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ORIGINAL RESEARCH ARTICLE

Re-admission and quality of life among patients with chronic obstructive pulmonary disease after telemedicine video nursing consultation - a randomized study

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ABSTRACT

Background: Our previous study showed a reduced cumulative length of re-admission stays due to chronic obstructive pulmonary disease (COPD) exacerbations during one year after telemedicine video consultation (TVC). The current study evaluated the effects of TVC on the length of re-admission stays within 12 months follow up post-TVC compared to phone call follow up or COPD usual care in a randomized study. Our secondary aim was to assess the impact of TVC on the frequency of re-admissions within 12 months of follow up. Patient satisfaction, hospital anxiety and depression scale (HADS) and COPD assessment test (CAT) scores were also evaluated.

Methods: The study was a prospective randomized study of COPD patients who after hospital discharge for acute COPD exacerbations, were randomized to monitoring by TVC at home compared to phone call follow up for two weeks by a specialist nurse at the hospital or usual COPD care. Prospectively, we compared the cumulative durations and frequencies of hospital re-admissions due to COPD exacerbations within 12 months follow up after TVC, phone call follow up or usual COPD care.

Results: Among 173 COPD patients followed for 12 months, 99 were re-admitted. The median cumulative length of re-admission stays per patient within 12 months post-TVC did not differ from those followed by phone calls or with usual COPD care. The number of patients re-admitted and the number of re-admissions due to COPD exacerbations were also equal in the three groups. Patient satisfaction was high among those followed by TVC and phone calls, and the HADS and CAT scores favorably declined from baseline to post-intervention in patients followed by TVC and phone calls.

Conclusions: The study could not demonstrate a beneficial effect of TVC on the cumulative length of re-admission stays or on the number of re-admissions within 12 months following an acute COPD hospital stay, as compared to those followed by phone calls or with usual COPD care. Patient satisfaction was high among those followed by TVC and phone calls, and the declines in HADS and CAT scores seem to be consequences of increased empowerment and competence for good self-care in COPD patients, remaining through the one-year observation period.

Key words: COPD; telemedicine video-consultation; hospital readmission stays; quality of life.

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Contributions: All authors have participated in the design of the study, the facilitation for data collection and interpretation of data. SS, contributed to data collection and quality control of data; drafted the manuscript, while all authors have made contributions to revisions of the manuscript. All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Conflict of interest: The authors declare that they have no competing interests, and all authors confirm accuracy.

Ethics approval and consent to participate: This study was approved by the Regional Board of Research Ethics in Norway (Committee's reference number: 2013/1886/Rek sør-øst). All participants signed a written informed consent to participate prior to the study.

Consent for publication: Written informed consent for the publication of study results was obtained from all participants.

Availability of data and material: The data used to support the findings of this study are available from the corresponding author upon request.

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Introduction

Chronic obstructive pulmonary disease (COPD) is a progressive lung disease causing significant and lasting morbidity, disability and increased mortality [1]. Acute exacerbations are common and require frequent and urgent hospital admissions with high social costs [2]. Patients discharged from hospital following COPD exacerbations have a high readmission rate [3]. Besides, as the severity of the disease increases, exacerbations are more frequent, and the hospitalisation frequency increases [2]. The rate of re-admission within one year in a Danish study was 46% [4], while British reports have suggested that 30% were re-admitted within 90 days [5]. For the individual patient with COPD exacerbation, the consequences can be severe, such as loss of pulmonary function [6], prolonged impairment, reduced quality of life [7] and increased risk of mortality [8]. Patients often are discharged in a vulnerable situation, at a high risk of relapse and need of re-admission. Telemedicine has been evoked as a potential tool in the care of COPD patients, as a supplement to usual care. Among the earliest experiences with the use of COPD video communication in Denmark, expanded telemedicine video consultation (TVC) with monitoring of the patient at home showed a borderline significant absolute reduction of about 10-14% in the early readmission risk by the TVC intervention, shorter hospital stay and earlier treatment of exacerbations with rapid efficacy and less drug use. Patient satisfaction was high [9]. Since then, several studies have been directed towards the ability of telemedicine monitoring of COPD patients to prevent exacerbations leading to hospital re-admissions, but with divergent results regarding health care outcomes [10-14]. The meta-analysis by Yang *et al*. [15], including a total of 31 reports over randomized controlled trials where comprehensive nursing intervention (CNI) and telemonitoring have been examined, concluded that both reduced all-cause readmissions, a key goal in the care of COPD patients. In COPD care there is a need for care delivery models that encourage prevention and self-management [16]. In a previous, retrospective study of COPD patients discharged from the hospital, we showed that the re-admission length within 12 months post-TVC was markedly reduced compared to pre-TVC. The patient satisfaction was high [17].

The main objective of this randomized, prospective study was to evaluate the efficacy on re-admissions of TVC at home as compared to telephone follow up or only best standard practice (BSP) COPD care. The major endpoints were the cumulative days and numbers of re-admission due to COPD exacerbation during the first year following discharge after hospitalization. Moreover, we wanted to assess patient satisfaction related to TVC, as compared to follow up by telephone call or BSP COPD care.

Methods

Study design

This study was conducted as a prospective, randomized unicenter study of a population of COPD patients discharged from Stavanger University Hospital, Norway, after treatment for an acute COPD exacerbation. Patients fulfilling the inclusion criteria were consecutively enrolled from December 2014 to March 2019 and randomized to 2 weeks of monitoring by TVC between the specialist respiratory nurse and the COPD patient at home, to telephone follow up from a specialist nurse or to a control group receiving BSP COPD care. Two weeks intervention was based on the benefits observed among the Danish patients who had the TVC equipment at home for about one week followed by at least one phone call [9] and our pilot study published in 2014 [17]. The main purpose was to teach patients to increase empowerment, self-care and correct medication in a more stabilized condition than the acute phase of hospitalization. Our primary endpoint was the cumulative number of days of re-admission due to acute COPD exacerbations during one year of follow up. The secondary endpoint included the frequency of hospital re-admissions due to COPD exacerbation during one-year follow up and the time to the first hospitalization. Admissions due to other causes than acute COPD exacerbations have not been included in this study. The index hospitalization was not included. Additionally, we wanted to assess the quality of life by the COPD assessment test (CAT) and the hospital anxiety and depression scale (HADS) [18] before and for 12 months post-intervention. Finally, all patients were requested to complete a questionnaire (Table 1) assessing patient satisfaction and impact on patient's quality of life. The questionnaire was similar to the one used in our pilot study [17] to patients monitored by TVC, a modified version to patients followed by telephone consultations or usual COPD care. The questionnaire was sent to the patient by mail one month post-discharge. All answers were registered anonymously.

Study population

All COPD patients living in the Southern part of the Rogaland County in Western Norway, with a habitual value of FEV_1 <50%, and/or emphysema with gas diffusion (DL_{CO}) <50% in a stable phase and/or chronic respiratory failure due to COPD, were screened and enrolled at discharge after an emergency hospitalization for COPD exacerbation at Stavanger University Hospital. Additional inclusion criteria comprised willingness to participate and age >40 years. Patients with active malignant or any other disease with a prognostic life expectancy shorter than 12 months, patients previously included in the study, residents of in-service-housing with care or nursing homes, inability to communicate and inappropriately available internet and telephone coverage were defined as exclusion criteria. Thus, patients with hearing impairment, aphasia or dementia were excluded from the TVC service and the study. Patients were also excluded if they were discharged to a service home with supervision or to a nursing home. Written informed consent to participation in the study and to publication of study results was obtained from each participant.

COPD exacerbation was defined as an increased need for COPD medication due to worsened dyspnoea, cough or increased amount of purulent sputum (not due to any other underlying lung or heart disease), with or without pneumonia.

Randomization procedure

Randomization was done at Stavanger Research Department *via* a computer-generated allocation sequence unknown to the research group.

Study participants who had given written informed consent were randomized immediately prior to discharge from the hospital to a randomization number, which identified a numbered, sealed envelope with written content of randomization result; TVC, telephone follow up or BSP COPD care.

Data collection

Baseline data

All baseline data were collected regarding demographics, co-

morbidity, risk factors including admissions due to COPD exacerbations the preceding 12 months, general condition, lung function test, blood gas values, BNP and maximum TnI during hospital stay, need for ventilatory support and COPD medication (before, during and after hospital stay).

Follow up data

After discharge from the hospital, patients were monitored for one year by reviewing hospital records by the project doctor regarding primary and secondary endpoints and confounding variables (other emerging diseases, smoking, introduction of ambulatory oxygen therapy, lung rehabilitation after the index stay).

Medical records were scrutinised for re-admissions due to COPD exacerbations for 12 months follow up. Length and frequency of hospital stay(s) due to COPD exacerbations, and clinical data were recorded. Finally, all patients were requested to complete a questionnaire concerning patient satisfaction and impact on patients' quality of life. The TVC nurse recorded the number of acute consultations during the period of home monitoring. CAT and HADS scores were registered at inclusion, within 3 weeks post-discharge and after 6 and 12 months.

Intervention

Treatment of COPD exacerbation was in accordance with Norwegian National guidelines for prevention, diagnosis and monitoring of individuals with COPD and included bronchodilators inhaled by nebulizer, systemic steroids, antibiotics, oxygen supply, chest physiotherapy and when needed non-invasive ventilatory support (NIV) according to BTS guidelines [19].

Telemedicine video-consultation, patient monitoring and follow up

The telemedicine equipment consisted of a tablet with a web camera and microphone, through which the patient at home and the specialist respiratory nurse in the hospital were able to communicate, and also comprised requisites to measure the patient's oxygen saturation and heart rate. The tablet was installed at the patient's home within 24 hours of discharge. The results were transferred to the hospital by a secure internet line. The patients contacted the nurse according to daily appointments for TVC on weekdays during the day-time for 2 weeks and in case of acute need for consultation whenever necessary, 24 hours a day.

As described in our pilot study [17], the nurse during the TVC made clinical observations according to a checklist shown in our previous publication [17], measured oxygen saturation and heart rate, and according to an algorithm advised the patient how to cope with COPD related symptoms, use of medication and how to maintain the activity of daily life and physical activity. The nurse could confer the patient with the doctor in the hospital, a physiotherapist or an occupational therapist, or advise the patient to consult a general practitioner or a home care nurse.

Telephone consultations

Patients randomized to follow up by telephone were contacted once a day by one of the two-trained nurses who evaluated the condition and advised on further handling according to the same template used in the TVC.

Statistical analysis

Anonymized data were continuously entered into the database, and double-checked for incorrect entries, before transferring to SPSS Statistics version 25 for statistical analyses. Differences in patient characteristics, frequency of re-admissions and cumulative number of re-admission days between the intervention and control groups were tested by chi-square test or Fisher's exact test for categorical variables and by One-Way Analysis of Variance or One-Way ANOVA on Ranks for continuous data, depending on whether data were normal or skewed. The Shapiro-Wilk test for normality was performed to study the distribution of parameters. Normally distributed data were given as mean±SEM, while variables with more skewed distributions were given as median and upper and lower quartiles (IQR). A $p<0.05$ was considered statistically significant. To examine the dependency of hospital re-admission days on potential determinants, a linear regression analysis was performed.

Table 1. Questions to patients regarding patient satisfaction and user friendliness of TVC equipment.

1.	How do you usually feel at discharge from hospital after COPD exacerbation? Very safe – Safe – Unsafe – Very unsafe
2.	At discharge this time I felt Very safe – Safe – Unsafe – Very unsafe
3.	Retrospectively, if you could choose, would you prefer a telephone consultation or a tele-video-consultation? I would prefer talking to the nurse by phone I would prefer the tele-video-consultation
4.	How do you consider the significance of the TVC /phone call follow up for your ability to cope with your COPD related problems? Great significance – some significance – no significance
5.	Which of the following statement fits you best concerning your experience of user-friendliness of the TVC equipment? It was easy to operate the TVC equipment It was a bit difficult to operate the TVC equipment I could not manage to operate the TVC equipment
6.	Who was operating the tele-video conferencing system at home? You, every time A friend or a relative operated the tele-video-conferencing system every time Different persons operated the tele-video-conferencing system every time The tele-video-conferencing system was not in use

Question 1-3 to all patients, question 4 to patients followed by TVC and phone-calls, question 5 and 6 to patients followed by TVC.

Multiple logistic regression analysis was further performed with a re-admission endpoint (yes/no) as the dependent variable, odds ratio presented at 95% confidence interval (CI). Potential prognostic indicators were implemented in these models as potential confounding factors. The statistical significance level was set to $p<0.05$. In the case of an expected 3-day reduction in the length of hospital stay in patients re-admitted within one year after TVC following a hospital stay due to acute COPD exacerbation, power calculation showed the need for a sample size of 180 patients in the study, randomized to 3 arms, (TMV, telephone follow up, BSP COPD care), to give a power of 80%. The calculations were performed for a significance level of 0.05.

The study was approved by the Regional Board of Research Ethics and conducted in accordance with the Declaration of Helsinki [20,21]. The legal and security aspects have been taken care of through data transfer, on the recommendation of the Norwegian Data Protection Authority (DPA), without objections.

Results

Patients demographics and clinical characteristics

A total of 180 patients were consecutively included in the study, out of whom 7 patients withdrew from the study at their own discretion. There was no intergroup difference in drop-out between the groups. The remaining 173 patients were randomized to the TVC group (n=57), the telephone group (n=59) or the BSP COPD care group (n=57). The patients were followed for 12 months or until death. Nineteen patients died during the 12-month follow up. Three of these belonged to the TVC group as compared to sixteen equally divided between the groups followed by telephone calls and BSP COPD care, respectively. The general baseline demographic and clinical characteristics of the study population are summarized in Table 2. There were no intergroup differences between the groups regarding demographics. The age was 68 (±1.16) years [mean (SEM)], and the majority of the participants were women. The co-morbidity was quite significant but did not differ between the groups. All patients in the three groups had a severely deteriorated lung function according to COPD Gold Guidelines stage III-IV. The FEV_1 value was 0.88 liter (l) (0.67-1.19) [median (25-75% percentiles)], [(38.0% of predicted value) (27.2-46.5%;] [median (25-75% percentiles)]. Forty-eight patients (27.8%) were classified in COPD Gold stadium IV, with $FEV_1 \leq$ 30% of expected. There was no intergroup difference regarding the need for ventilatory support at home. Forty-one percent of the entire population had been admitted within 12 months pre-intervention, with no intergroup difference (Table 2). At admission, there were no intergroup differences regarding ongoing COPD inhalation therapy. More than 70% of patients in each group inhaled long-acting muscarin antagonists (LAMA), and 68.2.% of patients inhaled combination products of long-acting beta-2-agonist and corticosteroid (LABA/ICS) as part of the ongoing regular medication, reflecting the high symptom burden of COPD in this population. During index admission, 91.9% of patients received treatment with nebulized ipratropium and salbutamol, 96% were treated with systemic corticosteroids, and 90.2% received antibiotics, with no intergroup differences in the in-hospital medical treatment. Ongoing regular medication was similar at inclusion and at discharge from index hospital stay. Respiratory failure with a need for oxygen supply during hospital stay was reported among 48 patients in the phone call follow up group (81.4%), and among 35 patients in the TVC and BSP COPD care groups (61.4%), and

Table 2. Baseline demographic and clinical characteristics.

Intervention group*	TVC (n=57)	Phone calls (n=59)	BSP COPD care (n=57)	p
Sex male[#]	15 (26.3)	21 (35.6)	26 (45.6)	NS
Age [mean (SEM)]	69.0 (1.169)	68.64 (1.161)	68.07 (1.134)	NS
Living alone[#]	28 (49.1)	19 (32.2)	24 (42.1)	NS
Home nurse[#]	9 (15.8)	17 (28.8)	12 (21.1)	NS
CAT score[3]	21.5 (0.93)	23.1 (0.81)	23.8 (0.98)	NS
Cardiovasculary disease[#]	20 (35.1)	27 (45.8)	25 (43.9)	NS
Heart failure[#]	3 (5.3)	10 (32.2)	6 (10.5)	NS
Depression[#]	17 (29.8)	14 (23.7)	16 (28.1)	NS
Osteoporosis[#]	9 (15.8)	16 (27.1)	14 (24.6)	NS
Current smoker[#]	13 (22.8)	17 (28.8)	17 (22.8)	NS
Ex-smoker[#]	57 (100.0)	59 (100.0)	55 (96.5)	NS
BMI (kg/m^2)°	22.5 (0.705) (n=56)	24.0 (0.653)	22.3 (0.738) (n=54)	NS
FEV_1 (liter)[§]	0.89 (0.68-1.23)	0.87 (0.67-1.20)	0.90 (0.69-1.18)	NS
FEV_1 (%)[4]	38.70 (31.80-46.25)	40.30 (26.28-47.08)	36.80 (26.50-46.30)	NS
LTOT at home[#]	6 (10.5)	15 (25.4)	10 (17.5)	NS
NIV at home[#]	1 (1.8)	5 (8.5)	3 (5.3)	NS
Previous acute NIV[#]	10 (17.5)	11 (18.6)	13 (22.8)	NS
Previous respirator[#]	5 (8.8)	5 (8.5)	11 (19.3)	NS
PAH#	4 (7.0)	5 (8.5)	5 (8.8)	NS
Admitted the preceding year[#]	26	25	20	NS

*Group 1 was followed by TVC, Group 2 by telephone contact and Group 3 by Best Standard Practise COPD care; [#][n (%)], p>0.05; °mean (SEM); [§]median (25-75% percentile); Age; one way analysis of variance, FEV_1; one way ANOVA on ranks and chi-square test for categorical variables; LTOT, long term oxygen treatment; NIV, non-invasive ventilatory support.

13.3% of all patients presented with pH <7.35 and hypercapnia in need of non-invasive ventilatory support, according to BTS guidelines [19]. During the TVC monitoring period 5 patients started systemic steroid therapy and additional 5 patients started combination therapy of systemic steroids and antibiotics. In the phone-call follow up group 11 patients received systemic steroid therapy, out of whom 5 patients also were treated with antibiotics. Four patients made 8 emergency calls during the TVC period. In the phone-call-follow up group 5 patients made 11 emergency calls.

Follow up data

Frequency of re-admission due to acute COPD exacerbations

Ninety-nine patients (57.2%) were re-admitted due to COPD exacerbation during the 12 months follow up period. They were older [age 69.8 years (±0.87)] [mean (SEM)] than those not re-admitted [66.9 years (±1.00)] [mean (SEM)], p= 0.03, however, there was no inter-group difference in age among the re-admitted. In the TVC group the re-admitted consisted of a relatively higher proportion of men as compared to the others. We noticed an equal distribution of re-admitted patients among the groups followed by TVC [n=32 (56.1%)], telephone calls [n=38 (64.4%)] and BSP COPD care [n=29 (50.9%)], p>0.05. Also, the total number of readmissions due to COPD exacerbations was equal in the groups (Table 3). Both the proportion of patients without any re-admission and the proportion with frequent ≥2 per year) re-admissions were equally occurring in the three groups compared (Table 3). Nor as early as 6 months following TVC could we observe any favor regarding the number of re-admissions in the TVC group as compared to the others (data not shown). In our population, a total of 41 % had been admitted within 12 months pre-intervention. Those who were re-admitted had a higher number of hospital stays the preceding year [1.22 (±0.141)] [mean (SEM)] as compared to those not re-admitted [0.61 (0.21)] [mean (SEM)], p= 0.01. They also had a lower FEV_1 of 0.80 l (0.61 -1.11) *versus* 0.96 l (0.82-1.26) [median (25-75% percentiles)], p<0.001. In the multiple regression analysis admittance due to COPD exacerbation in the previous 12 months was the strongest predictor for re-admission [Odds ratio (OR) of 1.35 (95% CI 1.04-1.75)], p=0.027. Higher age was associated with a minor increased risk of re-admittance in our study [OR 1.06 (95% CI 1.01-1.11), p=0.019. Patients who were readmitted *versus* those who were not did not differ in terms of sex, cardiovascular morbidity, blood gas values, smoking, or low BMI (<20).

