP

- Induction of T-cell apoptosis
  - Only 5% of lymphocyte load is treated with each cycle of ECP
- Induction of immunologic tolerance rather than immunosuppression
  - No altered T- and B-cell function in patients after ECP
  - Acquisition of a tolerogenic phenotype by immature dendritic cells
  - Increase in regulatory T-cells
- Conflicting effects on cytokine production
- “T-cell vaccination”
  - Th1 immune response against alloreactive T cells

ECP Process

- Removal of a certain percentage of a patient's blood (2-5% of total circulating leukocytes)
- Separation of blood into leukocyte-enriched (buffy coat) and –depleted components
- Buffy coat is exposed to UV light in the presence of 8-methoxypsoralen within the photoactivation chamber, which forms covalent bonds to DNA pyrimidine bases, cell surface and cytoplasmic components of exposed leukocytes
- Leukocyte apoptosis, changes in dendritic cells, cytokine production and induction of Tregs

ECP History in Lung Transplantation

- First report in 3 lung transplant patients with BOS published in 1995
- Initially used in the context of refractory BOS (stages 2-3) with demonstration of initial stabilization or improvement in FEV_1
- Literature suggested its efficacy in persistent acute rejection and early BOS, preventing further loss of lung function
- 2 recent larger studies suggested reduction in the rate of decline in lung function at all stages of BOS

Extracorporeal Photopheresis

Early C*linical Studies in Lung Transplantation*

- **Case series including 3-14 patients**

  Slovis. NEJM 1995;332:962—(n=3)

  Salerno. JTCS 1999;117:1063—(n=8)

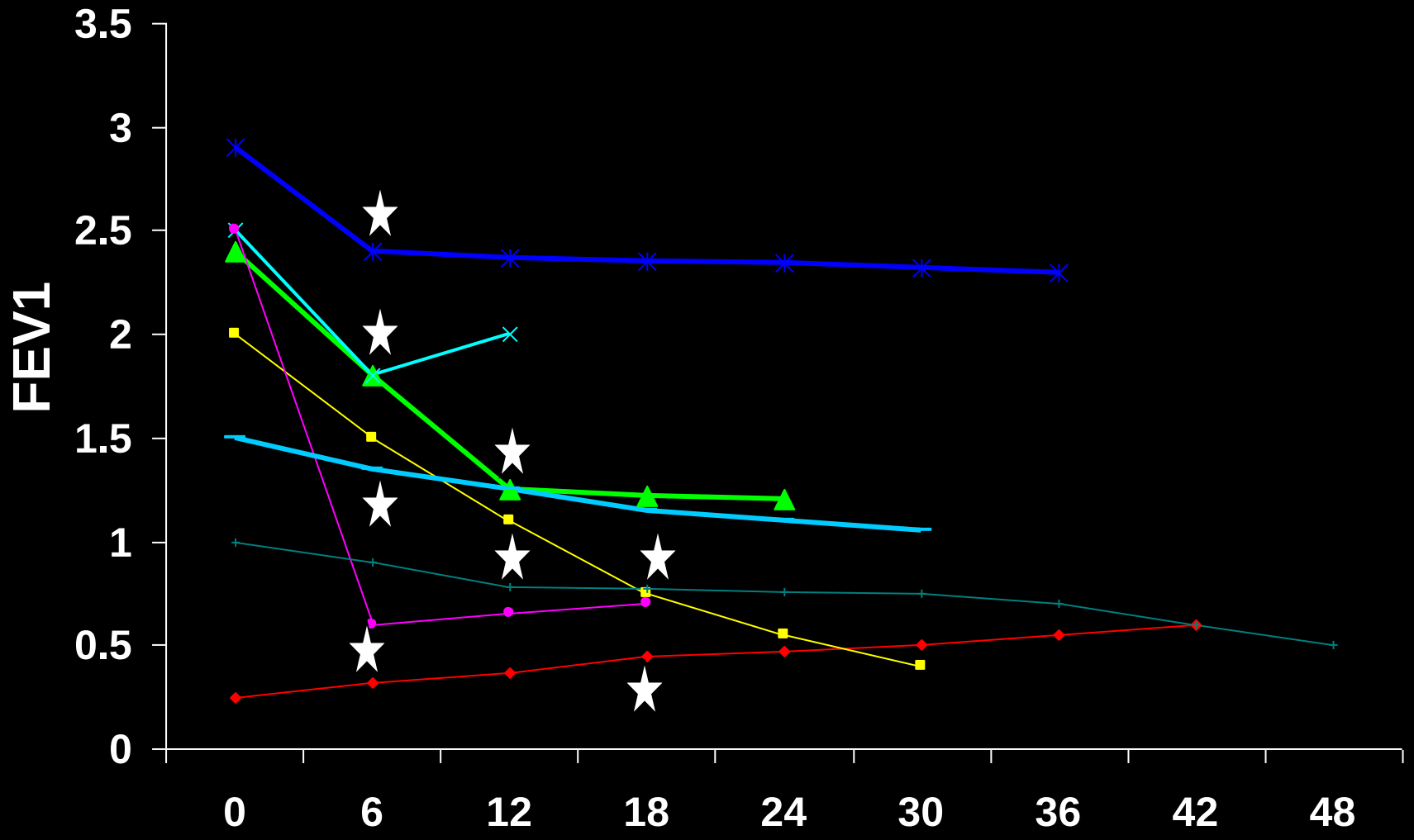
  O'Hagan. Chest 1999;115:1459—(n=6)

