P55 *ACHROMOBACTER XYLOSOXIDANS*: FOLLOW-UP OF 20 PATIENTS WITH CHRONIC INFECTION

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Background: *A. xylosoxidans* (Ax) is capable of persistent infection of the respiratory tract of Cystic Fibrosis patients although its contribution to pulmonary decline in this population is not clear.
Aim: To evaluate pathogenic role of Ax studying lung function and nutritional status in CF patients with chronic Ax infection.
Methods: Data (FEV1, FVC, BMI, sputum and number of IV therapy) of 20 CF patients in follow-up at our centre were studied retrospectively at the time of establishment of infection (T0), one year before (T-1) and one year after (T+1) and were then compared. Statistical analysis was performed by Student's T test. Mean age of the 20 (13 females) patients was 14.5 (range 6.2–23.3) at T0.
Results: Lung function showed a slight decrease in the year before the acquisition of Ax both in FVC (91.2±20.4 vs 86.1±12.6%/predicted $p=0.22$) and FEV1 (84.4±20.5 vs 79.1±16.3 %/predicted $p=0.09$), without reaching statistical significance. Respiratory data showed no deterioration in the year after infection: FVC (88.4±18.1 vs 86.1±12.6%/predicted $p=0.47$) and FEV1 (82.9±23.2 vs 79.1±16.3 %/predicted $p=0.26$). However, the number of respiratory exacerbations was much higher in the year after colonisation as demonstrated by the i.v. treatment mean days per patient (12.1±15.5 vs 3.1±6.5, $p=0.03$).
Nutritional status remained unchanged during the study period as demonstrated by BMI of T-1 vs T0 (18.1±2.9 vs 18.1±3.1 $p=0.77$) and T0 vs T+1 (18.1±3.1 vs 18.7±2.9 $p=0.07$).
Conclusion: The pathogenic role of chronic infection by Ax seems to be relevant in terms of therapeutic burden for patients in the short-term. A key factor would be monitoring the evolution of the patients chronically infected by Ax.

P56 OXIDATIVE STATUS CHANGE IN CYSTIC FIBROSIS (CF) AND ORAL ADDITION WITH WHEY PROTEIN ISOLATE WITH HIGH CONTENT OF CYSTEINE: PRELIMINARY OBSERVATIONS

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Oxidative status has a role in the progressive lung damage in CF. Glutathione is an important defence from pro-antioxidant agents and it is reduced in CF. Cysteine is the amino acid that gives to glutathione antioxidant status. The objective of this study is to reduce the oxidative status in CF with oral addition of whey protein isolate with high content of cysteine (PROther). We recruit CF patients older than 6 years, with a FEV1<70%, with a BMI <21 kg/m2 in adults and with a weight <25° centile in children. Oxidative status is estimated on a blood sample with d-ROMs test and BAP test that can measure oxidative stress and antioxidant status respectively. The study has started in May 2007 and will last for 12 months. Patients will be checked every three months. We have planed the enrolment of 50 patients at least. During the follow-up at every examination we will control oxidative status, clinical conditions (nutritional status, growth, lung function), compliance to the administration of PROther, alimentary intake and Quality of life. We recruited 32 patients still now. All cases show a pathological condition of oxidative status. Oxidative stress is increased in all patients and in 52% of cases is very serious. Antioxidant status is normal in 46% of cases and 14% show a high deficiency. Four patients deserted the study for a bad compliance to the administration of PROther not related to the product. In 6 patients we have done the first control after three months from the recruitment. All these cases show an improved oxidative status. Oxidative stress has become normal in one patient. Antioxidant status has become normal in 4 cases. All 6 patients report subjective clinical improvement. On the base of the clinical parameters, respiratory and nutritional conditions are stable in 4 cases and improved in 2. The quality of life test is better in all patients. Collected data confirm a high level of oxidative status in CF patients. Oral addition of whey protein isolate with high content of cysteine seems efficacious to improve the oxidative status. Oxidative status improvement could correlate to a clinical improvement. These observations coming from preliminary data must be confirmed. We think useful to continue the valuation of the efficacy of oral addition of PROther and we consider antioxidant therapy potentially important in CF.

