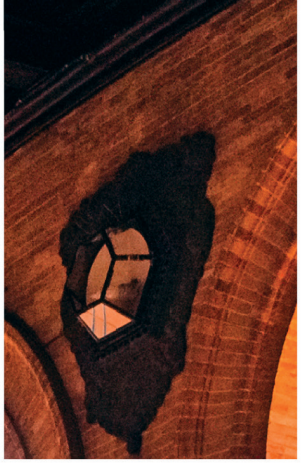
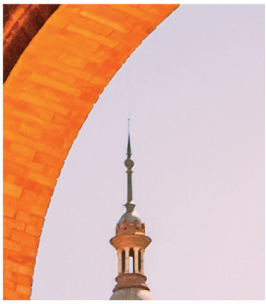
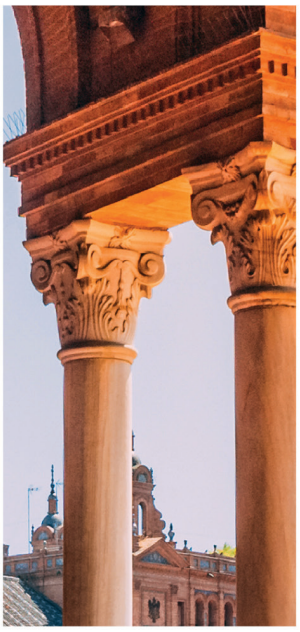
XI INTERNATIONAL WORKSHOP ON LUNG HEALTH

New Scenarios

Seville – Spain

January
18-20, 2024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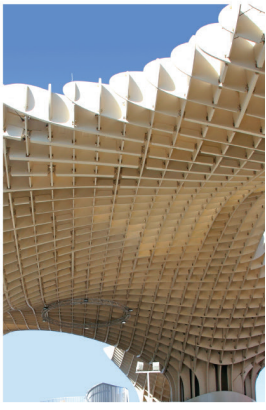
ABSTRACT BOOK

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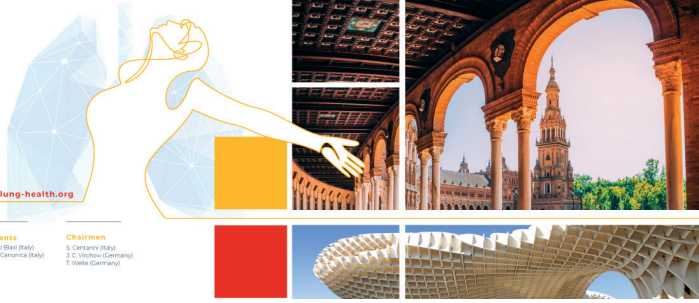

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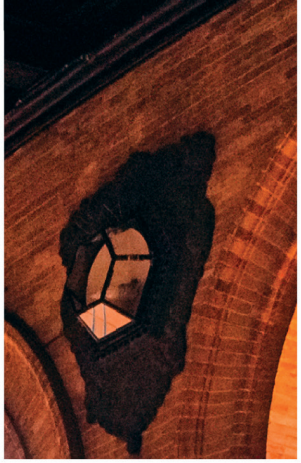
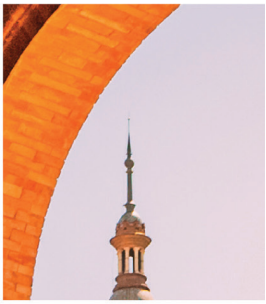
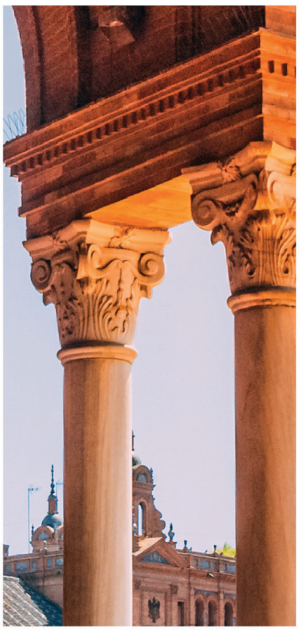


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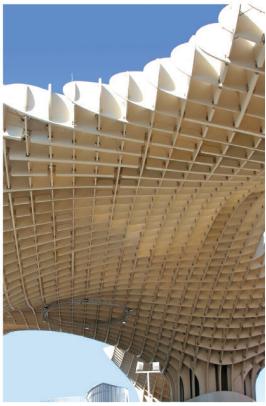
RISING STAR

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Mild/Moderate Asthma Network of Italy (MANI): First Data

Rising Star

Benedetta Bondi[1]; Irene Prediletto[2]; Matteo Bonini[3]; Giovanna Elisiana Carpagnano[4]; Puggioni Francesca[5]; Santus Pierachille[6]; Brussino Luisa[7]; Nucera Eleonora[8]; Scioscia Giulia[9]; Del Giacco Stefano[10]; Latorre Manuela[11]; Baiardini Ilaria[1]; Melissari Laura[1]; Candeliere Maria Giulia[1]; Terracciano Federica[1]; Mincarini Marcello[1]; Blasi Francesco[12]; Paggiaro Pierluigi[13]; Canonica Giorgio Walter[14]; Braido Fulvio[1]

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Background: Most asthmatics suffer from mild/moderate disease. The burden in terms of impact on health status and quality of life, exacerbations, lung function decline, and systemic corticosteroid use is largely unknown. Knowledge is also limited about the evolution of the disease. The Mild/Moderate Asthma Network of Italy (MANI) is a cluster-based, real world, cross-sectional and prospective observational study aimed to assess long term clinical evolution, phenotyping and therapeutic management of these patients.

Methods: A descriptive analysis of the first 700 enrolled patients was conducted to assess the relative prevalence of mild and moderate patients, the level of control, the demographic and clinical characteristics, the ongoing treatment, the exacerbation rate and use of oral steroid.

Results: Most of the sample were women (62.7%) and middle-aged (50±16.9). 12.1% of patients were active smokers, while 27.5% were former smokers. The mean FEV1% was 91.4 ±19.4, with a mean ACT of 21.1(± 3.73). 50.4% suffer from rhinitis while 13% from nasal polyposis. In the year before the enrolment 6.2% of

patients showed ED accesses, with asthma-related hospitalizations in 2.2% of cases. Exacerbations were recorded in 17.2% of patients and the need for the use of steroid per os in 14.2% of cases.

15.3% of patients were on treatment with Steps 1/2 according to GINA while 81.7% with Steps 3/4 and 3% with Step 5 drugs.

22.2% of Step ½ patients showed an ACT equal to 25, 61.1% between 20 and 24, while a 16.7% were uncontrolled (ACT<20). Among Step 3/4 patients, 20.6% showed optimal asthma control (ACT=25), 53.1% good control, while 26.3% were uncontrolled. Lastly, among patients step 5, 11.1% show an ACT equal to 25, 55.6% between 20 and 24, while 33.3% were uncontrolled.

Controlled and uncontrolled patients belonging to step 3/4 were compared. Uncontrolled patients showed a higher upper airways burden (CRSsNP 20.8% vs 3.1%, p<0.001; rhinitis VAS 5.06 ± 2.92 vs 3.31 ± 2.74, p=0.008, moderate persistent rhinitis 40.7% vs 18.4%, p=0.046). Conversely, mild intermittent (35.6% vs. 33.3) and mild persistent (37.9% vs. 14.8, p=0.046) rhinitis were more frequent in controlled patients. Uncontrolled patients complained more frequently for perennial rhinitic manifestations (77.4% vs 57.3% p=0.044), compared with controlled patients, who more frequently exhibit seasonal symptoms (42.7% vs 22.6%, p=0.044). Uncontrolled patients recorded lower AQLQ (4.45 ±1.19 vs 6.01± 0.83, p>0.001) and higher RAPP scores (20.9 ± 6.69 vs 14.1± 4.79, p>0.001) than controlled. A higher number of unscheduled visits (10% vs 0.8, p=0.002), higher use of systemic steroid during exacerbations (20.8% vs 8.8%, p= 0.03), more smoke exposure (20.3 vs 14.7, p=0.05), as well as higher IgE values (564± 829 vs 238± 282, p=0.012) and lower function tests (FEV1%, 83.1% vs 88.9% of predicted, p=0.05) were showed in uncontrolled ones.

Conclusions: The MANI study will provide important insights into mild and moderate asthma. The data collected on the first 700 patients, more than 80 percent of whom were treated according to GINA step 3/4, show that the burden in terms of poor control, impact on quality of life, healthcare resource, exacerbations, oral steroid use, and comorbidities are far from insignificant.

Prediction of Endothelial Dysfunction After COVID-19

Rising Star

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[1] *Dnipro State Medical University, Dnipro, Ukraine*

Background: One of the consequences of COVID-19 is an endothelial dysfunction but little is known about the predictors of its development and associated with it clinical signs.

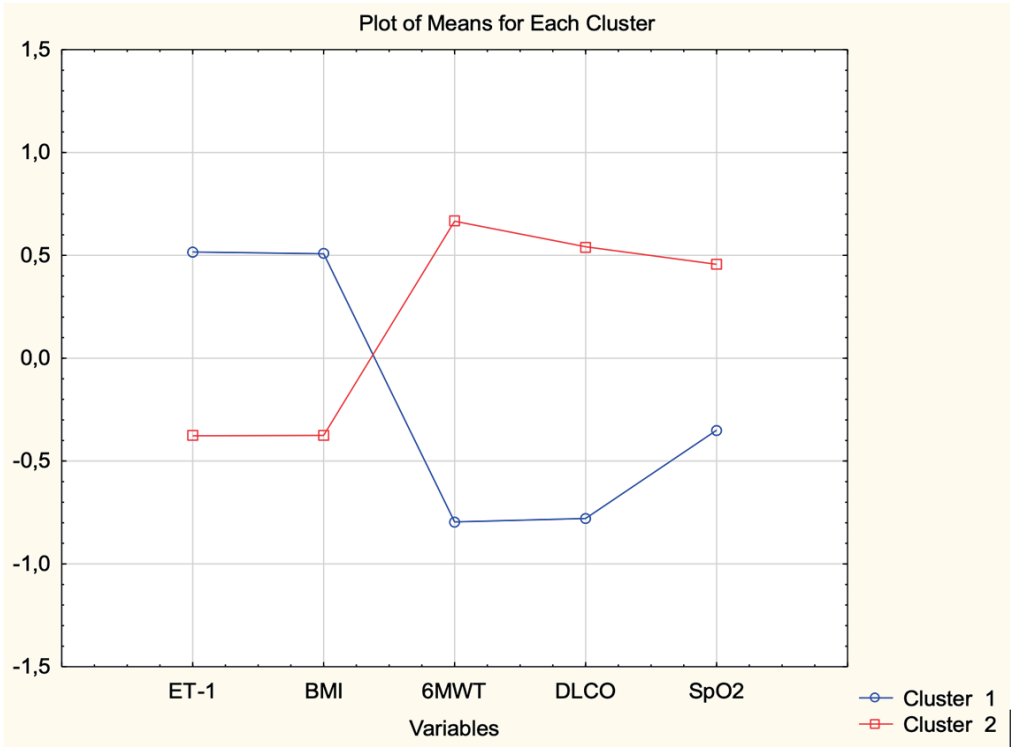
Aim: To determine whether endothelin-1 levels after COVID-19 are associated with the severity of COVID-19 pneumonia and the course of the post-COVID-19 period.

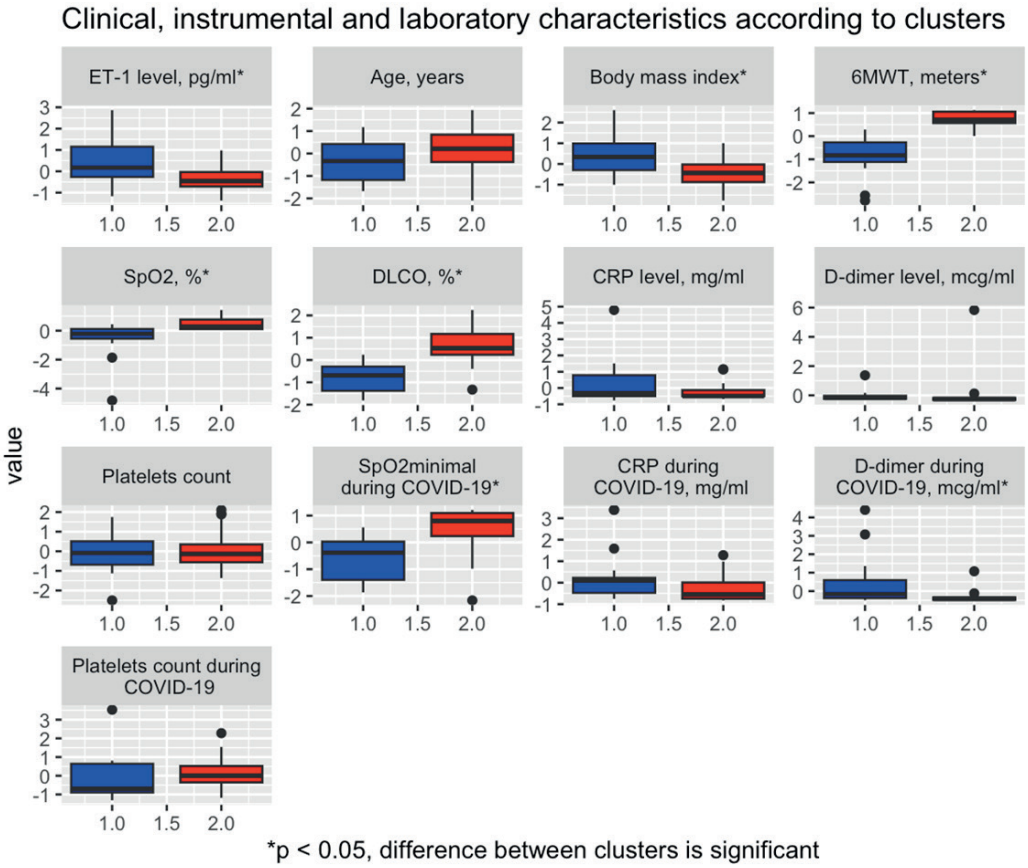
Material and Methods: The main group consisted of 40 patients (age – 58,0 (49,3; 64,5) years, men – 23 (57,5 %) who survived COVID-associated pneumonia and were experiencing dyspnea at the time of the study. They were investigated at 45,0 (40,0; 60;0) day from COVID-19 onset using the following methods: Modified Medical Research Council Dyspnea Scale (mMRC scale), 6-minute walking test (6MWT), pulse oximetry (SpO2), body mass index (BMI) calculation, diffusion lungs capacity measurement (DLCO), as well as laboratory methods (platelets counting, C-reactive protein (CRP), D-dimer, endothelin-1 (ET-1)). Anamnestic data of COVID-associated pneumonia course also were analyzed (minimal SpO2, CRP, D-dimer, platelets count). Patients with severe cardiovascular diseases, diabetes mellitus, or COPD were excluded from the study. U-test and cluster analysis were used as statistical methods.