In the multiple logistic regression model neither sex nor FEV_1, cardiovascular disease, low BMI, current smoking or living alone were associated with re-admission or time to re-admission. At the first re-admittance, 94 patients (95.0%) were in need of systemic corticosteroids, 85 (85,9%) of antibiotics and 75 (75.8%) of oxygen supply. We found no intergroup difference regarding the need for treatment with antibiotics (p=0.39), systemic steroids (p=0.28) and oxygen (p=0.67). Moreover, the patients in the three groups had equal levels of C-reactive protein (CRP), leucocytes, brain natriuretic peptid (BNP) and troponin I (TnI) at the first re-admittance. At twelve months follow up 10 patients in the TVC group had started home oxygen treatment, as compared to only 2 and 4 patients in the phone call follow up group (p=0.042) and the BSP COPD care group, respectively, while the total number of patients with long term oxygen treatment was equal among the groups. The patients in the three groups did not differ regarding the need for domiciliary help and home nursing, and they had an equal score on the medical research council dyspnea scale (MRC) of 3.5 in groups 1 and 4 in the two others. Nine and eleven patients in groups 1 and 2, respectively, had attended a pulmonary rehabilitation course during the 12-month follow up, as compared to only 4 patients in group 3.

Length of re-admission hospital stays and time to re-admission due to acute COPD exacerbations

The cumulative length of re-admission hospital stays (days; mean±SEM) due to COPD exacerbations within 12 months did not differ between the patients randomized to follow up by TVC, phone calls or BSP COPD care after the initial hospital stay for COPD exacerbation (Table 4). Nor as early as 6 months follow up could we observe any difference (data not shown). Moreover, the time to the first re-admission was similar in the three groups (Table 5). Those who had been admitted the year before the index hospital stay, did not reduce their re-admission stays during the following

Table 3. Patients with 0, 1 or >2 re-admissions due to COPD exacerbations within 12 months follow up after hospitalization with COPD exacerbation, according to mode of follow up.

Number of re-admissions	0	1	>2	Total number of re-admissions (n)
TVC (n=57) [n (%)]	25 (43.9)	15 (26.3)	17 (29.8)	71
Phone-calls (n=59) [n (%)]	21 (35.6)	18 (30.5)	20 (33.9)	93
BSP COPD care (n=57) [n (%)]	28 (49.1)	10 (17.5)	19 (33.3)	66

Number of patients with 0, 1 or ≥2 re-admissions within 12 months follow up after TVC as compared to phone calls or no extra-ordinary follow up; No intergroup difference in patients with > 2 re-admissions, p=0.88, chi square.

Table 4. Cumulative number of days in hospital per patient during re-admissions for 12 months follow up after hospitalization with COPD exacerbation, according to the mode of follow up (mean ±SEM).

Mode of follow up	TVC (n=57)	Phone-calls (n=59)	BSP COPD care (n=57)
Days in hospital	7.02±1.48	8.29±1.43	7.46±1.58

No intergroup difference regarding days in hospital 12 months following intervention, p=0.829 (one way analysis of variance).

year [paired *t*-test (two-tailed), p>0.05]. The number of hospital re-admission days was related to the number of COPD exacerbations in the previous 12 months (p=0.008), but not the time to re-admission (p=0.114).

Patient satisfaction, symptom burden and HADS score

The response rate to the patient satisfaction survey was 86%. While 23 patients in the TVC group responded retrospectively that they generally had felt safe or very safe when discharged from the hospital without TVC, the number doubled to 46 patients who reported safety when discharged to TVC at home, p<0.001. A similar observation was made regarding those who were discharged to follow up by phone calls, while there was no change in reporting a feeling of safety in patients in the usual COPD care group. Among patients followed by TVC, 77.6% found that TVC had great importance for the further management of their COPD-related problems, while 45.1% of patients followed by phone calls reported the same (p=0.002). Almost 96% of patients found the telemedicine equipment easy to operate, and 98% of patients reported that they handled the tele-video conferencing system on their own. Moreover, 97% of patients regardless of group preferred TVC over only phone calls. All patients in the TVC group would like to do another try and recommend TVC for follow up after a COPD exacerbation. Patients who were followed by regular phone calls had similar positive experiences. There were only a few technical issues; the TVC was occasionally cancelled due to internal IT issues. The HADS scores [mean (SEM)] were equal among the three groups at inclusion, p=0.673 (ANOVA) (Table 6). From baseline to post-intervention the scale values favorably declined among patients followed by TVC (p=0.059) and phone calls (p<0.01), but not among patients given only BSP COPD care (p=0.173) (paired *t*-test). The scores remained unchanged for the rest of the follow up period. Examining the hospital depression and anxiety scores separately, the anxiety score declined significantly from 6.02 (0.75) at baseline to 4.83 (0.61) [mean (SEM)] in the TVC group (p=0.028) and from 6.18 (0.70) to 4.58 (0.65) [mean (SEM)] in the phone call follow up (p=0.008) group following the intervention. The decreased levels remained unchanged throughout the observation period. A similar reduction was not found in the BSP COPD care group measured simultaneously. However, there was no intergroup difference in the change of the hospital anxiety score from baseline to post-intervention (p=0.128) or from baseline to 12 months follow up (p=0.549). A similar decrease in hospital depression score was not found, but patients in the BSP COPD as the only ones receiving care experienced an increase. Parallel to the decline in HADS-score from baseline to post-intervention, we found a similar decrease in the CAT-scores in patients followed by TVC and phone calls, reflecting an experience of decreased total subjective symptom burden of the COPD patient. In patients with CAT-scores at all 4 measurement points (n=37), the CAT-score declined from 20.8 (1.08) [mean (SEM)] to 14.1 (1.27) in the TVC group (p<0.001) and from 22.7 (1.07) to 19.1 (1.16) in the phone call follow up group (p<0.01), with no intergroup change. The decreased levels remained unchanged throughout the observation period; the patients still had lower CAT scores at 12 months follow up than at inclusion. A similar reduction was not found in the BSP COPD care group. At inclusion, the CAT scores [mean (SEM)] were equal among the three groups, p=0.198, Table 2.

Discussion

This randomized study could not demonstrate a reduction in either the length or the frequency of hospital re-admissions in patients with COPD during a 12-month observation period following TVC for two weeks after a hospital stay due to COPD exacerbation, as compared to follow up by phone calls or only BSP COPD care. Nor as early as after 6 months could we see any difference in the number of re-admissions or length of stay in hospital between the 3 groups. Our hypothesis of the reduced readmission hospital bed days for COPD exacerbations following TVC was derived from our findings in our previous retrospective observational pilot study [17] showing a markedly reduced number of hospital bed days following TVC as compared to the preceding 12 months without TVC. However, an equal frequency of re-admissions the year after as compared to the year before TVC was observed in our previous retrospective study.

The results presented in this report are based on the experience from the early start of TVC at our site and on the Danish pioneer study using similar equipment and short duration of intervention [9], demonstrating a 10-14% reduction in early re-admissions due

Table 5. Days from discharge after hospitalization for COPD exacerbation to first re-admission, according to the mode of follow up (mean ±SEM).

Mode of follow up	TVC (n=57)	Phone-calls (n=59)	BSP COPD care (n=29)
Days to first re-admission	01.56 (20.5)	85.42 (14.42)	98.72 (20.27)

p=0.786, one way ANOVA.

Table 6. HADS score (mean ±SEM) at baseline, post-intervention (3 weeks post-discharge), at 6 and 12 months follow up (for patients with four registrations).

	Baseline	Within 3 weeks post-discharge	6 months follow up	12 months follow up
Group 1 (n=39)	11.03 (1.15)	9.46 (1.14)	9.00 (0.98)	9.05 (1.13)
Group 2 (n=37)	11.08 (0.96)	8.78 (1.06)	8.57 (0.86)	9.14 (0.98)
Group 3 (n=33)	12.27 (1.15)	13.76 (1.32)	12.61 (1.20)	12.18 (1.45)

Group 1 was followed by TVC, Group 2 by telephone contact and Group 3 by Best Standard Practise COPD care; no intergroup difference in HADS score at baseline (p=0.673), one way ANOVA; change from baseline to within 3 weeks post-discharge: G1 p=0.059, G2 p<0.01, G3 p=0.173, paired *t*-test; changes from 3 weeks-post discharge to 6 months follow up: G1 p=0.584, G2 p=0.78, G3 p=0.439, paired *t*-test; changes from 6 months to 12 months follow up: Group 1 p=0.939, Group 2 p=0.438, Group 3 p=0.705, paired *t*-test; no intergroup difference in the change of HADS score from baseline to 3 weeks post-discharge (p=0.128); one way analysis of variance.

to COPD exacerbations in the TVC group as compared to a control group, with a use of TVC for only one week following discharge after hospital stay for COPD exacerbation.

Thus, the results of our prospective randomized study cannot position TVC as used in our model as an important contribution to the standard management of these patients. The reason for choosing this approach was the knowledge of COPD patients being in a vulnerable state when discharged from hospital after a COPD exacerbation, at high risk of prolonged impairment of health status, as the exacerbation is still ongoing at the time of discharge [22], and the patient is at a higher risk for a new event [2,23]. Moreover, at a time of expected high motivation among the patients, the specialist respiratory nurse in our TVC team not only daily monitored and advised each patient according to personal needs to improve the actual health condition, but as previously described, also great effort was invested in advising and teaching each patient to increase the empowerment and competence for good self-care, concerning correct medication use, inhalation technique, appropriate physical activity, pulmonary drainage, dealing with stress and anxiety to prevent and to cope with future exacerbations. However, our study has not been designed to directly evaluate the influence of TVC on each of those factors. As in our pilot study [17], an interdisciplinary team was available for consultation when needed, including among others a physiotherapist and an occupational therapist, who could for example easily facilitate home conditions.

Our approach differs from most studies exploring the effect of TVC in COPD, by not offering a long-term TVC for early detection of COPD exacerbation, but aiming to increase the patient's empowerment and competence for good self-care. The hypothesis in many studies has been that daily TM monitoring of patient's vital signs and symptoms would detect changes in the clinical status of COPD patients sufficiently early to improve care and decrease healthcare resource utilization by decreasing unscheduled visits to the family physician or specialist, home visits, ED visits, and hospitalizations [13,24].

The short duration of our study of only 2 weeks intervention could be considered as a limitation of the study design and negatively affect the results of the study, as compared to the beneficial outcomes observed in the long-term data collected by Dal Negro and Hodder, implementing several years of home telemedicine [25].

Even such long-term interventional studies have shown conflicting results. Recently, Pinnock *et al*. [26] published their findings from a large randomized study with patients with COPD recruited through general practice and reported that TM had no effect on hospital admissions or quality of life, and in keeping with this, Hamad *et al.* [27] failed to establish the value of TM in the early detection of COPD exacerbations. Also other randomized controlled trials have concluded that there were no between-group differences in hospital admissions [28,29]. The impact of TM on the length of hospital stay is also inconclusive with reports of a decrease [29,30].

A previous history of COPD exacerbation has been shown to be the most reliable predictor of new COPD exacerbations [2]. Moreover, data from the Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints (ECLIPSE) [2] showed that 33% with COPD stage 3 and 47% with stage 4, defined according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) [30], had ³2 exacerbations in the first year of follow up. Our observations are in accordance with these findings, as 32.4% of our patients, who are all characterized by COPD stage 3-4, with a median FEV_1 of 38 %, had ³2 re-admissions during the observation period. In our population, a total of 41% had been admitted within 12 months pre-intervention. Those who were re-admitted had a higher number of hospital stays the preceding year [mean 1.22 (SEM 0.141)] as compared to those who were not re-admitted [0.61 (0.21)], p= 0.01. They also had a lower FEV_1 of 0.80 l (0.61-1.11) *versus* 0.96 l (0.82-1.26) [median (25-75% percentiles], p<0.001. In the multiple regression analysis admittance due to COPD exacerbation the previous 12 months was the strongest predictor for re-admission [odds ratio of 1.35 (CI 1.04-1.75)], p=0.027. The number of COPD exacerbations the previous 12 months was also associated with the cumulative number of re-admission days (p=0.008). The frequency of exacerbations has been shown to contribute to disease progression [31]. Long-term data from previous research [32] investigating the natural history of the disease suggested a rapid decline in health status after the second severe exacerbation and high mortality following every severe exacerbation requiring hospitalization. In according with previous observations [9,33] higher age was associated with an increased risk of re-admittance in our study. Patients re-admitted as compared to those who were not, did not differ regarding sex, cardiovascular morbidity, blood gas values, smoking or low BMI (<20). In the multiple logistic regression model neither sex nor FEV_1, cardiovascular disease, low BMI, current smoking or living alone were associated with re-admission or time to re-admission.

For the majority of our patients, the need for re-admission has been decided by the occurrence of a serious event, as 85.9 % of patients re-admitted required antibiotic therapy, 95% needed systemic steroids and 75.8% needed oxygen therapy during the first re-admission. Thus, these re-admissions are hard to avoid, and the irreversible and progressive nature of COPD can contribute to the inevitable exacerbations and hospitalization. All of our patients had a serious burden of disease, possibly explaining the evitable and long hospital stays, necessary to cope with our seriously deteriorated COPD patients with complicated co-morbidity (Table 2). The high mortality rate also reflects this advanced disease condition with serious prognostic outcomes. The population of COPD patients in our study is therefore a topic for reflection when designing a study to show the effect of TVC on hospitalizations for COPD exacerbations. The serious burden of disease of the COPD patients in our study might have been the major reason why we could not show a beneficial effect of TVC on the total number of re-admission hospital days or the number of re-admissions due to COPD exacerbations. Moreover, since the implementation of the new "Coordination Reform" in the Norwegian health care policy in 2012, transferring more responsibility to the municipality health care system, the patients admitted to hospitals, present with an even higher burden of disease and higher treatment level, and they consequently spend more days in hospital to recover, why the length of the hospital stay will possibly not be influenced by TVC. The population in the Danish [9] study showing an early re-admission risk by the TVC intervention, was quite similar to ours. That study also failed to show a significant reduction in hospital stay length. Furthermore, the study's non-randomized interventional design made it vulnerable to imbalances in baseline prognostic factors. The target group for such an intervention model as ours should therefore be defined carefully in future studies, and a more flexible, individually adapted model for TVC monitoring of patients might even contribute to increased periods free of re-admissions, rather than the strict, pre-determined period of 14 days of TVC monitoring used in our study, irrespective of patient condition and needs. Despite our lack of demonstrating a protective effect of TVC regarding re-admittance due to COPD exacerbation, the patients reported a high degree of self-perceived patient satisfaction and increased coping skills following TVC, of major importance for the feeling of safety at home. For our COPD patients with a high prevalence of depression (Table 2), our interpretation is that the increased coping skills following TVC or phone call follow up have contributed to the reduced HADS scores observed post-follow up. The parallelly observed reduction of also the CAT score in these two groups mirrors the subjective experi-

ence of the decreased total burden of COPD symptoms and makes the strains of COPD in daily life easier to cope with. As the major benefit was related to the anxiety score, the feeling of safety seems to be of major importance for the daily level of functioning at home. However, experiences regarding self-perceived patient satisfaction and also impact on HADS score described in the literature have been diverse [34].

Conclusions

In this prospective, randomized study we could not demonstrate a reduction neither in the number of re-admission days nor the frequency of re-admissions due to COPD exacerbations for one year post-TVC for 2 weeks following hospitalization for COPD exacerbation, as compared to patients followed by telephone calls or "usual COPD-care". However, the patient satisfaction among patients followed by TVC was high, and the reduced HADS and CAT scores in patients followed by TVC and phone calls as compared to best standard practice COPD care is of major importance for the quality of life and the ability of coping with everyday life challenges among COPD patients. The benefits, remaining persistent throughout the one year observation period, seem to be the consequence of increased empowerment and competence for good self-care in the COPD patients. Other models of TVC follow up should be evaluated in future prospective, randomized studies.

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Abbreviations

BMI: body mass index;
BNP: brain natriuretic peptide;
BSP: best standard practice;
CAT: COPD assessment test;
COPD: chronic obstructive pulmonary disease;
DL_{CO}: diffusing capacity for carbon monoxide;
FEV_1: forced expiratory volume in first second;
HADS: the hospital anxiety and depression scale;
HR: hazard ratio;
LABA/ICS: long-acting beta-2-agonist and inhalation corticosteroid;
LAMA: long-acting muscarin antagonist;
LTOT: long-term oxygen treatment;
NIV: non-invasive ventilatory support;
OR: odds ratio;
SEM: standard error of the mean;
TnI: troponin I;
TVC: telemedicine video-consultation.

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ORIGINAL RESEARCH ARTICLE

Experimental studies and mathematical modeling of the viscoelastic rheology of tracheobronchial mucus from respiratory healthy patients

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ABSTRACT

Background: Tracheobronchial mucus plays a crucial role in pulmonary function by providing protection against inhaled pathogens. Due to its composition of water, mucins, and other biomolecules, it has a complex viscoelastic rheological behavior. This interplay of both viscous and elastic properties has not been fully described yet. In this study, we characterize the rheology of human mucus using oscillatory and transient tests. Based on the transient tests, we describe the material behavior of mucus under stress and strain loading by mathematical models.

Methods: Mucus samples were collected from clinically used endotracheal tubes. For rheological characterization, oscillatory amplitude-sweep and frequency-sweep tests, and transient creep-recovery and stress-relaxation tests were performed. The results of the transient test were approximated using the Burgers model, the Weibull distribution, and the six-element Maxwell model. The three-dimensional microstructure of the tracheobronchial mucus was visualized using scanning electron microscope imaging.

Results: Amplitude-sweep tests showed storage moduli ranging from 0.1 Pa to 10,000 Pa and a median critical strain of 4%. In frequency-sweep tests, storage and loss moduli increased with frequency, with the median of the storage modulus ranging from 10 Pa to 30 Pa, and the median of the loss modulus from 5 Pa to 14 Pa. The Burgers model approximates the viscoelastic behavior of tracheobronchial mucus during a constant load of stress appropriately (R^2 of 0.99), and the Weibull distribution is suitable to predict the recovery of the sample after the removal of this stress (R^2 of 0.99). The approximation of the stress-relaxation test data by a six-element Maxwell model shows a larger fit error (R^2 of 0.91).

Conclusions: This study provides a detailed description of all process steps of characterizing the rheology of tracheobronchial mucus, including sample collection, microstructure visualization, and rheological investigation. Based on this characterization, we provide mathematical models of the rheological behavior of tracheobronchial mucus. These can now be used to simulate mucus flow in the respiratory system through numerical approaches.

Key words: tracheobronchial mucus; rheological model; viscoelasticity.

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Introduction

Tracheobronchial mucus, also referred to as airway surface liquid, is a thin liquid layer with a thickness of 5-10 µm [1] that covers the surface of the airways and forms a blanket over the tips of the epithelial cilia [2]. It maintains a strong multifunctional protective barrier between the respiratory epithelia and the gas in the lumen [3,4]. Physiologically, tracheobronchial mucus ensures undisturbed ciliary interaction. Thus, it plays a vital role in protecting the lung from the continuous load of pathogens, particles, and chemicals in the inhaled air [5].