  Villanueva. Ann Transplant 2000;5:44—(n=14)

- **Reduced rate of decline in FEV_1 in most patients**
  - **More likely to be effective in earlier stages of BOS but stabilization of lung function observed in stage 3 BOS**

Extracorporeal Photopheresis

Salerno. JTCS 1999;117:1063



ECP. A 10-year Single Center Experience

Benden et al. Transplantation 2008; 86:1625

- **24 patients underwent ECP between 1997-2007**
- **12 cycles 4-6 weeks apart**
- **BOS grades**
  - **Stage 1 N=5**
  - **Stage 2 N=2**
  - **Stage 3 N=5**

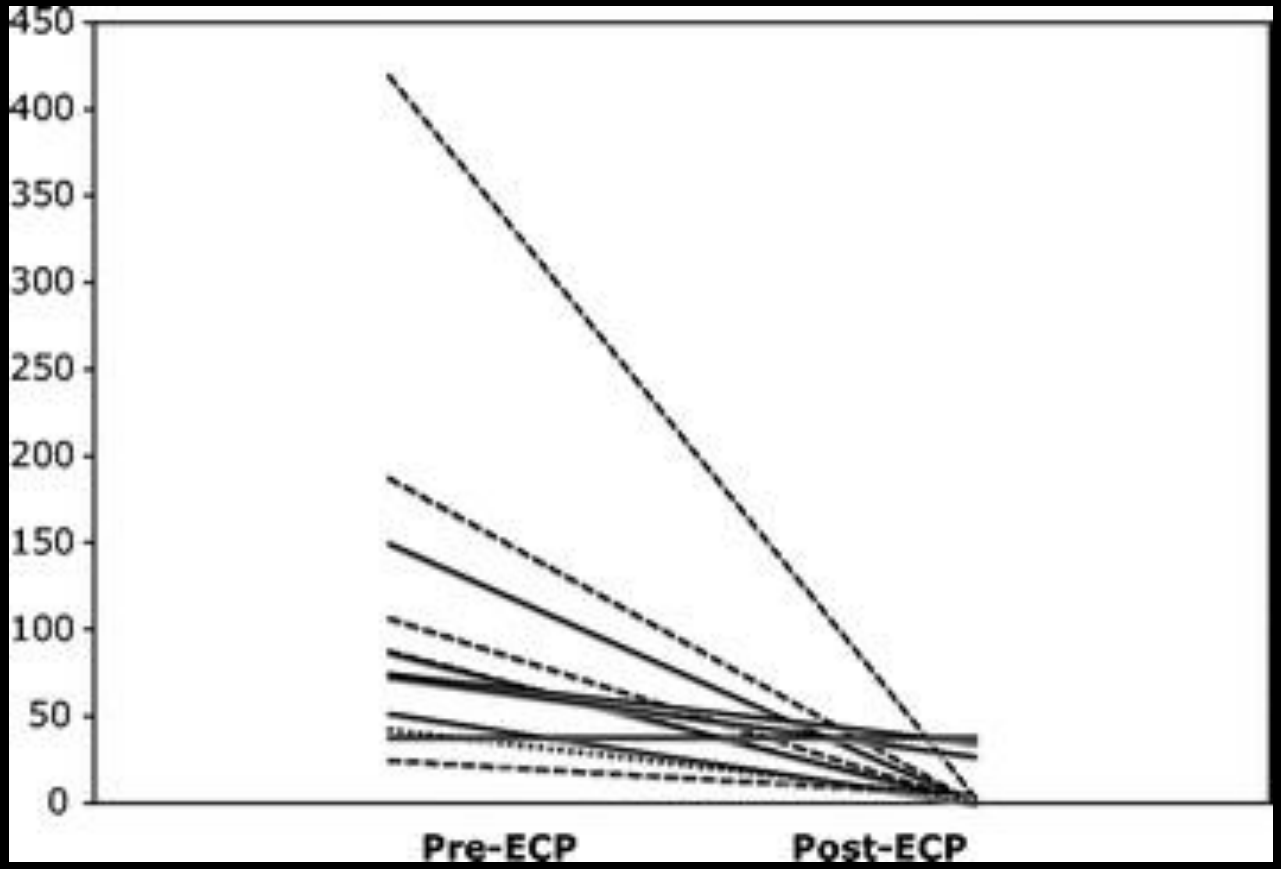
TABLE 1. Patient demographics

Total number of patients	24
Male/female	18/6
Mean age at transplant (SD), (yrs)	40.8 (12.7)
Diagnosis at transplant	
CF (%)	9 (37)
COPD (%)	7 (29)
IPF (%)	5 (21)
PAH (%)	3 (13)
Type of transplant	
Double lung (%)	21 (87)
Single lung (%)	3 (13)
Indication for ECP	
BOS (%)	12 (50)
Recurrent AR (%)	12 (50)
Mean baseline FEV_1 posttransplant (SD), (L)	3.1 (0.8)

CF, cystic fibrosis; COPD, chronic obstructive pulmonary disease; IPF, idiopathic pulmonary fibrosis; PAH, pulmonary arterial hypertension; ECP, extracorporeal photopheresis; BOS, bronchiolitis obliterans syndrome; AR, acute rejection; FEV_1, forced expiratory volume in 1 sec.

ECP. A 10-year Single Center Experience
Rate of Decline in FEV1 Before and After ECP