Results: Cluster analysis revealed that main group consisted of two heterogeneous subgroups. 1st subgroup included 17 patients. Among them 4 patients had 2 grade dyspnea by mMRC scale, 11 patients – 3 grade dyspnea and 2 patients – 4 grade dyspnea. 2nd subgroup included 23 patients. Among them 7 patients had 1 grade dyspnea by mMRC scale and 16 patients – 2 grade dyspnea.

According to cluster analysis, 1st subgroup had lower SpO2 and 6MWT results, worse DLCO and higher BMI at the moment of investigation. ET-1 level in 1st subgroup was higher and equaled 16,1 (12,2; 24,6) pg/ml. Whereas 2ndsubgroup had better SpO2 and 6MWT results, better DLCO and lower BMI at the moment of investigation. ET-1 level in 2nd subgroup was lower and equaled 10,0 (7,9; 14,1) pg/ml. The difference between subgroups was significant ($p<0,01$). Moreover, after comparing anamnestic data between two subgroups using U-test it was found that patients from 1stsubgroup had worse SpO2 as well as higher levels of D-dimer during COVID-19 pneumonia ($p<0,01$).

Conclusions: ET-1 level after COVID-associated pneumonia is associated with the severity of COVID-19 pneumonia and the course of post-COVID-19 period. These findings are important for the development of screening programs in post-COVID-19 period.





*p < 0.05, difference between clusters is significant

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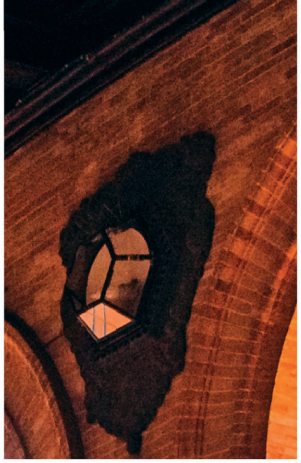
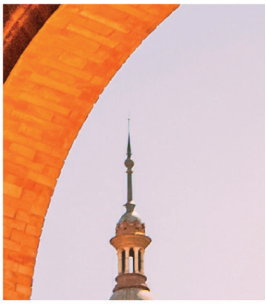
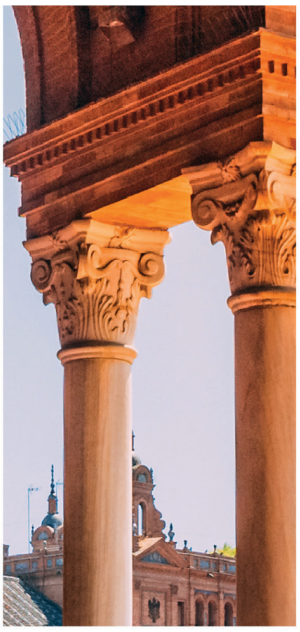


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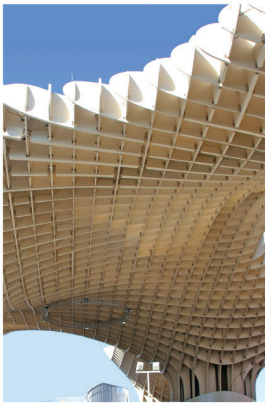

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Clinical, functional, radiological and quality-of-life characteristics in PI*SZ Alpha 1-Antitrypsin Deficiency compared to severe PI*ZZ, moderate PI*MZ genotype and common PI*MM COPD: A national retrospective registry-based analytical observational cohort study.

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Oral Communication Abstract Winner

Introduction: The compound heterozygous genotype PI*SZ of Alpha 1-Antitrypsin Deficiency (AATD) derives from the simultaneous presence of the allelic mutations “S” (Glu264Val) and “Z” (Glu342Lys) in the SERPINA1 gene. The PI*SZ genotype is associated with Alpha 1-Antitrypsin (AAT) levels between 25% and 40% of those detected in subjects with the PI*MM non-deficient genotype. To date only few studies in the literature have focused on PI*SZ, whose real severity level remains unclear. The aim of the study was to evaluate the clinical and radiological characteristics, the changes over time of respiratory function and the quality of life in a large cohort of AATD patients with the PI*SZ genotype, comparing these results with AATD patients with the severe PI*ZZ genotype, moderate PI*MZ genotype or common COPD without AATD (PI*MM genotype).

Methods: We included 792 patients, divided into 4 cohorts by genotype: PI*ZZ (n=355), PI*SZ (n=154), PI*MZ (n=183) and COPD (PI*MM; n=100). Clinical, demographic and radiological (HRCT) characteristics, pulmonary function tests and quality of life according to Saint George's Respiratory Questionnaire (SGRQ), AAT dosage were analyzed. Categorical variables were described as absolute and relative frequencies and compared using Chi-square test and Fisher's exact test. Quantitative variables were expressed as Mean and Standard Deviation (SD) or Median and Interquartile Range (IQR) based on their Gaussian distribution or not. Parametric and non-parametric data were compared by One-way Analysis of Variance (ANOVA) test and Kruskal-Wallis test. P-value <0.05 was considered statistically significant.

Results: 44% PI*SZ vs 20% PI*ZZ were healthy at diagnosis (p<0.0001). Among PI*SZ, diagnosis mainly resulted from family screening. Bronchial asthma was more frequent in PI*SZ group at diagnosis than in PI*ZZ group (11% vs 5%, p=0.01). Emphysema was less frequent in PI*SZ than in PI*ZZ group (15.6% vs 43.1%, p<0.0001) and was more associated with cigarette smoking (12% vs 6.5%) [Figure 1]. Furthermore, centrilobular and bullous emphysema of the upper lobes was more common among PI*SZ (as in PI*MM COPD), while basal panlobular emphysema was more common in PI*ZZ (p<0.05) [Figure 2]. The median AAT dosage was 25 mg/dl in PI*ZZ, 62 mg/dl in PI*SZ group (p<0.001). Among non-smokers, a higher prevalence of obstruction (FEV1<70%) was observed in PI*ZZ than in PI*SZ (34.4 vs 8.45%; p<0.0001). Cigarette smoking worsened obstruction, more in PI*SZ than in PI*ZZ (p<0.0001) [Figure 3]. Overall, FEV1 declined more rapidly in PI*ZZ than in PI*SZ, whose decline was just more accentuated than in PI*MZ [Figure 4]. Quality of life, assessed by the final SGRQ score, was better in PI*SZ (11.7) and PI*MZ (12.0) than in PI*ZZ and COPD PI*MM (both 29) (p=0.0001) .

Conclusion: In conclusion, the results show that the PI*SZ genotype is placed, in order of disease severity, between the intermediate PI*MZ and the severe PI*ZZ, albeit with a clinical trend more similar to PI*MZ than PI*ZZ. Cigarette smoking is the main risk factor for impaired lung function and for the onset or worsening of emphysema. In the absence of exposure to cigarette smoke, the PI*SZ genotype appears, in most cases, not associated with significant lung disease.

Severe Sepsis/Septic Shock Progression to Acute Respiratory Distress Syndrome in Intubated Patients with Ventilator-Associated Pneumonia:who are at risk and how improve the patients outcomes?

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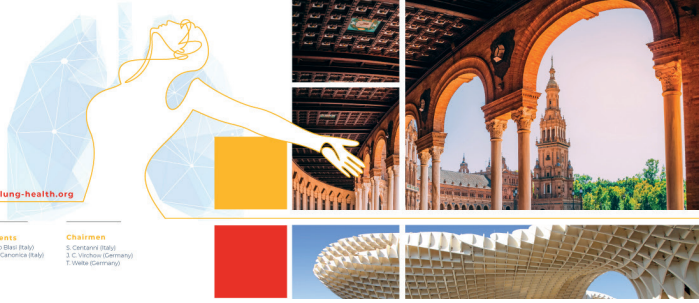
Background: Septic shock is acommon severe condition associated with high morbidity and mortality.Owing to early recognition ,prompt institution of antimicrobial treatment and advanced life support,most patients nowadays survive the early phase of resuscitation but then become highly susceptible to intensive care unit(I-CU)-acquired infections.Ventilator-associated pneumonia (VAP)accounts for the majority of ICU-acquired in-fections in septic shock patients and is associated with protracted ventilation and prolonged length of stay in the ICU and in hospital.Furthermore,sever sepsis/septic shock commonly progressed to acute respiratory distress ssyndrome(ARDS) which is highly linked to in hospital mortality.

Objective: We aimed to determine risk factors predicting development of sever sepsis/septic shock with furt-her progression to ARDS and in hospital mortalityin intubated critically ill patients with VAP and possibility reduction of ICU mortality through modification of risk factors.

Methods: This retrospective study carried out from January of 2018 to December of 2022 and involved 121 patients with VAP and 42 of them was developed septic shock with ARDS.All patients were admitted to the ICU of university teaching hospital,Baku city,azerbaijan.All demographic and clinical variables were compa-red between septic and non-septic VAP patients,and also between surivors and non-survivors.

Results: Comorbidity such as chronic obstructive pulmonary disease(COPD) with coexisting bronchiectasis was higher in patients with septic shock/ARDS(59.3% vs 18.9%;p<0.003;respectively).Prior use of antibi-otics (last 90 days)also was common for patients with VAP complicated with septic shock/ARDS(p<0.02). Gram-negative multi-drug-resistant (MDR) pathogens were common causative gaents in VAP patients and were responsible for complication as septic shock/ARDS(p<0.01).Most common causative infections agents in patients were:Acinotebacter baumannii(39/32.2%) followed by Pseudomonas aeruginosa(30/24.7%),fol-lowed by MRSA(10/10.0%),Escherichia coli and Klebsiella pneumoniae together(7/6.0%).80 of 86 isolated pathogens were MDR(93%).Severe malnutrition(albumin level <2.5g/l) was common among septic patients with progression to ARDS(p<0.001),and severe respiratory failure with PaO2/FiO2<250 was common maong septic patients(p<0.005)Mutlivariate analysis has showed the refractory septic shock with ARDS(non-respon-ding to vasopressors and systemic corticoteroids)(p<0.001),severe malnutrition (p<0.01),Acinotebacter bau-mannii infection(p<0.01),and severe refractory respiratory failure with PaO2/FiO2 <200(p<0.001) were asso-ciated with an increased risk of in ICU mortality of patients.

Conclusion: ICU admitted and intubated patients are at high risk for development of VAP and there were several risk factors wich were responsible for development of common complication such as septic shock with further progression to ARDS.By using retrospective approach to the patients records we identified bas-line variables that are independently associated with development of septic shock/ARDS and death in VAP patients.Our study has been showed that in patients with VAP presence of comorbidity such as COPD with coexisting bronchoectasis,severe malnutrition,prior use of antibiotics ,MDR pathogen isolation ,and severe respitarory failure were common risk factors associated with septic shock/ARDS.Severe refractory shock with ARDS,severe malnutrition,Acinotebacter baumannii infection ,and severe refractory respiratory failure with PaO2/FiO2<200 were significanlty associated with an increased risk of death in patients.Thus,importantly the identification of patients with VAP who are at high risk for development of septic shock/ARDS with highest probability to die may help ICU clinicians,to decide on the best management of VAP



Bronchiectasis in a patient with Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal-Dystrophy

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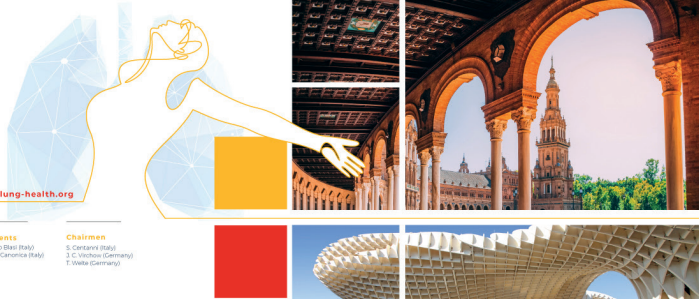
The rare monogenic syndrome Autoimmune Polyendocrinopathy-Candidiasis-Ectodermal-Dystrophy (APECED) leads to a defect in central immune tolerance with multisystemic autoimmunity manifestations. In several cohorts lung involvement as autoimmune pneumonitis has been described in up to 40 % of patients with bronchiectasis being the most frequent radiologic manifestation and rare fatal outcome due to respiratory and infectious complications being documented. The Sardinian population has a high incidence of APECED (1:14.000), although no cases of lung manifestation have been reported yet. Ferre et al. treated some of APECED patients with pulmonary involvement with lymphodepleting agents, demonstrating an ameliorating effect on clinical and functional parameters.