Tracheobronchial mucus mainly consists of water (90-95%), glycoproteins (2-5%), ions (1%), and molecules such as DNA and cell debris [6,7]. It contains two different families of glycoproteins: secreted mucins and cell-tethered mucins. Of these, mainly the secreted polymeric mucins influence mucus rheology [8]. Their chains have a high molecular weight of 200 kDa to 200 MDa and are large in size with diameters from 10 to 300 nm and lengths from 190 to 1500 nm [8,9]. By entangling and cross-linking, these mucins form a complex three dimensional network [6].

The network formed by linked mucins, causes a highly complicated rheological behavior. Mucus is non-Newtonian shear-thinning and non-linear viscoelastic [7,10-12]. Thus, it has properties of both viscous fluids and of elastic solids. Viscosity alone cannot describe this behavior adequately. Further, mucus behaves differently during loading and unloading. Such load changes are intrinsic to the breathing cycle, as the air flow stops and reverses at the end of each inspiration or expiration. Moreover, the reaction of mucus to applied forces, depends on its history of deformation. Strong deformations in the mucus, as they occur in the respiratory system for example during coughing, disrupt the fragile mucin network. This likely changes the flow behavior of the mucus.

These rheological characteristics directly affect the mucus flow [6], which is driven by a combination of mucociliary motion and shear forces exerted by the expiratory airflow [1]. During mucociliary motion, the thin layer of mucus traps pathogens contained in the respiratory air and then removes them by interacting with the cilia. Thus, the mucus layer operates as an indispensable coupler, transferring momentum from the tips of the cilia to the loaded pathogens. This creates mucus movement and thus transports the trapped pathogens. Shear-induced mucus transport, especially during coughing and sneezing, is one of the most important mechanisms in the clearance of potentially pathogen-contaminated tracheobronchial mucus [13] as it leads to aerosol and droplet excretion.

Changes in the amount and in the rheological properties of tracheobronchial mucus play an important pathophysiological role in the severity of symptoms in many respiratory diseases [6,14]. Such pathological changes occur in conditions such as bronchial asthma or cystic fibrosis [6,7]. Further, absence of mucus leads to a lack of particle transport, despite active ciliary motion [15]. Especially, the viscoelastic properties of tracheobronchial mucus affect its flow directly [6].

Both the physiological behavior of mucus and its pathological changes can be better understood with a profound knowledge of its physiological rheology. As such, a rheological characterization of tracheobronchial mucus opens up opportunities to improve both medical diagnosis [16] and treatment methods that use the respiratory mucosa as the application area. Further, a full characterization of the rheology of physiological mucus can build a reference base for pathological changes and provide data for numerical investigations of mucus transport and shear-induced aerosol generation in the upper airways [17,18].

Most recent studies investigated the rheological properties of tracheobronchial mucus, as well as mucus mimetics, only partly [12,19,20]. Oscillatory (investigating storage modulus G' and loss modulus G'') and/or continuous shear investigations (investigating viscosity) characterize only a subset of the complex rheological behavior [6]. However, numerical investigations, which can describe the more complex flow conditions in the human respiratory system based on experimental data from simplified tests on respiratory mucus, as well as the design of mucus simulants require a full characterization of both the viscous and the elastic behavior especially the interplay of these properties. Further, for numerical applications, mathematical models describing the rheological behavior are necessary. Due to the complexity of the mucus rheology, it is not possible to represent mucus behavior during a breathing cycle by a single model. Depending on the problem to be solved, models of the response of the mucus to stress or force loading or to strain or deformation loading, or combinations of these models are necessary.

Such models can be deducted from transient testing. These identify the interplay of viscous and elastic properties over time in simplified flow situations. Stress-relaxation tests investigate the material's response to an applied force, which is induced in the airways for example by coughing. Creep-recovery tests identify the response of the mucus to a defined deformation, which is induced in the airways for example by beating cilia. To derive statistically grounded models from experimental data of transient tests, a high number of investigated samples is necessary.

To collect such high sample numbers of human mucus, previously described tracheobronchial mucus collection methods [21,22] were not applicable. Common sample collection procedures such as the cytology brush method might damage the sample pre-testing via high shear forces. Further, saliva might contaminate the sample during the bronchoscopy. Additionally, an *in vitro* measurement environment does not completely reproduce physiological *in vivo* conditions (23). To overcome these limitations, a novel method to collect sample from endotracheal tubes without high shear forces and saliva contamination was developed within this study.

This project provides a full characterization of physiological, human mucus rheology. First, it describes the reproducible sampling method of collecting physiological, tracheobronchial mucus from endotracheal tubes. The mucus rheology is characterized via oscillatory tests and transient creep-recovery and stress-relaxation tests. Finally, mathematical models of the time-dependent mucus behavior are deducted. These include the Burgers model of stress loading, the Weibull distribution of stress release, and the six-element Maxwell model of stress relaxation. Visualizations of the microstructure of the mucus illustrate how the three-dimensional mucin network determines the complex rheological properties of tracheobronchial mucus.

Materials and Methods

Clinically used endotracheal tubes with adhering samples of tracheobronchial mucus were collected. The rheological behavior of the tracheobronchial mucus was investigated in amplitude-sweep tests, frequency-sweep tests, creep-recovery tests, and stress-relaxation tests. Then, transient test results were approximated by mathematical models: the Burgers model (creep-test), the Weibull model (recovery-test), and the six-element Maxwell model (relaxation-test). The process steps of this study as shown in Figure 1 are described in the following in detail.

Sample collection

Tracheobronchial mucus samples were collected from endotracheal tubes used in surgery by otorhinolaryngology specialists at

the University Hospital Regensburg. For this, anesthesiologists collected the tubes after the patients were extubated. Donors included in the study were over the age of eighteen and did not have any infectious respiratory disease. All donors gave informed consent regarding the biomedical research on tracheobronchial mucus. The institutional ethics commission of Regensburg (No. 22-2979-101) approved the protocol. The tubes were stored for transport in airproof plastic bags at a temperature of 5°C for a maximum of three days before the samples were analyzed.

Microstructure visualization

Images of the sample microstructure were captured with two scanning electron microscopes (SEM) (LEO 1455VP, Carl Zeiss Microscopy GmbH, Oberkochen, Germany; MIRA, Tescan GmbH, Dortmund, Germany). Tracheobronchial mucus has a high content of water. This water needs to be eliminated from the sample before visualization in a SEM. To visualize the cross-linked glycoproteins, which determine mucus's rheological behavior, the drying process needs to preserve the spatial structure of the mucus. To achieve this, mucus samples were pre-treated by freeze drying. A small amount of mucus of 1 g was freeze-dried over two days, using a vacuum of 0.31 mbar and a temperature of -6°C (Beta 1-8K, Martin Christ, Osterrode am Harz, Germany). To minimize loading of the sample and thus overexposure during high magnification in the MIRA SEM, these samples were gold-sputtered (coating thickness 5 nm) before scanning.

Rheological investigation

Before the rheological investigations, the integrity of each sample was assessed. For this, the tubes were investigated optically to ensure a sufficient mucus sample volume and to rule out blood contamination. A completely filled gap between cone geometry and peltier element defines a sufficient mucus sample (approximately 100 µL). Tubes with insufficient mucus volume, heterogenous mucus abnormalities or contamination were discarded.

The rheometer's (Discovery HR 30, TA Instruments, New Castle, DE, USA) inertia and friction were calibrated before each measurement sequence, which lasted a maximum of six hours and included three to eight samples. All measurements were performed on a cone-plate geometry with a cone angle of one degree and a cone base diameter of 20 mm. Samples were prepared according to the process illustrated in Figure 2. First, samples were carefully transferred from the endotracheal tubes to the temperature-controlled plate (Peltier element) of the rheometer using a spatula (Figure 2 A,B). Then, the upper cone was lowered to a truncation gap of 40 µm above the peltier element. Any sample protruding the measurement area was carefully removed (Figure 2C). Subsequently, the upper cone was lowered to the final measurement gap size of 20 µm between the tip of the cone and the peltier element. A low viscous silicone oil (5cSt, Carl Roth GmbH, Karlsruhe, Germany) was applied to the perimetral boundaries of the cone to prevent the sample from evaporating by sealing during the measuring procedure (Figure 2D). To simulate physiological conditions, the measuring temperature was set to 37°C with a tem-

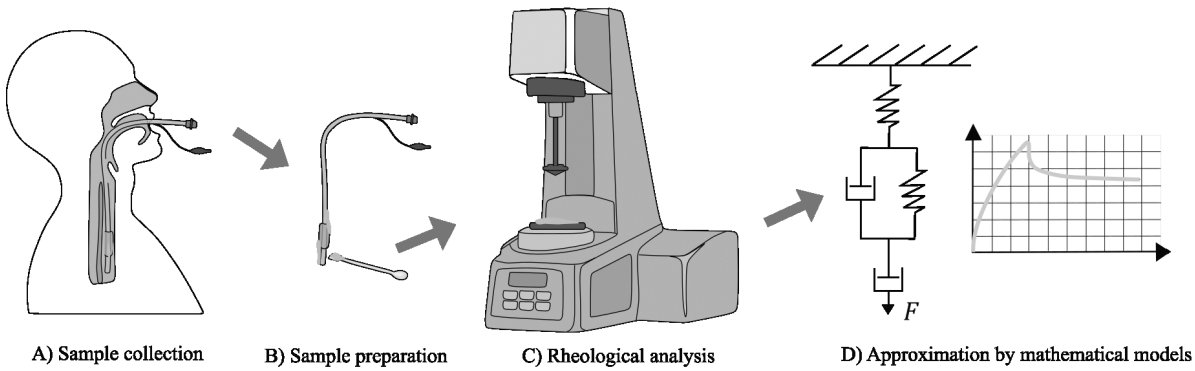

Figure 1. Overview of the study's methods. A) Sample collection; B) sample preparation; C) rheological analysis; D) approximation of experimental data with mathematical models.

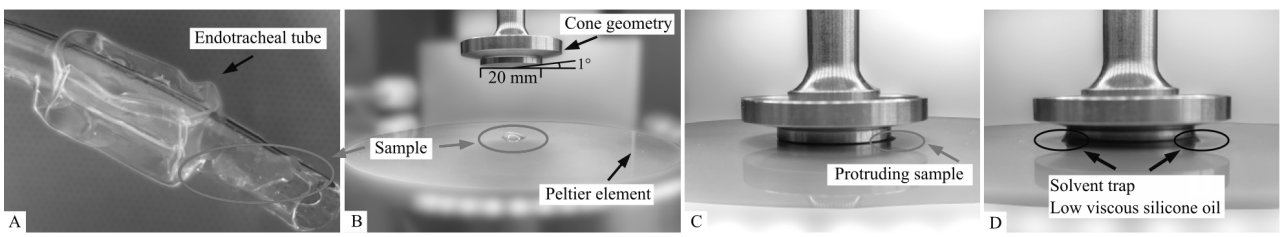

Figure 2. Rheological analysis. A) Sample collection from endotracheal tubes; B) rheometer setup with cone geometry and the sample loaded onto the Peltier element; C) sample protrudes once the cone is lowered; D) a solvent trap covers the sample during the measurement.

perature control system. In order to achieve a homogenous temperature throughout the sample, each sample was preheated for 180 seconds before the measurement.

In total four different rheological tests, which can be separated into two groups, were conducted: oscillatory tests and transient tests. The oscillatory tests include amplitude-sweep and a frequency-sweep tests. Transient tests were conducted as creep-recovery and stress-relaxation tests. Each rheological test was performed with a sample size of at least 20 subjects. Table 1 shows the number of investigated samples for each test. Due to the small volume of adhering mucus, only one sample was extracted per endotracheal tube. Only a single test was possible for each sample because the influence of the testing on rheological properties is unknown. In total 97 samples were measured in the rheological tests.

All measured quantities were first analyzed within TRIOS software (Version 5.1, TA Instruments, New Castle, United States). Subsequent statistical analysis and mathematical model fitting was performed using the MATLAB software (R2022b, Mathworks, Carlsbad, CA, USA). To fully characterize the rheological behavior of tracheobronchial mucus, four consecutive tests were conducted. Each test determines a different property: the amplitude-sweep test (Figure 3A) identifies the maximum applicable force, in which the applied strain does not disrupt the fragile microstructure. The frequency-sweep test (Figure 3B) provides a basic characterization whether viscous or elastic behavior is predominant. The creep-recovery test gives information of the interplaying viscous and elastic behavior at a defined deformation of the sample over time (Figure 3C). In addition, the stress-relaxation test (Figure 3D) provides information about the rheological behavior of a sample loaded with a defined force to complete the full characterization of the rheological behavior of tracheobronchial mucus. In the following, the tests and their parameters are described in detail.

Oscillatory tests

Oscillatory tests impose cyclically oscillating strain on a sample. The viscous as well as the elastic properties of the sample can be investigated. Within amplitude-sweep tests, the strain amplitude of a constant-frequency oscillation is gradually increased. This allows for the identification of a linear viscoelastic region (LVR). The frequency-sweep test investigates the stress induced in the sample by an oscillation with a strain amplitude within the LVR and varying frequencies.

Amplitude-sweep tests

The LVR is the region of applied strain in which the sample retains its microstructural properties. In the LVR, the shear moduli are constant and independent of the applied strain. The critical strain marks the limit of the LVR. Once the applied strain exceeds the critical strain, the structural properties of the sample are irreversibly destroyed. A correlation between structural properties and viscoelastic behavior is no longer possible. Thus, combinations of elasticity and viscosity laws based on Newton and Hook are no longer valid. To identify the bounds of the LVR, an amplitude-

Table 1. Breakdown of the collected tubes and measured samples in the rheological tests.

Rheological test	Number of samples
Amplitude-sweep test	21
Frequency-sweep test	36
Creep-recovery test	20
Stress-relaxation test	20
Total tubes collected	*179*
Total samples analyzed	*97*

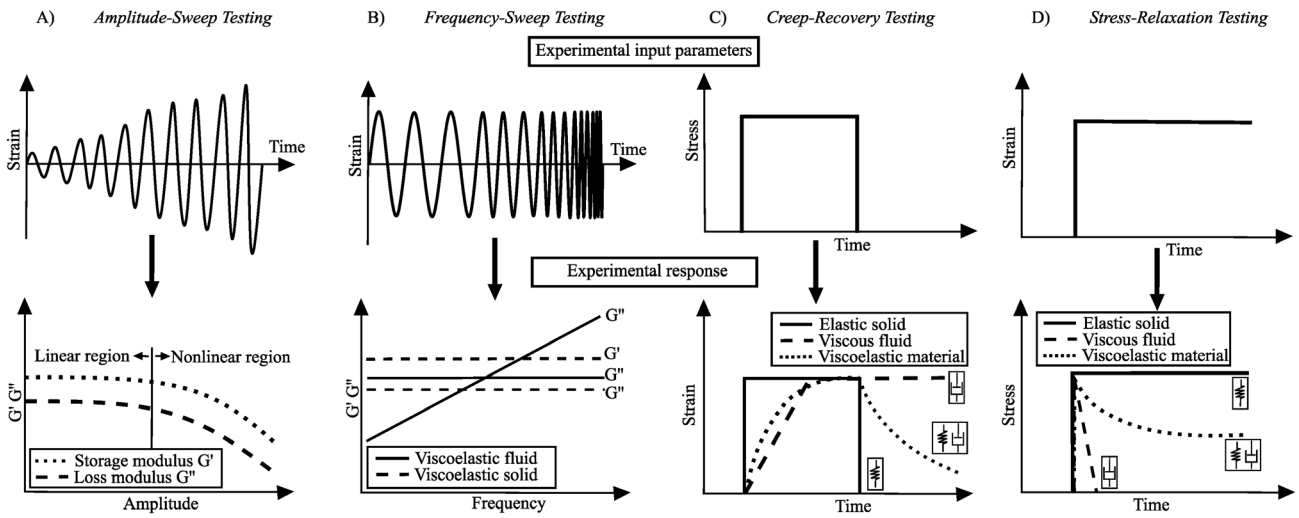

Figure 3. Schematic of the experimental input and output of an amplitude-sweep test (A), a frequency-sweep test (B), a creep-recovery test (C) and a stress-relaxation test (D). Exemplary behavior of storage and loss moduli is given for the oscillatory tests. For the transient tests, the experimental response of an elastic solid, a viscous fluid and a viscoelastic material is given.

sweep test was performed. For this, the sample was tested at a constant oscillation frequency of 10 rad/s and a varying oscillation strain amplitude ranging from 0.01% to 200%. The storage modulus G' was monitored with a sampling rate of 5 points per oscillation strain amplitude decade (0.1-1%, 1-10%, 10-100%, 100-1000%). Subsequently, the critical strain was identified as the strain value at which the storage modulus falls beneath its constant plateau for more than 10% of the plateau value. For each of the 21 samples, the critical strain was evaluated. Then, the averaged critical strain was assumed at the median of the individual critical strain values.

Frequency-sweep tests

Based on the averaged critical strain identified in the amplitude-sweep test, a strain amplitude of 2% was set for the frequency-sweep tests. The angular frequency was varied from 0.08 rad/sec to 100 rad/sec. Both the storage modulus G' and the loss modulus G'' were recorded with a sampling rate of 5 points per decade of the angular frequency (0.1-1 rad/sec, 1-10 rad/sec, 10-100 rad/sec). For each angular frequency, the medians of the storage and loss modulus were calculated to represent the frequency-dependent behavior of the mucus. As such, the storage modulus quantifies its elastic properties, while the loss modulus quantifies its viscous properties. The schematic of a frequency-sweep test in Figure 3B shows an exemplary behavior of a viscoelastic fluid and a viscoelastic solid.

Transient tests

Transient tests measure the time-dependent behavior of the mucus. For this, a constant load is applied to the sample, held for a specific time and released again. The time-dependent response of the sample after the load changes is measured. The type of load determines which quantities are measured. In creep-recovery testing, a constant shear stress is applied, and the strain response is measured. In stress-relaxation testing, a constant strain is applied and the induced stress is measured [24]. The schematic of transient tests in Figure 3 C,D shows the exemplary rheological behavior of a pure viscous material, an ideal elastic material, and a viscoelastic material. It includes the materials' responses to a strain load during stress-relaxation testing and to a stress load during creep-recovery testing. The critical stress, which limits the LVR, is not equivalent in oscillatory and transient tests. Thus, preliminary tests for determining the LVR for the transient tests were performed. To identify the critical stress in creep-recovery tests, and respectively the critical strain in stress-relaxation tests, the compliance curves of repeating transient tests with increasing stress/strain applications were analyzed. If the applied stress/strain is located within the LVR, the compliance curves overlap nearly. Loads exceeding the LVR cause the compliance curves to differ significantly. In the following, the measuring protocols for the creep-recovery test and the stress-relaxation test are presented.

Creep-recovery tests

Creep-recovery tests can be separated into two parts: the loading part (creep part) and the recovery part. The creep part involved loading a sample with a constant stress of 5 Pa for 300 s. The achieved deformation (strain) of the sample was monitored. To account for faster processes at the onset of the loading, a logarithmically increasing temporal sampling interval starting at 100 µs was used. Over a time of 300 s, the degree of elastic deformation and the rate of viscous flow was analyzed. During the relaxation phase, the stress load on the sample was removed, and the total recoverable elastic deformation was analyzed by monitoring the time-dependent strain $\varepsilon(t)$ over a time of 600 s. Again, a logarithmically increasing sampling interval starting at 100 µs was used.