Benden et al. Transplantation 2008; 86:1625



Decline in FEV1

Pre ECP 112 ml/mo
Post ECP 12 ml/mo
Mean change (95% CI)
100 (28-171) ml
P=0.011

ECP. A 10-year Single Center Experience

Benden et al. Transplantation 2008; 86:1625

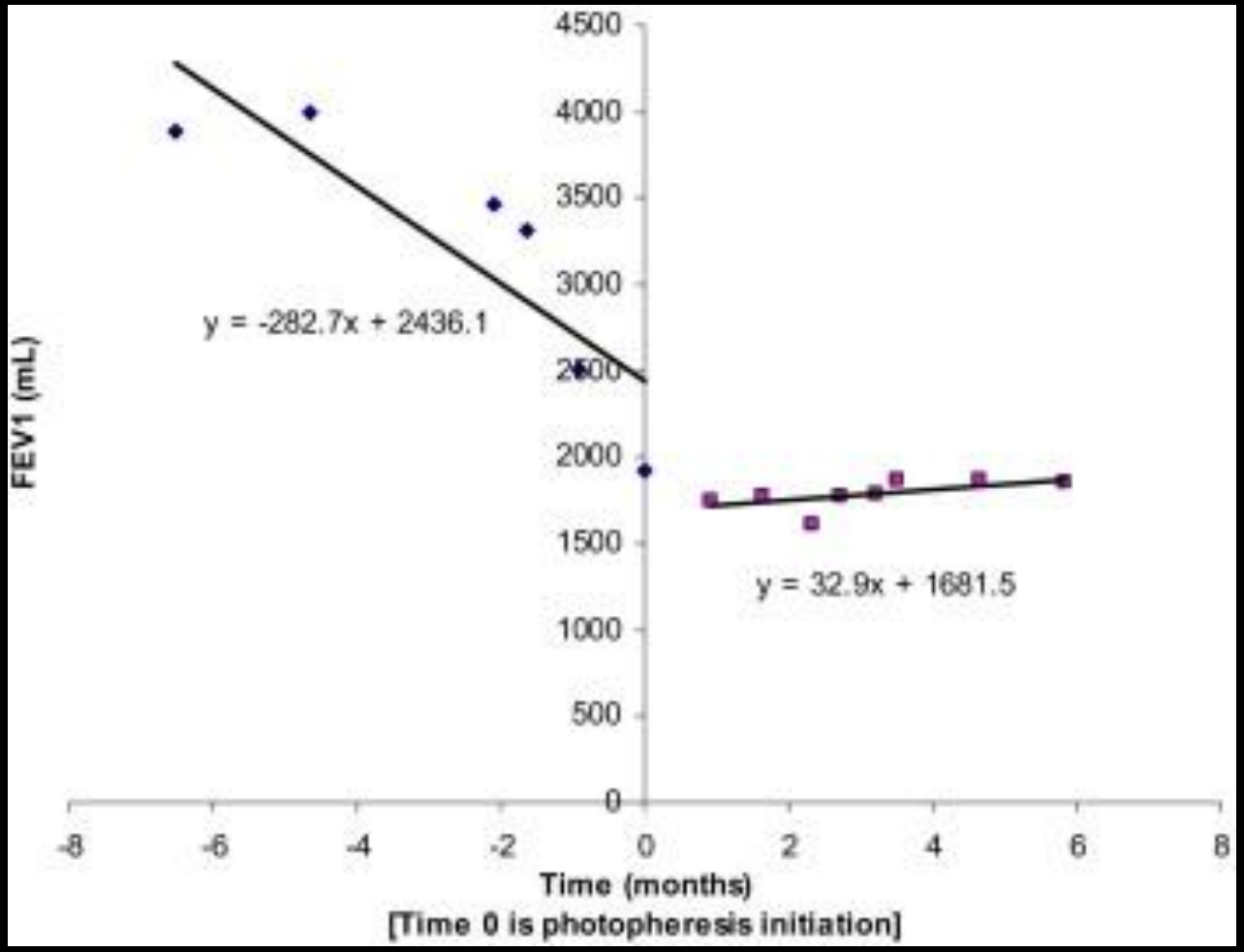
- ECP for recurrent acute rejection in 12 patients
- ≥ 2 biopsy proven episodes of acute rejection (≥ grade A2)
  - All except one had follow-up biopsy during ECP
  - Only 2 patients had an episode of ≥ grade A2 rejection
  - None developed BOS with clinical stabilization
- No adverse effects
- Median survival from LTx 7 yrs, from ECP 4.9 yrs

The Efficacy of Photopheresis for BOS

Morrell. JHLT 2010;29:424

- 60 patients with BOS between Jan 2000-Dec 2007
  - 34 early- (within 2 years) and 26 late-onset BOS
- Primary endpoint: rate of change in lung function before and after initiation or ECP
- BOS stage prior to ECP
  - Stage I: 8.3%, II: 33.3% and III: 58.3%
- ECP schedule (cycle=2 days)
  - 5 cycles first month, 4 cycles in next 2 months and 3 cycles next 3 months to complete 6 months

