SIFC
SOCIETÀ ITALIANA
PER LO STUDIO DELLA FIBROSI CISTICA

XXVII Congresso Italiano della Fibrosi Cistica

XVII Congresso Nazionale della Società Italiana per lo studio della Fibrosi Cistica

Napoli,
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ABSTRACT

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Detection and functional characterization of an ALU insertion in the *CFTR* gene

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Background: Rare mutations in the CFTR gene have been poorly studied making it difficult to determine a genotype-phenotype correlation, understand the effect of these mutations on CFTR activity, and choose possible therapeutic approaches. Furthermore, some of these mutations such as large insertion/deletions are challenging to be identified even by Next Generation Sequencing and different approaches need to be used for a correct genetic analysis. Here we report the identification and functional characterization of a rare event of an ALU insertion in the exon 15 of the CFTR gene.

Materials and Methods: MiSeq (Illumina), Nanopore, and Sanger sequencing methods and MLPA assay were used to identify *CFTR* mutations. Fluorescence-activated cell sorting and Fluorescence based assay was used to assess CFTR processing and function.

Results: *CFTR* gene sequencing performed by MiSeq revealed any SNVs of relevant clinical significance, while the CNV analysis showed a warning at amplicon 2 level of exon 15 of the gene, suggesting a likely deletion event, not confirmed by MLPA analysis, the gold standard for gene deletions/duplications analysis. At this point, the patient's diagnosis would be closed as negative. However, a deep analysis by Sanger and Nanopore sequencing showed the insertion of an ALU sequence in the exon 15. We hypothesize that this ALU insertion caused the amplification of one of the three amplicons of exon 15 to fail, resulting in a deletion signal. The functional analysis, based on halide sensitive YFP assay, performed by inserting the ALU sequence in the CFTR coding sequence, revealed that this mutated form of the CFTR protein is unable to function as chloride channel and it is not CFTR modulators responsive.

Conclusion: With these data, we want to emphasize that NGS results need to be carefully interpreted and corroborated by using different approaches to have a correct genetic analysis. Finally, this study confirms the importance of functional studies in the cystic fibrosis theratyping and personalized medicine (1, 2).

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Anti - *P. aeruginosa* antibodies in patients not chronically infected after early eradication treatment.

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Background: *P. aeruginosa* (Pa) lung infection causes a lung function decline and a systemic increase of anti-Pa serum antibodies. In the early phases of Pa infection early eradication treatment can clear the bacterium.
Aim: The purpose of this study was to evaluate, as marker of the eradication treatment in early stages of Pa infection, the anti-Pa immune response in patients not chronically infected.

Methods: Surveillance respiratory cultures are typically performed every three months and patients were classified according to their microbiological status (Leeds definition). A total of 135 sera from 75 not chronically infected patients (median age 8.62 years, range 0.86-32.9) in a regular follow-up in the period 2008-2016 were analyzed using Enzyme-Linked Immuno Sorbent Assay (ELISA) for the presence of IgG antibodies against Pa sonicated (St-Ag) (serogroups 1-17) (cut off >= 2.96 EU) and Pa Alkaline Protease (AP), Elastase (Ela), Exotoxin A (ExoA) (cut off borderline for titer > 500 and < 1250 and positive for titer >1250). Sera were taken at the time of Pa detection (T0) and after 6-12 months (T1) and they were diluted 1:100 for all the antigens used. The One way Anova test ant the t- test between groups was performed.

Results: At T (0) we analyzed 76 sera, the antibody titer was under the cut-off level for three out of four the antigens used (tab1). At T (1), we analyzed 58 sera and the antibody titer was significantly lower in subjects who did not showed Pa isolation during microbiological follow-up than in those with persisting Pa isolation for three out of four antigen used (tab1).

	Sera analyses (n)	IgG St-AG	AP	Ela	ExoA
T(0)§	76	1.79 ± 1.54	463 ± 702	441 ± 775	599 ± 786
T(1) after successful eradication§*	36	1.13 ± 0.96	343 ± 372	220 ± 331	380 ± 546
T(1) after unsuccessful eradication§*	22	1.97 ±1.64	508 ± 573	771 ± 944	980 ± 1162
P value**		P= 0.008	P > 0.05	P= 0.001	P= 0.005

§ Groups analyzed with the ANOVA * Groups analyzed with the t-test. **The result is significant at $p < 0.05$.

Conclusion: Antibody titers assessed before and after antibiotic therapy in patients with initial *P. aeruginosa* isolation showed a significant decrease in antibody titers against IgG St-AG, Ela and ExoA in patients clearing *P. aeruginosa* infection, whereas titers increased in patients in whom antibiotic therapy failed to eradicate the organism. Although serum antibody titers are on average low at the time of first *P. aeruginosa* isolation, they may be useful to monitor early Pa infection and to monitor early eradication treatment.
Funding: The work was funding by Tuscany Region grant K38.
The study received ethical approval from the Ethics Committee of Meyer Hospital and written patient consent was obtained.

Pancreatitis-Associated Protein in Neonatal Screening for Cystic Fibrosis: comparison between IRT/DNA/IRT2 and IRT/PAP/DNA protocols.

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Background: Pancreatitis-Associated Protein (PAP) is a secretory protein which is not measurable in blood in normal conditions and is increased in newborns with Cystic Fibrosis (CF).[1] Furthermore, previous studies have reported as PAP-based CF newborn bloodspot screening (NBS) protocols detect less CFTR-Related Metabolic Syndrome (CRMS)/ CF Screen Positive, Inconclusive Diagnosis (CFSPID).[1] In this ongoing study we compared IRT/DNA/IRT2 and IRT/PAP/DNA NBS protocols in Tuscany region.

Materials and methods: This prospective study started in June 1st 2020; we report the outcomes until May 31st 2021. In parallel to usual protocol (IRT/DNA/IRT2, protocol 1), PAP was assayed in newborns with IRT>99th percentile (IRT/PAP/DNA, protocol 2), calculated on the basis of newborns IRT cutoff values every four months. We defined an infant as CF NBS positive if PAP was > 1.8 µg/L for IRT value between 99th percentile and 100 µg/L or > 0.6 µg/L for IRT value >100 µg/L.[2]

Results: 193 subjects had IRT>99th percentile. We identified 3 CF and 9 CRMS/CFSPID with protocol 1 and one CF and 5 CRMS/CFSPID with protocol 2. In order to increase the sensitivity of protocol 2, we changed the cutoff as follow: positive for PAP > 1.8 µg/L and IRT between 99th percentile value and 90 µg/L or PAP > 0.6 µg/L and IRT value > 90 µg/L. In this way we identified all 3 CF diagnosis and the same 5 CRMS/CFSPID subjects (Table 1). Among 193 subjects with IRT > 99th, 61 (32%) were positive for PAP: 13 (21%) out of 61 had IRT > 90 µg/L and PAP > 0.6 µg/L, while 48 (79%) had IRT in the range 99th and 90 µg/L and PAP > 1.8 µg/L. We performed 61 sweat chloride tests with protocol 1 and 23 sweat chloride tests with protocol 2 after lowering IRT value at 90 µg/L.

Conclusions: our preliminary results show that PAP-based CF newborn bloodspot screening could reduce the number of sweat chloride tests and the detection of CRMS/CFSPID subjects. Further data and a longer follow up are needed to confirm our results and to identify the advantages of PAP test.

Table 1. CF and CRMS/CFSPID identified in the study.

		IRT	PAP	First CFTR variant	Second CFTR variant	Cl value at diagnosis (mEq/L)	Last Cl value (mEq/L), age (months)
CF	1	98	1,53	N1303K	N1303K	NA	/
	2	75	>max	L867X	G378X/I148T	109	/
	3	91	1,13	F508del	UNˆ	66-65	/
CRMS/ CFSPID	1*§	93	2,31	E585X	UNˆ	48-56	16 (18)
	2	47	0,60	F508del	(TG)12T5	50-36	45 (11)
	3	53	1,25	F1052V	621+3A>G	32	NA
	4	54	0,27	F508del	L997F	36-28	20 (8)
	5*	58	3,01	F508del	S912L	36-34	48 (9)
	6	58	1,11	N1303K	F508C	31-19	25 (6)
	7*	129	3,02	2789+5G>A	5T-12TG	39	34 (6)
	8*	54	3,20	F508del	L467P	31-24	NA
	9*	54	2,01	F508del	UNˆ	49-44	NA

Abbreviations: CRMS/CFSPID: CFTR-Related Metabolic Syndrome/ CF Screen Positive, Inconclusive Diagnosis; CF: Cystic Fibrosis; PAP: Pancreatitis-Associated Protein; IRT: immunoreactive trypsinogen; UN: undetected; NA: not available (quantity of sweat < 75 mg); >max: value beyond the upper limit of detection

* CRMS/CFSPID identified with both protocols.
ˆ after gene sequencing (detection rate 98%)
§ this subject was the only one with a conclusive diagnosis as healthy carrier

Funding: This work was supported by Tuscany Region (K36)
The study received ethical approval from the Ethics Committee of Meyer Hospital.

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Bronchial tolerance to colistin inhalation with I-neb system and standard nebuliser: a case report from Cystic Fibrosis Regional Centre of Verona

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Background

Colistin is regularly used as antipseudomonal therapy in Cystic Fibrosis (CF). Nebulized colistin is generally well tolerated; however it can cause adverse respiratory symptoms.
It is widely reported the challenge of a correct inhalation technique that involves all inhalation devices.
Efficient and breath-controlled nebulizers have been developed in recent years, such as the I-neb nebulizer: a portable, electronic, vibrating mesh nebulizer.
Based on the Adaptive Aerosol Delivery (AAD) technology, the I-neb AAD System has been designed to continuously adapt to changes in the patient's breathing pattern, to pulse aerosol only during the inspiratory part of the breathing cycle, and to deliver homogenously-sized aerosol particles.
In this manuscript we report a clinical case about the effects of 2 million international units (MIU) colistin (Promixin®, Zambon spa) nebulized with I-neb AAD system, compared to traditional systems.

Case Report

The study subject is a 25 year-old CF male (F508del homozygosis) with FEV_1 74% of predicted, with *Pseudomonas aeruginos*a (mucoid strain) chronic colonization, routinely treated with inhaled Tobramycin and Colistin since 2013, both delivered through a jet nebulizer-compressor system.
In March 2019 the patient was hospitalized for respiratory exacerbation. The subject reported a reduction of bronchial tolerance to nebulized colistin, with consequent hacking cough, sense of bronchial constriction, chest tightness in the last couple of months. Those symptoms were reversed by short-acting bronchodilator inhalation.
At the challenge test with colistin 2 MIU (delivered through standard jet nebulizer) there were no significant changes in the pulmonary function test (post inhalation FEV_1 -80 ml, -3%), nevertheless subjective feeling of chest discomfort had recurred. Therefore, this therapy was stopped for persistence of symptoms.
A second challenge test with Promixin® nebulized with the I-neb AAD system was performed. Good tolerability was recorded along with no significant fall in FEV_1 (FEV_1 post inhalation -60 ml, -2%) and absence of adverse respiratory symptoms. Promixin® was then prescribed for home treatment replacing the previous formulation.
After 3 months of use, no discontinuation of treatment occurred and the subject reported no further problems and good satisfaction about the new device. Remote download of inhalation data through Insight Online software confirmed the adherence and correct inhalation technique.

Conclusions

The use of Promixin® with I-neb AAD System allowed to better prevent adverse symptoms of colistin inhalation in patients with bronchial hyperreactivity. Clinical practice should consider new inhalation devices and further research is needed to investigate complex CF cases.
Patient gave consent for the publication of clinical data.

Growing number of adults with CF: emerging challenges

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With the advances in treatments, life expectancy in Cystic Fibrosis (CF) has improved dramatically in the last 4 decades, so we have to face with complications of adulthood management.
We present two clinical cases of a 47-year-old white male (pt1) (G542X / 2789+5G→A exon 14b) and of a 24-year-old white female (pt2) (F508del/F508del) with CF complicated by uncontrolled arterial hypertension (AH).

Pt1's medical history included severe obstructive ventilatory defect, chronic P. aeruginosa colonization, treatment for pulmonary NTM infection, selective left bronchial artery embolization and osteoporosis.
Pt2's medical history included severe obstructive ventilatory defect, chronic P. aeruginosa and MSSA colonization, ABPA, IGT, CF liver disease, LUMA/IVA treatment.
The patients received a diagnosis of systemic AH.
To exclude diseases or/and secondary AH, the patients underwent a carotid ultrasound, Kidneys artery and adrenal ultrasound, renal function, aldosterone-renin ratio and urinary albumin/creatinine ratio.
Pt1 started a pharmacological treatment with Losartan (starting dosage: 12.5 mg QD); even if the dosage was increased, holter monitoring of BP was still >140/90 mm Hg.
At this point, we speculated that NaCl supplementation could have interacted on the renin activity and therefore angiotensin II. So that we decided to replace NaCl with KCl. An attempt was made with KCl (1 pill=KCl 600 mg).
We established a dosage based on previous NaCl intake: the patient was taking 4 pills of NaCl (~Cl 68 mEq) so the equivalence would have been 8 pills of KCl (~Cl 64 mEq). However, considering the concomitant high K intake, we decided to prescribe only 2 pills of KCl and maintained 1 pill of NaCl. He continued Losartan 100 mg QD.
Based on pt 1's experience, we hypothesized AH linked to salt intake (2 pill of NaCl) and we adopted the same Cl supplementation. Both pts showed a normalization of BD values maintaining normal electrolyte measurements.