Stress-relaxation tests

In the stress-relaxation tests, a constant strain of 10% was applied to the sample. The deformation was kept constant for the measuring time of 300 sec during which the stress reaction was measured. Due to the mucus's viscoelastic properties, the sample creeped, and the measured stress decreased.

Mathematical characterization of transient tests

From the individual sample response curves of the transient tests, a median was calculated for each measured timestep to deduct average curves for the creep, recovery, and relaxation behavior of physiological tracheobronchial mucus. Mathematical models were fitted to the median data using a non-linear least square fit. In the following sections, the mathematical models for approximating the transient behavior are explained.

Mathematical modelling of creep-recovery tests

The viscoelastic behavior of a material can be modeled with a combination of springs and dashpots. Thereby, a dashpot represents a purely viscous sample. A spring models an ideal elastic material. With its spring constant E and the loaded stress σ_0, the strain ε of a spring follows Hooke's law:

Dashpots have Newtonian behavior. Thus, their strain rate $\dot{\varepsilon}$ results from the fluid's viscosity η, the loaded stress σ_0 and the time t since the load application:

$$\varepsilon(t) = \frac{\sigma_0}{E}. \quad \text{(eq.1)}$$

$$\dot{\varepsilon}(t) = t\,\frac{\sigma_0}{\eta}. \quad \text{(eq.2)}$$

The serial combination of one spring and one dashpot is called a Maxwell element (eq. 3). Its rheological parameters are the spring constant E_M and the dashpot viscosity η_M .

$$\varepsilon(t) = \sigma_0 \cdot \left(\frac{1}{E_M} + \frac{t}{\eta_M}\right). \quad \text{(eq.3)}$$

The parallel combination of one spring with one dashpot results in a so-called Kelvin element (eq.4). Its rheological parameters are the spring constant E_k and the dashpot viscosity η_K.

$$\varepsilon(t) = \frac{\sigma_0}{E_K} \cdot \left(1 - e^{\frac{E_K \cdot t}{\eta_K}}\right). \quad \text{(eq.4)}$$

The time-dependent strain ε(t) during the creep phase can be described by a combination of a Maxwell and a Kelvin element in series (eq. 5) which is then called the Burgers model [25].

$$\varepsilon(t) = \sigma_0 \cdot \left(\frac{1}{E_M} + \frac{t}{\eta_M} + \frac{1}{E_K} \cdot \left(1 - e^{\frac{-E_K}{\eta_K} \cdot t}\right)\right). \quad \text{(eq.5)}$$

The rheological behavior during the recovery phase after the load removal can be approximated by a Weibull distribution (Eq.6 (26, 27)). Thereby, the time-dependent strain ε(t) is described by the viscoelastic strain recovery ε_{ve}, the scale parameter η_r, and the shape parameter β_r. ε_∞ is the permanent strain remaining after the load removal, which is caused by viscous effects.

$$\varepsilon(t) = \varepsilon_{ve} \cdot e^{\left(-\left(\frac{t}{\eta_r}\right)^{\beta_r}\right)} + \varepsilon_\infty. \quad \text{(eq.6)}$$

Mathematical modelling of stress-relaxation tests

The time-dependent stress response $\sigma(t)$ to the continuous strain load ε can be expressed by a six-element Maxwell model, which is composed of three Maxwell elements combined in parallel (eq. 7) [28]. Thereby, σ_0 describes the initial stress caused by the constant strain at $t = t_0 = 0$ s.

$$\sigma(t) = \sigma_0 \cdot \left(e^{\frac{(-t-t_0)\cdot E_{M1}}{\eta_{M1}}} + e^{\frac{(-t-t_0)\cdot E_{M2}}{\eta_{M2}}} + e^{\frac{(-t-t_0)\cdot E_{M3}}{\eta_{M3}}} \right). \quad \text{(eq.7)}$$

The rheological constants of the six-element Maxwell model are the spring constants E_{M1}, E_{M2}, and E_{M3} and the dashpot viscosities η_{M1}, η_{M2}, and η_{M3}.

Results

In total 97 out of the 179 collected endotracheal tubes were measured in the rheological investigations (Table 1). They contained a sufficient volume of homogenous sample for non-destructive sample collection and showed no contamination. The eliminated tubes were contaminated by blood, had a heterogeneous composition, or contained an insufficient sample amount. Others were used for preliminary tests, to adjust measurement parameters such as investigated shear rates. The freeze-drying preparing the samples for SEM caused a sample weight loss of 83%. Figure 4 A,B show the foamy, three-dimensional structure of the tracheobronchial mucus's matrix spanned by glycoproteins in the non-sputtered samples. The protein fibers crosslink uncoordinatedly. In addition, cuticles are visible, which also crosslink three-dimensionally. Figure 4 C,D show the thin fibers of the glycoprotein network with a diameter of 180-450 nm as well as disrupted structures. The amplitude-sweep test was conducted on 21 samples to identify their LVRs. Once the applied strain amplitude exceeds the sample's critical strain, the sample's storage modulus G' decreases significantly. Figure 5 shows the response of the samples' storage moduli G' to an oscillating strain with amplitudes reaching from 0.01% to 200% at a constant frequency of 10 rad/s. The storage moduli range from 0.1 Pa to 10,000 Pa. The critical strain of each analyzed sample is derived from the point where the sample's storage modulus G' falls below its plateau value for more than 10%. The median of all samples' critical strain values is located at an

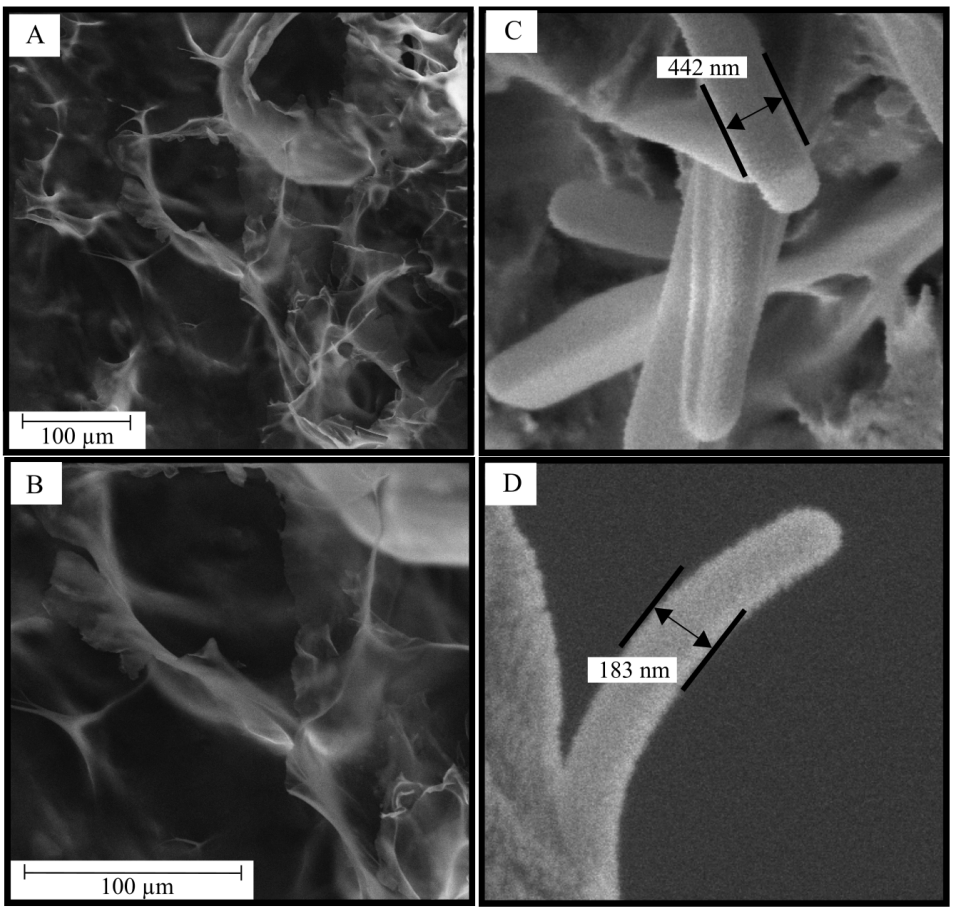

Figure 4. Scanning electron microscopic analysis of freeze-dried tracheobronchial mucus. A,B) Non-sputtered sample in a lower magnification to visualize the three-dimensional foamy microstructure; C,D) gold-sputtered sample in a higher magnification to show single fibers.

oscillation strain amplitude of 4%. The interquartile range (IQR) of the samples' critical strains reaches from 0.6% to 6.3%. The whiskers indicate the 1.5 x IQR and span a distance from 0.17% to 25.1%. The frequency-sweep test enabled to separate viscous and elastic properties of tracheobronchial mucus. Throughout all measured frequencies, the median of the elastic storage modulus was higher than the median of the viscous loss modulus at the same frequency. The strain amplitude for the frequency-sweep test was set to 2% to ensure measurements in the LVR. Figure 6 shows the frequency dependence of the storage modulus G' (Figure 6 left) and the loss modulus G" (Figure 6 right) of 36 tracheobronchial mucus samples. In both figures, the colored crosses represent the moduli of each sample at the measured frequencies. The red line connects the medians of the moduli at each measured frequency. Values exceeding 1.5 x IQR are marked as outliers and are shown as circles. Both the storage and the loss modulus increase with increasing frequency. The median of the storage modulus starts at 10 Pa at 0.08 rad/s and increases to 30 Pa at 100 rad/s. The median of the

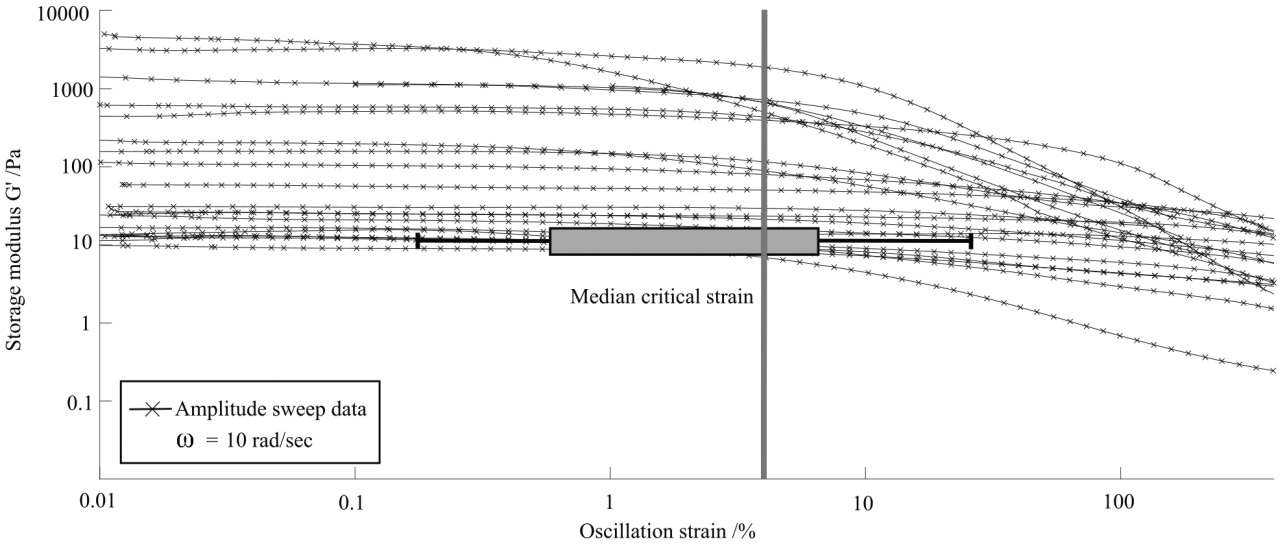

Figure 5. Amplitude-sweep test results: storage modulus G' plotted over the oscillation strain amplitude. The black crosses indicate the experimental data. The red line marks the median critical strain. The green box shows the critical strain interquartile range (IQR). The whiskers indicate the 1.5 x IQR.

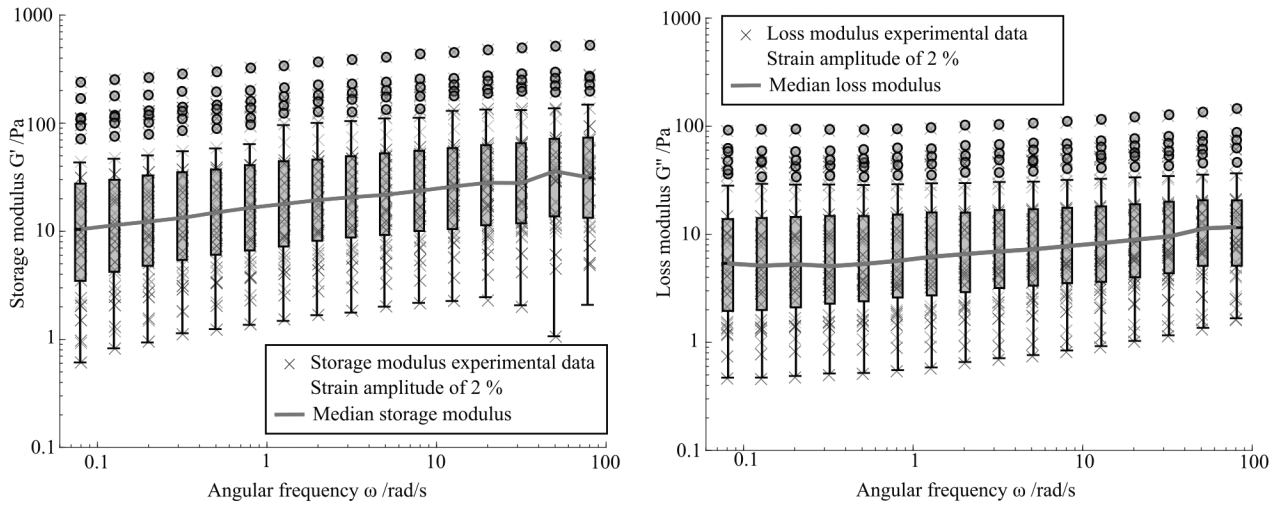

Figure 6. Frequency-sweep test results: storage G' and loss modulus G'' plotted over time. The crosses indicate the experimental data, while the red line shows the median of the data for the investigated frequencies.

loss modulus has lower values, starting at 5 Pa and ending at 14 Pa. The combination of viscous and elastic properties determines the time dependent behavior of the mucus. Transient testing (creep-recovery test, stress-relaxation test) can characterize this interplay over time. In the following, the results of the transient tests are presented. Mathematical model parameters for optimal approximations to the experimental data are presented in Tables 2 to 4. The creep curves of all samples showed a marked increase after the onset of loading. With time, the strain increase rates of all samples declined. A lower increase at the beginning led to an even lower increase rate after longer time, in the extreme to a nearly steady strain. Figure 7 shows the time-dependent strain during the creep part of the creep-recovery tests of 20 samples. The consecutive black crosses indicate the chronological strain sequence of each sample, after loading with a constant stress of 5 Pa. The resulting high gradients are well resolved by the high sampling rate at the beginning of the measurement. The red line connects the median of the strain of all samples at each time step. Two samples showed significantly higher strain exceeding 20 and were identified as outliers. The variance of the sample data is shown at every 15th time step with boxplots. The creep behavior of each sample was mathematically represented by the Burgers model. The black lines show the transient strain values predicted by an individual model for each sample. Across all individual models of the samples, the mean approximation coefficient of determination R^2 is 0.99. A Burgers model fitted to the median strains of all samples at each time step achieves an R^2 of 0.99. Table 2 shows the median Burgers model coefficients with 95% confidence intervals. The spring constant of the Maxwell element E_M resulted in 29 Pa and the dashpot constant of the Maxwell element η_M resulted in 695.3 Pa s. The spring constant of the Kelvin element E_K resulted in 7.179 Pa and the dashpot constant of the Kelvin element η_K resulted in 108 Pa s. The recovery curves of all samples showed a marked strain decrease during the first seconds. With time, the strain stabilized to a constant value. The time-dependent strains of the 20 samples during the recovery part of the creep-recovery test, after the continuous load of 5 Pa was lifted from the sample, are shown in Figure 8 over the measuring time of 600 sec. The black crosses indicate the strain recovery sequence for each sample over time. The two outliers identified in the creep part of the creep-recovery test persist in the recovery data. The variance of the sample data is shown at every 15th time step with boxplots in Figure 8. The recovery behavior of each sample was mathematically represented by the Weibull distribution. The black lines show the data predicted for each sample by a Weibull distribution fitted to the strain data of each sample. The individual fits have an average R^2

Table 2. Coefficients (in *italics*) of the Burgers model fitted to the medians of the experimental data of the creep part of the creep-recovery test. The upper and lower limits of the coefficients within a 95% confidence interval are given below.

$$\text{Burgers model: } \varepsilon(t) = \sigma_0 \cdot \left(\frac{1}{E_M} + \frac{t}{\eta_M} + \frac{1}{E_K} \cdot \left(1 - e^{\frac{-E_K}{\eta_K} \cdot t} \right) \right)$$

E_M (Pa)	η_M (Pa s)	E_K (Pa)	η_K (Pa s)
29 [27.2, 30.8]	*695.3* [675.1, 715.4]	*7.179* [6.848, 7.51]	*108* [98.97, 117]

Table 3. Dimensionless coefficients (in *italics*) of the Weibull model fitted to the medians of the experimental data of the recovery part of the creep-recovery test. The upper and lower limits of the coefficients within a 95% confidence interval are given below.

$$\text{Weibull model: } \varepsilon(t) = \varepsilon_{ve} \cdot e^{\left(-\left(\frac{t}{\eta_r}\right)^{\beta_r}\right)} + \varepsilon_\infty$$

ε_{ve}	η_r	β_r	ε_∞
333.9 [301, 366.9]	*921.5* [-607.8, 2451]	*0.08828* [0.0828, 0.0936]	*333.9* [301, 366.9]

Table 4. Dimensionless coefficients (in *italics*) of the six-element Maxwell model fitted to the medians of the experimental data of the stress-relaxation test. The upper and lower limits of the coefficients within a 95% confidence interval are given below.

$$\text{Six-element Maxwell model: } \sigma(t) = \sigma_0 \cdot \left(e^{\frac{(-t-t_0)\cdot E_{M1}}{\eta_{M1}}} + e^{\frac{(-t-t_0)\cdot E_{M2}}{\eta_{M2}}} + e^{\frac{(-t-t_0)\cdot E_{M3}}{\eta_{M3}}} \right)$$

σ_0(Pa)	E_{M1}(Pa)	η_{M1} (Pa s)	E_{M2} (Pa)	η_{M2} (Pa s)	E_{M3} (Pa)	η_M3 (Pa s)
1.19 [1.108, 1.272]	*0.993* [-2.074*10^6, 2.074*10^6]	*0.3312* [0.919*10^5, 6.919*10^5]	*0.05594* [-1.155*10^5, 1.155*10^5]	*1.758* [-3.63*10^6, 3.63*10^6]	*165.2* [-3.707*10^8, 3.707*10^8]	*0.5522* [-1.239*10^6, 1.239*10^6]

of 0.99. The red line connects the median strain of all samples at each time step. The fit of a Weibull distribution to the median strain values has an R^2 of 0.99. Table 3 shows the model parameters of the Weibull approximation of the median data. The viscoelastic strain recovery ε_{ve} resulted in a dimensionless value of 333.9, the scale parameter η_r resulted in a dimensionless value of 921.5, the shape parameter β_r resulted in a dimensionless value of 0.08828, and ε_∞ as the permanent strain caused by the viscous effects resulted in a dimensionless value of 333.9.