We present a case of a Sardinian APECED patient treated at the bronchiectasis clinic of IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy, with the aim to raise awareness on this underestimated cause of bronchiectasis and the necessity to screen these patients earlier for pulmonary involvement to pursue prompt diagnosis and better outcome.

A 49-year-old female originating from Sardinia from consanguineous parents was diagnosed with APECED syndrome in childhood (R139X/R139X genotype) and was referred to our bronchiectasis clinic in March 2023. Her brother and nephew were also APECED patients. Apart from typical APECED features, she presented also favism, gastoesophageal reflux, familial hip dysplasia and osteopenia. She reported recurrent respiratory infections since childhood, purulent sputum since 2018, and she was hospitalized in 2019 for pneumonia with a single episode of hemoptysis. From October 2022 she lamented worsening respiratory and systemic symptoms (night sweats, fever), as well as recurrent respiratory exacerbations treated with empiric antibiotics. On the first respiratory culture in January 2023 P. aeruginosa was isolated and on the chest CT in February 2023 diffuse cylindrical and varicoid bronchiectasis with tree-in-bud and mucous impaction were shown. She underwent etiologic screening for bronchiectasis with no evidence of another cause of disease and started a respiratory physiotherapy program despite costal fractures. At lung function tests, a moderate obstructive syndrome was recognized. After confirmation of chronic P. aeruginosa infection, two-week eradication therapy with endovenous meropenem was initiated in May 2023. Due to persistence of P. aeruginosa infection and two isolates of M. intracellulare on sputum cultures, she was hospitalized in August 2023 for a two-week treatment with inhaled colistin and the initiation of antimycobacterial treatment with azithromycin, rifampicin and ethambutol.

This is the first documented case of a patient with lung involvement by APECED in the Sardinian population and the first patient ever to enter a bronchiectasis program. After etiologic screening, APECED itself was indicated as the underlying cause of bronchiectasis. Infectious complications as chronic P. aeruginosa infection and M. intracellulare pulmonary disease were diagnosed and treated. Pulmonary involvement in APECED is an underdiagnosed entity and a watchful waiting approach with early radiologic screening at insurgence of respiratory symptoms should be implemented for these patients. Although lymphodepleting treatments have proven effective in patients with autoimmune pneumonitis, special attention should be put on management of possibly fatal infectious complications. Therefore, APECED patients with bronchiectasis could benefit from a multidisciplinary management and entrance in a bronchiectasis program.



Response to Nintedanib in progressive pulmonary fibrosis: an Italian monocentric real-world study.

Claudia De Petro[1,2]; Lucia Allavena[1,2]; Filippo Maraz[1,2]; Margherita Silani[1,2]; Antonella Arcadu[1,2]; Silvia Dellafiore[1,2]; Margherita Ori[1,2]; Crizia Colombo[1,2]; Letizia C. Morlacchi[1,2]; Marco Mantero[1,2]; Francesco Blasi[1,2]

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Introduction: The INBUILD study and subsequent real-life studies have demonstrated the effectiveness of Nintedanib in slowing the functional progression of progressive pulmonary fibrosis (PPF) without severe side effects. We collected data on PPFs followed at our Center with the aim to 1) describe the population in terms of demographic, radiological and clinical data; 2) evaluate the decline in lung function and any indirect signs of pulmonary hypertension one year after starting therapy compared to the previous 12 months.

Methods: We conducted an observational, retrospective and single-center study including consecutive patients with PPF who were prescribed Nintedanib from December 2018 to March 2023; PPF diagnosis was formulated after a multidisciplinary discussion following the INBUILD criteria and then revised for the ERS/ATS 2022. We collected demographic and functional data (FVC in mL and % of predicted and DLCO % of predicted) at time of initiation of antifibrosing therapy (T0), 12±6 months before (T-1) and after (T+1) introducing the same treatment. We included data on side effects, dose adjustment, radiological pattern at T0 and echocardiographic indirect signs of pulmonary hypertension (PH), calculated via composite endpoint (probability of PH and/or right ventricular dilation).

Results and Conclusions: 20 patients were included in the study, 16 (80%) female, mean age 64.7+9.7 years. 15 (75%) were affected by autoimmune diseases, with rheumatoid arthritis and scleroderma representing respectively 25% of the total. The remaining 25% were mainly affected by fibrotic hypersensitivity pneumonitis (FHP). 12 (60%) of patients showed UIP-pattern on high-resolution CT. Echocardiographic findings of right cardiac involvement were reported in 27% of patients at T-1,47% at T0 and 69% at T+1. At T0 mean FVC was 1955 mL(70.5%) SD=0,67 while DLCO 35.7% SD=1,53. Annual rate decline in FVC was -101mL before starting Nintedanib, in contrast to -10mL at T+1. DLCO mean decrease was -1.9% at T+1, compared to -11.8% at T-1 ($p<0.001$). We found no significant differences when stratifying by disease groups (autoimmune-ILDs vs other) and radiological pattern (UIP vs non-UIP). Side effects were observed in 16 (83%) of patients, the majority of whom experienced gastrointestinal involvement (10, 61%) which in 47% of cases led to a dose-adjustment. The reduction of the posology did not significantly affect the effectiveness of the treatment (measured as FVC and DLCO decline). Only one patient died because of pulmonary adenocarcinoma.
This is the first Italian study to evaluate both functional progression and right cardiac impairment one year after starting Nintedanib for PPF. Our population is predominantly made of women suffering from PPF in the context of a systemic autoimmune disease. These data are consistent with previous literature in confirming the effectiveness of Nintedanib in terms of slowing down functional decline over one year. The main side effects were gastrointestinal, managed by adjusting the dosage not impacting its effectiveness. Progression of indirect echocardiographic signs of pulmonary hypertension was observed at one year. Prospective and translational studies are warranted to expand these data and clarify the biological mechanisms.

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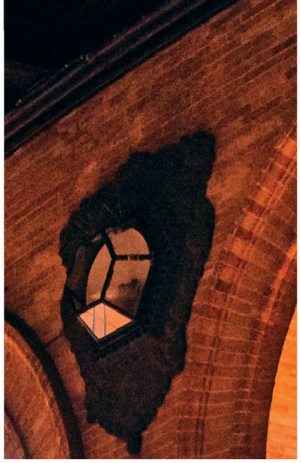
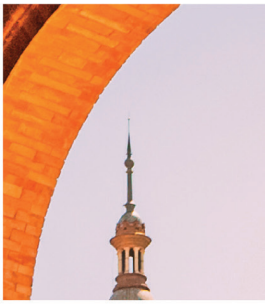
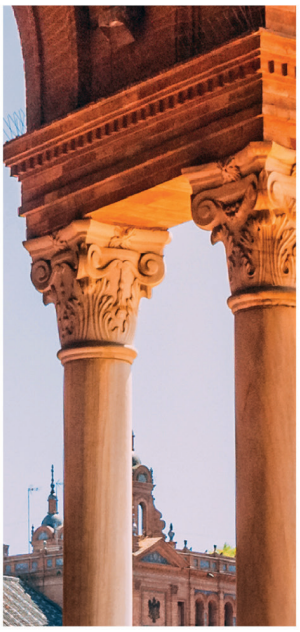


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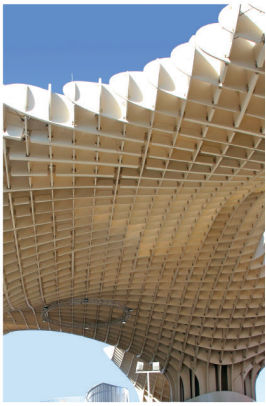
POSTER ABSTRACTS

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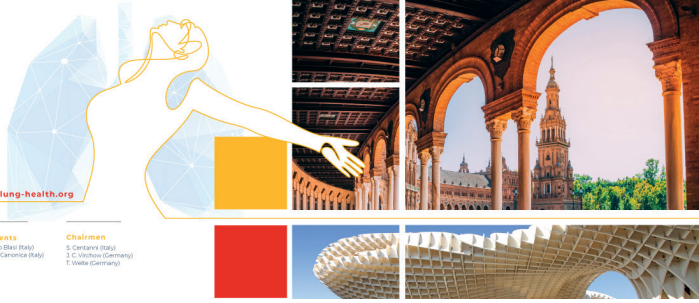

Levels of Inflammatory and Cardiac Biomarkers as a Predictor Factor for Complications and Outcomes in Hospitalized COVID-19 Patients

Poster Abstract Winner

Rovira-Ribalta Nona[1]; Cilloniz Catia[1,2]; Lopez-Aladid Ruben[1]; Motos Ana[1,3]; Bedini Josep Lluis[5]; Soler-Comas Alba[1]; Granero Sara[4]; Cabrera Roberto[1,2]; Kiarostami Kasra[1]; Llonch Blanca[1]; Fernandez-Barat Laia[1,3]; Torres Antoni[3,1]

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Background: SARS-CoV-2 physiopathology is linked to an uncontrolled response of the immune system besides a hyper-coagulopathy status. We aimed to characterize phenotypes according to inflammatory and cardiac biomarkers.

Methods: Patients admitted to the Hospital Clinic of Barcelona due to COVID-19 infection between 28th January and 14th June 2021 were prospectively included. A blood sample during the first 48h from hospital admission was collected for each patient to measure interleukin (IL)-6 and NT-proBNP. Biomarkers concentrations were quantified by bead-based multiplex assays (Millipore Iberica, S.A., Spain). For the analysis, patients were categorized into four groups depending on inflammation (IL-6 < or ³80 pg/mL) and cardiac phenotypes (NT-proBNP < or ³ 34.3 pg/mL). Clinical information was collected.

Results: One hundred sixty-nine patients were included (**Table 1**). Cardiovascular comorbidities were more present in the cardiac phenotype. Inflammatory phenotype' patients more frequently presented ARDS, while coagulation disorders were more commonly found in patients with both altered markers. Length of stay, ICU admission and IMV requirement were higher in the inflammatory phenotype, whereas mortality was higher when both phenotypes concurred.

Conclusions: High levels of inflammatory and cardiac biomarkers were associated with poor outcomes in hospitalized COVID-19 patients.

Characterization of the immunophenotype of circulating neutrophils in Bronchiectasis

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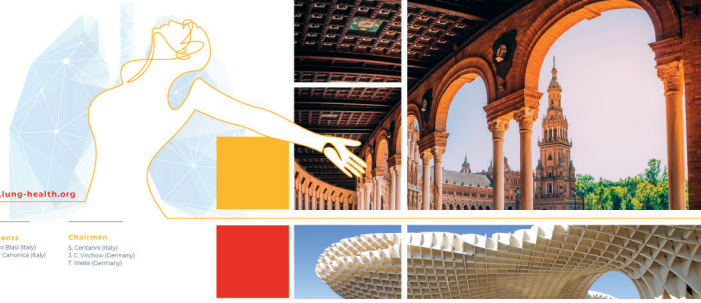
Poster Abstract Winner

Background: Bronchiectasis (BE) is an obstructive lung disease characterized by chronic cough and sputum production, recurrent bacterial infections and progressive lung damage. Considering that dysregulated immune responses represent a key pathogenetic mechanism in both BE and chronic obstructive pulmonary disease (COPD), the identification of the precise immunological features that characterize each disease entity will allow better patient stratification and facilitate the development of more targeted, personalized therapies. Also neutrophils play a crucial role in host defense responses, reprogramming their pro- inflammatory functions towards more effective anti-pathogen protective immunity represents an attractive therapeutic approach for the management of BE and COPD. Our aim was to comprehensively characterize the immunophenotype of circulating neutrophils in patients with BE and COPD and explore correlations with clinical and immunological disease parameters.

Subjects and Methods: We obtained peripheral blood from BE and COPD and Healthy controls (HC) (n=10 ± 3). Characterization of the immunophenotype of circulating neutrophils were investigated by single-cell cytometry by time-of-flight (CyTOF). Circulating neutrophils were also analyzed for phagocytosis and NETosis assays by flow cytometry.

Results: CyTOF analysis revealed distinct populations between HD, COPD and BE. Also, phagocytosis was decreased in circulating neutrophils of BE patients compared to individuals with COPD and HC.

Conclusion: Our studies reveal dysregulated neutrophil responses in BE compared to COPD and HC.