Absolute FEV_1 Pre- and Post-ECP Slope of Linear Regression Line



Patient Demographics

Morrell. JHLT 2010;29:424

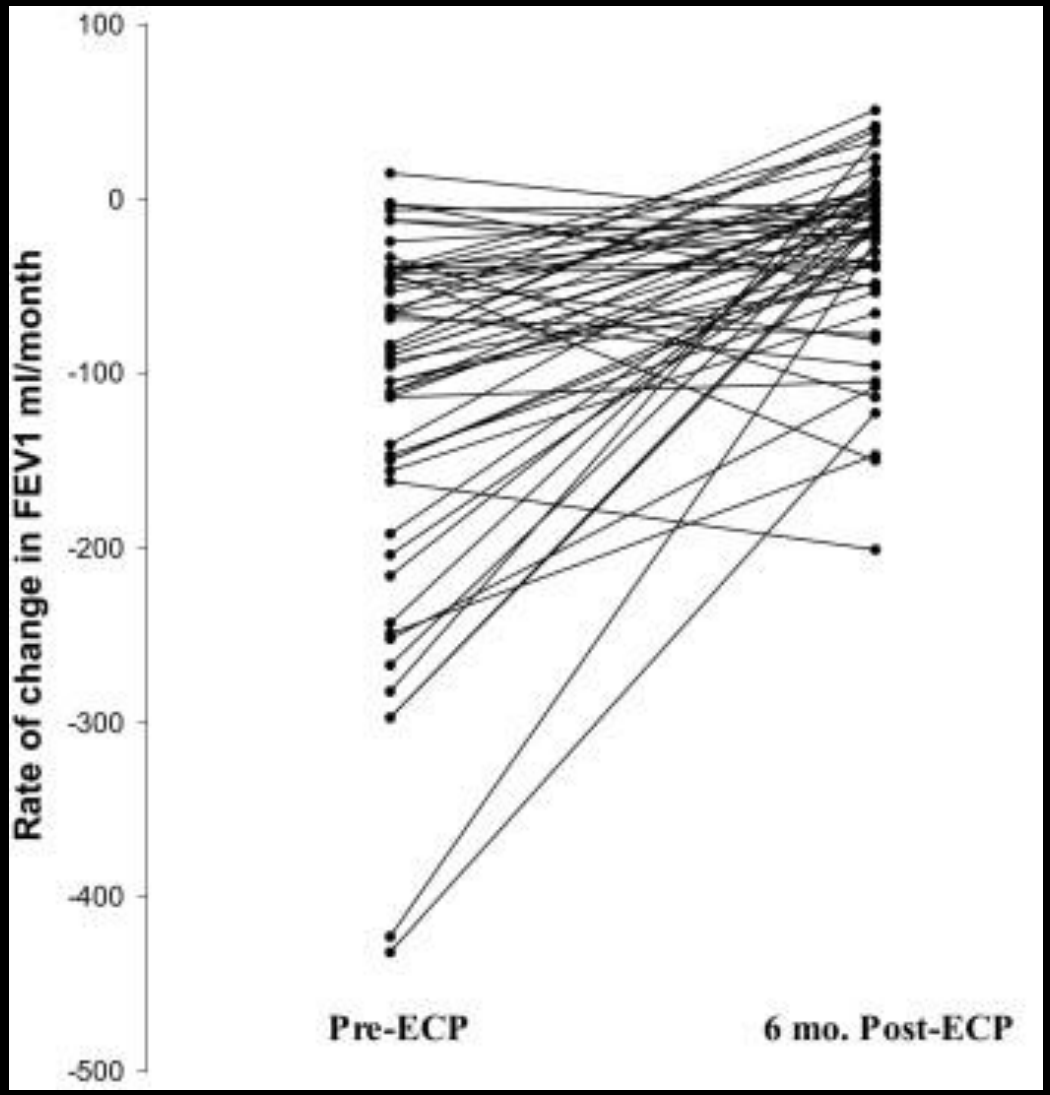
Demographics	Result No (%) or Median (Range)
Patients	60 (100)
Age (years)	58 (21-72)
Gender (male)	32 (53)
Pretransplant diagnosis	
COPD	26 (43)
CF	11 (18)
IPF	9 (15)
Type of Ltx (Bilateral)	57 (95)
BOS stage	
1	5 (8.3)
2	20 (33.3)
3	35 (58.3)
Prior ATG treatment	58 (96.7)