During the stress relaxation tests, the induced stress decreased markedly within the initial 10 seconds. After this decrease, the remaining stress, hereinafter called equilibrium stress, was nearly constant. Preliminary tests showed that an initially applied larger stress causes a higher equilibrium stress. Figure 9 shows the time-dependent stress during stress-relaxation tests while loading the samples with a constant strain of 10%. Boxplots indicating the IQR of the experimental data are shown for every 10th time step. Two outliers were identified in the stress-relaxation test. These are not visible in the graphic. The median stress of all samples at each timestep is visualized in red. The stress-relaxation behavior of each

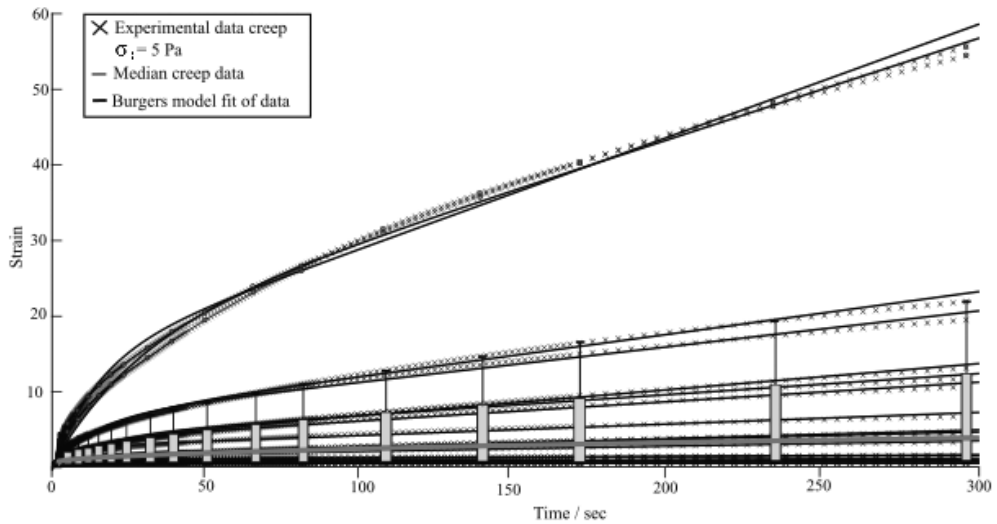

Figure 7. Strain response during the creep part of the creep-recovery test. The black crosses indicate the experimental data, the black lines the approximation by Burgers models fitted to each sample, and the red line connects the median strain values at each timestep.

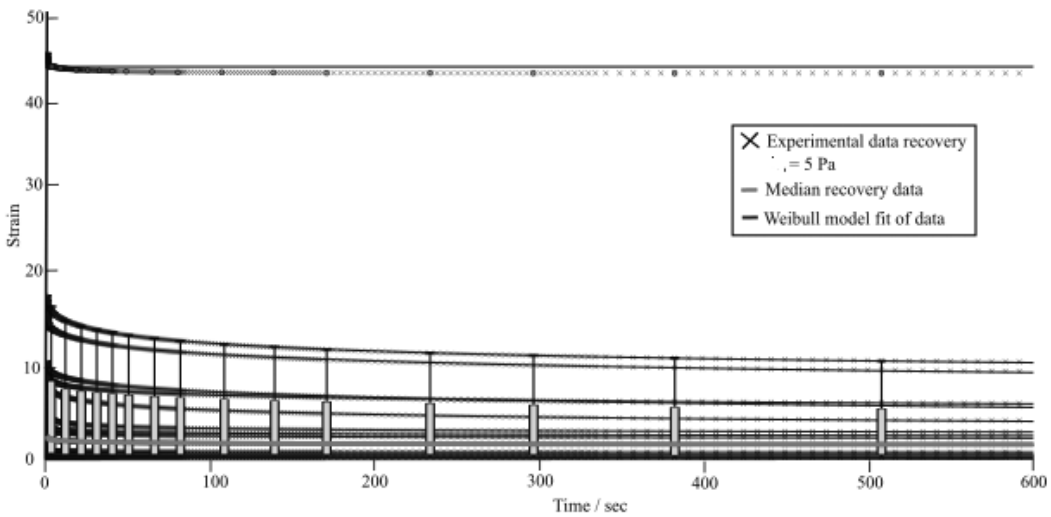

Figure 8. Strain response during the recovery-part of the creep-recovery test. The black crosses indicate the experimental data, the black lines the approximation by Weibull's models fitted to each sample, and the red line connects the median strain values at each timestep.

sample was mathematically represented by the six-element Maxwell model. The stress prediction by a six-element Maxwell model fitted to the median data is shown in green. Table 4 shows the coefficients of this six-element Maxwell model with 95% confidence bounds. The initial stress σ_0 resulted in 1.19 Pa, the spring and the dashpot constants resulted in 0.993 Pa and 0.3312 Pa s for the first Maxwell element, in 0.05594 Pa and 1.758 for Pa s the second Maxwell element, and in 165.2 Pa and 0.5522 Pa s for the third Maxwell element. The fit of the six-element Maxwell model to the median stress values has an R^2 of 0.91.

Discussion

Due to the sensible microstructure of the tracheobronchial mucus and the difficulties of collecting the sample [29], the rheological behavior varies. Thus, a large sample size is necessary to achieve reproducible results regarding the viscoelastic properties of tracheobronchial mucus. This is underlined further by the high ratio of endotracheal tubes that needed to be excluded from the study of nearly 55%. Therefore, the sample collection method potentially affects a high number of patients. Collecting the mucus samples from used endotracheal tubes makes it possible to obtain high sample numbers without any additional impact on patients' wellbeing. Further, this method ensures a defined localization of the collected sample in the trachea. Contamination by saliva can be neglected. Despite the high number of collected endotracheal tubes, the number of samples measured per test is limited. Thus, a pathological characterization of several diseases by mucus rheology requires a larger sample size.

The cross-linked three-dimensional network of glycoproteins in the tracheobronchial mucus could be visualized by SEM with the help of freeze-drying samples preliminarily. The weight loss and the SEM-images showed a successful and gentle freeze-drying process that preserved the three-dimensional microstructure of the mucus. The thin fibers span an unstructured network, which causes the viscoelastic behavior. The application of a small load causes the fibers to arrange in the strain direction. The critical strain marks the strain at which the fibers are fully aligned. Any additional deformation breaks the fibers, which renders the deformation non-reversible.

The complex viscoelastic behavior of tracheobronchial mucus results primarily from the cross-linking by covalent and non-covalent bonds between the macromolecules [20]. Within oscillation tests, this behavior can be modeled with a combination of the mucus storage G' und loss modulus G'', the complex modulus [30]. The validity of the complex modulus is limited to the LVR. Therefore, knowledge of the mucus's LVR is necessary. All samples showed an LVR in the amplitude-sweep-tests. Once the applied strain exceeds the critical strain, the storage modulus decreases. For the following frequency-sweep oscillatory tests a strain amplitude within the LVR needed to be set. Because of the small sample volume which could be obtained from each endotracheal tube, only one test per sample was possible. Thus, it was not possible to perform both amplitude- and frequency-sweep tests with one sample. The critical strain of each sample measured in the frequency-sweep test was unknown. Therefore, the strain amplitude for the frequency-sweep tests was deducted from the averaged critical strain distribution of all samples measured in the amplitude-sweep tests. To account for the large spread in critical strains, a strain amplitude of 2%, which is within the lower part of the critical strain IQR, was chosen. Despite being low, this strain amplitude might have exceeded the critical strain of individual samples in the frequency-sweep test. This potential excessive loading could have changed the molecular structure of these samples and could have led to errors in the frequency-sweep test results. While the values of the storage and loss moduli differ across the subjects, all samples showed an increasing trend for the storage and loss moduli with increasing frequency. The loss modulus being lower than the storage modulus characterizes the tracheobronchial mucus as mainly elastic at a strain rate of 2%. Outliers underline a wide scatter between individuals.

The novel transient rheological testing of human tracheobronchial mucus gives a statistically based insight into the interplay of viscous and elastic forces over time. Transferring these

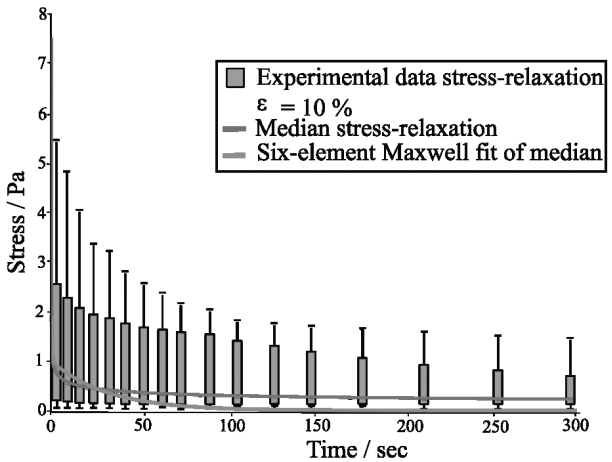

Figure 9. Stress results of stress-relaxation tests. The red line connects the median stress value at each timestep. The green line shows the stress curve predicted by the six-element Maxwell model fitted to the median stress values at each timestep.

results into mathematical models provides a basis for detailed investigations of flow phenomena in the human respiratory system such as mucus behavior during coughing or ciliary beating. Due to the variety of loads placed on the samples during the transient test, numerical models for a multitude of calculations could be deducted. Now, numerical approaches for simulating mucus behavior in different respiratory events, such as breathing at rest, coughing or ciliary motion, are available. During the creep-recovery tests at a constant stress load of 5 Pa, the mucus samples exhibited strain response curves that are characteristic for a viscoelastic fluid. At the onset of loading in the creep part of the test, a small amount of pure elastic deformation is seen in the nearly vertical strain increase. The following non-linear strain increase shows the viscoelastic behavior. Once the strain increase rate stabilizes to a constant value, the strain response is that of a pure viscous material. After the stress removal in the relaxation part of the test, the small amount of pure elastic deformation is visible in the first instantaneous strain decrease. With time, the strain decreases and settles to the non-recoverable strain caused by viscous flow. The ratios of recoverable, elastic strain to non-recoverable, viscous strain can be assessed reliably only in samples exhibiting high strain. Only a small portion of the strain is recoverable in these samples. Thus, the viscous influence has a higher impact on the viscoelastic behavior of the samples than the elastic influence. In both the creep and the recovery part of the creep-recovery test two significant outliers are visible. The constant load of 5 Pa causes a visibly higher strain in these samples. Upon load removal, these samples showed no remarkable recovery strain and a high permanent strain. Both the high strain values and the high non-recoverable strain indicate more viscous behavior in these samples. No difference in patient characteristics such as age or disease was apparent in the outlier samples. Thus, their different rheological behavior might be caused by the constant stress of 5 Pa inducing a higher strain than the critical strain of these samples. Overshooting the LVR causes permanent destruction in the mucus microstructure which affects its rheological properties. The Burgers model and the Weibull distribution represent the experimental data of the creep-recovery-tests well. The individual models and the models fitted to the median of the data at all measured frequencies have high coefficients of determination R^2 of 0.99. Thus, these models predict the mucus rheological behavior appropriately.

In the stress-relaxation test, the stress in the material decreases swiftly after loading the sample with a constant strain of 10%. The median stress settles at a low constant equilibrium stress of 0.4 Pa. Both these aspects indicate small molecules in the mucus microstructure, which can flow and relocate upon loading to decrease tension. The six-element Maxwell model approximation of the time-dependent stress response withing the stress-relaxation test showed visible differences to the experimental data. The stress predicted by the model falls below zero after 200 s. Thus, the model does not correctly predict the experimentally measured equilibrium stress. While this study focusses on physiological tracheobronchial mucus, further investigations of pathological changes in mucus's rheology will be conducted. For these studies, an even larger sample size, due to the high number of excluded samples, needs to be investigated.

Conclusions

In the present study, we assessed the steady as well as the time-dependent mechanical behavior of native tracheobronchial mucus. With a focus on the reliability of sample collection and on data reproducibility, the rheological behavior was characterized using amplitude-sweep, frequency-sweep, creep-recovery, and stress-relaxation tests. The amplitude-sweep test delivered an approximated critical strain. In frequency-sweep tests, the mucus was characterized as being mainly elastic. In transient tests, the averaged behavior as a response to deformation and force loading was investigated and approximated by common mathematical rheological models. Both the Burgers model of constant stress loading and the Weibull model of constant stress load removal show an appropriate approximation of the viscoelastic behavior of physiological tracheobronchial mucus. The six-element Maxwell model differs remarkably from the experimental data of stress-relaxation tests. With these results, we provide numerical models of the viscoelasticity of the physiological human tracheobronchial mucus. All model parameters are summarized in Tables 2 to 4. These models together with known forces or deformations can be used to simulate mucus flow in the respiratory system. Ultimately, the new numerical models enable realistic calculations of mucus flow during respiratory events such as breathing or coughing. This can improve our understanding of more complex flow phenomena such as pathogen transport or shear-induced aerosol generation. Further, it can provide insights into the mechanisms of respiratory diseases, aid in the development of new diagnostic tools and treatments, and thus ultimately improve patient outcomes.

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ORIGINAL RESEARCH ARTICLE

Utility of the 4C ISARIC mortality score in hospitalized COVID-19 patients at a large tertiary Saudi Arabian center

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ABSTRACT

Background: The International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) 4C mortality score has been used before as a valuable tool for predicting mortality in COVID-19 patients. We aimed to address the utility of the 4C score in a well-defined Saudi population with COVID-19 admitted to a large tertiary referral hospital in Saudi Arabia.

Methods: A retrospective study was conducted that included all adults COVID-19 patients admitted to the Armed Forces Hospital Southern Region (AFHSR), between January 2021 and September 2022. The receiver operating characteristic (ROC) curve depicted the diagnostic performance of the 4C Score for mortality prediction.

Results: A total of 1,853 patients were enrolled. The ROC curve of the 4C score had an area under the curve of 0.73 (95% CI: 0.702-0.758), p<0.001. The sensitivity and specificity with scores >8 were 80% and 58%, respectively, the positive and negative predictive values were 28% and 93%, respectively. Three hundred and sixteen (17.1%), 638 (34.4%), 814 (43.9%), and 85 (4.6%) patients had low, intermediate, high, and very high values, respectively. There were significant differences between survivors and non-survivors with regard to all variables used in the calculation of the 4C score. Multivariable logistic regression analysis revealed that all components of the 4C score, except gender and O_2 saturation, were independent significant predictors of mortality.

Conclusions: Our data support previous international and Saudi studies that the 4C mortality score is a reliable tool with good sensitivity and specificity in the mortality prediction of COVID-19 patients. All components of the 4C score, except gender and O_2 saturation, were independent significant predictors of mortality. Within the 4C score, odds ratios increased proportionately with an increase in the score value. Future multi-center prospective studies are warranted.

Key words: ISARIC; 4C; mortality; predictor; COVID-19; Saudi Arabia, utility.

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Ethics approval and consent to participate: Ethical approval was obtained from the institutional review board of the AFHSR (approval no; AFHSRMREC/2022/PULMONOLOGY-INTERANL MEDICINE/603).

Availability of data and material: The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Conflict of interest: The authors have no competing interests.

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Introduction

The COVID-19 pandemic spread rapidly worldwide, including in Saudi Arabia, leading to a severe health emergency [1]. The clinical presentation and progression of COVID-19 in patients are highly variable [2], making it difficult for physicians to triage patients and determine their risk of poor outcomes. While some patients may clearly present with severe disease, even patients presenting with mild symptoms may have rapid decompensation [3]. The variability in COVID-19 presentation necessitated the development of risk stratification tools that would allow early identification of COVID-19 patients at higher risk of mortality, using readily available objective criteria [3-5]. Accordingly, Knight *et al.* [6] utilized the International Severe Acute Respiratory and Emerging Infections Consortium (ISARIC) World Health Organization Clinical Characterization Protocol to develop and validate such a tool, the ISARIC 4C mortality score. The ISARIC mortality score utilizes variables that are readily available upon hospitalization, thereby avoiding reliance on parameters such as radiological imaging or those that only become available after hospital/ICU admission [7]. The model has been demonstrated to have a high discriminatory ability for in-hospital mortality and prognostically categorizes COVID-19 patients into four categories of severity with a uniformly increasing mortality risk (Supplementary Table 1).

After its development and validation of the original 4C score for the population in the United Kingdom, and for generalizability, it has been externally validated in many countries [5,8,9], as well as in Saudi Arabia [10,11]. However, the later studies either focused only on ICU patients [10] or reported the validation of the 4C score among heterogenous populations (both in-patients and out-patients) after the early wave of COVID-19 [11].

Despite that the 4C score has been seen before as a valuable tool for predicting mortality in COVID-19 patients, still there is a need to clarify its utility among more populations. This would be of particular importance if large numbers of COVID-19 patients are admitted, at different timeframes and all through different COVID-19 waves, into large tertiary referral centers.

Therefore, in the current study, we aimed to address the utility of the 4C score in a well-defined Saudi population with COVID-19 admitted to The Armed Forces Southern Region (AFSR), Saudi Arabia, over a 21-month period.

Methods

Study setting, design and population

Armed Forces Hospital Southern Region (AFHSR) is a tertiary hospital. The current study is a retrospective study that included all adults (>14 years old) with COVID-19 admitted to AFHSR, Khamis Mushayt, Saudi Arabia, between January 1, 2021 and September 30, 2022.

COVID-19 was confirmed by nasopharyngeal reverse transcription–polymerase chain reaction (RT-PCR). The criteria for admission were as per the COVID-19 management recommendations of the Saudi Ministry of Health [12]. After the completion of data collection, patients with missing variables that preclude the calculation of the ISARIC score were excluded.

Data collection

Demographic, clinical, laboratory, and outcome data were collected from electronic medical records. The demographic data included age, gender, and nationality. Clinical data included the main presenting symptoms, signs, admission data (ICU *versus* non-ICU), and comorbidities. Included comorbidities were chronic cardiac disease, chronic pulmonary disease, chronic kidney disease, chronic liver disease, diabetes mellitus (type 1 or 2), chronic neurological disease, connective tissue/rheumatological disease, malignant neoplasm, dementia, and HIV/AIDS. Laboratory data included basic investigations and inflammatory markers. Outcome data included mortality during hospitalization.

The 4C mortality score

For calculating the ISARIC score [6], the following variables were collected from the electronic database of the patients' medical records: age; gender; number of comorbidities; respiratory rate (RR), peripheral oxygen saturation (SpO_2) on room air, and Glasgow coma scale (GCS) at hospital admission; first available

Table 1. Demographic and clinical features of the study cohort.

Feature	n=1853
Age (years)	
Mean ± SD	57.20 ± 21.6
Median (range)	28.6 (15 - 109)
Gender	
Male	1045 (56.4%)
Female	808 (43.6%)
Nationality	
Saudi	1808 (97.6%)
Non-Saudi	45 (2.4%)
Respiratory rate	
0-20 cycles/min.	1040 (56.1%)
20-29 cycles/min.	783 (42.3%)
> 29 cycles/min.	30 (1.6%)
O_2 saturation	
> 92%	510 (27.5%)
< 92%	1343 (72.5%)
GCS	
= 15	1692 (91.3%)
< 15	161 (8.7%)
BUN	
< 7	1136 (61.3%)
7-14	494 (26.7%)
> 14	223 (12%)
CRP	
< 50	661 (35.7%)
50-100	573 (30.9%)
> 100	619 (33.4%)
No. of comorbidities	
0	735 (39.6%)
1	578 (31.2%)
≥2	540 (29.2%)
Clinical status	
Stable (non-ICU)	1505 (81.2%)
Critical (ICU)	348 (18.8%)
Outcome	
Alive	1541 (83.2%)
Dead	312 (16.8%)
4C score	
0-3	316 (17.1%)
4-8	638 (34.4%)
9-14	814 (43.9%)
>15	85 (4.6%)

blood urea level (mmol/L); and C-reactive protein (CRP) (mg/L).