A Qualitative Interview Study to Explore the Use of Adverse Event Mitigation Strategies Among Adults Receiving Amikacin Liposome Inhalation Suspension (ALIS) in Real World Settings

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Background: Amikacin liposome inhalation suspension (ALIS) is the first FDA-approved treatment as part of a combination antibacterial drug regimen for adult patients with refractory Mycobacterium avium complex lung disease (MAC-LD) who have limited or no alternative treatment options. This study used qualitative research methods via one-on-one patient interviews to gain insight into patient perspectives and practices used to mitigate adverse effects (AEs) that patients associated with ALIS in the real world.

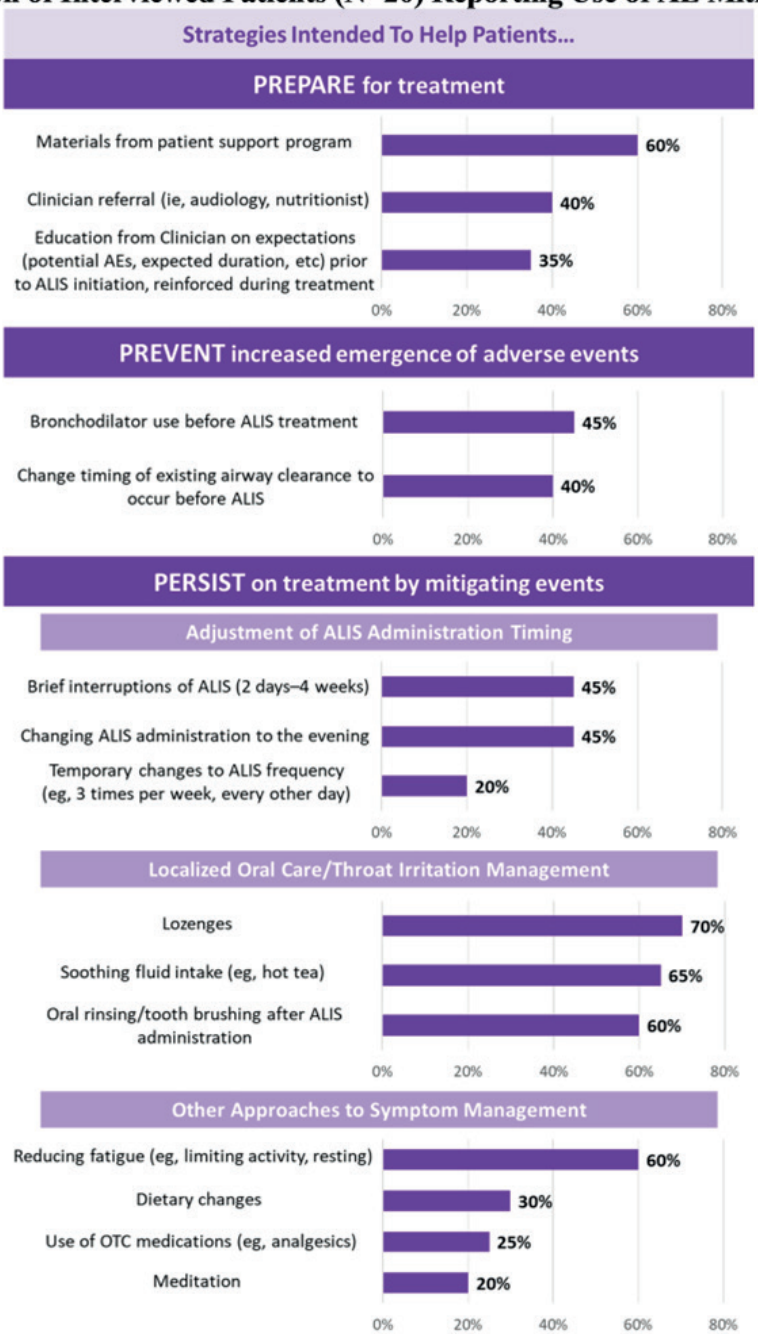
Methods: Adult patients in the United States were recruited through the patient support program. Patients who received ALIS for at least 7 consecutive days and self-reported a clinician-confirmed diagnosis of refractory MAC-LD were included. A predetermined sample size of 20 patients was targeted. Purposive sampling was used to ensure representation of patients with different durations of ALIS therapy. The study protocol was approved by an institutional review board. Research team members trained in qualitative data collection techniques used a semi-structured interview guide with open-ended questions and follow-up probes to conduct patient interviews via phone. Interview transcripts were coded and analyzed using ATLAS.ti v8.

Results: Study invitations were sent to 839 patients; 95 patients completed the screening survey and 41 were eligible based on their responses. Interviews were conducted with 20 patients (mean age, 48.7 years; 90% white; 80% women; mean ALIS duration, 5.45 months). At the time of interview, 15 patients (75%) had experience receiving ALIS for longer than 1 month, and 13 patients (65%) were currently receiving ALIS treatment.

Overall, patients described 44 unique AE mitigation strategies, which can be described using 3 categories (Figure). Most strategies were used to mitigate respiratory AEs. Common strategies (≥50%) included use of relevant informational materials, localized management of throat irritation, and symptom management to reduce fatigue. Concept saturation was achieved, as no new AE mitigation strategies were identified in the last 5 patient interviews.

Conclusion: Mitigation strategies intended to prepare patients for ALIS treatment, prevent the increased emergence of certain AEs, and mitigate impact of AEs on treatment persistence may have clinical relevance for treatment of MAC-LD with ALIS. This study collected real-world data from patients to identify the diverse set of AE mitigation strategies used by patients and identified potential opportunities clinicians can avail of and adopt in improving adherence to treatment with ALIS. These qualitative data can inform future studies to further quantify the effectiveness of different AE mitigation strategies in real-world settings.

Figure. Proportion of Interviewed Patients (N=20) Reporting Use of AE Mitigation Strategies



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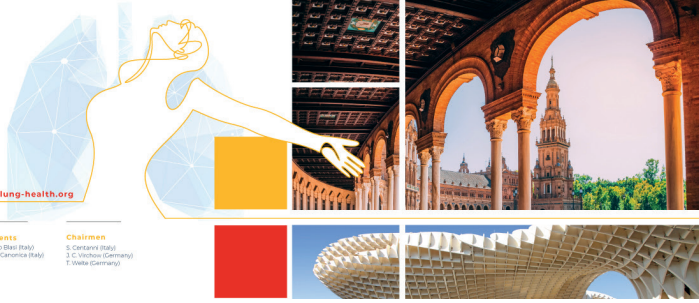
This study was funded by Insmed Incorporated.
Jui-Hua Tsai, Nancy Touba, and Kelly McCarrier are employees of OPEN Health, which received funding from Insmed Incorporated to conduct the research activities.
Jasmanda Wu, Mariam Hassan, and Mark Ballard are employees of Insmed Incorporated. Mark Ballard reports stock ownership in Insmed Incorporated.
Anjan Chatterjee is a former employee of Insmed Incorporated.
Juzar Ali is a consultant for Insmed and Oxford Immunotech and a member of the speakers bureau for Insmed and Oxford Immunotech.



CFTR Modulator Treatments Effects on Pulmonary Health: A Chest MRI Analysis in Cystic Fibrosis Patients

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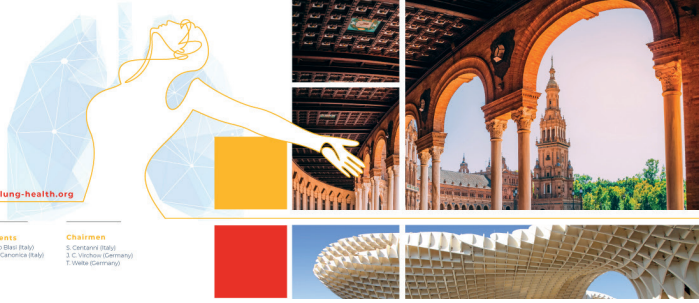
Background: Recent research has focused on identifying and proposing CFTR modulators (CFTRm) for commercialization, highlighting their efficacy in clinical trials. Effective monitoring is essential to prevent irreversible lung damage in patients with cystic fibrosis (CF). Chest Magnetic Resonance Imaging (MRI), a radiation-free modality, plays an increasingly important role in monitoring CF lung disease and may allow early disease detection and treatment adjustment.

Aim: To study the effects of dual and triple CFTR modulator therapies on pulmonary structural damage and inflammation on chest MRI at 12 months and to assess differences among treatments in patients with CF ≥12 years and homozygous for the F508del mutation.

Methods: 14 patients followed at the CF Center of Treviso (Italy) were first treated with Lumacaftor/Ivacaftor (LUM/IVA) before switching to Elexacaftor/ Tezacaftor/Ivacaftor (ETI). During the first year of each therapy, data from chest MRI (modified Brody and diffusion- weighted imaging scores), spirometry, sweat chloride test (SwCl) and pulmonary exacerbation rate (PEx) were evaluated.

Results: After 12 months of LUM/IVA, modest but not statistically significant improvements in MRI mBrody score (-2.25), ppFEV1 (+3.79), ppFEF25-75 (+7.21) were observed, in contrast to sweat chloride concentration (-16.07; p=0.005) and pulmonary exacerbation rate (-3.5/year; p<0.0001). DWI scores remained stable over the study period. ETI, however, had significant effects on all outcomes: MRI mBrody score (-13.43; p=0.0023; mean difference from LUM/IVA - 11.18 p=0.05), DWI score (-13.93; p=0.0005; mean difference from LUM/IVA -14. 79 p=0.0051), ppFEV1 (+11.98; p=0.0024), ppFEF25-75 (22.59; p=0.0296) and SwCl (-50.38; p<0.001), whereas significance was not reached for PEx rates.

Conclusion: During the observation period, LUM/IVA shows limited efficacy, but significantly reduces pulmonary exacerbations, leading to greater clinical stability and slower disease progression, despite what occurs in the natural history of CF. Even in clinically stable patients already on CFTRm, ETI significantly improves lung structure, function, and inflammation. These results underscore the potential of ETI in improving CF management and highlight the critical role of chest MRI in monitoring treatment responses.



Dipeptidyl Peptidase-1 Inhibition in Patients with Bronchiectasis with Eosinophilic Endotype From the WILLOW Trial

James D Chalmers[1]; Mark L Metersky[2]; Ariel Teper[3]; Carlos Fernandez[3]; Sebastian Fucile[3]; Melanie Lauterio[3]; Roald van der Laan[4]; Andrea Maes[3]; Loebinger Michael R[5]

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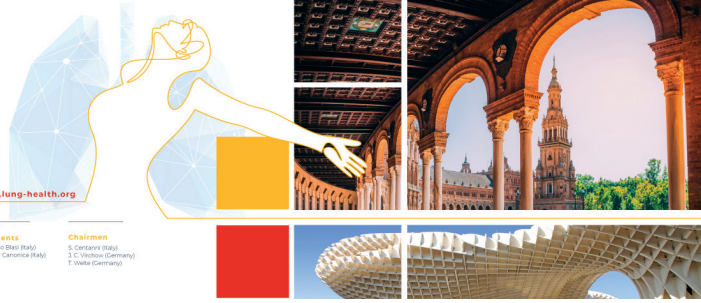
Background: Neutrophilic inflammation and neutrophil serine proteases, e.g., neutrophil elastase (NE), play key roles in bronchiectasis (BE). Blood eosinophilia is present in ~20% of BE patients. The significance of eosinophilic inflammation in BE is unclear. Brensocatib, an investigational dipeptidyl peptidase-1 inhibitor, prolonged time to first exacerbation (Ex) vs placebo in the phase 2 WILLOW study (NCT03218917). The aim of this analysis is to assess baseline characteristics and treatment outcomes by eosinophilic endotype (eosinophil count [EOS] ≥300 cells/µl) among WILLOW patients.

Methods: Adults with BE treated with once-daily brensocatib (10 mg or 25 mg) or placebo were analyzed by baseline blood EOS (<300 cells/µl or ≥300 cells/µl). Endpoints were time to first Ex, annualized Ex rate, change from baseline in FEV1, and treatment-emergent adverse events.

Results: Participants with baseline blood EOS ≥300 cells/µl (49/255) had greater BE Severity Index scores and were more likely to receive inhaled steroids or maintenance macrolides, or have P. aeruginosa in sputum. Brensocatib prolonged time to first Ex and reduced annualized Ex rates vs placebo in both subpopulations (Table). Safety finding were similar across the eosinophil subgroups and consistent with overall trial results.

Conclusion: Brensocatib treatment in patients with BE prolonged time to first Ex and reduced Ex rates vs placebo, regardless of eosinophilic subtype.



Efficacy and Safety of Dipeptidyl Peptidase-1 Inhibition with Brensocatib in the Frequent Exacerbator Phenotype: A Subgroup Analysis From the WILLOW Trial

Michael R Loebinger[3]; Mark L Metersky[4]; Ariel Teper[2]; Carlos Fernandez[2]; Sebastian Fucile[2]; Melanie Lauterio[2]; Roald van der Laan[1]; Andrea Maes[1]; James D Chalmers[5]

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Background: Neutrophil serine proteases (NSPs) such as neutrophil elastase (NE) are activated in the bone marrow by dipeptidyl peptidase-1. High levels of NSPs are associated with increased exacerbations (Ex) in patients with non-cystic fibrosis bronchiectasis (BE). Brensocatib is a reversible dipeptidyl peptidase-1 inhibitor that prolonged the time to first Ex vs placebo in patients with BE in the phase 2 WILLOW trial (NCT03218917). A subset of patients who experience consistently high Ex rates in BE has been recognized, termed “the frequent exacerbator phenotype”. The present analysis compares patient characteristics and outcomes in WILLOW subgroups based on history of Ex frequency in the year prior to study enrollment.