Life span for CF patients is actually getting significantly longer. Faced with the lengthening of patients' lives, we must treat common adulthood pathologist as AH. Our clinical case shows how sodium supplementation complicates the management of AH while the replacement of the supplementation with KCl ensured a stabilization of BP values because potassium can lessen the blood pressure-raising effects of sodium. However, it is very difficult to ensure adequate chlorine supplementation, as the formulations currently available are unbalanced for CF needs: to ensure optimal chloride supplementation there is the risk of administering an excessive amount of potassium. It is therefore necessary to create new formulations of chlorine supplements that meet the demands of FC patients.

We have signed informed consent from patients before submitting these Case Reports.

Clinical impact of *Aspergillus fumigatus* in children with cystic fibrosis

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Background. The clinical relevance of *Aspergillus fumigatus* (Af) in cystic fibrosis (CF) is controversial. Aim of the study was assessing whether allergic bronchopulmonary aspergillosis (ABPA) and sensitization to Af affected lung function, body mass index (BMI) and exacerbation rate.

Methods. Over the year 2020, demographic data, BMI and lung function of patients with CF aged 6-18 years followed in the CF Centre of Parma (Italy) were recorded. According to total IgE, specific Af IgE, Af precipitins and sputum culture, patients were classified as: non-Af, Af sensitized, Af colonized, ABPA or *Aspergillus* bronchitis. Most recent chest CT images were reviewed and scored by Bhalla system by a radiologist blinded to clinical information.

Results. Of 38 CF patients (13.5 ± 3.7 yrs), 8 (21%) showed Af sensitization, 7 (18.4%) fulfilled criteria for ABPA, 1 (2.6%) was Af colonized and 1 (2.6%) had *Aspergillus* bronchitis. Compared to the rest of patients, those with ABPA had lower BMI (16.1 ± 1.59 vs 19.1 ± 1.86, $p<0.005$) and higher number of exacerbations/year (4.43 ± 2.44 vs 1.74 ± 2.33, $p< 0.005$). While no difference was demonstrated in lung function, ABPA patients showed a FEV1 decline of 12% over the last three years (vs -0.16% in the rest of the cohort). Compared to non-Af patients, children with ABPA and Af sensitization had more abnormalities at chest CT scan (Bhalla scores: ABPA 14±3.6 vs Af sensitization 17.1±5.8 vs non-Af patients 22.2±2.8; $p<0.005$). Patients with Af sensitization showed more exacerbations/year than non-Af patients (3.5 ± 3.2 vs 0.9 ± 2.29, $p <0.005$).

Discussion. ABPA patients had lower BMI, greater FEV1 decline and higher exacerbation rate. While maintaining normal lung function, patients sensitized to Af have more lung abnormalities and exacerbations than children with no signs of Af. Not only ABPA but also Af sensitization may have relevant clinical impact on children with CF.

Psychological impact on parents of CRMS/CFSPID subjects compared to parents of Cystic Fibrosis patients

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Background: A cystic fibrosis (CF) transmembrane conductance regulator-related metabolic syndrome (CRMS)/CF screen-positive, inconclusive diagnosis (CFSPID) labelling leads to persisting uncertainty and distress for parents.[1,2] We report the preliminary results of a qualitative and quantitative study comparing the psychological impact on parents of CRMS/CFSPID and CF patients.
Methods: CRMS/CFSPID and CF subjects born in 2019-2020 and follow at 4 Italian CF Regional Centers were enrolled. In order to evaluate the psychological impact on parents, we used three tests as quantitative tool (Generalized Anxiety Disorder Scale, GAD-7;[3] the Patient Health Questionnaire-9, PHQ-9;[4] the Italian version of the Impact of Event Scale – Revised, IES-R) and a semi-structured interview as qualitative tool, according to Faye et al.[2] The areas investigated were: parental experience, representation of the child, description of relationships, future information, health professionals involved, perception of health status, beliefs. Each interview was recorded and then transcribed verbatim, removing identifiers. The present study was approved by the ethics committee of the CF coordinating centre (Florence, Italy) and subsequently by the ethics committees of all participating CF centres.
Results: Thirty-two families were enrolled: 16 CF patients (7 born in 2019 and 9 in 2020) and 16 CRMS/CFSPID (6 born in 2019 and 10 in 2020). The experiences of anxiety (GAD-7) and depression values (PHQ-9) were higher in parents of CF children (M=8.4 vs 5.35 and M=5.7 vs 4.1). Similar results were about measurement of the traumatic impact (IES-R): the avoidance (M=1.9 vs 1.8), intrusiveness (M=2.2 vs 1.9) and hyperarousal (M=2.3 vs 1.8) subscales. Analyzing the interviews, we emphasize as there was little involvement of the family pediatrician's in child care for both groups. Furthermore, both parents of CRMS/CFSPID and CF patients considered early to think about the future communication of the child's diagnosis and evaluated the child's health condition as close to being completely healthy.
Conclusions: our preliminary results highlight a negative psychological impact of a CRMS/CFSPID label on parents, with an emotional and affective representation similar to that of CF parents. The perception of disease severity is different, with a tendency to normalization for CF parents and to underestimate future progression of a CF diagnosis in CRMS/CFSPID parents.

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An Italian centre experience with Elexacaftor-tezacaftor-ivacaftor therapy in CF patients with advanced lung disease

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Background:
Elexacaftor-tezacaftor-ivacaftor (ELX/TEZ/IVA), a triple CFTR modulator combination, has proved to be highly effective in Phe508del homozygous and Phe508del/minimal function mutation compound heterozygous patients. We report here preliminary data on efficacy and safety of ELX/TEZ/IVA in selected patients with advanced lung disease after 6 and 12 months of treatment.
Materials and methods:
We collected prospective data on patients with CF and advanced lung disease who started ELX/TEZ/IVA within the compassionate use program between December 2019 and May 2020.
Results:
Over this time period, 8 patients (6 females, 4 Phe508del-homozygous, median age of 25.2 years [range 17.8;30.7], all with pancreatic insufficiency) started ELX/TEZ/IVA. Five patients were on continuous IV antibiotic therapy and 4 were on lung transplant waiting list.
At baseline (T0), median ppFEV1 was 38.2% [range 28.1;39], median BMI was 19.4 Kg/m^2 [range 18.2;21.3] and median sweat chloride concentration was 93.3 mEq/L [range 76.7;110]. Chest imaging was assessed using the morpho-functional MR-scoring-system for CF proposed by Eichinger [1]: at T0 median global MRI score was 22 [range 17;25]. We evaluated pulmonary function (ppFEV1, days on IV antibiotics), chest imaging and nutritional status at 6 (T6) and 12 (T12) months, whereas sweat chloride concentration was determined at T12.
During ELX/TEZ/IVA, ppFEV1 improved (median increase 23.4% [range 8;34.4] and 27% [range 8;35.9] at T6 and T12 respectively), and this was also the case for BMI (median increase at T6 0.92 [range – 0.9;4.2], at T12 1.4 [range 0.5;6.1]). In addition, continuous IV antibiotic therapy was withdrawn in all patients but one within 12 months from the onset of ELX/TEZ/IVA. We observed an improvement in the median global MRI score at T6 (median MRI score at T6 15 [range 11;18], with a 31.8% reduction from T0), which was confirmed at T12 (13 [range 11;17], with a 40.9% reduction from T0). Three lung transplant candidates were removed from the waiting list in consideration of their significant clinical improvement. Median sweat chloride concentrations were reduced at T2 by 52.4 mEq/L [range 27.7;70].
Treatment was well tolerated with no report of chest tightness or wheezing during the early phase of therapy. Biliary colic occurred in 1 patient, whereas no persistent increase in liver function tests was reported. None of our patients required treatment discontinuation due to severe adverse events.
Conclusions:
Our data confirm that ELX/TEZ/IVA treatment is safe, well tolerated and effective in CF patients with advanced lung disease and may reduce the need for lung transplantation.

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RADIOLOGICAL SCORES: ADDITIONAL OUTCOME MEASURES TO EVALUATE TREATMENT WITH ELEXACAFTOR/TEZACAFTOR/IVACAFTOR IN PATIENTS WITH CYSTIC FIBROSIS AND SEVERE PULMONARY DISEASE

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Background: Elexacaftor/Tezacaftor/Ivacaftor (ETI) is the third CFTR modulator approved by the FDA and EMA that targets the defects caused by the most common CFTR mutation, F508del. ETI was able to provide significant improvements in all outcomes studied compared with comparator regimens (placebo or ivacaftor/tezacaftor) in multinational phase II and III studies. These studies considered patients with moderately impaired lung function, and data on severe pulmonary condition are limited. Further investigations using new exploratory endpoints to assess effectiveness and safety in clinical practice may be indicated. The aim of our study is to evaluate the efficacy of triple therapy on clinical, nutritional and functional status and assess possible effects on lung inflammation and anatomical structure using MRI scores in severe F/MF patients older than 12 years of age in a real life setting of observation.

Materials and Methods: 16 patients (12 females, mean age 35.31) with severe pulmonary impairment (mean ppFEV1 [SD] 45.6 [9.07]), followed at the CF Center of Verona and Treviso (Italy), started ETI in compassionate use. At baseline PA colonised 12 patients (75%), MRSA and B. cepacia 2 (18.75%), M. abscessus 1 (6.25%). 4 patients (25%) were on continuous antibiotic therapy. Lung function measurements, number of exacerbations and hospitalisations, BMI, CFQ-R, MRI scores (mBrody and DWI scores) and sweat chloride were assessed for almost 12 months after initiation of ETI.

Results: After 12 months of observation statistically significant improvements were found in ppFEV1 (+ 11.71 from baseline; $p<0.0001$) ppFVC (+11.61 from baseline; $p<0.0001$), $ppMMEF_{75-25}$ (+6.14 from baseline; $p=0.0009$), BMI values (+0.99; $p<0.0001$) and in sweat chloride concentrations (-61.17; $p<0.0001$). A reduction in the rate of pulmonary exacerbations was also seen (-0.32/month; $p = 0.0022$) and there were no hospitalisations after the start of therapy. There was a clinically significant change in the Respiratory domain of the CFQ-R questionnaire (+29.76; $p =0.0007$). MRI mBrody and DWI scores decreased during the observation period (-5.88; $p =0,04$ and -7.5; $p =0.0039$ respectively). Among the 16 patients, 2 had mild adverse events, none of them discontinued therapy.

Conclusions: These preliminary data show that ETI is effective in patients with severe disease and provide respiratory, nutritional benefit, reduce the rate of exacerbations and hospital admissions and decrease sweat chloride levels. An improvement in radiological scores was also seen, underlining that fewer pulmonary exacerbation and a reduction in lung function decline may have an important impact on chest imaging in patients using ETI.

Impact of COVID-19 pandemic on parents of children with CF: an observational study

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Background COVID-19 pandemic has disrupted children and families' everyday life. Several studies documented its impact on people with cystic fibrosis (pwCF) and their caregivers, who are already at increased risk to develop psychological symptoms of stress, depression and anxiety. Kazak et al. (2021), developed the COVID-19 Exposure and Family Impact Scale (CEFIS), aimed to evaluate how pandemic affects pediatric patients and their caregivers. Aim of the study was to assess the exposure and impact of COVID-19 pandemic on a group of Italian parents of children with CF.

Material and methods Parents of children with CF aged 4-12 years were enrolled. Exclusion criteria were: a) COVID-19 infection within two months for both parents and children; b) pre-existance of other chronic diseases. Participants completed the following self-report questionnaires: Generalized Anxiety Disorder-7 (GAD-7), Patients Health Questionnaire-9 (PHQ-9), COVID-19 Exposure and Family Impact Scale (CEFIS). The Italian translation of CEFIS was performed, following the FDA and EMA guidelines. This measurement has 3 scales: *Exposure* (experience with potentially traumatic events related to pandemic; Yes/No responses), *Impact* (perception of how pandemic affected everyday life, suggesting negative impact with a mean score >2.5; 4-point Likert Scale) and *Stress* (individual and family level, 10-point Likert Scale).