Results (I)

Morrell. JHLT 2010;29:424

- **6-month pre and post-ECP treatment**
  - **Pre-ECP mean rate of decline in FEV_1 -116 ml/mo**
  - **Post-ECP mean rate of decline in FEV_1 -28.9 ml/mo**
  - **Mean difference in rate of decline 87.1 ml/mo (95% CI 57.3-116.9 ml/mo, p<0.0001)**
  - **Decline in FEV_1 in a 6-month period 696 ml vs 173 ml**
- **When FEV_1 was entered as 0 in patients who died after initiation of ECP, mean difference in rate of decline was still significant (58.7 ml/mo, p=0.003)**
- **When 5 BOS stage I patients were excluded, mean difference in rate of decline remained significant**

Change in Rate of Decline in FEV_1

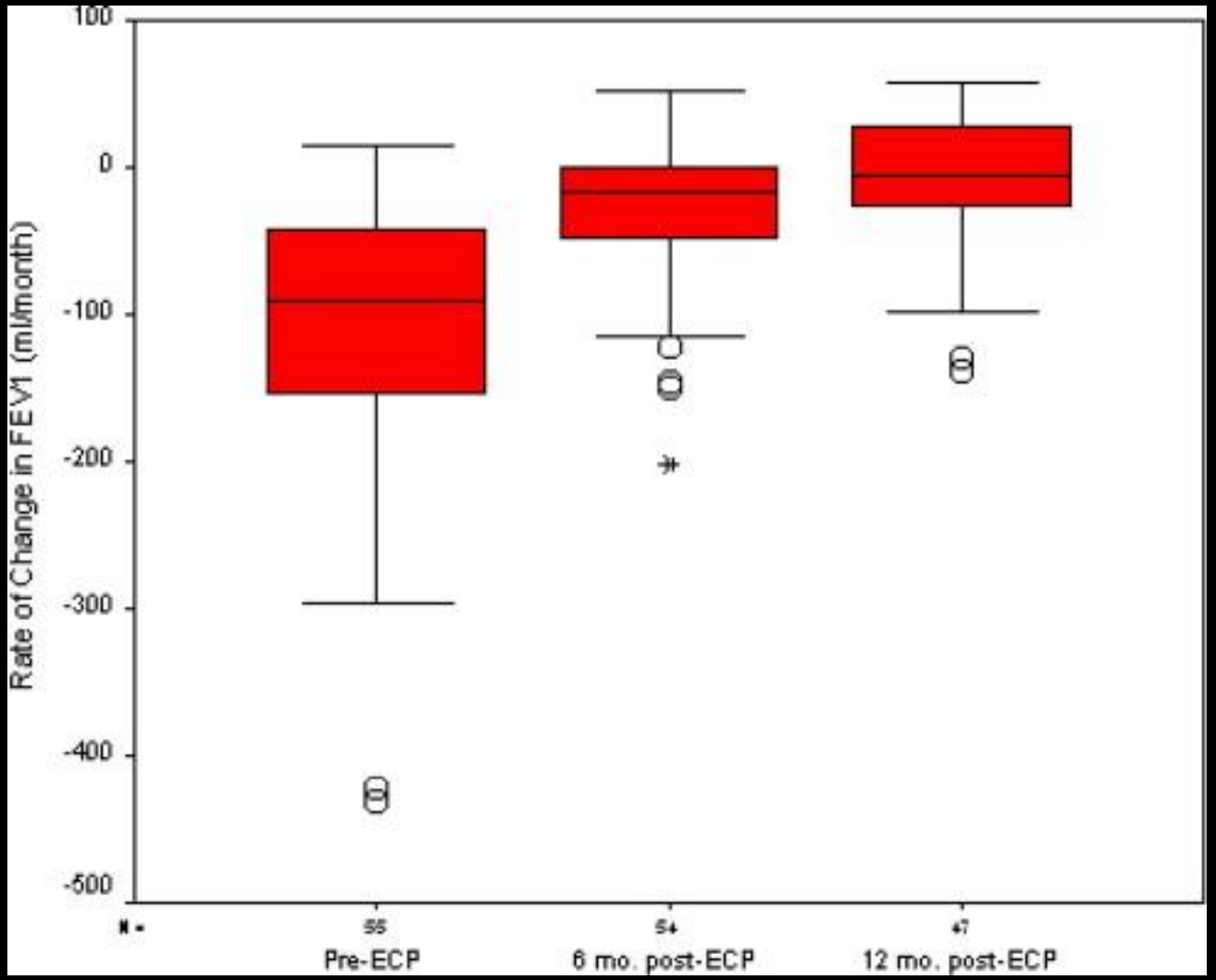


Results (II)

Morrell. JHLT 2010;29:424

- **Rate of decline was reduced after initiation of ECP in 44 patients (79%)**
  - **14 (35%) of these patients had an improvement in FEV_1 with an increase above pre-ECP values**
  - **Mean rate of increase in these patients was 20.1 ml/mo and mean gain in lung function in 6 mo was 120.6 ml**
- **Clinical characteristics were not predictive**
- **12-month efficacy in the mean rate of FEV_1 decline**
  - **-21.4 ml/mo and decline of 128.4 ml in 12 month period**
  - **Mean difference pre and post-ECP 94.6 ml/mo ($p<0.0001$)**

Rate of Decline in FEV_1 Pre-ECP, 6 months and 12 months Post-ECP



Safety and Tolerability

- 10 of 60 patients had complications
- 8 (13%) with indwelling catheter related bacteremia
- 1 with partially occlusive thrombus in SVC
- 1 with transient hypotension during ECP
- No malignancies

Guidelines On The Use of Therapeutic Apheresis in Clinical Practice-Evidence-Based Approach

Apheresis Applications Committee of the American Society for Apheresis

Disease	Modality	Category	Recommendation Grade	Page
Lung Allograft rejection	**ECP**	**2**	**1C**	**126 Refs 173, 174, 400-412**