Methods: Adults with BE in the WILLOW study, treated with once-daily brensocatib (10 or 25 mg) or placebo were stratified by history of 2 or ≥3 Ex in the prior year. Endpoints included time to first Ex, annualized Ex rate, change from baseline in FEV1, and treatment-emergent adverse events.

Results: Consistent with greater disease severity, a greater proportion of patients with ≥3 Ex in the prior year (n=84) had higher BE Severity Index (BSI) scores, received maintenance macrolides, or had P. aeruginosa cultured from sputum at baseline (BL), than patients with 2 Ex (n=171). Having ≥3 Ex at BL was also associated with higher levels of NE at BL than patients with 2 Ex. Brensocatib treatment resulted in prolonged time to first Ex and reduced Ex rates across both Ex groups. The hazard ratios vs placebo (95% CI) for time to first Ex in the subgroup with history of 2 Ex were 0.53 (0.30–0.93) and 0.59 (0.33–1.071) and for the ≥3 Ex group were 0.60 (0.21–1.71) and 0.78 (0.33–1.83), for patients treated with 10 mg and 25 mg brensocatib respectively. Annualized Ex rates in the brensocatib groups were lower than those in the placebo groups (38% lower with the 10 mg dose and 22% lower with the 25 mg dose for the 2 Ex group; 45% lower with 10 mg and 26% lower with 25 mg for the ≥3 Ex group). Safety in both Ex subgroups was consistent with overall trial results.

Conclusion: Consistent with overall WILLOW study results, brensocatib treatment prolonged time to first Ex and reduced Ex rates as compared to placebo in both Ex subgroups. Results support the potential of brensocatib as a treatment for patients with BE experiencing Ex. The phase 3 ASPEN trial (NCT04594369) is a larger study that is currently ongoing to further evaluate these findings.

Presence and Extension of Mucus Plug in Bronchiectasis Define a Specific Inflammatory Endotype

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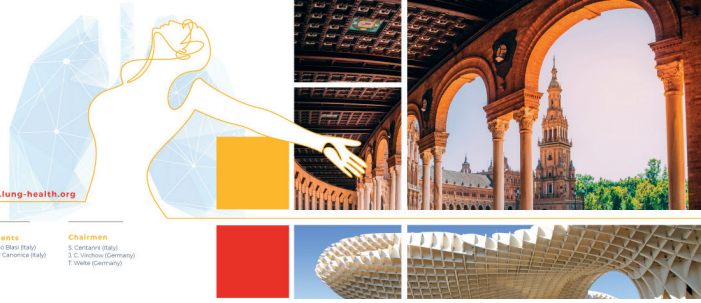
Mucous plug (MP) is one of the most prevalent radiological patterns on chest CT in bronchiectasis. We speculate that its presence and extension could be associated with a specific inflammatory endotype and airway microbiome profile.
To prove this hypothesis, a prospective, cohort study was conducted in Milan (Italy) and Barcelona (Spain) from 2008 to 2019. Consecutive adults with bronchiectasis who underwent both chest CT and serum and sputum analysis during stable state were enrolled. Two radiologists with 5 years of experience in chest radiology assessed presence and extension of MP at the chest CT. Blood eosinophils, sputum and serum inflammatory markers as well as sputum microbiome were evaluated. Patients were divided into Group A if MP was present in at least 10 bronchopulmonary segments and Group B if MP was absent or present in less than 10 segments.
137 patients (73% female, median age of 64 years) were enrolled. The median [IQR] level of aNE in sputum was 10.3 [3.1 - 22.4] ug/mL, with high levels associated with the extension of MP (P: 0.046) at the univariable binary logistic model. Patients in Group A (n = 50) showed higher levels of sputum aNE (14.2 [6.3 – 33.2] ug/mL VS. 8.6 [2.6 – 19.0] ug/mL, P: 0.014), sputum cathepsin-G (102.0 [63.2 - 217.6] ng/mL VS. 66.0 [0 – 124.6] ng/mL, P: 0.009) and serum IL-10 (34,587.2 [15,326.4 – 64,290.2] pg/mL VS. 19,716.2 [8,596.7 - 32,177.1] pg/mL, P: 0.041) in comparison to those in group B (n = 87). In terms of T2-high inflammation, Group A patients had higher levels of IL-5 (106.3 [72.8 - 156.2] pg/mL VS. 52.8 [33.4 - 105.7] pg/mL, P: 0.019), IL-13

(12,827.8 [11,078.1 – 17,317.1] pg/mL VS. 8,868.9 [6,581.0 - 11,465.0] pg/mL, P: 0.006) and extracellular ADP (216.9 [96.4-367.8] ng/mL VS. 105.6 [173.7-53.0] ng/mL, P: 0.024) than those in Group B, while blood eosinophils did not differ significantly (130 [53-245] VS. 150 [100-270], P: 0.193) between the two study groups. In terms of airway microbiome, Group patients A had a lower evenness (0.67 [0.53-0.86] VS. 0.82 [0.66-0.90], P: 0.037) and a lower Shannon diversity index (3.8 [2.3-5.5] VS. 5.0 [3.7-6.0], P: 0.013).

Presence and extension of MP seems to be associated with specific inflammatory and microbial features in bronchiectasis.



The Impact of Extrafine Beclometasone/Formoterol/Glycopyrronium on ability to carry out activities of daily living in Chronic Obstructive Pulmonary Disease (COPD) in an Italian Context of Real Life: The TRITRIAL Study

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Rationale: The ability to carry out activities of daily living in patients with moderate-severe COPD is a fundamental outcome for evaluating the impact of the disease on patients's quality of life. In this study we evaluate the results of TRITRIAL study in terms of daily living activities (through the CAT items) in patients with COPD treated with extrafine triple therapy.

Methods: TRITRIAL was a longitudinal, multicenter, prospective, 12-month observational study conducted to evaluate the effect of extrafine BDP/FF/G on the health status (CAT score) of patients with COPD aged ≥ 40 years and with a history of at least 1 moderate or severe exacerbation. The CAT (COPD Assessment Test) questionnaire evaluates, through 8 items, the various symptomatic aspects that can impact the patient's quality of life: activities, leaving home and energy, and expresses the patient's ability or otherwise to carry out daily life activities. The questionnaire was self-administered electronically. Higher scores represented a higher impact of the pathology on the patient's normal activities.

Results: A total of 656 patients were enrolled, with a mean age of 71.2 years (SD 9). The CAT score at baseline was 22.8, at 12 months it was 16.4 with a reduction of 6.3 points ($p<0.0001$). Domains related to activities of daily living at baseline were: activities 2.91 vs 2.29 at 6 months [mean difference -0.65 ($p<0.0001$)] and 2.13 at 12 months [mean difference -0 .76 ($p<0.0001$)]. Leaving home 2.39 vs 2.01 at 6 months [mean difference

-0.44 (p<0.0001)] and 1.73 at 12 months [mean difference -0.67 (p<0.0001)]. Energy 3.07 vs 2.53 at 6 months [mean difference -0.54 (p<0.0001)] and 2.3 at 12 months [mean difference -0.76 (p<0.0001)]. The ability to perform activities of daily living in these patients improved from baseline to follow-up visits.

Conclusions: The present study demonstrated that extrafine BPD/FF/G significantly improved patient perception of being able to perform activities of daily living, over time, in patients with moderate to severe COPD. Results collected from COPD patients were consistent with the CAT score.

Efficacy of Oral Lyophilisate Inmunotherapy Against House Dust Mites in Asthmatic Patients

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Introduction: In several clinical studies, the oral lyophilisate immunotherapy (OLI) against house dust mites has evidenced less asthma exacerbations and reduction of inhaled corticosteroids (IC).

The main objective was to evaluate the efficacy and security of OLI in asthmatic and mites sensitized patients.

At this moment, there is no definite position regarding guidelines for OLI against mites.

Methods: In the study, it was included 34 patients with asthma and a positive sensitization to house dust mites. This patients were treated with oral lyophilizate immunotherapy for 24 months (September 2018 to December 2022).

It was obtained the next items: FEV1, severe and moderate asthma exacerbations, Asthma Control Test (ACT), inhalate corticosteroids dose and the number of exacerbations during the next two years.

Results: It was included 34 patients (29 women) and the middle age was 46 years old (18-64). At baseline, 5.9% of patients were included step 1 of GINA; 20,6% step 2; 29,4% step 3; 38,3% step 4 and 5,9% step 5.

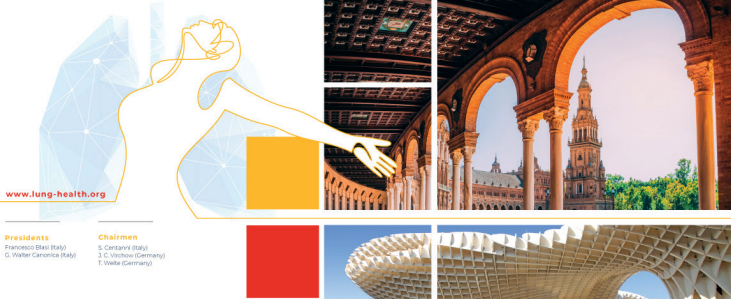
At commence, 91,17% of total patients used long-acting beta agonists (LABA) with IC; 2,9% long-acting muscarinic antagonists (LAMA) with LABA; and 32,4% used antileukotrienes.

The results were (before and after treatment): FEV1 91% vs FEV1 98% (p=0,034); exacerbations per year 1.23 vs 0.41 (p=0.037), hospitalizations per year 3 vs 0 (p≥0,05), inhaled corticosteroids doses (budesonide or equivalent) 800mcg/day vs 600mcg/day (p=0.025), ACT 16 points vs 22 points (p=0.001).

The main adverse effect was oral itching (11 patients). The multivariate regression showed significant differences in steps 3 and 4 of GINA (p=0,009).

Conclusion: There are significant differences in lung function, exacerbations, asthmatic symptoms and inhaled corticosteroids doses.

Oral lyophilisate immunotherapy against house dust mites could be recommended in 3 and 4 steps of GINA. It has demonstrated few serious adverse events.



The Efficacy of Biologic Drugs In Severe Asthma Elderly Patients

Gianluca Imeri[2]; Roberta Biza[1,2]; Roberta Trapasso[2,1]; Luca Novelli[2]; Benedetta Cavazzutti[1,2]; Francesco Caglioni[1,2]; Ileana Curtò[1,2]; Greta Chiodini[1,2]; Carlo Catani[1,2]; Lavinia Bellini[2]; Ludovica Piazzoni[2,1]; Fabiano Di Marco[1,2]

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Backgrounds: Elderly patients can develop more severe and difficult-to-treat asthma compared to younger patients. This is due to several factors, such as comorbidities, polypharmacy, age-related changes in the anatomy and lung function, different response to drugs and, last but not least, the social and psychological impact of aging. Data regarding the efficacy and safety of biological drugs in elderly asthmatics are very few.

Objective: To assess the efficacy of biological therapy for severe T2 asthma (omalizumab, mepolizumab, benralizumab and dupilumab) under real-life conditions in patients older than 65 years. The primary outcome consisted in reduction of exacerbation rate. Secondary outcomes included variation in disease control and lung function (measured with Asthma Control Test and FEV1) and reduction in long-term oral costicosteroid (OCS) therapy.

Methods: Data on clinical features, comorbidities, treatment, biomarkers, asthma exacerbations and disease control were retrospectively collected of all patients with severe asthma receiving biological therapy (prescribed at least 6 months before enrollment) who were followed by the Severe Asthma Outpatient Clinic at our hospital (ASST Papa Giovanni XXIII, Bergamo, Italy). End of the enrollment was October 2023.

Results: Of 104 patients with severe asthma being treated with biologics, 36 patients (35%) older than 65 years were included. Clinical features and outcomes were evaluated in the whole population and in the two subgroups of patients (under-65 and over-65 years). 51 were men (49%), with a BMI of 25±4 kg/m2, without significant differences in the two subgroups. Before the initiation of biologics all patients had a median of 3 (2-4) exacerbations per year, poor symptoms control with a median ACT of 14 (11-18) and a mild airflow obstruction with a FEV1 Z score of -2.48 (-3.45 to -1.54). There weren't statistically significant differences for these findings in the two subgroups, even if patients under 65 years had a slightly worse airflow obstruction (FEV1 Z score -2.72, -3.62 to -1.52, versus -2,35, -3,12 to -1,55, p 0,358). The primary outcome was met without differences in both subgroups, with a median reduction in the exacerbation rate at 6 months of -3 (-2 to -4). An improvement in both symptom control and lung function was seen in all patients, without significant differences in the subgroups. ΔACT in the overall group was +6 (+2 to +11); ΔFEV1 Z score in the overall group was +1.19 (+0.27 to +1.83), while the increase in FEV1 absolute value in the overall group was +0.49L (+0.06L to 0.79L). The reduction in OCS therapy at 6 months was greater in patients under-65 years (-6.25mg, -10mg to -2.5mg) versus patients over-65 years (-2.5mg, -5mg to 0mg) and this difference was statistically significant (p 0.008).