P57 CYTOKINE PROFILES IN DIFFERENT MATRIXES (SERUM, SPUTUM AND EXHALATE) OF CYSTIC FIBROSIS PATIENTS

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The hallmarks of cystic fibrosis (CF) lung disease are bacterial infections by opportunistic pathogens and chronic inflammation, characterized by polymorphonucleate neutrophils predominance, progressing to obstructive lung disease and bronchiectasis.
High levels of sputum tumor necrosis factor (TNF)-α and interleukin (IL)-8 and serum IL-6 have been found in CF patients. The aim of this study was to analyze the major cytokines such as IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-10, interferon (IFN)-γ, the chemokines IL-8, monocyte chemoattractant protein-1 (MCP-1) and the growth factors epidermal growth factor (EGF) and vascular endothelial growth factor (VEGF) before and after antibiotic therapy in serum, sputum and exhalate in order to clarify the process involved in the CF inflammation and to evaluate which is the best matrix which can define this process.
We considered 10 CF patients (median age 19.5± 4, 6 M, 4 F) who were admitted at the CF Center of the University of Milan for i.v. antibiotic therapy during acute respiratory exacerbation. Before and after treatment all patients underwent routine laboratory determinations, sputum culture and standard spirometry. Serum, sputum and exhalate interleukins, chemokines and growth factors were analyzed simultaneously by means of the Evidence® biochip array (Randox) on semiautomated instrument. Results at admission and the percentage of significant changes after six months are reported in the table. After treatment, chemokines and growth factors decreased in a different manner for the considered matrix, only VEGF seemed to be always significantly decreased. No significant change was found for IFN-γ, IL-6 and IL-4.

	pg/ml	IL-2	IL-4	IL-6	IL-8	IL-10	VEGF	IFN-γ	TNF-α	IL-1α	IL-1β	MCP	EGF
Serum	Mean	5.8	4.1	34.7	378	1.5	187	3.41	8.06	0.68	2.28	367	135
	SD	4.6	3.5	69.0	935	1.4	128	3.59	5.83	0.74	2.82	286	107
	change (%)	−26					−41		−34			−28	−56
Sputum	Mean	6.9	12.2	10.5	21852	6.2	2297	1.66	153	102	1344	66	493
	SD	11.0	6.1	12.4	15540	10.9	1412	5.71	239	123	1103	72	548
	change (%)						−78			−41	−56	73	−10
Exhalate	Mean	2.1	4.6	0.2	0.4	0.6	12.2	3.43	1.79	0.43	1.24	2.47	0.60
	SD	4.0	4.9	0.3	0.2	1.1	32.2	9.74	3.93	0.22	2.11	3.94	0.25
	change (%)				−17	−52	−75			−12	−59		

In conclusion, antibiotic therapy in CF patients could be monitored by cytokine profiles in sputum and serum, while exalate levels are too low to be useful. VEGF, a growth factor involved in tissue remodeling, needs further studies.

P58* CYSTIC FIBROSIS RELATED DIABETES IS ANTICIPATED BY REDUCED INSULIN SECRETION DURING OGTT

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Diabetes in Cystic Fibrosis (CFRD) is increasingly common with advancing age because of a combination of insulin resistance and insulin secretory defects. Many patients are normoglycemic or even hypoglycemic after overnight fast, and there are repeated changes of glucose tolerance status from normal to diabetes and vice-versa, for many years and for unclear reasons. These features render difficult the prediction of CFRD development.
This study aimed to detect predictive factors of CFRD development in patients routinely undergoing yearly Oral Glucose Tolerance Test (OGTT) evaluations.
Starting from 2002, all patients followed at the CF Center in Milan aged >10 years and without established CFRD undergo OGTT yearly. Among those who received their first OGTT between 2002 and 2004, 14 had developed definitive diabetes by April 2007. Each of them was matched with patients of same sex and age, who underwent an OGTT in the same month and year but did not develop CFRD ($n=20$). Logistic regression, controlled for age, sex and follow-up time, was used to identify CFRD predictors among factors including glucose, insulin and c-peptide concentrations and area under the curve (AUC) during OGTT, insulin sensitivity indexes (HOMA and QUICKI).
In the group that developed CFRD, baseline glucose concentration was increased (92±6 vs 72±3 mg/dl, mean±SEM, $p=0.034$) whereas insulin and c-peptide concentrations were similar (5.4±0.61 vs 7.8±1.4 μU/ml, and 1.4±0.1 vs 1.4±0.2 ng/ml). Glucose ($p=0.010$) and insulin AUCs ($p=0.030$) were the most important