The 4C Mortality Score ranges from 0 to ≥15 and it divides patients into four risk groups: low (0-3), intermediate (4-8), high (9-14), and very high-risk groups (≥15).

Study outcomes

The primary outcome of the study was the performance of ISARIC score in our settings by evaluating its discriminatory ability of survivors and deceased in all-cause hospital mortality outcome. The secondary outcome was the comparison between subjects with scores above and below the optimal cut-off value of ISARIC.

Ethical considerations

Ethical approval was obtained from the institutional review board of the AFHSR (approval no; AFHSRMREC/2022/PULMONOLOGY-INTERANL MEDICINE/603). The study participants were fully informed about the study procedures.

Statistical analysis

Data were verified, coded by the researcher, and analyzed using IBM-SPSS 24.0 (IBM-SPSS Inc., Chicago, IL, USA). Descriptive statistics: means, standard deviations (SD), medians, inter-quartile range (IQR) and percentages were calculated. Significance test: Chi-square/Fisher's exact test was used to compare the differences in frequency between groups. Test of normality, Shapiro-Wilk or Kolmogorov Smirnoff was used to test the normality of continuous variables. For continuous variables with two categories, independent sample *t*-test/Mann Whitney U test was used to compare the difference in means/median as appropriate. The clinical and demographic factors with proven statistical significance were included in the multivariable logistic regression models. Multivariable logistic regression analysis was calculated to investigate the independent significant predictors of mortality [odds ratio (OR) 95%, confidence interval (CI) 95%]. The receiver operating characteristic (ROC) curve depicted the diagnostic performance of the 4C Score for mortality prediction, analyzed as area under the curve (AUC), standard error (SE) and 95% CI. Validity statistics [sensitivity, specificity, positive and negative predictive value (PPV, NPV)] were calculated. A $p<0.05$ was considered significant.

Results

Demographic and clinical features

There were 2,148 confirmed COVID-19 admissions during the study period. Of these, 150 had insufficient data to calculate a score, 100 were discharged against medical advice, and 45 were transferred to other hospitals. Accordingly, the study finally included 1,853 patients (Figure 1). The vast majority of the patients were Saudis (97.6%), and 56.4% of patients were males. A total of 1,118 /1,853 (60.3 %) patients had one or more comorbidities. The most commonly encountered comorbidity was diabetes mellitus (DM), where 899/1853, 48.5% of patients suffered from it. Among the study cohorts, 18.8% needed ICU admission. During the study period, 1,541 (83.2%) survived, while 312 (16.8%) patients died. Table 1 depicts the demographic and clinical characteristics of the cohort.

The ISARIC 4C score

The average age of the study subjects was 57.2±21.6 years. With regards to comorbidities, 39.6%, 31.2%, and 29.2%, had 0, 1, and ≥2 comorbidities, respectively. With regards to ISARIC score, 316 (17.1%), 638 (34.4%), 814 (43.9%), and 85 (4.6%) of patients had low, intermediate, high, and very high values, respectively. Table 1 shows these results.

Comparison between survivors and non-survivors

Table 2 details the differences between survivors and non-survivors. For comorbidities, there were significant differences between the survivors and non-survivors between patients with all comorbidities, except those with chronic liver disease, connective tissue disease, and HIV. There were significant differences between survivors and non-survivors with regard to all variables used in the calculation of ISARIC 4C score. There were significant differences between survivors and non-survivors among patients within each category of the ISARIC score. Characteristically, high-risk and very high-risk patients were 64.4% and 15.4% among patients who died, respectively, while among patients who survived the categories high risk and very high risk were only 39.8% and 2.4%, $p<0.001$.

Predictors of mortality

Multivariable regression analysis revealed that clinical status, and all components of the ISARIC 4C score, except gender and O_2 saturation, were independent significant predictors of mortality. Thus, 6 out of 8 components of the 4C score were independent predictors of mortality. For the 4C score, characteristically odds ratios increased proportionately with the increase in the value of each score category. The odds ratio was 6.598 (95% CI 1.032-8.334), $p<0.001$ for the category 4-8, 15.480 (2.702-28.635), $p<0.001$ for the category 9-14, and 23.676 (4.541-72.582), $p<0.001$, for the category >15, respectively. Table 3 details these data.

Diagnostic criteria of the 4C score

The ROC curve of ISARIC score had AUC of 0.73 (95% CI: 0.702–0.758, $p<0.001$) (Figure 2). The sensitivity and specificity with scores >8 were 80% and 58%, respectively; the PPV and NPV were 28% and 93%, respectively (Table 4).

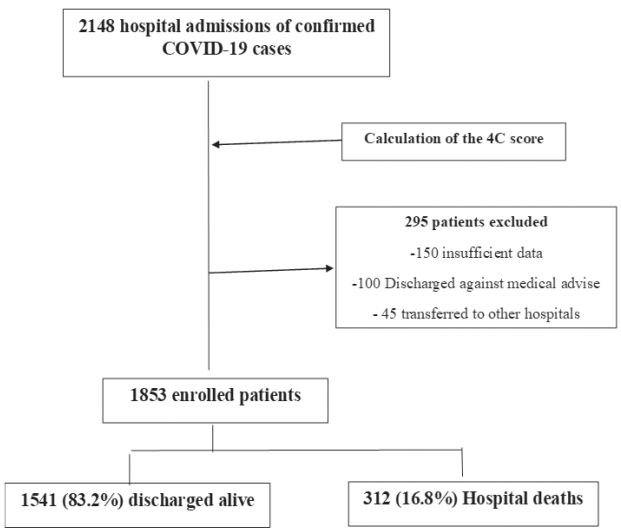

Figure 1. Flow chart of the studied patients.

Discussion

The current study was conducted to address the utility of the ISARIC 4C mortality score among COVID-19 inpatients admitted to a large Saudi Arabian tertiary referral hospital between January 1, 2021 and September 30, 2022. Our data showed that the 4C mortality score is a valid tool to prognosticate mortality among hospitalized COVID-19 patients. We observed an overall AUC of 0.73 (95% CI: 0.702-0.758, p<0.001) which is identical to the initial derivation research of Knight and coworkers [6].

The 4C score has been validated outside of the United Kingdom in many countries, including Canada [8,13], Italy [5], Japan [9], as well as in Saudi Arabia [10,11]. Characteristically, the 4C score has shown utility all over the study period (21 months), during which many changes occurred with regard to the COVID-19 timeline [14,15]. Changes over time in the dominant strain of

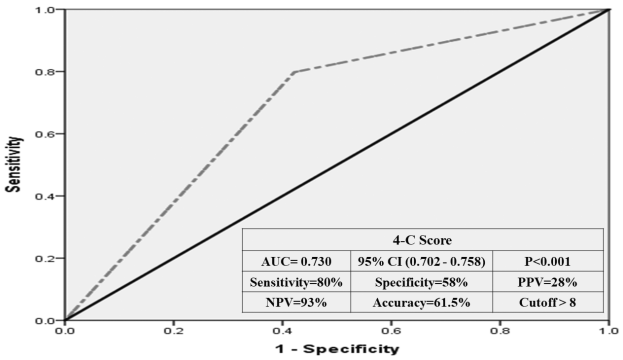

Figure 2. Receiver operating characteristic of the ISARIC 4C score.

Table 2. Determinants of mortality among the studied Cohort (n=1,853).

	Alive (n=1541, 83%)	Dead (n=312, 17%)	p
Age/years (median - IQR)	55 (30)	73.5 (19)	<0.001*
Age groups			<0.001**
<50	622 (40.3%)	23 (7.3%)	
50-59	250 (16.2%)	42 (13.5%)	
60-69	255 (16.5%)	64 (20.5%)	
70-79	239 (15.5%)	79 (25.3%)	
≥80	175 (11.4%)	104 (33.3%)	
Gender (M/F)	849/692	196/116	0.012**
Nationality (Saudi/Non)	1499/42	309/3	0.065**
No. of comorbidities			<0.001**
0	671(43.5%)	64 (20.5%)	
1	482 (31.3%)	96 (30.7%)	
≥2	388 (25.2 %)	152 (48.7%)	
Respiratory rate			<0.001**
0-20 cycle/min	913 (59.2%)	127 (40.7%)	
20-29 cycle/min	612 (39.7%)	171 (54.8%)	
>29 cycle/min	16 (1%)	14 (4.5)	
O_2 saturation (<92%)	1071 (69.5%)	272 (87.2%)	< 0.001**
Glasgow coma scale (<15)	76 (4.9%)	85 (27.2%)	< 0.001**
Blood urea nitrogen			
<7	1034 (67.1%)	102 (32.7%)	
7-14	367 (23.8%)	127 (40.7%)	<0.001**
>14	140 (9.1%)	83 (26.6%)	
C-reactive protein			
< 50	603 (39.1%)	58 (18.6%)	
50-100	494 (32.1%)	79 (25.3%)	< 0.001**
> 100	444 (28.8%)	175 (56.1%)	
Clinical status (critical)	87 (5.6%)	261 (83.9%)	< 0.001**
4 C score			<0.001**
0-3	314 (20.4%)	2 (0.6%)	
4-8	577 (37.4%)	61 (19.6%)	
9-14	613 (39.8%)	201 (64.4%)	
>15	37 (2.4%)	48 (15.4%)	

*Mann Whitney U-test was used to compare the differences in median between groups; **Chi-square test was used to compare the differences in frequency between groups; ***Fisher's exact test was used to compare the differences in frequency between groups.

SARS-CoV-2, vaccine distribution, and treatment practices (*e.g.*, use of steroids) could all potentially impact the predictive ability of a mortality risk score [8].

In the current study, the AUC was almost identical to those by Knight *et al.* [6] and Jones *et al.* [8], but lower than in others: van Dam *et a.* [4] and Wellbelove *et al.* [16]. Despite that the current study was conducted among the Saudi population, our AUC was lower than those observed among other studies that addressed the 4C score among Saudi patients [10,11]. This variation among studies – although minimal – utilizing the same prediction model may reflect the variations in the studied populations, with regard to their demographic characteristics, hospitalized or out-patients, clinical severity, and sample size. For example, in our study, the age range was so wide (from 15 to 109 years). On the other hand, other studies from Saudi Arabia had reported data for patients only admitted to the ICU [10] or data of both hospitalized and home-isolated patients [11].

An important finding was highlighted in the current study. There were rising mortality rates across groups of severity, that is, a directly proportional relationship between mortality risk and increase in score. This is in agreement with those observed by the original study [6] and Aletreby *et al*. [10]. This reflects that the model performs optimally, especially when taking into consideration that the higher mortality rates were higher within all groups in our study compared with the original study. Our finding was not in concordance with those observed by Mohamed and coworkers [11], who found that the 4C Score underestimated mortality risk among the very high-risk group with overestimation in other risk groups.

The diagnostic parameters of 4C scores >8 were the sensitivity, specificity, PPV, and NPV of 80%, 58%, 28%, and 93%, respectively. Compared with our study, an Italian study [5] reported almost identical sensitivity (88.1%) and specificity (55.9%). The same study considered this score as the most accurate mortality predictor compared with other scores like COVID-19-Gram Critical Illness Risk Score [17], Quick COVID-19 Severity Index [18], and the National Early Warning Score [19].

On the other hand, different cut-off values and diagnostic parameters were found among the original British study [6] Saudi [10,11] and international studies [8,9,20]. One of the most important diagnostic parameters is NPV, which indicates the probability of survival in patients with scores ≤8. In our model, NPV was 93%, which provides a reasonable risk probability to guide clinical decision-making.

Our results have shown significant differences between survivors and non-survivors among patients within each category of the 4C score. Moreover, multivariable regression analysis revealed that all components of the ISARIC 4C score, except gender and O_2 saturation, were independent significant predictors of mortality. In another ward, 6 out of 8 components of the 4C score were independent predictors of mortality. Hypoxemia, being a non-significant independent predictor of mortality, might be explained by the phenomenon of "happy hypoxemia" observed in patients with COVID-19. In patients with COVID-19, arterial hypoxemia is induced by intrapulmonary shunting, dysregulated hypoxic pulmonary vasoconstriction, impaired lung diffusion, and formation of intravascular microthrombi [21]. At the stage that COVID-19 patients are admitted to the hospital with hypoxemia (and the 4C score is calculated), viral replication is well underway. Furthermore, as in the first days of the disease, the lung mechanics are well-preserved and there is no increased airway resistance or dead space ventilation. Thus, the respiratory center does not sense an uncomfortable sensation of breathing. However, sudden and rapid respiratory decompensation may occur, and tachypnea and

Table 3. Independent predictors of mortality: multivariable logistic regression.

Predictor	Odds ratio (95% Confidence interval)	p
Age groups		
<50	1 (Reference)	0.001
50-59	2.892 (1.242-3.881)	0.004
60-69	3.324 (1.335-5.022)	0.006
70-79	4.676 (1.615-6.433)	<0.001
≥80	5.805 (1.743-7.574)	<0.001
Gender (male)	0.906 (0.692-1.186)	0.471
Clinical status (critical)	7.009 (1.882-11.987)	<0.001
No. of comorbidities		
0	1 (Reference)	<0.001
1	1.792 (1.042-2.481)	<0.001
≥2	2.020 (1.729-2.361)	<0.001
0-20 cycle/min	1 (Reference)	0.001
-29 cycle/min.	1.892 (1.242-2.881)	0.003
>29 cycle/min.	6.805 (1.743-9.574)	0.006
Glasgow coma scale (< 15)	3.324 (1.835-6.022)	<0.001
O_2 saturation (< 92%)	1.272 (0.870-1.860)	0.214
Blood urea nitrogen		
<7	1 (Reference)	0.009
7-14	1.419 (0.896-2.246)	0.136
>14	2.414 (1.372-4.247)	0.002
C-reactive protein		
<50	1 (Reference)	<0.001
50-100	1.484 (0.848-2.597)	0.167
>100	2.676 (1.615-4.433)	<0.001
4C score		
0-3	1 (Reference)	<0.001
4-8	6.598 (1.032-8.334)	<0.001
9-14	15.480 (2.702-28.635)	<0.001
>15	23.676 (4.541-72.582)	<0.001

Table 4. Diagnostic criteria of 4C score for mortality prediction.

Diagnostic criteria	4C score
Area under the curve	0.730
95% CI	0.702-0.758
Standard error	0.014
p-value*	<0.001
Cut-off	8
Accuracy	61.5%
Sensitivity	80%
Specificity	58%
PPV	28%
NPV	93%
False discovery rate	20%
False omission rate	6%

*Null hypothesis: true area=0.5; sensitivity, true positives/all diseased; specificity, true negatives/all non-diseased; PPV, positive predictive value (true positives/all test positives); NPV, negative predictive value (true negatives/all test negatives).

hyperpnea might be the most important clinical warning signs of impending respiratory failure in COVID-19 patients [21].

With this regard, our results are in agreement with those by Mohamed and coworkers [11], who observed that among the eight components of the 4C score, only hypoxia, tachypnea, high BUN, and CRP were the significant independent predictors of mortality. The proliferation of COVID-19 risk models is evidence of the need for an accurate, accessible, and generalizable tool [22] and our data add to the body of evidence supporting the use of the 4C score. Despite that we did not compare between 4C score and other mortality prediction scores in the current study, our data might support the findings of studies [5,16-18, 22] which showed that the 4C mortality score outperformed existing scores in COVID-19 patients.

The current study has many implications for daily clinical practice, as shown in the recent literature [22-27]. In their analysis, Sellers *et al*. [23] questioned if the 4C mortality score may be used to predict which patients with moderate to severe COVID-19 would benefit the most from remdesivir at the time of hospital admission. Their results have shown that driven by patients who were categorized into the intermediate-risk and high-risk mortality groups using the 4C mortality score, patients in the remdesivir group had a longer time to recover compared to patients in the standard of care group (6 days vs 4 days) [23]. Automated calculation of the 4C score in electronic medical records could be used to guide resource management and support clinical decision-making such as early admission, treatment initiation [11, 23], and admission to the ICU [10]. This is of crucial importance in large tertiary hospitals where large numbers of COVID-19 patients could represent a burden on those healthcare centers.

Similar to the COVID-19 situation, the potential for application of the 4C score in other common, but potentially fatal respiratory infections, exists. A larger prospective validation study of the 4C mortality score versus established scoring systems is needed to confirm its utility in undifferentiated respiratory infection, focusing on the potential for the ongoing utility of the 4C mortality score, even after the pandemic has ended and the incidence of COVID-19 is much lower. A recent meta-analysis [25] was conducted to externally validate various prognostic models and scoring rules for predicting short-term mortality in patients admitted to hospitals for COVID-19, among 46,914 patients across 18 countries. While the prognostic value of the included models varied greatly between the data sources, the Knight 4C Mortality Score and Wang clinical model appeared most promising [25].

This study has some potential limitations to be considered while interpreting the results. First, the inherent limitations of the retrospective study design are applicable. Second, our study was performed in a single medical center, limiting the generalizability of the results. However, our cohort of patients with COVID-19 was relatively large and has been recruited in one of the tertiary referral hospitals in Saudi Arabia.

Further multicenter studies with a larger sample size and including those with varied severities are required to validate the score in the larger Saudi population and possibly explore predictors of mortality in COVID-19 patients. Recently, the 4C score was prospectively validated to predict clinical deterioration and mortality in a large prospective second-wave validation cohort of adult hospitalized patients with COVID-19, in the UK [27].

Conclusions

In conclusion, our data support previous international and Saudi studies that the 4C mortality score is a reliable tool with good sensitivity and specificity in mortality prediction of COVID-19 patients. All components of the 4C score, except gender and O_2 saturation, were independent significant predictors of mortality. Within the 4C score, odds ratios increased proportionately with an increase in the score value. Future multi-center prospective studies with larger sample sizes are warranted to support our results and to address the validity of the scoring system on different COVID-19 strains.

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ORIGINAL RESEARCH ARTICLE

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Nebivolol: an effective option against long-lasting dyspnoea following COVID-19 pneumonia - a pivotal double-blind, cross-over controlled study

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ABSTRACT

Background: Pulmonary microvascular occlusions can aggravate SARS-CoV-2 pneumonia and result in a variable decrease in capillary blood volume (Vc). Dyspnoea may persist for several weeks after hospital discharge in many patients who have "radiologically recovered" from COVID-19 pneumonia. Dyspnoea is frequently "unexplained" in these cases because abnormalities in lung vasculature are understudied. Furthermore, even when they are identified, therapeutic options are still lacking in clinical practice, with nitric oxide (NO) supplementation being used only for severe respiratory failure in the hospital setting. Nebivolol is the only selective β_1 adrenoceptor antagonist capable of inducing nitric oxide-mediated vasodilation by stimulating endothelial NO synthase *via* β_3 agonism. The purpose of this study was to compare the effect of nebivolol *versus* placebo in patients who had low Vc and complained of dyspnoea for several weeks after COVID-19 pneumonia.