Conclusion: This study suggests that biological therapy in severe asthma is equally effective in elderly patients as compared to under-65 patients. Further research is needed to better evaluate long-term outcome (i.e. ACT, FEV1 and OCS therapy).

Use of Dupilumab in Asthma Relapse After Lung Transplant

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Backgrounds: Dupilumab is a fully human monoclonal antibody against the IL-4 receptor alpha subunit and blocks the action of both IL-4 and IL-13. It has shown great potential in the treatment of severe eosinophilic asthma, as well as in other conditions such as nasal polyposis. However, its use in lung transplantation (LuTx) has not been described yet. We present the use of dupilumab in a LuTx recipient, who suffered an asthma relapse shortly after surgery.

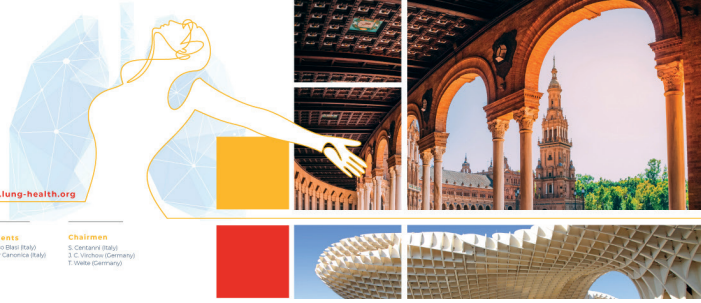
Methods: A 37-year-old man, who underwent bilateral LuTx in April 2023 for sarcoidosis, was hospitalized because of acute respiratory failure one month after transplantation. His past medical history included obesity/overweight and severe asthma being successfully treated with dupilumab; this biological drug was discontinued after transplant surgery.

After discharge, one month after LuTx, in May 2023, he started complaining of progressive dyspnoea on exertion, cough, wheezing and a significant FEV1 decrease; no fever was reported. After an initial course of oral antibiotics and steroid taper on, with subsequent temporary benefit, on May 29th he was hospitalized because of acute respiratory failure; he was diagnosed with massive embolism and anticoagulant therapy was promptly initiated. However, despite initial improvement, severe wheezing occurred and gas exchange started deteriorating again: steroid dosage was increased and he was adapted to non-invasive ventilation. Underlying clinical conditions (especially rejection and/or infection) were ruled out by several investigations. We concluded for high suspicion of asthma flare-up. Therefore, in June 2023, based on the benefit–risk assessment, we restarted the subcutaneous administration of dupilumab (300 mg once every two weeks after an initial loading dose of 600 mg).

Results: After discharge, we noticed a progressive functional recovery, with normal gas exchange on room air both at rest and on exertion; therapy was well-tolerated and no side effects or other respiratory exacerbations were reported.

Conclusions: Although dupilumab is considered to be both safe and non-immunosuppressive, given its immunomodulatory nature, there might be concerns when it is used for immunosuppressed patients.
To our knowledge, our case is the first to report the use of dupilumab in the treatment of an asthma relapse in a LuTx recipient. Further studies are needed to assess the efficacy and the safety of biological treatments in these patients.

Conflict of Interest
We hereby certify that there is not any actual or potential conflict of interest.



Asthma and Treatable Traits in a Candidate for Lung Transplant: a Case Report

Irene Tomarelli[1]; Serena Piccirillo[1]; Irene Sini[1]; Letizia Morlacchi[1]; V Rossetti[1]; A D'Adda; M Cavallini[1]; M Mantero[1]; Francesco Blasi[1]

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Introduction: "Treatable traits" are specific disease characteristics that are clinically relevant and modifiable through pharmacological or non-pharmacological interventions. This concept was originally proposed in 2016 by Agusti et al. as a way toward precision medicine of airway diseases. Chronic pulmonary diseases are ideally suited for precision medicine because they likely represent a continuum of different diseases that may share biological mechanisms ("endotypes") and similar clinical features ("phenotypes") requiring "individualized" treatment. We present a case from our clinical practice where the application of such principles allowed our patient to gain important time while on the waiting list for lung transplant (LuTx).

Methods: A 55-year-old female known for bronchiectasis from 2005 and chronic respiratory failure in oxygen long-term therapy since 2019 was referred to our Centre in Novembre 2021and subsequently listed for LuTx in March 2023. Her past medical history included respiratory colonization by Pseudomonas aeruginosa with frequent pulmonary exacerbations and hospitalizations; eosinophilic asthma in chronic therapy with oral corticosteroid (OCS) and previous allergic broncho-pulmonary aspergillosis (ABPA); malnutrition and sarcopenia. The patient was considered eligible for LuTx but her estimated time on the waiting list was very long due to several reasons, including anthropometry (height 159 cm), rare blood type in our region (B negative) and immunization (previous blood transfusion and two pregnancies). Therefore, we focused on managing treatable traits to optimize her clinical conditions, trying to "buy" some time. The patient was successfully adapted to non-invasive ventilation (NIV) and airway clearance technique and respiratory physiotherapy were improved. Considering the presence of eosinophilic asthma in March 2023 the patient started subcutaneous administration of Benralizumab (30 mg every four weeks for the first three doses, then 30 mg every eight weeks). Extra-pulmonary comorbidities such as malnutrition and sarcopenia were also treated with a personalized diet. In October 2023 - after 18 months on the waiting list - she successfully underwent LuTx.

Results: The assessment and management of treatable traits during the eighteen months of waiting list led to less exacerbations and a better nutritional and general performance status. A slight improvement in functional tests was also reported (Figure 1). We believe that these achievements were fundamental in terms of giving our patient more time while on the waiting list but also in determining a more favorable course after the transplant.

Conclusions: Chronic pulmonary diseases are complex and we often deal with an overlap of different conditions. They also have heterogeneous clinical features, underlying once again the importance of a patient-specific approach. Treatable traits may contribute to move forward in the field of precision medicine of airway diseases. In our case, not only we avoided further deterioration of the patient's respiratory condition, but we were also able to improve the patient's general status while she was waiting for her lung donor.

Scoping Review of the Effectiveness of Noninvasive Ventilation in the Management of COVID-19 Patients

Ahmad Alessa[1]

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In 2020, COVID-19 caused a global pandemic that caused healthcare professionals to be on the frontline. Due to respiratory failures associated with this condition, strategies were needed to improve the respiration of patients diagnosed with COVID-19 disease. An intervention that was extensively adopted as a substitute for invasive ventilation is noninvasive ventilation (NIV). However, there is limited evidence on the effectiveness and safety of this intervention. The aim of this scoping review was to map the existing literature on the use of NIV for COVID-19 patients and identify gaps in knowledge. A systematic search using appropriate keywords was conducted on three selected electronic databases; PubMed, Cochrane Library, and CINAHL by two independent reviewers. After applying the inclusion and exclusion criteria, a total of 30 studies were used for the scoping review. Data was extracted from the studies and the results were presented and discussed. The results of the scoping review showed that some studies presented evidence that supported the effectiveness of NIV. However, some other studies could not provide strong evidence for the efficiency of NIV based on statistical grounds. Also, no negative consequences were identified from the studies regarding the use of NIV in managing patients with COVID-19. Hence, the findings from this study suggest that even though NIV improved the conditions of patients, more studies of high-level and high-quality ratings are needed to provide strong evidence regarding its efficiency.

Scoping Review of the Effectiveness of Noninvasive Ventilation in the Management of COVID-19 Patients

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This study aimed to explore the outcomes of using HFNC for patients with COVID-19. Forty-two studies were scanned using a scoping review, of which 22 were found eligible, satisfying the inclusion and inclusion criteria. Multiple patient outcomes were considered, including recovery time, oxygenation levels, reduced need for intubation in the future, ICU avoidance, and chances of respiratory distress. The findings suggest that HFNC remains more effective in treating patients with COVID-19-induced respiratory problems than traditional methods by indicating significantly improved oxygenation, reduced recovery time, reduced respiratory distress levels, and the need for invasive methods in the future. However, a few complications were also notable while considering its implementation on a wider scale, the most prominent being particle dispersion or airborne infection. However, the studies indicate that the complications and risks can be mitigated using precaution. The research seeks the validation of its findings through more comprehensive research in the future

Table 1. Baseline characteristics and outcomes according to study groups.

	No abnormalitiesa n= 65	Inflammatory phenotypeb n=35	Cardiac phenotypec n=41	Inflammatory and cardiac phenotyped n=28	p-value
Baseline characteristics					
Sex, male	37 (57)	25 (71)	24(59)	19 (68)	0.45
Age, years	60 [40 – 60]	71 [63 – 73]	66 [61 – 72]	74 [57 – 79]	**<0.001**
Comorbidities, n (%)					
Cardiopathy	4 (6)	1 (3)	14 (34)	7 (25)	**<0.001**
Liver disease	1 (1)	5 (3)	1 (1)	2 (1)	0.041
Kidney disease	5 (8)	3 (9)	5 (12)	3 (11)	0.88
Chronic respiratory disease	7 (11)	4 (11)	7 (17)	8 (29)	0.15
Active malignant neoplasia	1 (2)	1 (3)	3 (7)	4 (14)	0.070
Immunodeficiency	4 (6)	4 (11)	1 (2)	1 (4)	0.38
Arterial hypertension	13 (20)	12 (34)	24 (59)	14 (50)	**<0.001**
Diabetes mellitus	5 (8)	9 (26)	8 (20)	7 (25)	0.064
Obesity (BMI >25 kg/m2)	26 (65)	13 (69)	20 (67)	17 (81)	0.619
Alcoholism	9 (14)	4 (11)	5 (12)	3 (11)	0.973
Smoker	18 (28)	16 (46)	13 (32)	14 (50)	0.108
Biomarkers concentrations at hospital admission					
IL-6, pg/mL	43 [33-50]	152 [101-280]	31 [20-52]	152 [111-270]	**<0.001**
NT-proBNP, pg/mL	<34.3	<34.3	36 [35-117]	53 [35-131]	**<0.001**
Complications and treatment during hospital admission, n (%)					
Corticosteroids treatment	54 (83)	31 (89)	33 (81)	27 (96)	0.24
Acute cardiac injury	2 (3)	2 (6)	5 (12)	4 (14)	0.17
Coagulation disorder	3 (5)	8 (23)	9 (22)	9 (32)	**0.004**
PTE	0 (0)	5 (14)	6 (14)	4 (14)	0.016
Acute liver injury	2 (3)	4 (11)	3 (7)	2 (7)	0.44
Acute kidney injury	3 (5)	3 (9)	6 (15)	7 (25)	0.031
ARDS	16 (25)	22 (63)	15 (37)	17 (61)	**<0.001**
Outcomes n (%)					
Length of hospital stay, days	6 [4-9]	11 [5-32]	8 [6-16]	12 [8-24]	**<0.001**
ICU admission	13 (20)	19 (54)	11(27)	13 (46)	**0.002**
Length of ICU stay, days	5 [3-9]	15 [6-33]	12 [3-24]	7 [5-25]	0.11
Requirement of IMV	2 (3)	10 (29)	4 (10)	5 (18)	**0.002**
IMV length, days	30 [7-52]	32 [21-36]	18 [9-26]	24 [20-32]	0.57
In-hospital mortality	0 (0)	3 (9)	4 (10)	6 (21)	**0.004**
90-days mortalitye	0 (0)	4 (12)	5 (13)	7 (25)	**0.002**

Treatment of Latent Tuberculosis Infection: Completion Rate and Adverse Events in Patients with Different Comorbidities

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Background: Screening for latent tuberculosis infection (LTBI) is important to detect and provide treatment to those subjects who are at risk of developing active tuberculosis (TB). In high-risk subjects, even more than in the general population, it is essential to diagnose and treat LTBI before it becomes a life-threatening active disease.

Aims: The aims of this study are to show the tolerability of LTBI treatment, to evaluate its completion rate and to describe the most frequent adverse events (AEs) according to the underlying medical conditions.

Methods: We conducted a retrospective, observational, cohort study on 25127 patients diagnosed with LTBI and who were referred to Villa Marelli outpatient clinic in Milan from 1992 to October 2023.

Results: Out of a total of 25127 subjects, 1297 refused treatment while 18920 completed the prescribed regimen. During LTBI treatment, 3606 reported AEs.

HIV+

157 subjects were HIV+. 151 started LTBI treatment, 114 completed it and 14 subjects reported AEs. The most common AEs in this subgroup were nausea and vomit (3.31 %) and increased serum liver enzymes (2.65 %).

Autoimmune conditions

1292 subjects were affected by autoimmune conditions (psoriasis, rheumatoid arthritis, Chron's disease, ulcerative colitis, vasculitides). Out of these, 1169 started the treatment and 1093 completed it. The most common AEs were increased serum liver enzymes (8.55 %) followed by nausea and vomit (5,82 %).