Category 2: Disorders for which apheresis is accepted as a second-line therapy, either as a standalone treatment or in conjunction with other modes of therapy

Recommendation Grade: Strong recommendation, low quality evidence; from observational studies or case series

Implications: Strong recommendation but may change when higher quality evidence becomes available

J Clin Apheresis 2010;25:83-177

Extracorporeal Photopheresis (ECP)

- Autoimmune diseases
  - Scleroderma: Category 4, grade 1A
- Graft versus host disease (skin vs non-skin)
  - Category 2 and 3; grade 1B and 2C
- Cutaneous T-cell lymphoma (erythrodermic versus non-erythrodermic)
  - Category 1 and 3, grade 1B and 2C
- Prophylaxis and treatment of heart transplant rejection
  - Category 1 and 2, grade 1A and 1B
- Lung transplant rejection
  - Category 2, grade 1C

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- **Frequency**
  - **Variable: Biweekly to every 2 weeks, larger intervals of every 4-6 weeks reported**
  - **Generally weekly cycles for 4-6 wks, then every other week for 6 weeks followed by monthly cycles**

- **Duration and discontinuation**
  - **Optimal duration unknown**
  - **Number of treatment cycles varied between 6-24**
  - **Long-term continuation may be necessary in responders**

Conclusions

- **BOS is the single most important cause of limited long-term survival after lung transplantation**
- **There are limited treatment options for BOS, none of which have been approved**
- **Photopheresis is one treatment option for BOS, which has been shown to result in preservation of lung function with low side-effect profile**
  - **Accepted as second-line therapy and recommended strongly by the American Society of Apheresis**
  - **ECP should be made available for patients with BOS**