Results Twenty parents (F 90%) of children with CF (M/SD age = 8/2.9) completed the measurements. Two parents were affected by COVID-19 more than two months before the evaluation. A wide percentage of parents showed clinical scores for both anxiety and depression (80% and 65%, respectively). The 30% showed "moderate/severe" anxious and depressive symptoms. Mean stress scores indicated elevated stress both at individual and familial level (M/SD = 7.2/1.6; 7.1/1.5, respectively). Participants reported a variety of COVID-19 related events, including: stay at home orders (90%), missing an important family event (60%), and inability to visit other family members (55%) (Table 1). Concerning Impact of pandemic related events, mean score was 2.54 (SD=0.7), suggesting negative consequences on ordinary activities.

Conclusions One year after COVID-19 pandemic, psychological wellbeing of parents of children with CF appears vulnerable, with elevated levels of stress and high anxiety and depression. The adverse effects of pandemic add to an already at-risk condition for parents, who struggle along childhood with the considerable emotional fatigue associated to the adaptation to the diagnosis process. A measure able to evaluate how families continue to be impacted by COVID-19 could be of great value in facilitating the delivery of high-quality healthcare.

TABLE 1 – Percentage of respondents that endorsed each item (Exposure Scale)

1.	*Our school/childcare closed*	90%
2.	*We had a stay at home order*	50%
3.	*Children's education disrupted*	25%
4.	*Missed/cancelled important event*	55%
5.	*Unable to care for/visit family*	25%
6.	*Someone kept working*	10%
7.	*Family income decreased*	15%
8.	*Cut back hours at work*	50%
9.	*Required to stop working*	10%
10.	*We self-quarantined*	5%
11.	*Difficulty getting other essentials*	5%
12.	*Someone is healthcare/first respon*	90%
13.	*Lived separately health safety job*	5%
14.	*Difficulty getting healthcare*	25%
15.	*Someone exposed to COVID-19*	45%
16.	*Difficulty getting food*	50%
17.	*Someone had COVID-19*	25%
18.	*Someone moved back home*	15%
19.	*Difficulty getting medicine*	35%
20.	*Lost job permanently*	60%
21.	*Ordinary visits disrupted*	35%
22.	*We had to move out of home*	25%
23.	*Someone hospitalized COVID-19*	10%
24.	*Someone in intensive care*	5%
25.	*Someone died from COVID-19*	0%

Impact of daily therapeutic regimen discontinuation in a F508del/G542X adult with severe cystic fibrosis in treatment with elexacaftor-tezacaftor-ivacaftor

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Background
CF transmembrane conductance regulator (CFTR) modulators have proved to potentially improve clinical outcomes in different subsets of patients. The continuous development of more effective drug combinations leads to important results in quality of life and clinical symptoms which could lead patients to reduce treatment regimen burden. This easily predictable effect is posing a risk for adherence especially in severe fragile CF patients.
By now there are no data on CFTR modulators long-term effect and their impact on adherence to airway clearance techniques (ACTs), aerosol therapy, physical activity and consequently on the possibility to a-priori discontinue daily treatment regimen.
Here we present the case of a patient with severe CF who started therapy with elexacaftor-tezacaftor-ivacaftor (Trikafta) combination and simultaneously interrupted airway clearance therapy, mucolytics and physical activity prescribed.

Case Report
50 year-old male, late CF diagnosis at 21 years-old, genotype F508del/G542X, chronic Pseudomonas Aeruginosa colonization, best FEV_1 % of predicted ($ppFEV_1$) of 38, body mass index (BMI) of 25.6 Kg/m^2 and chronic respiratory failure with 2 lt/min nocturnal and 3 lt/min on physical activity oxygen therapy started Trikafta in October 2019 on compassionate protocol. Clinical objective and subjective patients reported improvements are shown in Table 1. Since then the patient completely stopped daily ACTs, inhaled antibiotics and all kind of physical activity reporting maintenance of aerosol therapy only. On May 2021 patient was admitted to our hospital with C-reactive protein (CRP) of 141 mg/lt, 24H need of 1 lt/min oxygen therapy, increased thick mucus and respiratory distress. CT scan reported extended parenchymal consolidation of right middle and basal lobe, diffuse accentuation of interstitial texture of right inferior lobe, increased endobronchial mucoid impaction with "tree-in-bud" representation and evident areas of air-trapping in the right lung field. Treatment consisted of intravenous antibiotics, airway clearance with non-invasive ventilation (NIV) support three-times a day premedicated with bronchodilators, inhaled corticosteroid and anticholinergics. Patient completely recovered with increase of $ppFEV_1$ to 50, and ppFVC to 69. Maintenance of ACT with NIV twice a day, restart of structured physical activity and inhaled antibiotics were prescribed as home routine program.

Conclusions
The beginning of a CFTR modulator therapy needs to be carefully supervised in order to maintain patient adherence to daily therapeutic regimen. Reduction or interruption in routine airway clearance and mucolytic therapies should not be driven only by patient self-reported improvements but also by multiprofessional radiological and clinical reasoning.
Patient gave consent for the publication of clinical data.

Table 1. Effect of Trikafta on different clinical and subjective outcomes

	PRE Trikafta	SIX MONTHS AFTER STARTING Trikafta
Sputum	70 ml/day, thick, dark yellow	30 ml/day, light yellow, watery
Oxygen therapy	2 L/m nocturnal 3 L/m physical activity	1 L/m nocturnal 2 L/m physical activity
Anthropometrics	Weight 78.7 Kg BMI 24.8 Kg/m^2	Weight 81.1Kg BMI 25.6 Kg/m^2
Spirometry	FEV_1 38% FEF_{25-75} 16% FVC 52%	FEV_1 47% FEF_{25-75} 22% FVC 62%
6MWT	Distance: 600 meters SpO_2min 82% Borg Dyspnea: 6 Borg Fatigue: 8	Distance: 660 meters SpO_2min 91% Borg Dyspnea: 6 Borg Fatigue: 6
Cough	Daily productive wet cough (also nocturnal during exacerbations)	Absence of cough
Pain	NO	Knees, hands and tibiotarsal bilateral arthralgias (NRS-pain 8)
N° of antibiotics courses per year	3 Endovenous 3 Oral	2 Endovenous 1 Oral

Examples of theratyping using rectal organoids of rare CFTR variants: a clinical, regulatory and organizational challenge

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Background

Despite the existence of four CFTR targeted therapies, none have been approved for individuals with rare variants because the associated molecular defects were not known. An effort should be devoted to fill this gap and primary cell model reproducing the genomic and functional landscape of an individual are emerging as a suitable strategy. Currently report in the literature point to primary cultures derived from nasal and rectal samples as suitable models to address this challenge. These cells are cultured in vitro and tested with selected compounds with a procedure named "theratyping". In this preliminary study we report examples of theratyping derived from intestinal organoids of patients carrying rare and uncharacterized CFTR variants that were tested for their response to currently available therapies in order to identify drugs of potential clinical benefit based on the in vitro response.

Materials and methods

We focused on treatment with lumacaftor and ivacaftor and the triple modulator combination tezacaftor, elexacaftor and ivacaftor as well as some experimental compounds. Testing was performed using Forskolin induced swelling (FIS) assay on 3D intestinal organoids and short-circuit currents (Isc) measurement in monolayers of organoid-derived cells.

Results

We present for the discussion theratyping data for patients carrying the CFTR genotypes R74W+D1270N+V201M/ CFTRdelee22-24; W57G/A234D; 3849+10kbC->T +/+; L227R+/+, G542X / G85E; W1282X+/+ variants showing the impact of different treatment to the functional response. All patients signed the informed consent for the project CFTR 0028 approved by the local ethics committee.

Conclusions

Recently, the FDA agreed to extend the list of CF-causing mutations for which the triple combination treatment could be clinically beneficial based on *in vitro*, cell-based studies. We bring to the discussion these examples and the relevant organizational and technical challenges. A personalized medicine approach for these patients should be considered in association with the development of a defined procedure for regulatory agencies that should consider the results of *in vitro* assays for the prescription of rather expensive treatments for patients that, due to extremely rare incidence of their variants, cannot benefit for the results derived from a classical clinical trial.

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Microbiological Comparison between Upper and Lower Airways in Patients with Cystic Fibrosis

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Background: The correlation between upper (UAW) and lower airways (LAW) may be important in CF lung disease. We analyzed UAW and LAW using microbiological and molecular approaches. Furthermore, we compared the performances of different nasal lavage techniques.

Materials and methods: LAW specimens were sampled as sputum or throat swab and UAW specimens were collected by nasal lavage with two methods, Mainz and Ryno-set, using randomization. We performed microbiological analyses on all samples, and molecular tests (BIOFIRE® FILMARRAY® Pneumonia plus) on a selected group of samples.

Results: Between December 2020 and June 2021 in CF center of Florence 108 patients (median age 15, range 1-58, 56% male) not chronically colonized by *P. aeruginosa* were enrolled. A higher prevalence of *S. aureus* (76 %) and *P. aeruginosa* (10 %) was observed in LAW cultures, whilst *Enterobacteriaceae* were mostly present in the UAW (10 %). 51 nasal lavages were sampled with Mainz approach and 57 with Ryno-set method: 6 samples were positive to *P. aeruginosa* with the former technique, instead samples collected with the latter approach were negative for the bacterium (table 1).
We performed multiplex PCR panels on 12 paired samples: we found no viruses, 10 samples were positive for bacteria species. Results obtained with microbiological and molecular methods were concordant in most cases (92%), but these panels don't test for a variety of culturable pathogens.

Table 1. Comparison of Pathogens Based on Culture Site and on Nasal Lavage Sampling Method

					Mainz Method				Ryno-set Method			
	UAW (n=108)		LAW (n=108)		UAW (n=51)		LAW (n=51)		UAW (n=57)		LAW (n=57)	
Pathogen	n	%	n	%	n	%	n	%	n	%	n	%
S. aureus	61	56.48%	82	75.93%	28	54.90%	42	82.35%	33	57.89%	40	70.18%
MRSA	6	5.56%	6	5.56%	4	7.84%	1	1.96%	2	3.51%	5	8.77%
P. aeruginosa	6	5.56%	11	10.19%	6	11.76%	7	13.73%	0	0.00%	4	7.02%
Enterobacteriaceae	11	10.19%	8	7.41%	6	11.76%	2	3.92%	5	8.77%	6	10.53%
Others non fermenting Gram-negative bacteria	4	3.70%	4	3.70%	3	5.88%	2	3.92%	1	1.75%	2	3.51%

Conclusions: Evaluation of UAW and LAW paired samples confirms different microbiota. We delineated a strong correlation between results obtained with microbiological and molecular approach. The two method of UAW lavage showed different performance, but further data are need in order to exclude bias between the groups.
Funding: This work was supported by Tuscany Region (K37, K35)
The study received ethical approval from the Ethics Committee of Meyer Hospital and written patient consent was obtained.

SUPPORTING PARENTAL PSYCHOLOGICAL WELLBEING IN INFANCY WITH CYSTIC FIBROSIS: A COMBINED PSYCHOLOGICAL-PHYSIOTERAPEUTIC HOME-VISITING INTERVENTION

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Background Care of infants with Cystic Fibrosis (CF) can be particularly challenging for parents, due to uncertainty in clinical progression and adherence to overwhelming treatment schedules. Main aim of this pilot study was to consider the effects of a combined home-visiting psychological/physiotherapeutic intervention, developed at the Bambino Gesù Children's Hospital of Rome (Italy), to provide suitable clinical support to parents of infants and toddlers with CF.

Materials and methods Six mothers (M/SD age = 33/6) and 5 fathers (M/SD age = 35.5/4) were involved (M/SD infants age =12.7/10.7 months). Weekly combined psychological-physiotherapeutic home-visits were conducted for a mean period of 8 months. Psychological intervention mainly focused on the emotional processing and adaptation to diagnosis, coping strategies, psycho-education and parental self-efficacy. Physiotherapeutic intervention focused on prevention of pulmonary exacerbations, inhalation therapy and chest physiotherapy. Parents completed the self-report questionnaires: Generalized Anxiety Disorder-7 (GAD-7, anxiety); Patients Health Questionnaire-9 (PHQ-9, depression); Parenting Stress Index (PSI-SF) before and after the intervention.

Results The 100% of parents completed all the planned sessions. A decrease in anxiety and stress levels was observed after the intervention: at baseline, 46% of parents showed moderate/severe and 18% mild anxiety, while 36% showed "no symptoms". After the intervention, 18% showed moderate/severe and 27% mild anxiety; 55% was asymptomatic. At baseline, the 9% of the sample showed moderate/severe and 36% mild depression; 55% reported no symptoms. After the intervention, 18% showed moderate/severe and 45% mild depression; 33% had no symptoms. Parental distress (PD-PSI) was reduced from 18% to 0% and maternal global stress (PSI total index) from 33% to 17%.