Methods: Patients of both genders, aged ≥18 years, non-smokers, who had a CT scan that revealed no COVID-related parenchymal lesions but still complaining of dyspnoea 12-16 weeks after hospital discharge, were recruited. Spirometrical volumes, blood haemoglobin, SpO_2, simultaneous diffusing capacity for carbon monoxide (CO) and NO (DL_{CO} and DL_{NO}, respectively), DL_{NO}/DL_{CO} ratio, Vc and exhaled NO (eNO) were measured together with their dyspnoea score (DS), heart frequency (HF), and blood arterial pressure (BAP). Data were collected before and one week after both placebo (P) and nebivolol (N) (2.5 mg od) double-blind cross-over administered at a two-week interval. Data were statistically compared, and $p<0.05$ assumed as statistically significant.

Results: Eight patients (3 males) were investigated. In baseline, their mean DS was 2.5±0.6 SD, despite the normality of lung volumes. DL_{CO} and DL_{NO} mean values were lower than predicted, while mean DL_{NO}/DL_{CO} ratio was higher. Mean Vc proved substantially reduced. Placebo did not modify any variable (all p=ns) while N improved DLco and Vc significantly (+8.5%, $p<0.04$ and +17.7%, $p<0.003$, respectively). eNO also was significantly increased (+17.6%, $p<0.002$). Only N lowered the dyspnoea score (-76%, $p<0.001$). Systolic and diastolic BAP were slightly lowered (-7.5%, $p<0.02$ and -5.1%, $p<0.04$, respectively), together with HF (-16.8%, $p<0.03$).

Conclusions: The simultaneous assessment of DL_{NO}, DL_{CO}, DL_{NO}/DL_{CO} ratio, and Vc confirmed that long-lasting dyspnoea is related to hidden abnormalities in the lung capillary vasculature. These abnormalities can persist even after the complete resolution of parenchymal lesions regardless of the normality of lung volumes. Nebivolol, but not placebo, improves DS and Vc significantly. The mechanism suggested is the NO-mediated vasodilation *via* the β3 adrenoceptor stimulation of endothelial NO synthase. This hypothesis is supported by the substantial increase of eNO only assessed after nebivolol. As the nebivolol tolerability in these post-COVID normotensive patients was very good, the therapeutic use of nebivolol against residual and symptomatic signs of long-COVID can be suggested in out-patients.

Key words: Nebivolol; COVID-19; vascular effects; lung perfusion; capillary blood volume (Vc); simultaneous DL_{CO} and DL_{NO} assessment.

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Conflict of interest: All authors declare no conflict of interest. RWD is Associate Editor of *Multidisciplinary Respiratory Medicine.*

Ethics approval and consent to participate: The study was approved by the Ethical and Scientific Commission of the National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology during the session held on May 2nd, 2021. At recruitment, all subjects gave their informed consent; their consent for the anonymous use of their own data for research purposes was also included.

Availability of data and materials: The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Introduction

The clinical impact of SARS-CoV-2 infection widely ranges from mild involvement of upper airways to severe interstitial pneumonia and hypoxemic respiratory failure, not infrequently fatal [1-7]. The crucial pathogenetic events occurring in the lung are high local concentration of cytokines, chemokines and IgM-mediated immunocomplexes that induce a tremendous recruitment of inflammatory cells [2,8-9]; diffuse damage at alveolar level [10]; microvascular thrombosis and capillary occlusion at variable extent [11-13]; activation of platelets and tissue factors further causing coagulation and micro-thrombosis [2].

Though variably mixed and mostly occurring in the acute phase of pulmonary infection, these tissular changes can partially persist over of the following healing and recovering phase, and can contribute to substantial alterations in alveolar-blood gas exchange, being dyspnoea the mayor clinical sign reported [14]. Dyspnoea is in fact complained by a considerable proportion of patients for several weeks after their ‘’apparent recovery” from COVID-19 pneumonia. Unfortunately, though dyspnoea can affect daily activities persistently in these subjects, its underlying causes still are poorly investigated in clinical practice [15]. Usually, in clinics, after the exclusion of any cardiac or psychologic cause (the two causes most frequently suggested), respiratory investigations are mostly limited to the assessment of spirometrical lung volumes and of diffusing capacity for carbon monoxide (DL_{CO}) in a smaller proportion of cases [16-19].

However, lung volumes are of limited value in the majority of cases, while the current assessment of DL_{CO} is unable to discriminate abnormalities occurring at the alveolar level (i.e., the membrane diffusing conductance - DM) from those attaining the vascular side of the blood gas exchange (i.e., such as the pulmonary capillary blood volume - Vc) [20-23]. In fact, due to the much faster binding of NO with intracapillary haemoglobin (Hb), also the assessment of diffusing capacity for carbon monoxide (DL_{NO}) was recommended in these cases [24-26] even in patients with minimal or no abnormalities in their chest computed tomography (CT) [23]. Recently, the simultaneous assessment of DL_{CO} and DL_{NO} proved suitable and reliable for investigating the underlying causes of long-lasting dyspnoea in out-patients defined “recovered” from COVID-19 pneumonia, being the reduction of capillary blood flow assessed in these cases strictly related to their dyspnoea score (DS), regardless of their normal lung volumes [27].

Unfortunately, once these abnormalities documented, specific therapeutic options are still missing to date in these cases. Currently, inhaled NO supplementation is only used in hospital setting in the aim to induce a strong vasodilation at pulmonary level in most severe cases of respiratory failure [28-29]. Nebivolol is the only selective β_1 adrenoceptor antagonist capable of inducing nitric oxide-mediated vasodilation by stimulating endothelial nitric oxide synthase *via* β_3 agonism [30-33].

The aim of the present study was to investigate *vs* placebo the effect of nebivolol *vs* placebo in affecting the long-lasting pulmonary blood volume reduction assessed in patients “radiologically recovered” from COVID-19 pneumonia, but still complaining dyspnoea for several weeks.

Methods

Out-patients aged ≥18 years previously defined “recovered” for COVID-19 pneumonia, but still complaining dyspnoea for 12-16 weeks after discharge were investigated between 1st September 2021 and 15th March 2022, after their informed consent. All patients suffered from COVID pneumonia originally affecting ≥50% of their lung volume (CT documented) and during their hospitalization they received high flow oxygen. At recruitment, patients had to provide a CT scan performed in the previous two weeks and showing the absence of any residual COVID-related parenchymal lesions.

Exclusion criteria were the refusal of the informed consent; subjects aged <18 years; current and former-smokers; subjects with main comorbidities affecting lung diffusion (i.e., blood Hb <12 g/L; heart failure; lung fibrosis; vasculitis; COPD; diabetes; renal and liver failure); persisting COVID-related parenchymal lesions; physical and/or cognitive limitations enabling lung function measurements and other procedures of the study.

Clinical and lung function variables collected in each patient before and after both treatments were:

- age (in years);
- gender;
- BMI;
- Hb (blood haemoglobin, in g/L);
- SpO_2 (O_2 saturation, in %);
- VC (vital capacity) and FEV_1 (forced expiratory volume in 1 sec); both reported as % predicted);
- DL_{CO} (diffusing capacity for carbon oxide; in % predicted);
- DL_{NO} (diffusion capacity for nitric oxide; in % predicted);
- DL_{NO}/DL_{CO} ratio (in % predicted);
- Vc (capillary blood volume; in % predicted);
- eNO (exhaled NO, in ppm);
- DS (dyspnoea score);
- dyspnoea duration after discharge (in weeks)
- systolic blood pressure (S-BP, in mmHg)
- diastolic blood pressure (D-BP, in mmHg)
- heart frequency (HF, in beats/min)

A Platinum DX Elite Plethysmography (MedGraphics, Saint Paul, MN, USA) was used for assessing spirometrical volumes. DL_{CO}, DL_{NO}, DL_{NO}/DL_{CO}, Vc, and eNO were obtained by means of the “Stand-Alone” Hypair Compact System (MGC Diagnostics International, Sorinnes, Belgium). This equipment consents the simultaneous assessment of DL_{CO} and DL_{NO} during the usual single breath manoeuvres [26,34]. According to standard procedures, measure of DL_{CO} and DL_{NO} required breath-hold times of 10 and 5 sec, respectively [20-23,27].

The dyspnoea duration after discharge was measured in weeks. Current dyspnoea was graded in each patient by means of the modified British Medical Research Council (mMRC) dyspnoea score [35].

Study design

This was a double-blind cross-over study. All lung function parameters, together with the DS, HF, S-BP, D-BP were collected before and after nebivolol 2.5 mg od, and before and after undistinguishable placebo, both randomly administered for one week, with a two-week interval in between.

Statistics

Continuous data were presented as means and standard deviation (SD), while gender as absolute frequency. Differences in all variables were tested by *t*-test for continuous data and $p<0.05$ was accepted for statistical significance.

All statistical calculations were carried out by means of STATA (StataCorp. 2017. Stata Statistical Software: Release 15. StataCorp LLC., College Station, TX, USA), $p<0.05$ was assumed as the limit of statistical significance.

Ethics statement

At recruitment, all subjects gave their informed consent; their consent for the anonymous use of their own data for research pur-

poses was also included. The study was approved by the Ethical and Scientific Commission of the National Centre for Respiratory Pharmacoeconomics and Pharmacoepidemiology during the session held on May 2nd, 2021.

Results

A total of eight out-patients were investigated. No significant comorbidities were recorded. Patients' general characteristics assessed in baseline are reported in Table 1 together with mean values for their blood Hb, lung volumes, S-BP, D-BP and HF. Mean dyspnoea duration and mean current DS score are also reported in the same table. In baseline, all parameters were in their normal range, except HF that was high when compared to usual resting conditions. All patients were showing a higher DS that despite the absolute normality of their lung volumes.

DL_{CO} and DL_{NO} mean values were lower than predicted in baseline, while mean DL_{NO}/DL_{CO} ratio was slightly higher. Mean Vc proved highly lowered than predicted, while the mean eNO value was at the lower limit of the normal range.

Table 2 reports mean values ± SD for each variable of lung diffusion measured before and after placebo (P), and before and after nebivolol (N), together with the corresponding statistical comparisons and significancy. N, but not P, improved significantly DL_{CO} by 8.5 ($p<0.04$) and and Vc by 17.7% ($p<0.003$), respectively, while the DL_{NO}/DL_{CO} ratio was lowered even if the variation did not reach the statistical significancy. To emphasize that eNO was significantly increased by 17.6% ($p<0.002$), thus confirming the ability of N to increase the NO expression at pulmonary vascular level in these cases.

Changes observed in DS, S-BP, D-BP, and HF with both treatments are reported in Table 3. Only N minimized DS by 76% from the corresponding mean basal value ($p<0.001$), while P was completely ineffective from this point of view (p=ns).

Finally, S-BP and D-BP were significantly lowered only after N by 7.5% ($p<0.02$) and 5.1% ($p<0.04$), respectively, while mean HF was lowered by 16.8% ($p<0.03$). Mean changes obtained in S-BP and D-BPs were mild, while those in HF were more pronounced. However, these changes, likely also related to the nebivolol β_1 adrenoceptor antagonism, had been perfectly tolerated by all patients.

Discussion

Further to alveolar damage, pulmonary microvascular thrombosis and occlusions (such as: lesions to the capillary endothelium; angiogenesis within the inter-alveolar septa; capillary microthrombi) represent the main pathogenetic events complicating the SARS-CoV-2 infection at variable extent and duration.

These events can lead to reduction of Vc in the lung [2,10-13] and frequently contribute to the occurrence of persisting alterations

Table 1. General characteristics of the sample at recruitment. Data are reported as means ± SD while comorbidities as relative frequency.

n	8
Males/females	3/5
Age (y)	50.5 ± 17.2
BMI	24.4 ± 2.8
Hb (g/L)	13.9±0.4
SpO_2 (%)	96.8±1.1
VC (% pred.)	95.7±11.1
FEV_1 (% pred.	93.2±10.6
Systolic BAP (mmHg)	132.3±4.6
Diastolic BAP (mmHg)	77.3±3.4
HF (b/min)	96.4±8.1
Dyspnoea duration after hospital discharge (weeks)	13.2±2.7
Dyspnoea score	2.5±0.6
DL_{CO} (% pred.)	72.1±14.7
DL_{NO} (% pred.)	73.1±15.5
DL_{NO}/DL_{CO} (% pred.)	121.6±3.6
Vc (% pred.)	45.0±7.9
eNO (ppm)	5.2±0.6

Table 2. Mean values ± SD for each variable of lung diffusion measured before and after placebo (P), and before and after nebivolol (N), with corresponding significance of statistical comparisons.

	Pre-P	Post-P	p	Pre-N	Post-N	p
DL_{CO} (% pred.)	72.1±14.7	72.5±17.0	ns	70.9±13.7	76.0±14.5	0.04
DL_{NO} (% pred.)	73.1±15.5	73.4±13.5	ns	74.2±15.5	73.2±14.8	0.75
DL_{NO}/DL_{CO} (% pred.)	121.6±3.6	123.2±4.5	ns	120.6±7.8	117.5±6.3	0.31
Vc (% pred.)	45.0±7.9	44.4±8.7	ns	44.1±8.6	51.9±9.0	0.003
eNO (ppm)	5.2±0.6	5.0±0.5	ns	5.1±0.6	6.0±0.9	0.002

Table 3. Mean values ± SD for dyspnoea score, systolic BAP, diastolic BAP and HF measured before and after placebo (P), and before and after nebivolol (N), with corresponding significance of statistical comparisons.

	Pre-P	Post-P	p	Pre-N	Post-N	p
Dyspnoea score	2.5±0.6	2.6±0.4	ns	2.5±0.8	0.6±0.3	0.001
Systolic BAP (mmHg)	132.3±4.6	134.3±5.4	ns	134.6±5.2	124.2±6.7	0.02
Diastolic BAP (mmHg)	77.3±3.4	78.4±4.1	ns	78.6±3.9	74.7±3.0	0.04
HF (b/min)	96.4±8.1	97.1±9.2	ns	95.7±7.7	78.6±8.9	0.03

in alveolar-blood gas exchange [14] and dyspnoea, both long-lasting even beyond the healing and recovering phase of COVID-19 pneumonia.

From a general point of view, two are the critical issues in these cases: first, the assessment of these disorders, and second, their therapeutic approach. Their assessment is difficult indeed in clinical practice due to technological and methodological limits. Spirometrical measurements (such as: lung volumes) are unable to identify these disorders while the sole measure of DL_{CO} is insufficient to recognize these abnormalities specifically [16-23]. As mentioned above, also the DL_{NO} assessment is recommended in these cases [23-26]. Unfortunately, specific dedicated technologies are not currently available in clinical practice and require high specialist skills, longer time and higher costs.

The recent technological opportunity that allows the simultaneous assessment of DL_{CO} and DL_{NO} represents a novel, easier, and reliable methodological approach for measuring and discriminating the damage occurred at the alveolar level from disorders occurred at the vascular side of the alveolar membrane, included the quantification of the pulmonary capillary blood volume [24-26]. This method proved particularly suitable for investigating also in clinical practice the hidden alveolar and capillary damage due to COVID-19 pneumonia together with the so-called "unexplained" causes of long-lasting dyspnoea, such as the mayor symptom complained by these patients [15,27]. This method was adopted in a recent study aimed to investigate from this point of view a selected sample of patients defined "radiologically recovered" from COVID-19 pneumonia and with no residual CT pulmonary abnormalities even if still complaining significant dyspnoea and tachycardia for more than 12 weeks from their hospital discharge. Regardless of their normal lung volumes, a substantial reduction of pulmonary capillary blood volume was documented in these cases, this limitation resulting strictly related to the current patients' DS [27].

As mentioned above, once identified the hidden damage, a further crucial point is to be faced: such as, the problem of the therapeutic approach aimed to improving the pulmonary capillary blood volume and the persistent dyspnoea in these cases. At present, specific pharmacologic opportunities are practically missing for outpatients as NO supplementation via inhalation is in fact only limited to most severe cases of respiratory failure to be managed in hospital setting and aimed to stimulate a strong vasodilation at pulmonary level both in adults and in children [28,29].

However, the increasing awareness of the essential role of NO in different physiological processes stimulated multiple pharmacological strategies for different diseases [36-39]. Further to old NO donors (such as sodium nitroprusside, nitroglycerin and isosorbide dinitrate), new molecules were developed in the last decades, in particular newer vasodilating β-blockers that increase NO bioavailability substantially [40,41]. Moreover, the interest on NO pulmonary effects was further expanded due to the NO ability to attenuate the effects of the platelet activating factor, that is a further pathogenetic determinant of capillary obstruction [29], particularly in COVID patients [2].

The original hypothesis of the present study was the assumption that nebivolol, due to its peculiar mechanism of action, would provide an interesting opportunity for intervention against the COVID-induced alterations of lung capillary bed and related persisting dyspnoea, otherwise therapeutically "orphan". On the other hand, nebivolol is the only selective β_1 adrenoceptor antagonist that is capable to induce nitric oxide-mediated vasodilation by stimulating endothelial nitric oxide synthase *via* β_3 agonism [30-33] and endothelium-dependent vasodilation mediated *via* the L-arginine/NO pathway [41,42]. The vasodilatory mechanism of action strongly differentiates nebivolol from all other vasodilatory β-blockers (such as labetalol and carvedilol) that act via α1-receptor antagonism [32,33].

It was also documented that nebivolol is capable to provide anti-thrombotic, anti-platelet and anti-aggregation activity associated to its enhanced NO bioactivity [43]. In particular, while endothelial-derived NO acts as a major vasodilator, cyclic guanosine monophosphate (cGMP) and protein kinase (PKG), that are its downstream effectors, are also provided with peculiar vasodilatative, anti-proliferative, anti-coagulant, and anti-inflammatory effects on pulmonary vasculature [44].

Data from the present study showed for the first time at our best knowledge that nebivolol, but not placebo, affects the hidden abnormalities in pulmonary capillary vasculature induced by COVID-19 pneumonia substantially and significantly. In other words, nebivolol proved effective in increasing the patients' pulmonary capillary blood volume persistently reduced by COVID-19 infection. This therapeutic effect, assessed experimentally after a low dose (2.5 mg od) administered for a short period (one week) empirically decided, is supported by the basic pharmacology of nebivolol and confirms the original hypothesis of the study. In particular, the significant increase of the exhaled NO release at pulmonary level (eNO) assessed after nebivolol further confirms the therapeutic mechanism of action of this molecule at pulmonary level. On the other hand, it was showed that β_3-adrenergic receptor agonists produce a significant reduction in pulmonary vascular resistance in experimental studies on pulmonary hypertension (PH), thus emerging as an innovative potential approach for managing PH patients [45].

Moreover, it should be emphasized that the efficacy of nebivolol on pulmonary capillary blood volume proved strictly correlated to the drop in patients' dyspnoea score. This outcome further confirms the relationship existing between the documented pulmonary capillary alterations and the persistence of dyspnoea, even in the absence of lung volume limitations in this kind of patients.

The present study has some limitations: i) the small sample of patients investigated; ii) the dose of nebivolol and the duration of treatment, both empirically decided; iii) the lack of a documented dose-dependent effect of nebivolol.

Point of strengths are: i) the strict selection of patients investigated aimed to avoid any clinical confounding factor; ii) the adoption of the simultaneous assessment of DL_{CO} and DL_{NO} that presently represents the most appropriate method for assessing and discriminating the pathologic damage occurring at the alveolar and at the vascular pulmonary level; iii) the very first application of this investigational method in clinical pharmacology; iv) the excellent correspondence between the pharmacology of nebivolol and results obtained.