predictive variables, respectively directly and inversely related to CFRD development (pseudo R^2 for the model: 0.581, $p < 0.001$). Glycated hemoglobin and baseline glucose concentrations were directly related with outcome at univariate analysis whereas c-peptide concentrations were inversely related. In contrast, no relationship emerged between insulin-sensitivity indexes and outcome. Anthropometric (weight, height z scores, BMI) and pulmonary function indexes were also unrelated.
Conclusions: Defects in insulin secretion are determinants of subsequent CFRD development. The evaluation of insulin concentrations during OGTT may be helpful in CFRD prediction.
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P59 CONTINUOUS SUBCUTANEOUS GLUCOSE MONITORING IN CYSTIC FIBROSIS (CF) PATIENTS

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Objectives:
1. To study the effectiveness and reliability of the continuous monitoring of blood glucose (CGMS) in CF patients, to be able to identify at an early stage any condition of glycemic intolerance (IGT) or even diabetes.
2. To evaluate if the pre-diabetic treatment with insulin may lead to an improvement of CF pts glyco-metabolic control and of other clinical parameters such as BMI and FEV1.

Materials and Methods: We evaluated 10 CF pts (5 M and 5 F) with standard OGTT or altered baseline glycemic values. These pts had also shown a decrease in FEV1 and BMI values during the 2 years before the beginning of the study.
A microdialysis fiber was inserted subcutaneously into the periumbelical region and perfused with a buffer solution. Glucose concentrations in the dialysate were measured every 3 minutes by the glucose sensor over a 48-h period, during which 6 capillary blood samples were also collected before and after the 3 mean meals to evaluate the correlation between CGMS and traditional methods. The pts diagnosed for Cystic Fibrosis Related Diabetes (CFRD) as a result of monitoring, began insulinic therapy. After a follow-up period of 14 months glycaemia, FEV1 and BMI were evaluated again for each of them.
Results: Both the insertion of the fiber and the wearing of the device were well tolerated by the pts. Subcutaneous glucose levels were well correlated with capillary glucose measurements ($r = 0.88$, $P < 0.001$) over a wide range (45–250 mg/dl) for up to 48 h. An analysis of 120 relevations showed a linear relationship between the CGMS and serial capillary blood glucose levels, and 98.33% of the data fell in the A and B regions of the error grid analysis. The results of CGMS for 48 hours confirmed the presence of IGT in all pts and identified early CFRD in 6 pts who had glycemic peaks > 200 mg/dl. After they were given insulinic therapy they showed an improvement of the glyco-metabolic control and an increasement of 6% of BMI values during the 14 months of follow up. FEV1% values were unchanged.
Conclusions: The CGMS demonstrated high reliability and provided much more informations about glycemic excursions and glucose trends than the traditional diagnostic methods, making it possible to identify earlier the CFRD in CF pts and begin as soon as possible an individual insulinic treatment.

P60 EXCEPTIONALLY EARLY OCCURRENCE OF EBV RELATED LYMPHOMA AFTER LUNG TRANSPLANTATION

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We basically describe the case of a CF pt that developed fatal EBV related lymphoma 4 months after lung transplantation. A 17 years old female CF pt underwent bilateral sequential lung transplantation uneventful in May 2006. All other recipients from the same multi-organ donor are currently alive and well with no evidence of lymphoproliferative disease. Standard immunosuppression was instituted with Tacrolimus, Azathioprine and Prednisone. In October 2006 the pt was readmitted to the hospital with a decrease of FEV1 of > 10%, increased inflammation index, anemia, low platelets count, fever (39–40º). Chest x-ray and CT showed diffused peribronchial infiltrates. Physical and abdominal examination was negative; abdominal echography was also negative. Wide spectrum antibiotics were administered. Bacteriology, virology and fungal exams were performed, but all proved negative, including the search for EBV and CMV. Still, high fever (39–40º) persisted along with lymphocytosis and neutropenia. With the suspect of CMV infection Ganciclovir (10 mg/kg/die IV) and immunoglobulins were administered. Immunosuppression was discontinued. Ten days after admission, without any clinical improvement, the spleen became palpable and a laterocervical lymphonodus evident. A biopsy was immediately performed; abdominal echography and CT were also performed. Multiple lymphadenopaties were revealed, along with hepatosplenomegaly and moderate pleural effusion. EBV related lymphoma was suspected on the basis of these findings and Retuximab therapy was started. The clinical setting deteriorated over the following days and multiple organ failure developed. The patient died on the 18th day after admission.
Necropsy confirmed clinical findings, and in situ hybridization confirmed the expression of EBV genome in over 90% of the large B Lymphoma cells.
We believe it is important to be aware that Lymphoma can develop also in the early postoperative period after lung transplantation. Although it is common knowledge that lymphoproliferative disease can occur in as much as 10% of lung transplanted patients, this usually occurs years after the transplant. The early occurrence of this dramatic complication certainly entails exceptional severity and difficult diagnostic problems, which might be facilitated by its awareness.