Conclusions A combined home-visiting psychological-physiotherapeutic intervention appears to be a considerable tool supporting psychological wellbeing of parents with infants and toddlers affected by CF, with a decrease in anxiety and stress levels. Increased depression may suggest the emotional parental fatigue experienced in elaboration and adaptation to the diagnostic processes. These processes appear to be highly challenging during infancy and toddlerhood.

Yield of lung pathogens comparing induced sputum with mannitol powder versus spontaneous sputum.

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Background

Isolation of bacteria from the lower airways is difficult in children and adult cystic fibrosis (CF) patients who do not cough up sputum. Several studies have compared yields of pathogens comparing different microbiological methods to obtain samples from lower respiratory airways. These studies showed that induced sputum (IS) has the same ability to recover lung pathogens as spontaneous sputum (SS) and BAL and it is recommended as non-invasive collection method for those patients who have declining lung function, particularly those with persistently negative cough swabs and in poor expectorating subjects. There is a growing evidence that CF patients on CFTR modulators show a reduced sputum production.

In this study we used for the first time mannitol powder as substitute of hypertonic saline in induced sputum procedure.

Methods

In this study 20 CF patients (age range: 30.4 years) previously tolerant to mannitol powder test were enrolled to compare spontaneous sputum and induced sputum to yield lung pathogens.

This IS procedure consisted in inhalation of 10 cps mannitol powder with a pre and a post-test spirometry. We collected a pre-test sputum sample and the total sputum till the end of IS procedure. A VAS scale was used to evaluate patients' discomfort after IS procedure.

Results

18 out of 20 patients (pts) completed this study; none of them was classified as poor expectorating subject based on medical history; 5/18 on CFTR modulators active treatment; FEV1 (%pred): <40 (2/18), 40-80 (10/18), >80 (6/18)

Main results of this study:

- patients in which IS resulted in more germs identified (multiresistant *Pseudomonas aeruginosa*, *Stenotrophomonas maltophilia*, MRSA, *Scedoporium spp*) and/or higher CFU/ml than spontaneous sputum (11/18)
- patients in which IS resulted in less germs identified (*Pseudomonas aeruginosa* and *Staphylococcus aureus*) and/or lower CFU/ml than spontaneous sputum (2/18)
- patients in which IS resulted in equivalent bacterial culture results as spontaneous sputum (5/18)
- 4/18 pts reported discomfort after induced sputum procedure (VAS score ≥8/10)
- 18/18 patients showed a higher sputum production after IS procedure
- IS with mannitol powder was able to capture germs responsible for chronic lung infection (14/18)

Conclusions

The results of this pilot study confirm that IS performed with mannitol powder is safe and tolerable and is superior to spontaneous sputum in detecting lower airway infection in CF patients. These results should be confirmed comparing this technique with IS after hypertonic saline.

The Lung Clearance Index in the clinical monitoring of patients with Cystic Fibrosis

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Background: Lung disease remains the leading cause of mortality in Cystic Fibrosis patients. Pulmonary exacerbations cause loss of respiratory function, resulting in a deterioration in quality of life and, ultimately, in survival. FEV1 is used as a measure of lung function, but it does not detect the structural damage that can be underlined with HRCT (High Resolution Computed Tomography), and it does not monitor the progression of the disease.
Lung clerance index (LCI) measured through the Multiple Breath Washout (MBW) test is an outcome of respiratory function that correlates most with the airway alterations evidenced by HRCT. It was shown by a lot of studies that LCI is more sensitive than FEV1 in identifying small airway ventilatorial inhomogeneity.
LCI can detect changes in respiratory function early in response to antibiotic therapy after an acute episode of pulmonary exacerbation. In the literature there are etheorgenic data regarding LCI before and after an antibiotic treatment, showing extreme variability of the absolute value of the LCI.
The aim of the study is to consider LCI as the main outcome in the evaluation of the response to antibiotic therapy and also to identify the clinical response to therapy through the value of the lung clerance index (LCI). It's important to analize correlation between different respiratory function indices (FEV1, FEF 25-75 and LCI) to identify the one with most sensitivity.

Material and Methods: 40 subjects (M 14; F 26) (age 19.07 ± 8.54 pediatric and adult age) with documented pulmonary exacerbation (Fuchs's criteria) executed spirometry and LCI in the 48 hours prior to the start of intravenous antibiotic therapy and at the end of treatment (of variable duration 14 to 21 days)

Results: FEV1 (pre 72.6 post 73.92) LCI (pre 13.50 post 12.81) FEF 25-75% (pre 56.64 post 60.45). The variations in spirometric and LCI values are not statistically significant, and show an improving trend after treatment, due to a positive effect of drugs on the drainage of bronchial secretions with a consequent reduction in inflammation of the small airways.

Conclusion: *Multiple breath washout* is a good tool to evaluate early assessment of lung damage. LCI has a clinical importance to play a role in therapeutic decisions. Its relevance in a short-term timing still remains to be explored.

A case of pseudo-papillary pancreatic tumour in an asymptomatic cystic fibrosis patient.

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We present the case of a 35-year-old Bangladesh woman. Her eldest daughter was lung transplanted at age of 8 ys old for severe CF disease (R1162X/R1162X genotype); she had already performed CFTR genetic analysis (32 mutations panel), finding R1162X/- genotype. Patient's medical history included mellitus diabetes diagnosed during the second pregnancy.
In February 2021, due to the onset of back pain, an abdomen CT scan was performed **(Figure 1 a)** with the evidence of a hypodense solid pancreatic lesion with polylobate contours (d:5.5x5cm); the pancreas was diffusely hypotrophic and hypodense, with contextual calcifications **(Figure 1 b)**. A PET revealed a weak uptake (SUV max 3.5) at the site of pancreatic lesion. An ultrasound endoscopy confirmed the iso-hyperechoic lesion, inhomogeneous and with irregular margins (d 45 mm), infiltrating Wirsung duct and the splenic vein.
Therefore, we performed multiple sweat tests (77-84 mEq/l) and CFTR gene by NGS analysis that showed R1162X/13TG-5T genotype. Confirmation of segregation by parental CFTR mutation testing has not been possible (parents are living in Bangladesh). Mutations associated with hereditary pancreatitis (PRSS1, SPINK1, CTRC, CASR) were excluded.
Chest CT scan excluded lungs involvement, whereas fecal pancreatic ELASTASE-1 showed exocrine pancreatic insufficiency.
In March 2021 she underwent a laparoscopic distal spleno-pancreatectomy. The histological examination revealed a solid pancreas pseudopapillary neoplasm (NPP) **(Figure 2-5).**
Based on the clinical picture, CFTR gene analysis and pathological sweat tests, a diagnosis of CF was made.
CF patients' Life span is actually getting significantly longer, so CF physicians must treat common adulthood diseases as cancers. A significantly increased risk of gastrointestinal neoplasms (especially intestinal) is described in CF patients compared to the general population so that endoscopic screening from 40 years of age is recommended; it's also possible an increased risk of pancreatic neoplasms, but till now it's less clear.
Although most pancreatic cancers are sporadic, up to 10% may be associated with genetic factors. Among the predisposing mutations (such as PRSS1, SPINK1, CTRC), a statistically significant association is described between del508F, W1282X, ΔI507, S549R and an increased risk of pancreatic adenocarcinoma.
Chronic inflammation linked to chronic pancreatitis, the deficient antineoplastic and pro-apoptotic role of CFTR and the deficiency of selenium and vitamin E conditioning a deficiency in the concentration of cellular glutathione with its antioxidant/antineoplastic role (secondary to pancreatic insufficiency) would be at the basis of the increased risk of neoplastic transformation.
Our clinical case is a late diagnosis in a parent of a young CF patient; it supports the hypothesis that pancreatic tumor risk is increased in CF patients; particularly, this is the first reported case of NPP associated with CF.
This finding, if confirmed in subsequent epidemiological studies (possible thanks to the increase of CF adult population), would suggest the need of dedicated tumor screening tests.
Informed consent was obtained from the patient before submitting this Case Report.

TRIKAFTA IN CYSTIC FIBROSIS PATIENTS: A PROMISING TRIPLE COMBINATION THERAPY

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Background. Elexacaftor-Tezacaftor-Ivacaftor is a recently approved triple combination therapy for the modulation of Cystic Fibrosis Transmembrane Conductance Regulator (CFTR), containing two correctors and a potentiator of the channel (1). In June 2021, its use was approved in all Italian patients aged 12 years and older with one F508del mutation and one minimal function mutation (F/MF) or two F508del mutations (F/F) in the CFTR gene. In Italy, triple combination therapy was already approved as compassionate use before this date (2). We present a one-year case-control study of 26 patients enrolled at Palermo Regional Reference Center for Cystic Fibrosis.
Materials and Methods. All recruited patients were 18 years and older. 13 of them had at least one copy of the F508del mutation: in particular, 5 were homozygous for the above mutation (F/F), 3 were heterozygous (F/No gating no RF) and 5 had an F508del mutation and a minimal function mutation (F/MF). This group of patients had the worst clinical condition and those with a predicted forced expiratory volume in 1 second (FEV1) of 40% or less were enrolled in the study and received Elexacaftor-Tezacaftor-Ivacaftor combination therapy. The remaining 13 patients had less critical genotypes and better clinical condition, so they did not receive any treatment. Sputum samples were collected from all patients in the two groups. The samples were inoculated into enriched and selective agar media after dilution. The isolated microorganisms were identified by MALDI-TOF *Bruker*, while the susceptibility tests were performed using BD Phoenix or Microscan *Walkaway*.
Results. A number of 120 strains were collected and divided into: *S. aureus* (50), *P. aeruginosa* (38), *A. niger* (1), *A. xylosoxidans* (5), *C. albicans* (1), *C. freundii* (1), *C. lusitaniae* (1), *C. parapsilosis* (1), *E. cloacae* (1), *E. coli* (3), *K. pneumoniae* (2), *P. mirabilis* (1), *S. maltophilia* (1) and *S. pneumoniae* (1). Only 2 patients among those treated had respiratory exacerbations in twelve months; overall, all showed a significant reduction in airway colonization. 41.5% of samples collected in the treated group showed complete negativity of sputum (**P <0.05**), in contrast to the untreated patients who had recurrent respiratory colonization and consistently positive sputum samples.
Conclusions. While the clinical and instrumental benefits of combination therapy are well established, further studies are needed to investigate how these drugs, which alter the properties of airway mucus, can lead to a significant reduction in microbial colonization and subsequently in pulmonary exacerbations in CF patients (5).

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Meningoencephalitis in Cystic Fibrosis patient in treatment with Elexacaftor-Tezacaftor-Ivacaftor combination therapy

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Introduction: Anxiety and depressive symptoms are very common in adult cystic fibrosis (CF) patients, ranging from 8% to 33% (1). Even if novel CFTR modulators hold great promise for individuals with CF, few informations are known about their effect on mental health. Psychiatric disorders are not reported such as adverse events in studies involving Lumacaftor, Ivacaftor or Elexacaftor (2): nevertheless, being CFTR expressed also in the brain, these drugs could affect neural function and subsequently mental health (3). We present the case of a 50-year-old man, with CF, who developed meningoencephalitis and subsequent behavioral disorders, 6 months after starting Elexacaftor-Tezacaftor-Ivacaftor combination therapy.

Case-report: F. is a 50 year old man affected by CF (homozygous for Phe508del CFTR), with a history of anxiety disorder, treated with benzodiazepines. In 2016, Lumacaftor-Ivacaftor therapy was given as compassionate use, without a real clinical and instrumental benefit. In November 2020, he started compassionate use of Elexacaftor-Tezacaftor-Ivacaftor combination therapy, with subsequent improvement of general clinical conditions and respiratory function parameters. In May 2021, the patient developed sudden paranoia with unwarranted feelings of being persecuted, for about 5 hours, with no memory of what happened. Two days later, after a new episode of *delirium* lasting more than 12 hours, a new psychiatric therapy with haloperidol was started, on suspicion of neurotic syndrome; after 5 days new episode, so the patient was hospitalized. He had generalized tonic-clonic seizures documented by simultaneous EEG monitoring; no brain lesions at CT scan. Brain MRI showed an inflammatory process affecting meninges in the occipito-parietal area on the left and some cortical furrows in the bilateral frontal area. On suspicion of meningoencephalitis, therapy with Vancomicin, Meropenem, Ceftriaxone and Acyclovir was started, contextually with anti-epileptic one. CSF cell count and film-array: negative. CSF chemical-physical examination: increase in proteins and slight increase in glucose. After 48 hours, Elexacaftor-Tezacaftor-Ivacaftor combination therapy was stopped, due to the significant increase in transaminases and creatine-phosphokinases levels. During hospitalization, no other seizures and/or acute psychiatric events, with EEG normalization. At the brain MRI, repeated after one month, persistence of millimetric areoles of inflammation in the bilateral fronto-parietal area. Elexacaftor-Tezacaftor-Ivacaftor combination therapy is still stopped.