Cancer

41 subjects were affected by cancer (multiple myeloma, leukaemia, lymphoma, breast cancer, endometrial cancer, lung cancer, laryngeal cancer, prostate cancer, pancreatic cancer, melanoma, thyroid cancer). All patients started LTBI treatment and 33 subjects completed it. AEs were reported in almost one-third of patients. The most common AEs were equally: increased serum liver enzymes (9.76 %), nausea and vomit along with nervousness, insomnia and sleepiness.

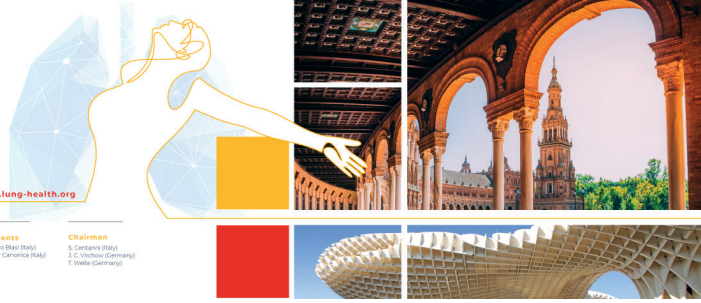
Transplant recipient candidates

190 subjects were transplant candidates (kidney, liver, lung, pancreas or heart). Only 1 patient refused LTBI treatment and, out of the subjects who started it, 160 completed it while 58 reported AEs. The most common AEs were nausea and vomit (7,94%) and astenia (13%).

Conclusions: AEs associated with LTBI preventive treatment are highly heterogeneous. The overall prevalence of AEs was 15.13%. We detected the highest prevalence of AEs among cancer patients (31.71%) and transplant candidates (30.69 %), followed by autoimmune diseases (26 %) and HIV+ patients (9.27 %).

Among HIV+ patients and transplant candidates, nausea and vomit were the most prevalent AEs: 3,31 % and 7,94 % respectively. In neoplastic patients, the most frequent AEs were both laboratory test alterations along with nausea, vomit and nervousness, insomnia or sleepiness. Patients affected by autoimmune diseases and transplant recipient candidates had a wider range of AEs including hypertension, tremor and anaphylactic shock which were absent in the other subgroups.

To conclude, we can state that preventive TB treatment is overall well tolerated and completed also in presence of significant comorbidities. However, AEs are reported in up to almost a third of specific subgroups. Correct monitoring and effective treatment of AEs is of paramount importance because premature discontinuation of LTBI treatment is ineffective.



Sedation With Propofol in Patients with Interstitial Lung Disease

Celia Rodríguez Dupuy[1]; Vicente Roig Figueroa[1]; Blanca De Vega Sánchez[1]; Carlos Disdier Vicente[1]; Santiago Antonio Juarros Matínez[1]; Soraya Fernández Gay[1]

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Propofol is a drug used for sedation during flexible bronchoscopy (FB), characterized by a rapid onset of action and ultra-short effect, with various modes of administration. Complications arising from its use include desaturation, respiratory arrest, bradycardia or hypotension.

Methods: Retrospective descriptive study of FB with the use of propofol in our center. The presence of desaturation (decrease >4% in satO2 or satO2<90% transiently and lasting more than 1 minute), and tolerance (assessed through tachypnea, tachycardia, agitation or other clinical symptoms that cause discomfort) were compared. patient and/or bronchoscopist) in patients with a diagnosis of ILD vs patients without ILD.

Results: Of our sample (N=90), 32.2% were women and 67.8% were men, without significant differences. The dose of propofol and the mean duration of the procedure were 0.163 mg/kg/ml (±0.07) and 32.93 minutes, respectively. 2.2% desaturations and 2.2% regular tolerance occur.

The sample was divided into two groups: Group A (diagnosis of ILD N=42) and Group B (Absence of diagnosis of ILD N=48). The overall mean DLCO and KCO were 77.58 (±23.02) and 96.55 (±21.16). In group A, only 45.2% (N=22) had altered DLCO diffusion (mild, moderate and severe: 11, 9 and 2 respectively). 8.9% of the sample was being treated with home oxygen therapy, with an average flow of 2.13 l/min.

Just 2 patients within group A presented desaturation. There were no significant differences in complications, tolerance or mortality between both groups.

The endoscopic procedures associated with the highest desaturation rate were bronchoalveolar lavage (35.6% p=0.026), with no differences between groups. There were also no differences in tolerance or complications related to the decrease in DLCO or previous treatment with oxigen therapy.

A Case of Systemic Sclerosis with Interstitial Lung Disease after Covid 19 Infection

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Introduction: SARS-CoV-2 infection is primarily a respiratory disease, but it has now become clear that it is a systemic disease due to the wide range of symptoms and organ involvements (1). It has been linked to hyperinflammation in multiple organs due to cytokine storm and molecular mimicry. It has been shown that SARS CoV2 can trigger autoantibody production and in genetically predisposed patients may cause the onset of systemic autoimmune rheumatic diseases (SARDs) because the virus appears to perturb self-tolerance, suggesting also the potential existence of underlying immune dysregulations in individuals with COVID-19 (1-3). However, their incidences and risks have rarely been quantified.

We report a case of mild COVID-19 infection complicated by autoantibody production, cutaneous and respiratory symptoms and subsequently diagnosed with systemic sclerosis (SSc).

Case Report: A 79-year-old male, no smoking, with no history of any autoimmune diseases and in good health became sick on the 12th of December 2020 with mild symptoms: tiredness ever, cough, and sore throat. Oropharyngeal swab for SARS-CoV-2 tested positive. He did not require hospitalization. After 4 months from mild infection of SARS CoV2 infection, the patient began to present Raynaud's phenomenon, tiredness and continued to present cough. Physical exam findings of puffy fingers, sclerodactyly of the fingers, and skin hyperpigmentation. Nailfold capillaroscopy showing a classic SSc capillary pattern with frequent giant capillaries, mild disorganization of the capillary architecture, and moderate loss of capillaries (fig.1). Lab tests showed antinuclear antibody (ANA) titer > 1:160; anti-PM/Scl 75 and PM/Scl 100 tested positive, anti-Scl-70, anti-Jo 1, anti-RNA-polymerase III and other autoantibodies tested negative. Pulmonary function testing showed reduced diffusion capacity of 69% predicted with normal lung mechanics and volumes. High-resolution CT scan of the chest showed initial interstitial lung disease (fig. 2 and 3). Echocardiography showed normal systolic artery pressure. and Schirmer test was negative. The rheumatologist confirmed the diagnosis of SSc and multidisciplinary team decided to start a calcium channel blocker and immunosuppressive therapy (mycophenolate mofetil 1,500 mg twice daily).

Conclusion: This case report describes the onset of clinical symptom and autoantibodies of SSc after a mild COVID-19 infection. The relationship between COVID-19 and the appearance of autoimmunity is complex and again unclear. Is necessity to investigate and to test autoantibodies in all patients that present with unclear and new symptoms after a COVID-19 infection.

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Anemia as a Comorbidity in COPD Patients

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Introduction: Anemia is common in patients with chronic diseases and associated with impaired long-term survival and quality of life. The prevalence of comorbid anemia in patients with COPD ranges from 7.5% to 34%, depending upon the populations selected and diagnostic tools employed to determine the level of hemoglobin. The true prevalence of anemia in patients with COPD, its impact on quality of life, healthcare utilization, and mortality in patients with COPD is unknown. The prevalence of coexisting anemia in COPD is highly variable and depends on the severity of the lung disease, the presence of other comorbidities, and other factors such as socioeconomic status and race.

Material and method: The design is a cross-sectional study, including 220 patients with stable COPD as investigated group (IG), aged 40-75 years and 58 non-COPD subjects, matched by gender, age, body mass index (BMI), smoking-status, as control group (CG). All study subjects underwent pulmonary evaluation (dyspnea severity assessment, baseline and post-bronchodilator spirometry, gas analyses, chest X-ray, 6-minute walk distance, modified Medical Research Council dyspnea questionnaire, St. George's Respiratory Questionnaire), and laboratory analyses (blood count, sedimentation rate, c-reactive protein (CRP), routine biochemistry). Patients were classified as anemic based on hemoglobin (Hgb) levels (Hgb<12/13 g/dl, female patients/male patients, according to The World Health Organization). Patients with known causes for anemia were excluded.
Results presented statistically significant difference between presence of normocytic anemia in IG 13.6% (n=30) vs. CG 3% (n=3) ($p<0.05$). There was a significant linear positive correlation between anemia and GOLD stage ($R=0.174$; $p<0.05$). With decrease of FEV1(GOLD1→GOLD4), the frequency of anemia increased significantly. According to gender anemia was more frequent in male 9% (n=20), vs. female 4.5% (n=10) ($p<0.05$). Anemia was associated with higher levels of serum C-reactive protein in COPD patients with anemia 10.5mg/L, vs COPD patients without anemia 2.3mg/L ($p<0.05$). Anemic participants were older with worse airflow obstruction and they had a higher prevalence of cardiac and metabolic comorbidities. Anemia was strongly associated with 6-minute walk distance (β, −62.34; 95% confidence interval [CI], −84.12 to −36.63), St. George's Respiratory Questionnaire (β, 3.82; 95% CI, 1.06–6.62) and modified Medical Research Council dyspnea questionnaire (β, 0.31; 95% CI, 0.12–0.45). There was a significant linear positive correlation between anemia and BMI ($p=0.012$)

Conclusion: Comorbid anemia in patients with COPD was associated with greater healthcare resource utilization, impaired quality of life, older age, and male gender. Moreover, anemia in patients with COPD is an independent prognostic predictor of premature mortality and a greater likelihood of hospitalization. Based on the findings from the existing literature, more work is necessary to establish the true prevalence of anemia in COPD. More prospective clinical studies are needed to improve the management of COPD patients with comorbid anemia.

Cachexia in Chronic Obstructive Pulmonary Disease (COPD)

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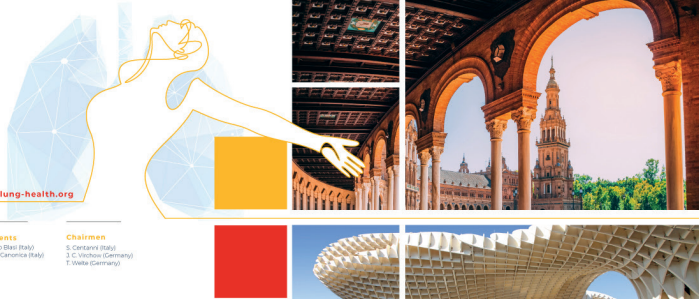
The prevalence and mortality of chronic obstructive pulmonary disease (COPD) in elderly patients are increasing worldwide. Low body mass index (BMI) is a well-known prognostic factor for COPD. Cachexia and muscle wasting are well recognized as common and partly reversible features of COPD, adversely affecting disease progression and prognosis. There is considerable heterogenecity in the rate of lung function decline in COPD, the determinants of which are largely unknown. Observational studies in COPD indicate that low BMI is associated with worse outcomes, and overweight/obesity has a protective effect - the so-called "obesity paradox". We aimed to determine the relationship between BMI and the rate of FEV1 decline. The design is a cross-sectional study, including 220 patients with stable COPD as investigated group (IG), aged 40-75 years and 58 non-COPD subjects, matched by gender, age, BMI, smoking-status, as control group (CG). All study subjects underwent pulmonary evaluation (dyspnea severity assessment, baseline and post-bronchodilator spirometry, gas analyses), BMI measurement. We analyzed BMI in 4 categories: BMI-I (< 18.5 or < 20 kg/m2), BMI-II (18.5 or 20 to < 25 kg/m2), BMI-III (25 to < 29 or < 30 kg/m2) and BMI-IV (≥29 or ≥ 30 kg/m2). The analysis indicated incorrect distribution of frequencies for BMI (kg/m²) values for Shapiro-Wilk W=0.9746; p=0.00007, which is why appropriate non-parameter statistical tests were applied to the analyses. For p<0.05, no significant difference was established between the four IG subgroups in relation to the height of the BMI (Kruskal-Wallis H test: p=0.0291). Additional analysis in both groups indicated an average BMI of 25.4±3.8 kg/m² with a min/max of 17.6 /35.5 kg/m² in IG vs. 26.2±2.5 kg/m² with a min/max of 19.4 /33.2 kg/m² in CG. 50% of IG participants were less than 25.3kg/m² for Median IQR=25.3 (22.9-27.4), and in 50% of CG it was Median IQR=29.2. For p<0.05, the analysis indicated a significant association between the nutrition of subjects and the subgroup (GOLD 1→ GOLD 4) to which they belonged (Fisher Freeman Halton test: p=0.023). With decline of FEV1, BMI also declined. Analysis between the two (IG/CG) groups indicated that, for p<0.05, there is a significant association between nutrition and the group to which the respondents belong (Pearson Chi-square test: X2=8,691; df=2; p=0.0129). CG respondents were 2,648 times more frequent obese compared to IG [OR=2.65 (1.37–5.13) 95% CI]. In this review, recent insights are presented in the frequency of cachexia in COPD. In mild to moderate COPD, higher BMI was associated with a less rapid decline of FEV1 in male patients whereas this association was minimal in female patients. This gender-specific BMI effect was independent of COPD severity and smoking status. These novel findings support the obesity paradox in COPD: compared to normal BMI, low BMI is a risk factor for accelerated lung function decline, whilst high BMI has a protective effect. The relationship may be due to common but as-of-yet unknown causative factors; further investigation into which may reveal novel endotypes or targets for therapeutic intervention.



