Title: Heterogeneity within chronic lung allograft dysfunction: A BAL analysis

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Body: It became clear that patients suffering from irreversible Chronic Lung Allograft Dysfunction (CLAD) after lung transplantation (LTx) can be subdivided in at least two phenotypes based on pulmonary function (Restrictive Allograft Syndrome, RAS vs. Bronchiolitis Obliterans Syndrome, BOS). Underlying mechanisms remain elusive A retrospective analysis of our LTx cohort (2003-2012) was performed (n=380) to identify all patients with an irreversible FEV1 decline. They were further classified as BOS or RAS patients according to the classical definitions. BAL was performed with 2x50 cc saline at the moment (±1 months) of CLAD diagnosis. Classical BAL cellular analysis was done and IL-6 and IL-8 levels were measured using ELISA (Invitrogen). C-reactive protein was measured in serum (Tina-quant CRP latex assay). 25 RAS patients were identified, of whom 20 BAL samples at diagnosis were included and compared with 52 BAL samples of 79 BOS patients. We could identify significant differences in % BAL neutrophils (p=0.035), macrophages (p=0.0010), eosinophils (p=0.025), total cell count (p=0.031) and IL-6 (p=0.0092) (table 1). Serum CRP was higher in RAS compared to BOS (p=0.0013). More RAS patients (15/20) were already under active azithromycin before diagnosis of CLAD compared to BOS (22/52) (p=0.013). There was no difference in immunosuppression. Significant differences in the BAL cellular profile were detected, which may point to different mechanisms.