Conclusions: further studies are necessary to demonstrate if the Elexacaftor-Tezacaftor-Ivacaftor combination therapy can worsen psychiatric disorders in patients with CF, but especially it is important to understand if this therapy might be a trigger for neurologic infections, whose first clinical manifestation can be a psychiatric disorder.

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E' stata ottenuta autorizzazione alla descrizione del caso clinico da parte del paziente.

Mucoceles in 3-years-old patient with Cystic Fibrosis: a really rare complication in paediatric age

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Introduction: cystic fibrosis (CF) is a genetic inherited condition in which the secretions are abnormally thick and sticky; chronic sinusitis and nasal polyps are a frequent complaint in CF patients, with a reported occurrence of about 40% over 5 years. Mucoceles are a well-known complication of sinusitis in adults but they are very rare in pediatric age (1). We present a case of bilateral maxillary mucoceles in a child, who underwent functional endoscopic sinus surgery (FESS) with good results in terms of safety and efficacy.
Case-report: E., 3-years-old, second child born full-term from a eutocic delivery, by non-consanguineous parents. Delayed emission of meconium (after 48 hours); during the third day of life, an apnea crisis. First and second screening test for CF were positive. Genetic tests were positive for CF with the following mutation: DF508/N1303K, in compound heterozygosity. Sweat test was positive (Cl 111 mg/dl with 179 mg of sweat). In the first two years of life, the child was hospitalized several times, for dyspnea and respiratory flare-ups, with sputum methicillin resistance *Staphylococcus aureus* (MRSA), *Klebsiella pneumoniae* and *Pseudomonas aeruginosa* detection. From March 2020, frequent mucosal rhinorrhea, associated with catarrhal cough and mild dyspnea; on July, during an ENT examination, chronic nasal inflammation and stenosis of the left nasal cavity were found, with a translucent and regular "formation": for this reason, instrumental investigations were planned. On mass facial computed tomography (CT), finding of "slightly hyperdense material conglomerate in two rounded masses, surrounded by hypodense mucous material; nasal deviation to the right and partial erosion of the nasal septum. Walls of the ethmoidal cells markedly thinned and partially eroded. Frontal and sphenoid sinus not yet pneumatized". On the magnetic resonance imaging, visualization of "mucocele-like pseudocystic expansion of both maxillary sinuses; hyperintense material in T1-weighted sequence, hypointense in T2-weighted one, with significant impregnation after contrast medium intravenously". The patient underwent FESS with bilateral antrostomy, emptying of the maxillary sinuses occupied by dense and yellowish secretions, removed during surgery. Nasal culture was positive for MRSA, tracheal aspirate culture was positive for *Candida albicans*, so we started intravenous antibiotic therapy with Cefepime and Ambisome for a week. Regular post-operative course.
Conclusions: In all patients with CF, the presence of persistent nasal obstruction, associated with poor growth and poor quality of life, requires a specialist otolaryngology visit; if nasal endoscopy or CT show anatomic obstruction, surgery with FESS is required (2).

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E' stata ottenuta autorizzazione alla descrizione del caso clinico dai genitori della piccola paziente.

The complex management of drug therapy in Cystic Fibrosis (CF) patients

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Background: Non tubercolar micobacteria are ubiquitous microrganisms that can cause respiratory infections in about 13% of CF patients, expecially *Mycobacterium avium complex* and *Mycobacterium abscessus*. The eradication of these germs is extremely difficult and, often, we have to use more than one drug. Prevalence of this condition has been increasing, because of the increasing life expectancy of CF patients, and a quicker and more precise diagnosis. The use of drugs in CF patients is dependent from concomitant bacterial colonizations that are present in their respiratory tract, the number of respiratory exacerbations and the possibility to use new combination therapies that act on the CFTR channel.
Case report: We present the case of a 30-year-old woman affected by a complete form of CF (homozygosity DF508), in order to underline the complex management of her drug therapy. Cronic colonization of the sputum with *Stenotrophomonas maltophilia* and *Pseudomonas aeruginosa*, treated with nebulized Colimycin and Tobramycin. In January 2016, infection by *Mycobacterium abscessus complex* was diagnosed, so endovenous antibiotic therapy with Amikacin was started; due to the several respiratory exacerbations and the reduction of $VEMS_1$, in April 2016, therapy with Ivacaftor/Lumacaftor was started for compassionate use, until July 2016. Contextually, Amikacin was replaced by Moxifloxacin (one of the few compatible drugs with Ivacaftor/Lumacaftor therapy), with no real clinical benefit. In October 2017, due to clinical worsening and reduction of respiratory parameters, Ivacaftor/Lumacaftor therapy was stopped and Clarithromycin was introduced. In November 2018, for the serious malnutrition, gastrostomy was placed. In November 2019 episode of hemoptysis to which followed bronchial angiography. Chest CT scan showed two excavated nodular formations (max 25 mm), connected to the bronchial tree. In December 2019 positive sputum for MDR *Mycobacterium abscessus complex*, so antibiotic therapy was modified again: Rifampicin, Ethambutol and Claritrhomycin were started. In February 2020, Claritrhomycin was stopped and Trimethoprim/Sulfamethoxazole was added. In May 2020, new worsening of general clinical conditions with further reduction of $VEMS_1$, so Ivacaftor/Tezacaftor/Elexacaftor combination therapy was started for compassionate use and for incompatibility with the last one, Rifampicin was stopped. Subsequent improvements of general clinical conditions, of respiratory parameters, reduction of respiratory exacerbations and number of hospitalizations, with BMI and CFQ-R score increasing. Negativization of the sputum for mycobacteria.
Conclusion: In our patient, we demonstrate that knowing the main drug interactions between antibacterial drugs and the most recent modulator therapy are fundamental for the choice of therapies to eradicate atypical mycobacterium infections.

È stata ottenuta autorizzazione alla descrizione del caso clinico da parte della paziente.

The new Elexacaftor-Tezacaftor-Ivacaftor combination therapy: a case report

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Introduction: The new Elexacaftor-Tezacaftor-Ivacaftor combination therapy has recently demonstrated, in cystic fibrosis patients, to improve: lung function, rate of pulmonary exacerbations, sweat chloride concentration, BMI and CFQ-R score (1,2). From 2019, in the USA, the use of this drug is allowed in all patients ≥12 years of age with one copy of the F508del mutation associated to any other type (1,3). Only in June 2021, in Europe, its use has been approved for people ≥12 years of age with two F508del mutations or with one F508del mutation and a minimal function one (4). We present the case of a 18-year-old girl who started compassionate use of Elexacaftor-Tezacaftor-Ivacaftor combination therapy, about one year ago, with a remodelled dosage according to her very low weight.

Case-report: G. is a 18 years old girl, affected by CF in heterozygosity form (F508del/del ex2) associated with a central form of GH deficiency, in endocrine replacement therapy. Poor weight gain from the first years of life so, at 8 years old, she underwent surgery for the positioning of a PEG, with poor compliance. She also developed psoriasis and CF related diabetes mellitus. In May 2020, she started compassionate use of Elexacaftor-Tezacaftor-Ivacaftor combination therapy, with dosage remodelling according to the very low weight of the patient (20 kg, -10.27 z-score): a tablet of Elexacaftor 100 mg-Tezacaftor 50 mg-Ivacaftor 75 mg in the morning and a tablet of Ivacaftor 150 mg in the evening, every other day. No clinical and biochemical adverse effect have been showed, except for a minimal increase in alkaline phosphatase. After 2 months from the start of the therapy, negativization of sweat test (Cl 46 mEq/L with 124 mg of sweat) was demonstrated. In December 2020, a weight gain of about 4 kg and reduction of the cough, with progressive improvement of respiratory parameters (+12% of FEV_1 values) were showed. During last clinical control (April 2021), the patient had a weight of 27 kg (-6.7 z-score), she underlined an important reduction of the cough and an almost absence of daily bronchorrhea. Further improvement in respiratory parameters (FEV_1 51%) has been evaluated but especially in her quality of life (CFQ-R score: 100).

Conclusions: Elexacaftor-Tezacaftor-Ivacaftor combination therapy has demonstrated, also in our case, to improve spirometric and auxological parameters although used at half the dosage. The approval of the ethics committee was fundamental from this point of view.

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E' stata ottenuta autorizzazione alla descrizione del caso clinico da parte della paziente.

ELEXACAFTOR-TEZACAFTOR-IVACAFTOR IMPROVES HEALTH RELATED QUALITY OF LIFE IN PATIENTS WITH SEVERE LUNG DISEASE: A FIRST CASE SERIES IN ITALY AFTER ONE YEAR

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Background: Elexacaftor-Tezacaftor-Ivacaftor (ETI) is a newly approved modulator therapy in Europe that contains two correctors and a potentiator of the CFTR channel. In 2020, in Italy, Vertex Pharmaceuticals launched a compassionate use program for people with cystic fibrosis (pwCF) who have at least one F508del mutation. Aim of our observational pilot study was to monitor both physical and mental health outcomes in a small sample of pwCF who received ETI for one year.
Materials and methods: Six pwCF were enrolled in the compassionate use program in April 2020. Baseline measures of physical health (FEV_1, BMI) were collected from most recent chart review; mental health and daily functioning measures were collected within two days of initiation of ETI. Assessments included: CFQR-14+ (HRQoL), PHQ-8 (depression), GAD-7 (anxiety). Physical and psychological outcomes were measured again at 15 days and 3, 6, 9, 12 months after starting ETI.
Results: In April 2020, six pwCF were approved for ETI compassionate use program [F/M=2/4, *X*-age=30.2 *(SD=7.3)*]. At enrollment, two were being evaluated for lung transplant and three were on the lung transplant waiting list. ETI was well-tolerated, with no side effects reported over one year. Improvements were noted across all health outcomes after 15-days and remained stable at 12-months: $ppFEV_1$ (average +19.2%); BMI (average +1.4 kg/m^2); sweat chloride (average -19 mEq/1). Symptoms of depression and anxiety were below the clinical cut-off at baseline and remained stable at 12-months (average: 4.7 to 4.0 on PHQ-9, 4.0 to 4.0 on GAD-7). At 12-months, a general trend of improvements in HRQoL was documented across the domains of the CFQ-Rs, with remarkable increase of Vitality, Social and Role (20 points). A dramatic increases of Physical Functioning and Health Perceptions was found (40 points). The Treatment Burden and Respiratory domains improved too (10 points) (Tab.1).
Conclusions: Compassionate use of ETI provided clinically robust benefits, with a favourable safety profile. $ppFEV_1$, BMI and sweat chloride improvements were observed after 15-days and maintained stable up to one year, consistently with the literature. It is not yet clear how improvements in CFTR activity will affect individuals who already have severe lung disease in the long term, but our data show mid-term benefits on key health outcomes. Symptoms of depression and anxiety were stable after one year, accompanied by substantial increases in domains of HRQoL, such as Physical Functioning and Health Perceptions, Vitality, Social, Role. Future research will require larger sample sizes to assess the long-term improvements.

	$ppFEV_1$		BMI		Physical		Health		Vitality		Social		Role	
	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post	pre	post
CASE 1	39	47	19.6	21	25.0	83.3	0.0	88.9	33.3	83.3	44.4	83.3	33.3	91.7
CASE 2*	25	34	22	23.8	29.2	54.2	33.3	55.6	58.3	75	44.4	50	66.7	91.7
CASE 3	31	60	19.9	20	16.7	100	22.2	100	83.3	100	66.7	83.3	41.7	75
CASE 4	31	43	17.2	18	83.3	100	77.8	77.8	91.7	66.7	83.3	77.8	91.7	100
CASE 5	38	89	18.4	21.4	29.2	95.8	33.3	88.9	50	100	22.2	77.8	50	66.7
CASE 6*	27	33	23.6	27	58.3	79.2	55.6	88.9	66.7	83.3	255.6	83.3	91.7	83.3
MEAN	31.8	51	20.5	21.9	40.3	85.4	37.0	83.3	63.9	84.7	52.8	75.9	62.5	84.7
SD	7.3	21.1	2.4	3.1	25.4	17.6	26.9	15.3	21.5	13.3	21.0	13	25.1	12.3

**for this case the number of pulmonary exacerbations was higher*

Tab.1

Nasal symptoms prevalence in adults with Cystic Fibrosis using 22-item Sinonasal Outcome Test (SNOT-22)

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Introduction
Nasal obstruction, chronic rhinosinusitis and nasal polyposis are frequent CF patients with a potentially high impact on their quality of life. The prevalence of chronic rhinosinusitis in adults with CF varies between 80 and 100%. A series of questionnaires and screening tools have been proposed over the years to analyze the symptoms of chronic rhinosinusitis. The SNOT-22 is a 22 items-questionnaire among the best known and studied, validated in Italian and with specific and studied clinimetric properties. A SNOT-22 score greater than 21 is highly indicative of chronic rhinosinusitis in adult patients with CF.