Dyslipidemia in COPD Patients

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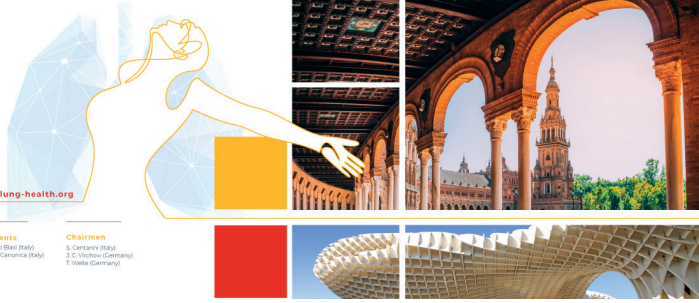
Introduction: Chronic obstructive pulmonary disease (COPD) is a progressive inflammatory lung disease that causes obstructed airflow limitation from the lungs. COPD is currently the third leading cause of death worldwide and is characterized by airway inflammation, alveolar destruction, and airflow limitation. It is prone to the viewpoint that systemic inflammation maybe complicated in the pathogenesis of majority comorbidities.

Material and method: The study was conducted at the General Hospital "8th September", Skopje, in the period 2018-2020 as a continuum of our investigation of the impact of cardiovascular comorbidities on COPD. The design is a cross-sectional study, including 220 patients with stable COPD as investigated group (IG), aged 40-75 years and 58 non-COPD subjects, matched by gender, age, BMI, smoking-status, as control group (CG). All study subjects underwent pulmonary evaluation (dyspnea severity assessment, baseline and post-bronchodilator spirometry, gas analyses), BMI measurement, laboratory analyses with attention to lipid profile (cholesterol, triglycerides, LDL = low density lipoprotein, HDL = high density lipoprotein).

Results: For $p<0.05$, the analysis indicated a significant difference between the four IG subgroups in terms of triglyceride level (Kruskal-Wallis test: $H(3)=12,842$; $p=0.005$). Analysis in IG/CG indicated an average triglyceride level of 1.34±0.74 (mmol/L) in IG vs. 1.41±0.69 (mmol/L) in CG. For $p>0.05$, there was no significant difference between IG and CG respondents in relation to triglyceride value (Mann-Whitney U Test: $Z=-1,484$; $p=0.1377$). For $p>0.05$, there was no significant difference between the four IG subgroups in terms of cholesterol level (Kruskal-Wallis test: $H(3)=2,303$; $p=0.512$). Analysis in IG/CG indicated an average cholesterol value of 4.88±1.07 (mmol/l) in IG vs. 4.79±1.12 (mmol/l) in CG. For $p>0.05$, there was no significant difference between IG and CG subjects in relation to cholesterol levels (Mann-Whitney U Test: $Z=1,187$; $p=0.235$). The proportion of hypercholesterolemia, hypertriglyceridemia and combination (hypercholesterolemia + hypertriglyceridemia) was consequential in: a) GOLD1 - 19 (33.33%) vs. 4 (7.02%) vs. 5 (8.77%); b) GOLD2 - 24 (38.71%) vs. 9 (14.52%) vs. 2 (3.23%); c) GOLD3 - 14 (26.92%) vs. 4 (7.69%) vs. 5 (9.62%); and d) GOLD4 - 21 (42.86%) vs. 1 (2.04%) vs. 1 (2.04%). For $p>0.05$, there was no significant association between the GOLD subgroup of IG, which included respondents and the dyslipidemia status for the Fisher Freeman Halton test: $p=0.190$.

Conclusion: Chronic obstructive pulmonary disease - associated chronic illnesses and systemic comorbidities pose a significant problem in the risk assessment and affect the integrated treatment plans.



The Role of Small Airways Disfunction in EGPA: Preliminary Results From a Multicentric Study

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Small airways disfunction (SAD) is a physiopathological trait of asthma, with a prevalence of over 90%[1] and a significant impact in term of exacerbation risk and symptom control.

Asthma is one of the most frequent manifestations of EGPA and over 57% of EGPA patients have a severe form of asthma, as defined by the ERS/ATS statement [2]. Little is known about the functional characteristics of asthma associated with EGPA, especially about the prevalence of SAD.

The aim of this multicentric retrospective study was to evaluate the prevalence of SAD, defined by any alteration in FEF25-75, R5-19, AX and X5, in asthmatic patients with EGPA and to compare their functional characteristics with a matched group of asthmatic patients with severe eosinophilic asthma (SEA). The secondary aim was to evaluate the impact of SAD disease control (ACT and ACQ7) in these different conditions.

We present the results from the 35 patients enrolled at ASST Papa Giovanni XXIII hospital (BG, Italy), 16 with EGPA and 19 with SEA, matched by sex, age and anthropometric characteristics. We found similar functional characteristics between SEA and EGPA groups with a prevalence of SAD of 66% in the whole sample, 68% in the EGPA group and 63% in the SEA group (p= 0.736). We also confirmed the impact of SAD on asthma control, with ACT values significantly lower (p = 0.012) in patients with SAD [24 (22-25) vs 22 (16-24)] both in EGPA [24 (22-25) vs 22 (16-24)] and SEA patients [25 (25-25) vs 22 (17-25)]. Similar results were found for ACQ7 questionnaire, with values significantly higher (p = 0.017) in patients with SAD [0.7 (0.28-1.50) vs 0 (0.00-0.01)] independently from the presence of EGPA [0.7 (0.28-1.50) vs 0 (0.00-0.01)] or SEA [0.6 (0.1-1.5) vs 0.0 (0.0-0.1)].

The main limitation of our study was the small sample of patients, something that we hope to overcome once the data from the other severe asthma centres will be available.

In conclusion, our study shows how asthma in EGPA is functionally comparable with SEA, both in terms of SAD prevalence and its negative impact on asthma disease control assessed with ACT and ACQ7.

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[2] Chung et al., “International ERS/ATS Guidelines on Definition, Evaluation and Treatment of Severe Asthma.”

Assessment of Diaphragmatic Ultrasound in Patients with Acute Respiratory Failure: Dysfunction and Clinical Correlates

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Background: Diaphragmatic ultrasonography is a non-invasive, repeatable and rapid tool to assess diaphragmatic function. In invasively ventilated patients, diaphragmatic dysfunction -defined as an excursion < 10 mm and/or a thickening fraction (TF) < 20%- can identify patients at risk of difficult weaning. Diaphragmatic function in spontaneously breathing patients with acute respiratory failure (ARF) is still poorly investigated. The present study was designed to describe the diaphragmatic function in patients admitted with ARF, investigating correlations between diaphragmatic excursion and clinical variables and to assess the prevalence of diaphragmatic dysfunction and its association with in-hospital mortality.
Material and Methods: We enrolled consecutive patients admitted in the Pulmonary Unit of Hospital Sacco with a diagnosis of ARF of any entity or diagnosis between January and June 2023.
For each patient, the same operator conducted the following assessments: recorded the patients' medical history, performed a blood gas analysis (ABG), completed the respiratory distress score (evaluated by assessing the respiratory rate and the use of accessory muscles), assessed dyspnea using the visual analog scale (VAS) and performed a diaphragmatic ultrasound upon admission (T0) and at the time of the discharge (TD). Each ultrasound included: the thickness of the diaphragm, the thickening fraction (TF) - assessed at the end of a tidal volume expiration (E-VT) and at total lung capacity (TLC) - as well as the maximal excursion, measured as the distance between the maximum point (at TLC) and the minimum point (at the end of expiration) on the diaphragmatic line using M-Mode with a convex probe.
Results: In total, 43 patients werer recruited, and 33 had complete data on ultrasonographic evaluation. Mean (SD) age was 76 (14) years with 54% being men, and with average hospitalization stay of 9 days. Upon admission, 5 patients (11%) exhibited diaphragmatic dysfunction and the mean excursion was 3.5 cm (SD 1.8), with a Δ% at discharge of +51% ($p < 0.01$). During the hospital stay, no significative variations of thickness at EVT and at TLC were measured, but a more higher entrance TF was associated with a reduced TF at the discharge ($R^2 = 0,404$; $p < 0.001$). Considering the clinical variables, only the respiratory distress score at admission to the ward correlated weakly and inversely with the excursion ($p < 0.01$, r2 0.24). 28% of all deaths presented diaphragmatic dysfunction.
Conclusion: During acute phase, accessory muscles can provide an adequate tidal volume, explaining the lack of correlation between excursion and clinical parameters. Conversely, reduced excursion was found to be associated with higher distress, maybe representing an ultrasound index of the involvement of accessory muscles. In our population, the prevalence of diaphragm dysfunction was low and didn't impact in-hospital mortality, possibly due to heterogeneity of the admission diagnoses of the patients included in the study.

No external funding or financial support were received for the present study

Familial Pulmonary Fibrosis Due to SFTPC Mutation and Eosinophilic Granulomatosis with Polyangiitis: a Unique Contemporary Diagnosis of Two Rare Diseases

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Introduction: Familial pulmonary fibrosis (FPF) is defined as any fibrosing interstitial disease (ILD) in at least two first- or second-degree blood relatives. Two classes of genetic variants have been associated with FPF: common variants (allele frequency >1%) and rare variants (allele frequency <0.1%). Among rare variants, mutations of the surfactant and telomerase genes have the greatest phenotypic expression. Eosinophilic granulomatosis with polyangiitis (EGPA) is a rare ANCA-associated necrotizing vasculitis affecting small to medium-sized vessels. To date, associations of the two pathologies have not been described.

Clinical Case: In December 2021, in the context of a health screening, a 52-year-old Caucasian man had a chest X-ray with evidence of bibasal interstitial thickening. Since he was asymptomatic, he underwent a chest high resolution computed tomography (HRCT) in November 2022 only. HRCT was suggestive for combined pulmonary fibrosis and emphysema (CPFE) (Figure 1). In February 2023, histology from a transbronchial lung cryobiopsy was compatible with a secondary UIP pattern due to the presence of multinucleated giant cells and mild lymphocytic infiltrates. A positivity for p-ANCA (Myeloperoxidase-MPO) was also found with a pathologic titre of 12 IU/ml (cut-off >5 IU/ml). CPFE with autoimmune background was thus diagnosed and therapy with Nintedanib (300 mg/day) and prednisone 25 mg/day to be gradually reduced to 6.25 mg/day over 2 months was recommended. The patient, still asymptomatic, refused the treatment.

In March 2023, the patient came to our center for second opinion. He was asymptomatic, bilateral velcro crackles could be appreciated at auscultation. Never smoker, he denied exposure to toxic inhalants, allergies, Raynaud's phenomenon, premature hair graying and other comorbidities. However, his father died of unspecified pulmonary disease at 45 years-old. Spirometry was normal, diffusing capacity for carbon monoxide was moderately reduced (44%). Curiously, exercise respiratory failure was found at the 6-minute walking test in room air (SatO2 min: 84%, time <90%: 72%). MPO-ANCA positivity (15 IU/ml) was confirmed and mild-moderate microhematuria was observed.

Given the young age, the histological-radiological pattern and the dubious family history, a genetic test was proposed, which made it possible to confirm FPF, revealing the presence in heterozygosity of the autosomal dominant rare pathogenic variant (class 4) c.334G>A (p.Ala112Thr) in exon 4 of the SFTPC (Surfactant Protein C) gene. At the same time the rheumatologist ordered a renal biopsy in the suspicion of EGPA (repeated p-ANCA positivity, microhematuria in serial urine tests), which finally confirmed also this diagnosis. After multidisciplinary discussion, genetic counseling for FPF was offered to the patient and first-degree relatives. The patient started rituximab therapy for EGPA and was referred for pulmonary transplant evaluation.

Conclusion: The contextual diagnosis of FPF and EGPA was not described before. In case of suspicion of FPF it is useful to propose a genetic test. The multidisciplinary discussion and the transversal research approach is fundamental for the management of patients affected by fibrosing ILD and, in this case, has allowed the simultaneous diagnosis of two rare diseases and the timely activation of the appropriate therapy.

AUTHOR INDEX

NOTES

XI INTERNATIONAL WORKSHOP ON LUNG HEALTH

New Scenarios

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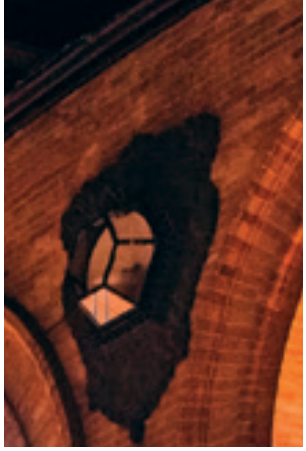


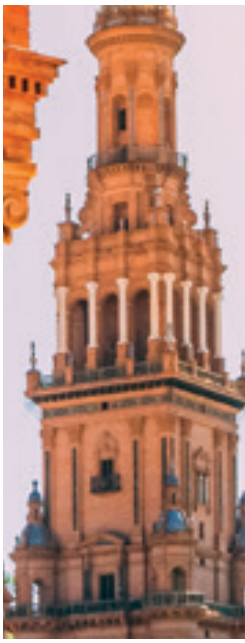

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