P61 TOTIRESISTENT *BURKHOLDERIA CEPACIA* COMPLEX SEPSIS IN A 62-YEAR-OLD WOMAN WITH CYSTIC FIBROSIS

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Colonization of cystic fibrosis (CF) airways with *Burkolderia cepacia* complex (Bcc) is associated with an accelerated pulmonary deterioration and increased mortality. Bcc sepsis is one of the most dramatic events that can occur in a patient chronically infected.
We describe the case of a 62-year-old woman with CF (diagnosed at the age of 50), with type II chronic respiratory insufficiency in long term oxygen therapy and nocturnal non-invasive ventilation, severe obstructive respiratory impairment (FEV_1 29% of the predicted value), totiresistant *B. cenocepacia* (genomovar III) chronic pulmonary infection. On July 2007 she presented with obnubilation, worsened general and respiratory conditions and pyrexia; blood culture detected Bcc septicaemia. The organism was resistant to all antibiotics singly and synergically *in vitro* tested, and the sepsis occurred while she was being treated with intravenous ceftazidim and oral co-trimoxazole.
Multiple antibiotics, including levofloxacin per os, ceftazidim i.v., meropenem as continuous intravenous infusion associated with high-dose i.v. methylprednisolone were administered.
Despite the fact that Bcc was resistant to all tested antibiotics, her clinical conditions progressively improved and she overcame the acute Bcc sepsis.
The exact mortality rate associated with Bcc septicaemia in CF patients is not known, but it is thought to approach 100%.
We speculate that the intensive antibacterial therapy, in particular the continuous intravenous infusion of meropenem, and the anti-inflammatory effects of high-dose corticosteroids, could significantly contribute to the survival of the patient.
Moreover, the favourable outcome of this case highlights that the resistance to antibiotics detected *in vitro* does not always correspond to clinical inefficacy.

P62 FUNCTIONAL ENDOSCOPIC SINUS SURGERY (FESS) IN PATIENTS WITH CYSTIC FIBROSIS (CF)

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Objective: To determine the effectiveness of FESS through the reduction of symptoms and the improvement of related clinical parameters in children and young adults with CF and sinonasal disease (SND).
Materials and methods: 12 children and young adults (15 years median age; range 7–38) with medically refractory SND were examined before and after FESS. The main outcome measures were sinonasal symptoms, spirometric values (forced expiratory volume in 1 second, FEV1, and peak expiratory flux, PEF), and number of hospitalizations. The extent of polyposis was graded endoscopically and on computer tomography images. The sinonasal symptoms were inquired through a questionnaire pre- and postoperatively.
Results: The mean follow up time after surgery was 15.1 months. Postoperatively, polyp recurrence was seen in 5 pts of 12. Before surgery, bilateral nasal polyposis was an endoscopic finding in 11 pts of 12, and 50% of them had polyps occluding the middle meatus (grade 2 polyposis). 4 pts had undergone previous polypectomy in other centers. The symptoms complained were nasal obstruction (100%), nasal discharge and postnasal drip (67%) and anosmy (50%). Only 2 pts complained headache. After FESS, 4 pts reported no nasal obstruction and marked decline in the frequency of nasal discharge and postnasal drip (25%). Headache shows no improvement.
Spirometric values and the number of pulmonary exacerbations were found to be related to the severity degree of lung disease. On the basis of these observations CF