Objective
To estimate the prevalence of chronic rhinosinusitis symptoms in adults with CF followed at Verona Regional Cystic Fibrosis Centre.

Material and Methods
Observational retrospective one-year analysis was performed from 2019 to 2020 among clinically stable adult CF patients. Respiratory function indices, anthropometric data, bacterial colonization status, sino-nasal disease history, routine airway clearance techniques, routine nasal cleaning and SNOT-22 were collected and a stratified correlation analysis was performed. The study was conducted at Verona Regional Cystic Fibrosis Centre.

Results
One hundred sixteen patients (59 female) aged 36.1(SD 10.9, range 18-65) years with mean ppFEV$_1$ 69.6(25) and mean ppFVC 90.4(19,6) completed SNOT-22. Mean SNOT-22 score was 23.7(16). Cough was considered the most severe symptom followed by need to blow the nose, nasal obstruction and taste/smell impairment. Nasal disease was already diagnosed in 54 patients (46%) which correlated with a significantly higher SNOT-22 score. Nasal polyposis was the most diagnosed disease (70%) followed by chronic rhinosinusitis (30%). Items frequency and SNOT-22 total score were not significantly different according to severity of pulmonary impairment, history of nasal surgery, Pseudomonas Aeruginosa colonization, BMI, type of routine airway clearance technique, type and frequency of nasal irrigations. SNOT-22 cut-off score of 21 was able to significantly detect nasal disease in concordance with patient diagnosis and with data from literature along with superimposed values of sensitivity and specificity.

Conclusion
Sinonasal symptoms are widely common in CF adults along with high incidence of nasal polyposis. SNOT-22 is a feasible, simple, easy-to-administer, inexpensive useful test to detect nasal conditions. SNOT-22 score 21 is a practical and sensible cut-off that could lead CF clinical practice to nasal symptoms.

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Adaptive Aerosol Delivery (AAD) system use during the advanced stage of disease

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BACKGROUND

The administration of inhaled therapy with antibiotics in Cystic Fibrosis is maintained until the most advanced stages of the disease, even when lung function no longer guarantees optimal intake. Adaptive Aerosol Delivery (AAD) system with digital platform offers the possibility to assess the adequacy of aerosol therapy even in the most compromised patients.

CLINICAL CASE

45-year-old woman with Cystic Fibrosis in an advanced stage of the disease, on the waiting list for bipulmonary transplant, with chronic respiratory failure. Clinical characteristics: FEV_1 0.67 liters (27% of predicted) - FVC 1,1 liters (49% of predicted), need for non-invasive ventilation 16-18 hours/day with Oxygen 2 L/min, Oxygen Therapy (3 L/min at rest - 5 L/min while walking), chronic respiratory infection by *Pseudomonas aeruginosa*, pancreatic insufficiency, Body Mass Index 18.5 Kg/m^2.

In the past, several aerosolic therapy challenges with different inhaled drugs had failed due to bronchial hyperactivity; since 2018 in therapy with Colistin and AAD system with satisfactory tolerance.
During hospitalization it was verified that the inhalation session time was more than 5 minutes; then the data was extracted to analyze filter efficiency, inhalation duration and rest time. A training session was carried out with the dedicated software.
Due to the respiratory pattern compromised by the severe respiratory failure, the duration of inhalation and the time of rest cannot be changed; on the other hand, it should be noted that the completed inhalation are 100%. To the other side, while wih other aerosol systems the drug would be lost for 60% (rest time), the AAD allows for complete inhalation.

CONCLUSIONS

The AAD system delivers the drug only in the inspiratory phase, thus allowing complete administration of the drug even to patients who need longer and more frequent breaks.
Being able to observe all the characteristics of the session, it is possible to verify that the treatment is optimized for each specific patient, without only taking into account the inhalation time (the only parameter that can be monitored with other devices).

Patient gave written informed consent to the use of his data.

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Mental health perception and Quality of Life in patients with Cystic Fibrosis before and during the Covid19 outbreak.

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Background. In the general population, COVID-19 pandemic caused many changes in life routine including an increased risk for mental illness symptoms.[1] We aimed to study the impact of the COVID-19 outbreak in mental health perception and quality of life (QoL) in Cystic Fibrosis (CF) population.

Methods. We analysed the data of 42 patients with CF [23 M, mean age 28.8 ± 9.2 yrs (11.1-47.3 yrs), 10 patients age<21y, 32 patients≥21y] who completed Patient Health Questionnaire 9 (PHQ-9), General Anxiety Disorder 7 (GAD-7) and Cystic Fibrosis Questionnaire-Revised (CFQ-R) before and during COVID 19 outbreak. We focused on the Respiratory and Emotional domain of CFQ-R.

Results. Results are shown in Table 1. No patient acquired SARS-CoV2 infection. We found no statistical relevance in the scores before and during COVID-19 pandemic for all three questionnaires regardless of sex and age. Even if there was no perceived well being loss related to COVID pandemics we found a statistically relevant difference between males and females for all the three questionnaires ($p<0,05$) and a difference in the respiratory domain of CFQR between age groups ($p<0,04$) pre-COVID19. A significant correlation was found between CFQ-R results and the PHQ-9 ($p<0,001$) and GAD-7 data ($p<0,001$).

Discussion. No significant difference was found in depression and anxiety symptoms before and during COVID-19 outbreak in this specific population, in contrast to the data obtained from the general population. CF patients usually refer to doctors for medical advice and are already used to social distancing, hygienic measures and segregation in order to protect themselves from respiratory infections. Therefore, COVID-19 outbreak has not resulted in major changes in daily routine and QoL of these patients. Anxiety and depression symptoms were prevalent in female patients in accordance with previous studies indicating a female tendency to a lesser mental health perception.[2] Younger patients had better respiratory health perception at baseline confirming previous literature results.

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Table1.

			PHQ-9					
			Before COVID19	**During COVID 19**				
		patients	**Mean ±SD**	**Mean ±SD**	**p value**			
Whole Sample		42	4.7±4.3	4.7±4.6	ns			
Gender	**Male**	23	3.2±2.6	3,2±2,7	ns			
	Female	19	6.5±5.3	6.4±5.7	ns			
Age	**<21yrs**	10	2.6±2.5	3.2±3.5	ns			
	≥21yrs	32	5.4±3.1	5.1±4.8	ns			
			GAD-7					
			Before COVID19	**During COVID 19**				
		patients	**Mean ±SD**	**Mean ±SD**	**p value**			
Whole Sample		42	5.8±4.8	5.8±5.2	ns			
Gender	**Male**	23	4.5±3.8	4.1±4.4	ns			
	Female	19	7.5±5.5	7.8±5.4	ns			
Age	**<21yrs**	10	3.6±3.1	5.4±5.4	ns			
	≥21yrs	32	6.5±5.1	6.4±5.2	ns			
			CFQ-R Respiratory domain			**CFQ-R Emotional domain**		
			Before COVID19	**During COVID19**		**Before COVID19**	**During COVID19**	
		patients	**Mean ±SD**	**Mean ±SD**	**p value**	**Mean ±SD**	**Mean ±SD**	**p value**
Whole Sample		42	73.4±12.8	76.6±14.6	ns	75.8±19.1	73±20.5	ns
Gender	**Male**	23	78.6±10.3	78.2±14.2	ns	82±16.2	80.6±17.9	ns
	Female	19	67.2±13	74±15.1	ns	68.3±20	63.7±19.9	ns
Age	**<21yrs**	10	80.4±12.6	82.7±14.9	ns	80.3±17.9	77.3±22.9	ns
	≥21yrs	32	71.3±12.3	74.7±14.2	ns	73.5±21.1	74.5±21.1	ns
			Gender			**Age**		
			male	**female**	**p value**	**<21**	**≥21yrs**	**p value**
PHQ-9	**Mean ±SD**	**Before COVID19**	3.2±2.6	6.5±5.3	**<0.02**	2.6±2.5	5.4±4.6	ns
		During COVID19	3,2±2,7	6.4±5.7	**<0.04**	3.2±3.5	5.1±4.8	ns
GAD-7	**Mean ±SD**	**Before COVID19**	4.5±3.8	7.5±5.5	**<0.05**	3.6±3.1	6.5±5.1	ns
		During COVID19	4.1±4.4	7.8±5.4	**<0.02**	5.4±5.4	6.4±5.2	ns
CFQ-R Respiratory domain	**Mean ±SD**	**Before COVID19**	78.6±10.3	66.4±12.7	**<0.002**	80.4±12.6	71.3±12.3	**<0.04**
		During COVID19	78.2±14.4	74.2±15.9	ns	82.7±14.9	74.7±14.2	ns
CFQ-R Emotional domain	**Mean ±SD**	**Before COVID19**	78.6±10.3	66.4±12.7	**<0.002**	80.3±17.9	73.5±21.1	ns
		During COVID19	78.2±14.4	74.2±15.9	ns	77.3±22.9	74.5±21.1	ns

Impulse Oscillometry (IOS) technique application and assessment in an outpatient setting of Cystic Fibrosis pediatric patients

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Background: Pulmonary function testing is central in CF management and it becomes challenging when addressing uncooperative patients. IOS has been applied in young uncooperative patients affected by different respiratory illnesses, detecting underlying bronchial and respiratory mechanics alterations, but its routine use it's not widespread in CF patients.
Materials and methods: our aim was to test feasibility of IOS in our pediatric outpatient clinic and to assess correlations between 5 Hz resistance (R5), 5 Hz reactance (X5) values and spirometry parameters. We performed IOS and spirometry (Vyntus IOS, Vyaire Medical) on the same day in children in stable conditions; GLI were applied as reference values.
Results: 109 stable pediatric CF patients were tested (mean age 11.5±3.5, F 54.1%). IOS quality was assessed by the software as good in 65% of tests, moderate in 35% of tests (because only 3 manoeuvres were performed instead of 5). No patient performed IOS with poor quality manoeuvre.
Median [IQR] R5 and X5 were 101 [83-121] and 92 [69-133] %pred respectively. Median [IQR] FEV1, FVC and FEF25-75 were 100 [86-109], 101 [92-111], 86 [65-103] %pred respectively.
R5 fairly to moderately inversely correlated (S_R) to FEV1%pred (r -0.5, p<.0001) FVC%pred (r -0.4, p<.0001), FEF25-75%pred (r -0.45, p<.0001). R5 and X5 moderately inversely correlated (S_R 0.7, p<.0001).
IOS parameters did not correlate to age.
Conclusions: IOS was a feasible, well tolerated, non-invasive tool, with good quality performances in our cohort. The correlation to spirometry parameters was fair to moderate. This was a preliminary assessment to understand correlations with spirometry and feasibility of the technique. Our results encourage us to perform IOS also in toddlers and preschoolers, who cannot perform a good quality forced spirometry manoeuvre. Moreover its application to treatment response monitoring should be evaluated.
IOS may be considered a novel and complementary insight in functional status of children with CF and further evaluations are needed.

Can CFTR modulators cause an increase in haemoglobin?

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Background: CFTR is an anion channel expressed on the plasma membrane of erythrocytes and is reduced by 70% in patients with CF. CFTR modulating drugs enhance or even restore the stability, expression, and function of defective CFTR. Phase IV pharmacovigilance studies reported many unexpected effects, such as the increase of haemoglobin (Hb) concentrations over time, associated with CFTR modulators Ivacaftor and Lumacaftor/Ivacaftor. We evaluated the correlation between Hb levels and modulators therapy with lumacaftor/ivacaftor in a cohort of CF children/adolescents through a retrospective study.

Materials and methods: We enrolled 20 children (10 males, average age 11.58 years; range 5.5-16.33) followed at the Pediatric Unit of Regional Centre for Cystic Fibrosis of the Federico II University of Naples, treated with CFTR modulators (Lumacaftor/Ivacaftor). Only one girl had to interrupt the treatment for an adverse reaction. For each patient we considered the Hb values at baseline and after regular time intervals (15 days, 1-3-6-9-12 months) from the beginning of the treatment. We calculated the mean and standard deviation of the Hb values and statistical analysis was performed with a t-student test for paired data. The alpha level was set at 0.05.

Results: Table 1 reported study results.

	MALE Hb m ± sd	P value T0 vs Tx	FEMALE Hb m ± sd	P value T0 vs Tx	TOTAL Hb m ± sd	P value T0 vs Tx
T0	12.55±1.07		13.08±1.48		12.82±1.29	
T0.5	14.36±0.75	<0.05	14.42±1.94	<0.05	14.39±1.49	<0.05
T1	13.42±0.58	<0.05	13.21±1.61	0.065	13.34±1.08	<0.05
T3	13.96±0.74	<0.05	13.31±0.89	0.27	13.65±0.86	<0.05
T6	14.05±1	<0.05	13.19±1.33	0.28	13.64±1.22	<0.05
T9	13.95±1.34	<0.05	13.26±1.60	0.13	13.61±1.47	<0.05
T12	13.96±1.33	<0.05	13.42±1.38	0.16	13.71±1.34	<0.05

m: main; sd: standard deviation; Hb: Haemoglobin; T0: time before modulator introduction; T0.5: day 15; T1-3-6-9-12: months 1-3-6-9-12

In patients receiving Lumacaftor/Ivacaftor we observed a significant increase in Hb values already in the first days after the introduction of the drug which remained constant over a year treatment. Hb value increase remained persistently significant in males but not in females. All patients provided informed written consent for data publication.

Conclusions: In according to the study by Gifford et al. [1] we observed an increase in Hb values more in males than in females constantly over time. Gifford et al. hypothesized that this difference was a consequence of the menstrual cycle, however we enrolled girls in prepuberal age, so this cannot be the only explanation. Our results suggest that CFTR modulators could favourably affect erythrocyte development, function and /or survival. Hb increase could be linked to the reduction of chronic inflammation in patients who take modulators. Further studies will be needed to understand the possible mechanisms involved in Hb changes in patients taking CFTR modulators.

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Adherence to remote monitoring in patients with Cystic Fibrosis during Covid-19 pandemic

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Background

At Ancona Cystic Fibrosis (CF) Center, the remote monitoring (RM) service has been systematically offered since 2018 to a small group of patients with advanced lung disease.
During 2019, the concomitant improvement of the operator's skills, the lack of universally accepted criteria for the inclusion of CF patients in RM program [2] and the advent of Covid-19 pandemic led to a progressive increase in the number of patients in RM. Therefore, all CF patients in charge at our centre, most prone to exacerbation and without age limits were progressively equipped with at-home spirometry device.

Materials and methods

RM service includes the supply of a tablet connected spirometer. The data collected by the patient are sent to a digital platform and can be accessed by the CF team.
The frequency of data recording is established by the CF physician on individual basis in accordance with disease severity.
In stable conditions the patient is invited to send at least 1 spirometry per month. If the patient perceives a deterioration of the clinical state, he is invited to increase the frequency of data collection. Adherence rate to RM is calculated as the % of patients adherent to delivery times to the totality of patients on RM.
The aim of this study was to evaluate patient's adherence to the RM service.

Results

To date (June 2021) 86 out of 180 CF receive a RM service.
Adherence to RM service increased during the Covid-19 pandemic. The table shows adherence data before and during Covid-19 pandemic:

Months	Active remote monitoring	Adherence rate range
May 2019 –Feb 2020	32	9% -28%
Mar-2020 – May 2020	47	**49% - 70%**
Jun-2020	59	**46%**
Jul-2020 – Sep 2020	66	**36% - 41%**
Oct-2020	69	**39%**
Nov-2020 – Jun 2021	86	27% - **49%**

Covid-19 pandemic seems to be the most important factor influencing adherence to RM: the highest adherence values in fact corresponds to the Covid- 19 peaks and the lowest adherence values are recorded during the summer.

Conclusions

Our data show an increasing trend possibly related to Covid-19 pandemic, in fact the highest % of adherence to RM service corresponds to pandemic waves in our Region. These data arise the question of disease awareness despite external events. RM service should be part of a routine practice for CF patients as it can help patients and health care teams to capture initial signs of pulmonary exacerbation [1].

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Feasibility and reliability of Telemonitoring in people with cystic fibrosis. A one-year experience

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Background: Pandemic put a strain on continuity of care for patients with cystic fibrosis [1](pwCF). For this reason, we decided to activate a remote surveillance programme to guarantee clinical support and monitoring during the pandemic. With this project, we aimed to explore the feasibility of telemedicine[2] in pwCF with a significant therapeutic load, and to assess adherence to treatments and reliability of spirometry performed at home.

Methods: PwCF were enrolled if the following criteria were met: age >12y, FEV_1 >40% pred. at least 1 hospitalization in the previous year, and ability to perform spirometry. Patients were asked to download a mobile app (e-Care) that connected the portable spirometer with a webplatform, where clinical data were stored. Each day, patients entered the value of the oxygen saturation and answered questions regarding sleep and airway secretions; they were asked to send their spirometry tests to the CF centre once per month, and were randomly divided in four groups, each one scheduled at different days within the same month. If requested by the CF team, patients were allowed to send further tests. Data were collected from June 2020 to June 2021.

Result: 70 patients were recruited (37 famales), aged 10.8-29.73: 22.9% (16/70) refused to join the programme (7 without reasons), 7 left during the study period, 1 died and 1 was inserted in the lung transplant waiting list. Of the 336 spirometry tests scheduled, 79.7% were available for analysis; of these 36% did not meet the ATS/ERS criteria and 9.3% of tests was requested as a further by the CF team. With regard to spirometry, compared to the maneuver guided by physiotherapist in the clinic, we found that average FEV_1 performed at home with the portable spirometer was underestimated by 0.16, 95%. Limits of Agreement (LoA):-1.63; 1.31 L compared to the value obtained in the clinic. The bias improved if the maneuver was guided by a physiotherapist remotely: -0.12, 95% LoA [-0.68; 0.43] L. One full-time physiotherapist was necessary to manage the entire telemonitoring programme.

Conclusion: Telemonitorig is feasible in a large CF center, however several pitfalls can be identified. PwCF should receive more training before doing spirometry alone, thus returning to the clinic reliable spirometry tests. The project shows also poor adherence behaviors, which should be further explored.

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Clinical characteristics and outcome of SARS –CoV-2 infection in patients with cystic fibrosis managed at home

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Background: The presence of co-morbidities, such as Cystic Fibrosis (CF), has been identified as a risk factor for severe disease in patients with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection. [1-3] We evaluated clinical presentation, management and outcomes of CF patients with SARS-CoV-2, managed at home thanks to telemedicine.

Methods: We identified all CF patients with SARS-CoV-2 infection via a positive nasal/throat polymerase chain reaction (PCR) test and followed at CF centre of Florence, Italy. Cases were recorded from 1 November 2020 up to 30 of May 2021. We enrolled only CF patients managed at home. Data collected included CFTR genotype, pancreatic and microbiological status, age at SARS-CoV-2 infection, pre-existing CF related diabetes (CFRD), BMI and FEV_1 for patients aged 6 years and older, pre and post infection and usual medication.

Results: 18 (5.1%) out of 352 CF patients suffered from SARS-CoV-2 infection. 13 (72.2%) out of 18 (10 males, mean age at SARS-CoV-2 infection: 27 years, range 3 months-59 years) were managed at home. We excluded the remaining 5 patients who needed hospitalisation. Key characteristics and outcomes of enrolled CF patients are reported in Table 1. Nine (69%) out of 13 was pancreatic insufficiency. No patients had CFTR-RD. We compared FEV_1 and BMI at a mean period of 33 days (range 17-50 days) before infection and at the first visit after negative PCR test, which was performed after a mean period of 50 days (range 7-116 days). No significant worsening was reported (Table 1). No patients received azithromycin acutely or antiviral therapy. One child aged 4 years needed to antibiotic and corticosteroid medication for increased cough and wheezing in the first 24 hours. Two adult patients took antibiotic therapy in presence of increased cough. We report a mild course of SARS-CoV-2 infection, although in our cohort 3 patients were older 50 years,[4] one adult patient had chronic Burkholderia gladioli infection[5] and severe lung disease and 10 (77%) out of 13 patients were males.[6] Furthermore, we focus on other seven cases of CF patients with asymptomatic SARS-CoV-2 infection.[7]

Conclusions: Management at home alleviated the anxiety of patients and their families, reduced the risk of hospital cross-infection and avoided further overcrowding the hospital. The telemedicine can be a tool to follow CF uncomplicated patients with SARS-CoV-2 infection.

Patient	First CFTR variant	Second CFTR variant	Sweat chloride at diagnosis (mEq/L)	Age at SARS-CoV-2 infection (years)	Symptoms	Sat02	Microbiological status	Pre infection FEV1 (%)	Post infection FEV1 (%)	Pre infection BMI	Post infection BMI
1	2789+5G>A	1602delCT	104	54	Fever	98	Burkholderia gladioli	33	36	27.67	27.67
2	F508Del	CFTR Dele 2	125	14	None	94	MSSA	40	37	18.13	22.05
3	F508Del	N1303K	112	26	None	97	MSSA	53	53	25.51	25.21
4	E585X	Dele 22-24	101	10.5	Cough	98	MSSA	86	95	17.04	17.71
5	R347H	G542X	97	59	Myalgia, fever	98	MSSA	51	63	21.89	21.74
6	F508Del	A1006E	85	4.5	Cough, wheezing	98	MSSA	na*	na*	16.02	15.6
7	F508Del	(TG)12T5	73	10	None	98	MSSA	126	98	19.07	18.5
8	F508Del	G542X	106	30	None	98	Stenotrophomonas maltophilia.	72	76	19.72	20.26
9	G178R	L1065P	104	40	Cough, fever myalgia	98	MSSA	87	92	26.96	26.6
10	F508Del	G542X	102	3 months	None	98	Normal flora	na*	na*	4.44*	5.23*
11	F508Del	D192G	68	57.5	Cough	97	Pseudomonas aeruginosa	44	42	19.14	19.53
12	F508Del	F508Del	121	31	None	98	MSSA	61	65	20.27	20.13
13	F508Del	L1065P	90	13.8	None	98	MSSA	72	77	19.83	19.11

Abbreviations: SARS-CoV-2: severe acute respiratory syndrome coronavirus-2; MSSA: Methicillin-sensitive Staphylococcus aureus; $FEV_{1:}$ predicted forced expiratory volume in one second; BMI: body mass index; CFTR: cystic fibrosis transmembrane conductance regulator; na: not available
*children aged < 6 years
˚we refer to the weight given the age of the child

Table 1: key characteristics and outcomes of enrolled CF patients diagnosed with SARS-CoV-2 infection

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Cystic Fibrosis and Elexacaftor-Tezacaftor-Ivacaftor: new nutritional challenges.

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Background

Malnutrition has always been related to poor pulmonary function and reduced survival in Cystic Fibrosis (CF) [1].
Over the last decades, aggressive interventions and new CFTR (Cystic Fibrosis Transmembrane conductance Regulator) modulators have improved nutritional outcomes in people with CF, resulting in a decrease in underweight and an increase in overweight and obesity [2].
For CF patients, the nutritional aim is to reach and maintain a normal Body Mass Index (BMI): the relation between an excessive weight or a rapid weight gain and the pulmonary function remains unknown but a status of overweight or obesity is likely associated with cardiometabolic risks and does not offer any benefits in comparison to a condition of normal weight [3, 4].

Materials and methods

From October 2019 to July 2021, 18 patients (7 males and 11 females) over 12 years old have been treated with Elexacaftor-Tezacaftor-Ivacaftor at Cystic Fibrosis Center of Ancona. They have been monitored to define their nutritional status through the assessment of their anthropometric parameters at several times, i.e. at baseline (T0) and 1 (T1), 3 (T3), 6 (T6), and 12 months (T12) after the start of the treatment.

Results

The median weight gain was 0,7 kg (mean ± SD: 1,03 ± 1,67 kg), 1,7 kg (mean ± SD: 2,36 ± 2,96 kg), 3 kg (mean ± SD: 3,93 ± 4,39 kg), and 3 kg (mean ± SD: 3,55 ± 4,65 kg) at T1, T3, T6, and T12 respectively.
The median BMI was 20,36 kg/m^2 (mean ± SD: 20,4 ± 1,96 kg/m^2), 20,64 kg/m^2 (mean ± SD: 20,8 ± 1,95 kg/m^2), 21,57 kg/m^2 (mean ± SD: 21,18 ± 2,29 kg/m^2), 21,77 kg/m^2 (mean ± SD: 21,97 ± 2,58 kg/m^2), and 21,12 kg/m^2 (mean ± SD: 21,62 ± 2,94 kg/m^2) at T0, T1, T3, T6, and T12 respectively.
The nutritional status of the CF patients is outlined in Table 1.

Table 1. Numbers of underweight, with a normal weight, overweight or obese patients at T0, T1, T3, T6, and T12. Data are collected up to July 2021.

BMI [kg/m^2]	T0	T1	T3	T6	T12
Underweight (BMI < 18,5 kg/m^2)	2	2	2	2	2
Normal weight (BMI 18,5-24,9 kg/m^2)	15	15	14	11	7
Overweight (BMI 25-29,9 kg/m^2)	1	1	1	2	1
Obesity (BMI > 30 kg/m^2)	0	0	0	0	0
	18	18	17	15	10

Conclusions

The results detailed above suggest that:
1. the majority of patients have gained weight and increased their BMI during the observation time;
2. the weight gain and median BMI have increased after 6 months and reduced or remained stable after 12 months from the start of the treatment and this can be related to nutritional interventions;
3. despite the adequate nutritional status at T12, regular assessments of anthropometric parameters and dietary habits are needed to avoid rapid or excessive weight gain through personalized nutritional interventions.

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Is the Brody score a valid outcome measure in the era of ELX/TEZ/IVA therapy?

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Background

Cystic fibrosis (CF) patients on CFTR modulators show a good clinical response supported by an improvement of FEV1 (%pred), decreased pulmonary exacerbations, decreased sweat chloride and improved BMI. Moreover, in our experience, patients on ELX/TEZ/IVA show improved lung CT scan. To our knowledge, this evidence was not reported in ELX/TEZ/IVA literature.
Here we show chest CT scan results obtained in 4 pancreas insufficient CF patients (1 adolescent F/F, 3 adults F/MF) on ELX/TEZ/IVA not compassionate use.

Materials and methods

All patients underwent clinical and instrumental monitoring (chest CT scan, spirometry) at baseline and 6 months after ELX/TEX/IVA treatment.
The chest CT scan was carried out with a low dose volumetric technique in inspiratory and expiratory with a third-generation dual-energy tomograph (DECT). Each exam was then reported with both a traditional report and a modified Brody score.
Informed consent was obtained from all patients for data publication.

Results

Table 1: main results

	FEV1 (%pred), baseline	**Delta FEV1(%) 6 mo after**	BMI baseline	BMI 6 mo after	SW CL, baseline	**Delta SWCl (mmol/L) 6 mo after**	Pulm exacerb, 6 mo before	Pulm exacerb, 6 mo after
Case 1	70	**+32.4**	22.17	23.5	119	**-69**	3	0
Case 2	48	**+25**	19.78	20.96	140	**-59**	2	1
Case 3	50	**+42**	21.39	21.88	155	**-69**	5	1
Case 4	70	**+52.8**	19.79	20.88	94	**-53**	5	0

Clinical parameters (Table1) are in accordance with published data.
Six months after the start of therapy inspiratory scans show a widespread reduction in both central and peripheral mucoid impacts, a reduction in the thickening of the bronchial walls with re-expansion of the atelectasis and resolution or reduction of parenchymal thickening. In expiratory scans, the areas of air trapping resulted reduced. Despite a global improvement in CT scans at 6 months, Brody's score did not reflect such findings.

Conclusions

The lack of or the reduced improvement of the Brody score can be explained by the reopening of the atelectasis. As a result, the Brody score that take into account the atelectasis, worsened at this stage compared with the score at baseline. Based on these results, under a radiographic point of view, the Brody score did not prove to be a valid outcome measure in patients receiving ELX/TEZ/IVA therapy. In our opinion, further research is needed to define a CT scan score more specific in this cohort of patients.

Characterization of three novel CFTR insertions and therapeutic response to modulatory treatment

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Background: Cystic Fibrosis (CF) is caused by pathogenic variants of Cystic Fibrosis Transmembrane conductance Regulator (CFTR) gene. A great international effort is underway in order to functionally and clinically characterize the greatest possible number of variants. CFTR gene analysis is an important inclusion criteria for clinical trials or treatment protocols. Despite of the increasingly powerful methods of mutational search, some patients remain without one or both pathogenic variants found even after in-depth genetic analysis, with diagnostic, prognostic and therapeutic impairment. Mutation-specific precision therapies of CF are currently in clinical use for some pathogenic variants. However, CFTR function and relation with clinical status remain poorly understood for a large group of rare ("orphan") variants. Patients showing an *ex vivo* response to theratyping are eligible to effective treatments where this approach is already approved (as in US) and will become eligible as soon as it will be authorized in other Countries.
Materials and methods: We present three patients diagnosed as CF based on positive sweat tests and severe clinical symptoms, with one p.Phe508del mutated allele evidenced at a first level genetic test. A full genetic and functional analysis allowed to select and characterize three novel insertions [1], strictly related, in the CFTR gene. The establishment of ALI-differentiated cultures generated from patient-derived nasal epithelial Conditionally Reprogrammed Stem Cells (CRC model) [2] proved useful to functionally characterize the insertions and test clinically approved drugs.
Results: The analysis showed a rearrangement at the level of the polymorphic (TG)mTn tract and the presence of an insertion of part of intron 10 within the (TG)m repeat of intron 9 of the CFTR gene, preceded by abnormal poly-T stretch **(**different in length in the three cases). These three large molecular insertions are novel CFTR pathogenic variants, similar to each other, but with a different number of inserted nucleotides. They show the same effect of a complete exon 10 skipping in the mRNA, resulting in a pathogenic effect of mutational class II. The analyzed genotypes resulted to respond to Trikafta. Interestingly, also the Lumacaftor+Elexacaftor+Ivacaftor combination showed high efficacy in restoring CFTR protein maturation and function in all genotypes analyzed, with potential therapeutic implications.
Conclusions: The discovery of novel rare pathogenic variants of CFTR, as well as their experimental functional characterization, are mandatory to ameliorate our diagnostic, prognostic and, in the era of CF personalized medicine, therapeutic ability. The concept of theratyping, predicting the optimal therapeutic treatment from patient-specific *ex vivo* cells, resulted to be fully validated and feasible by the CRC model, allowing the extension of personalized CF therapy to an increasing number of patients/genotypes.

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Implementation of a telemedicine service during COVID-19 pandemic in a large CF Center in Italy

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Background. At the beginning of COVID-19 pandemic, hospital attendance was identified as a risk factor for exposure to SARS-CoV-2 infection in vulnerable populations including adults with cystic fibrosis (CF). As a consequence, CF centers had to face the need to avoid presence visits and set up a remote follow-up. Telemedicine has been found as a valuable tool to offer alternative options for routine care in CF, when in-person appointments are difficult. We present our experience in implementing telemedicine in our adult CF Center in Milano (Lombardia, Italy), one of the worst-hit area since the beginning of the pandemic.
Methods. Consecutive adults with CF were included during clinical stability at the Adult CF Center, IRCCS Ca' Granda Ospedale Maggiore Policlinico, Milan from December 2020 July 2021. Inclusion criteria were: patients living at long distance from the CF Center; patients with ppFEV1 <50 or 3+ pulmonary exacerbations during the previous 6 months; patients treated with Elexacaftor/Tezacaftor/Ivacaftor on compassionate use. Patients were exluded if not willing to partecipate or in case lack of access to basic technology.
The intervention consisted in a virtual visit (VV) led by a trained chest physiotherapist (CPH) via a telematic platform (Microsoft Teams, Microsoft) or telephone call; median duration ranged from 30 to 45 minutes*; took place 5 days a week with 3 dedicated slots*. During VV the interviewer investigated current clinical state, occurrence of pulmonary exacerbations or worsening of symptoms during the previous six months; strategies of airway clearance and adherence to standard therapy were also assessed. Table 1 summarized the list of items checked each time.
Results. We included 141 patients (median age 39 years, male 53.9%) that received a median of 1 VV in the study period. Of these patients, 75(53.2%) rescheduled their VV within the next three months. In addition, 18 patients (12.8%) were promptly seen face-to-face for acute need. A sub-group of 45 patients was equipped with home spirometry. Median ppFEV1 was 1.58 l/min.
Conclusions. This is the first report of the implementation of a CPH-driven telemedicine service in a large CF adult Center in Italy. In the context of COVID.19 pandemics, VV have been a good answer to the needs of the CF multidisciplinary team and help to preserve CF care model. Multicenter studies and long-term observation are now expected to explore association of telemedicine with relevant clinical outcomes.

Table 1

Virtual clinic checked items
Clinical stability or exacerbation
Symptoms: presence of cough; mucus: amount, quality and colours Dyspnoea (MRC)
Strategy of mucus clereance; proper use and timing of inhalation therapy
Use of LTOT and any changes
Exercise tolerance, following activity program: frequency, intensity, and modalities
Quality of night rest, devices CPAP /NIV

Cardiovascular Involvement in Cystic Fibrosis Patients: Monocentric Experience in a Cohort of Adult Patients

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Background: Cystic Fibrosis (CF) is an autosomal recessive genetic disease occurring in 1:2500 individuals. The channelopathy is characterized by a mutation of the CFTR gene that causes a deficit of the membrane protein forming the chlorine channel, which is also fundamental in the regulation of other ion channels. Cystic Fibrosis has multi-organ involvement and affects all exocrine secretion cells as well as all structures in which the CFTR channel is present, including the heart. The purpose of this study is to evaluate the impact of Cystic Fibrosis on heart rhythm and electrocardiographic alterations.
Materials and Methods: Clinical records of 83 patients with CF and 1 with Primary Ciliary Dyskinesia admitted to the Infectious Diseases Ward in 2017 and 2018 have been analyzed. For each patient, the first 12-lead ECG available in the database of the Cardiology Department of Careggi Hospital have been analyzed focusing on the study of heart rate in relation to respiratory function and genetic mutation. Statistical analysis was performed by Fisher's exact test.
Results: Clinical record of 84 patients with an average age of 35 years ± 20 years have been studied, among which 52% were women. Numerous comorbidities have been found pancreatic insufficiency in 79% of the patients, osteoporosis in 46%, hepatopathy in 17%, CF-related diabetes in 42% of cases, VTE in 11% and neoplasms in 18%. 33% of the patients have a heart rate discrepancy with FEV1 values, either because they have excessively tachycardia associated with preserved ventilatory capacity (1%), for bradycardia (8%) or 70% have a frequency within normal limits in the presence of altered respiratory exchange.
Heart rhythm disturbances suggest a possible dysautonomia and a primitive effect of the altered ionic membrane currents of cardiomyocytes at the level of the conduction tissues. Overall, cardiovascular involvement was rare and not determining the prognosis, except in cases of pulmonary embolism with hemodynamic involvement. In addition, cardiomyopathic evolution was absent.
Conclusions: The study does not suggest an involvement of primitive heart disease or risks of life-threatening arrhythmias. The young age of the patients and the duration of the follow-up do not allow to completely exclude a possible later involvement that could emerge with the progressive improvement of the prognosis and specific treatments. Thus, the role of the cardiologist is mainly related to the surveillance and prevention of thromboembolic events, the control of symptoms related to changes in rhythm and the management of possible pulmonary hypertension.

Pharmacokinetics considerations for Isavuconazole management in Cystic Fibrosis lung transplant patient with *Aspergillus* tracheobronchitis

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Background: Cystic Fibrosis (CF) patients undergo lung transplant for end-stage pulmonary disfunction. *Aspergillus spp*. tracheobronchitis can occur as post-transplant complication and airway pre-transplant colonization (approximately 50%) makes CF population at high risk. Azoles represent the therapy of choice for treatment of fungal infections but their pharmacokinetic is impaired in CF because the disease can involve many organs leading hepatobiliary dysfunction, malabsorption, hypoalbuminemia and increased renal drug elimination. Currently, there are no specific recommendations for the use of Therapeutic Drug Monitoring (TDM).

Materials and methods: A 37 years old male received bilateral lung transplantation. He carried CF-related liver disease and pancreatic insufficiency. Tacromilus was given as immunosuppressant drug. Following a critical fall of FEV1, a CT scan detected ground-glass opacities and *Aspergillus flavus* was isolated from broncho-alveolar lavage. Therapy with inhaled amphotericin B 5mg/ml bid and voriconazole 200 mg bid was started. Low voriconazole plasma levels were registered with TDM. Bronchoscopy showed bilateral pseudomembranes on bronchial anastomosis and intermediate right bronchus stenosis requiring balloon recanalization. Despite the optimization of therapy, both voriconazole and tacrolimus did not reach sufficient plasma concentrations. Voriconazole was switched to Isavuconazole (ISA), known for having less Drug-Drug interactions (DDIs) and for its optimal oral availability. ISA loading dose was administered intravenously for 200 mg q8 hours for 6 doses then switched to maintenance dose of 200 mg qd orally. After 35 days the patient was hospitalized again for malaise and lack of FEV1 improvement. We collected plasma samples twice weekly and timepoints included ISA pre-dose and 1h and 2h post-dosing. Simultaneously Tacrolimus was dosed. The measurement of the ISA serum concentration was performed on a HPLC system (Agilent Technologies, Waldbronn, Germany).
Results: TDM analysis showed that ISA therapeutic interval (3-8 µg/ml) was reached only during intravenous administration, whereas plasma levels remained below the inferior threshold during the oral maintenance phase.
Conclusions: The risk of DDIs in transplant recipients mandate TDM as a crucial tool to control drug exposure levels in order to optimize drug efficacy and safety and prevent emergence of resistance. ISA is >99% protein bound, and is eliminated predominantly by the liver. Thus, it's clear how the ISA pharmacokinetics can be altered in CF people, especially with oral administration. With this case we want to stress the importance of TDM for all antifungal agents in CF transplant population in order to improve the management of DDIs so as to increase the probability of therapeutic success.
The authors obtained the patient's consent

Note:

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