Conclusions

Patients "radiologically recovered" from COVID-19-induced pneumonia can be frequently characterized by persistent reduction of pulmonary capillary blood volume and long-lasting dyspnoea as the major clinical sign. To note that these abnormalities would be unexplained and neglected in clinical practice unless investigated by means of a proper methodological approach, such as the simultaneous assessment of both the DL_{CO} and DL_{NO}.

Due to its peculiar mechanism of action, nebivolol 2.5 mg od proved effective in increasing pulmonary capillary blood volume and the corresponding dyspnoea substantially, both persisting for several weeks after hospital discharge in patients previously

defined ''recovered'' from COVID-19 pneumonia. Nebivolol seems to provide a novel and effective option against these pulmonary abnormalities in clinical practice, even if still off-label. Finally, nebivolol was well tolerated in all patients investigated though normo-tensive.

The multifaceted pharmacological action of nebivolol (such as, the vasodilatative, anti-coagulant, anti-inflammatory and antioxidant activities) are regarded as likely contributing to minimize the abnormalities in lung capillary volume that can frequently persist in out-patients after COVID-19 pneumonia.

Further studies are needed for confirming the present pivotal results.

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Review

Physical exercise in asthma adolescents: a concept review

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ABSTRACT

Background: Asthma is a frequent pathological condition during childhood and adolescence. Young asthmatics demonstrate decreased aptitude for physical activity and a limited exercise capacity. Lower hospitalisation rates, reduced school absenteeism, fewer medical examinations, and limited use of bronchodilators have been documented in children and adolescents with bronchial asthma who engage in physical exercise regularly. Structured physical exercise protocols should be encouraged as they can work as a synergistic therapeutic option in addition to regular pharmacologic treatment. This article outlines the most suitable exercise training techniques for young patients with bronchial asthma and their effects on health status.

Key words: childhood asthma; asthma in adolescence; physical exercise.

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Introduction

Physical activity is a physiological need for the human body. This crucial assumption is frequently neglected in the current lifestyle, particularly in children and teenagers with bronchial asthma. Bronchial asthma is a heterogeneous chronic inflammatory disease of the airways which is characterised by variable airflow limitation, wheezing, dyspnoea, sensation of chest tightness, and cough. These symptoms occur more frequently at night or early in the morning. The manifestation of these symptoms which are often reversible and can be due to several "triggers" [1] may vary in severity. Physical exercise is one of the most frequent triggers faced by young asthmatics and can contribute to progressive deconditioning and reduction of cardiorespiratory capacity. In other words, a vicious circle can be established: the occurrence of asthma symptoms leads to a reduction in physical activity and deconditioning. These factors may cause a progressive increase in asthma symptoms triggered by even lower physical efforts [2,3]. Furthermore, the limitation in sports activity significantly worsens the quality of life in young asthmatics. This is due to the reduction in muscular tone, sleep quality, cognition, and school performance. Emotional problems, such as frustration, sadness, anger, fear, shame, and difficulties in relational life are also frequent consequences [4]. Moreover, parents' fear that exercise might aggravate asthma symptoms or trigger a respiratory crisis frequently discourages many young asthmatics from exercising regularly or playing sport [3,5].

Despite the lack of specific guidelines, the current literature strongly recommends that asthmatic patients should practice regular physical activity because this improves wellness and reduces the incidence of exacerbations in young asthmatics. It has been demonstrated that exercise performed under medical supervision should be considered a highly valuable adjunct therapy in asthma treatment. Furthermore, regular physical activity is associated with a reduction in corticosteroid assumption [6,7]. Aerobic exercise improves cardiopulmonary health in asthmatics and has a positive effect on bronchial hyperreactivity and inflammation. Regular practice of aerobic activity since childhood or adolescence improves pulmonary development and causes a minor loss in lung function in adulthood [8,9].

Considering the data presented thus far, a rather important question arises: is regular daily physical activity enough to obtain specific benefits in health status?

The answer may be deduced by exploring the distinction between physical activity and exercise [10]:

- **Physical activity** is defined as any body movement produced by skeletal muscles that requires energy waste (World Health Organization -WHO) [11]. To obtain healthy benefits, it is necessary to practise aerobic physical activities at a moderate intensity for at least 150 min per week or, at least, 75 min per week at high intensity or an equivalent combination of both. Therefore, the most common daily activities such as walking at a leisurely pace, doing household chores, *etc*. are 'light intensity' physical activities which, although preferable to a total sedentary lifestyle, do not reach the threshold level of intensity of effort which correlates positively with healthy benefits. Therefore, physical activity does not qualify as rehabilitative therapy and should not be considered a specific "healthy" practice. However, it is an integral part of the activities that have an impact on health, and that's why it should be encouraged in the context of the promotion of a healthy lifestyle.
- **Exercise**, on the other hand, is a subset of physical activities, in which the exercises are well-defined through four parameters: quantity, duration, intensity, and frequency of repetition [10]. It is a type of physical activity which is planned, personalised and, therefore, structured to obtain specific outcomes for healthy purposes. Examples of physical exercise are personalised activity programs for rehabilitative or preventive purposes. In the context of chronic illnesses such as bronchial asthma physical exercise is effective in improving health status and it can be considered therapeutic exercise or "the drug of movement" [12]. Exercise is considered a healthy intervention which contributes, together with pharmacological therapy, to the prevention of exacerbations and to the maintenance of optimal health status in asthmatic patients [13]. However, physical exercise is rarely compared to pharmacological treatment. This is due to several reasons: i) insufficient awareness of the effectiveness of exercise practice on behalf of doctors and patients; ii) insufficient knowledge of the effect of exercise-based treatment on asthma; iii) lack of adequate doctors' theoretical and practical training; iv) inadequate description of exercise-based treatments in clinical trials and published reviews [14,15].

More deep and widespread knowledge of the preventive and therapeutic role of physical exercise should be encouraged as it would represent another effective medium and long-term option for young asthmatics. As it is directed to the prevention of exacerbations and delaying asthmatic evolution, it would be synergistic with the appropriate pharmacological treatment. However, it should be underlined that the simple prescription of "physical exercise", without any further detail, is an absolutely insufficient indication and it is useless for the achievement of specific outcomes in young asthmatics [16].

Although contraindications to prescribing physical exercise are limited in patients with bronchial asthma, an adequate assessment of clinical conditions and of lung function should be carried out before starting any exercise program. Furthermore, it is always recommended to dedicate some time to inform patients and his/her parents about the components and the steps of the exercise program, besides the potential benefits. It is also important to listen to the patient's concerns and preferences in order to implement strategies that would increase long-term adherence to treatments and outcomes. Finally, it is fundamental to agree with the patient and/or with the patient's parents on the most personalised therapeutic program that is considered the most adequate to his/her cognitive, cultural, socio-economic, and environmental characteristics [12,17].

Can exercise stop asthma symptoms?

Though asthma inflames the airways, regular exercise can actually decrease inflammation. Some types of exercise can reduce or prevent asthma symptoms. They work by making the lungs stronger without worsening inflammation. Specifically, these activities minimize symptoms because they:

- **Increase endurance.** Over time, working out can help the airways build up tolerance to exercise. This makes it easier for the lungs to perform activities that usually make the subject winded, like walking upstairs [19].
- **Reduce inflammation.** Though asthma inflames the airways, regular exercise can actually decrease inflammation. It works by reducing inflammatory proteins, which improves how airways respond to exercise [20].
- **Improve lung capacity.** The more the subject works out, the more the lungs will get used to optimally utilise oxygen. This decreases the effort exerted in breathing on a daily basis [18,21].

- **Strengthen muscle.** When his muscles are strong, the body functions work more efficiently during everyday activities [22].
- **Improve cardiovascular fitness.** Exercise improves the overall conditioning of the heart, improving blood flow and the delivery of oxygen [23].

In addition to physical activity, breathing exercises can also reduce asthma symptoms. These methods help by opening the airways, moving fresh air into the lungs, and reducing the effort required for breathing.

Examples of breathing exercises for asthma include:
- diaphragmatic breathing
- nasal breathing
- pursed lip breathing

However, it's still important to take pharmacological medications as directed. This is the best way to control asthma symptoms, especially during exercise [22].

The physical exercise program: from processing to performance

Although there are no specific evidence-based guidelines for physical exercise in young patients with bronchial asthma, structured protocols are available for adapted physical activity. Some systematic reviews and meta-analyses suggest that an exercise program that increases significantly in asthma-free days, improves aerobic capacity, maximum muscle work capacity, exercise tolerance, and lung minute ventilation [24].

A single Cochrane review [25] concerning the role of exercise training in asthmatic patients is available. All the studies included in this review suggest that exercise improves asthma-related symptoms and cardiopulmonary wellness [22]. Other studies demonstrate that the increase in physical activity obtained by exercise training leads to the reduction of ventilatory requirements induced by mild-to-moderate exercise, thus reducing the likelihood of exercise-induced asthma [7]. Moreover, a 12-week aerobic training programme demonstrated significant reductions in bronchial hyperresponsiveness and serum pro-inflammatory cytokines that were associated with an improvement in the quality of life (QoL) questionnaire and with a reduction of asthma exacerbations in patients with moderate-to-severe persistent asthma [20].

The mechanisms by which a physical exercise program would be of therapeutic value in young patients suffering from bronchial asthma are reported below [4,23].

- The improvement in lung function with a consequent reduction of dyspnoea;
- The stimulation of the immune system, which in turn reduces the vulnerability to colds or other respiratory infections that are known to be asthma triggers.
- An increase in the levels of endorphins, thus contributing to improving mood, reducing stress, and containing depressive and/or anxious state.
- It contrasts a sedentary lifestyle and unhealthy weight, often related to poor asthma control (Table 1).

The personalised training session

The treatment based on therapeutic physical exercise protocols adapted to young patients suffering from bronchial asthma stems from aerobic exercises, intended to: i) improve the degree of tolerance to a continuous effort – that is similar to daily activities; ii) improve joint mobility, in particular of the shoulder girdle, humeral and rib cage; iii) increase muscular resistance by means of exercises affecting muscle strength, and muscle relaxation. It is possible to start with 10-15 min of specific or variable intensity warm-up, in order to induce a "refractory period" during which the occurrence of exercise-induced bronchoconstriction is limited [21,26]. The principles of prescribing physical exercise in young asthmatics are based on: frequency (how often); intensity (how demanding); time (how long); type (mode); total volume (total quantity); progression (the way you grow): the combination of these parameters defines the principle of exercise prescription (FITT-VP) [27] (Table 2).

Table 1. Steps of a physical exercise intervention.

Evaluate
- Analysis of reports and collection of information on the health status
- Assessment of motor skills through entrance tests
Establish
- The short- and long-term goals
Decide
- The most suitable exercise program

Table 2. Recommendations of the FITT model for subjects with asthma.

	Aerobic exercises	Resistance exercises	Flexibility exercises
Frequency	3-5 days/week	2-3 days/week	>2-3 days/week, more effective if daily
Intensity	Start with moderate intensity (40-59% of FRC or of Vo2 R). If well tolerated, increase after one month to 60-70% of FRC or of Vo2 R	Force: 60-70% of 1RM for those who start exercising with weights; 80% for those who have been doing it for some time. Resistance: <50% of 1 RM.	To the point of a feeling tightness or mild discomfort
Duration	Gradually increase up to at least 40 min per day	Strength: 2-4 series, 8-12 repetitions Resistance: <2 series, 15-20 repetitions	10-30 s duration for static stretch; 2-4 repetitions of each exercise
Type	Aerobic activity using the major muscle groups (walking, running, etc.)	Weight-lifting machines, free weights or natural load exercises	Static and dynamic elongation and PNF technique

1RM, maximum single repetition; FCR, reserve heart rate; PNF, proprioceptive neuromuscular facilitation; FITT-VP, frequency-intensity-time-type–Total volume-progression.

Methods of exercise

Aerobic exercises should be first proposed through walking and common specific tools should be used, such as the treadmill, the bike, and the ergometer. The specialist's evaluation of compliance in terms of intensity workload, duration, frequency and type of activity, is crucial. The procedure may initially provide a constant load intensity, which can be gradually increased, at such point, the interval training technique might also be used (Figure 1).

Joint mobility exercises can be performed with a stick or with graduated elastic bands which are important for maintaining the correct posture and for performing thoracic respiratory dynamics more efficiently, as well as avoiding any damage and joint stiffness. Dynamic and isometric free body resistance exercises can be performed by means of dumbbells, medicine balls, and graduated elastic bands, in order to improve the tone and muscular trophism of the limbs. Exercises for specific muscle districts and general movements that simulate daily activities can be performed in order to improve muscle strength. Stretching exercises are also useful for maintaining a correct posture, avoiding the condition of muscle hypertonia, reducing anxiety, and promoting breathing [22,29].

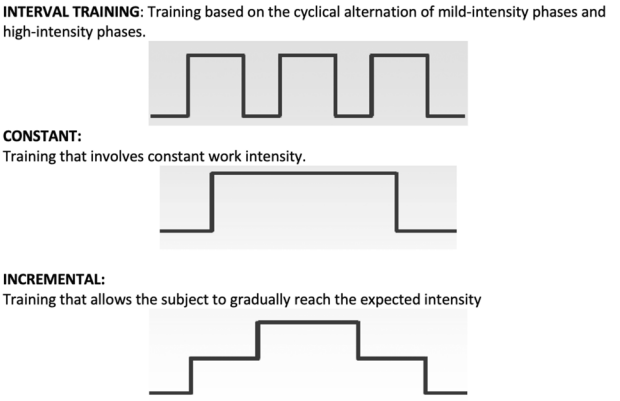

Figure 1. The training mode.

Posture and balance

- Exercises oriented to maintain posture should be of progressive difficulty. For example, attempting to shift from the bipodalic support with semi-spread legs to the bipodalic support with the feet aligned one in front of the other, to the monopodalic support.
- Make movements that "stimulate" the centre of gravity. For example, by walking in a straight or circular line.
- Stress the postural muscles. For example, by walking on the forefoot, or on the heels.
- Reduce the sensory information that controls balance. For example, walking with eyes closed attempting to maintain one's equilibrium, thus eliminating visual interference [29] (Figures 2 and 3).

Figure 2. Correct posture in children.

Breathing exercises

Breathing exercises are also widely used in clinical practice as part of asthma management in children and adolescents. However, it is quite difficult to quantify its effect in this population because in the available studies, these techniques were never used alone but in conjunction with other exercise types. Inspiratory muscle training (IMT) seems to improve inspiratory and expiratory muscle strength, but its utilisation in the paediatric population is not a standard procedure. It has been shown that IMT in children with asthma can improve the strength of inspiratory and expiratory muscle, even if the clinical improvement post-treatment is still uncertain given the lack of specific literature about this intervention in paediatric populations [30]. Finally, in adolescents with bronchial asthma education in terms of correct breathing is essential for optimising respiratory dynamics. From this point of view, it is necessary to pay attention to the coordination between inhalation and exhalation manoeuvres, also using semi-closed labial breathing and thoracic and diaphragmatic breathing techniques in order to increase ventilation and to achieve a correct automatism of in- and expiratory muscles. In our experience, the value of respiratory training is mirrored by a better perception of the respiratory effort, a lower degree of dyspnoea, a more efficient voluntary management of breathing during exercise and during asthma attacks, and a lower degree of anxiety.

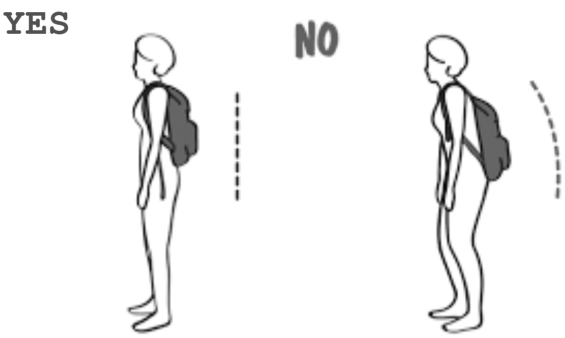

Figure 3. When carrying a backpack, it is important to keep it on both shoulders in order to balance the load.

Techniques to reduce exercise-induced asthma

Exercise-induced asthma (EIA) usually occurs within the first 5 to 10 min of physical exercise and is more likely to occur during or after regular-paced activities in cold, dry air [15,31]. Therefore, some general and practical tips have been proposed intended to reduce EIA impact in young individuals that are summarised hereafter:

- warm-up and cool-down before and after exercise.
- choose activities that do not require exposure to cold, dry air.
- participate in activities with short bursts of exercise (such as tennis and football) rather than exercises involving long-duration pacing (such as cycling, soccer, and distance running).
- breathe through a scarf or through the nose. This helps warm up the airways when exercising in cold air.
- use any prescribed medications as directed.

Conclusions

Asthma is a frequent pathological condition during childhood and adolescence that affects up to 25% of children in Western urban environments. It is a widespread perception that young asthmatics have a reduced aptitude to physical activity and a limited exercise capacity. Although there is no definitive evidence in the literature, lower hospitalisation rates, lower school absenteeism, a reduced need for medical examinations, and reduced use of bronchodilators have been reported in asthmatic children and adolescents who are regularly practising physical exercise regardless of the pharmacological therapy used. Comparative and controlled research in physical exercise should be reinforced and should encourage the adoption of physical exercise protocols in young asthmatics. This is a valuable therapeutic option that is synergic with the effects of regular pharmacological treatment.

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CASE REPORT

Germline variant of *CTC1* gene in a patient with pulmonary fibrosis and myelodysplastic syndrome

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ABSTRACT

Introduction: Telomeropathies are associated with a wide range of diseases and less common combinations of various pulmonary and extrapulmonary disorders.
Case presentation: In proband with high-risk myelodysplastic syndrome and interstitial pulmonary fibrosis, whole exome sequencing revealed a germline heterozygous variant of *CTC1* gene (c.1360delG). This "frameshift" variant results in a premature stop codon and is classified as likely pathogenic/pathogenic. So far, this gene variant has been described in a heterozygous state in adult patients with hematological diseases such as idiopathic aplastic anemia or paroxysmal nocturnal hemoglobinuria, but also in interstitial pulmonary fibrosis. Described *CTC1* gene variant affects telomere length and leads to telomeropathies.
Conclusions: In our case report, we describe a rare case of coincidence of pulmonary fibrosis and hematological malignancy caused by a germline gene mutation in *CTC1*. Lung diseases and hematologic malignancies associated with short telomeres do not respond well to standard treatment.

Key words: *CTC1* gene; interstitial pulmonary fibrosis; myelodysplastic syndrome.

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Contributions: MD, MiD, designed the study, analyzed and interpreted the data, and wrote the manuscript; ZV, SK, IB, SP, performed the genetic analysis; LČ, collected patient's data. All the authors read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

Ethics approval and consent to participate: No ethical committee approval was required for this case report by the Department, because this article does not contain any studies with human participants or animals. Written informed consent was obtained from the patient who was enrolled in accordance with the Helsinki Declaration.

Introduction

Human telomeres consist of long TTAGGG sequence repeats that are bound and stabilized by two nucleoprotein complexes required for the protection and replication of chromosome ends [1]. A protein complex "shelterin" is comprised of six telomere-specific proteins (TRF1, TRF2, POT1, Rap1, TIN2 and TPP1), and a heterotrimeric "CST" complex is composed of the proteins Ctc1, Ten1 and Stn1 involved in telomere maintenance [2,3]. Genomic alterations in these proteins are causative of a number of disorders known as telomeropathies. Telomeropathies are closely associated with premature aging and a reduction of cell ability to cope with recurrent damage. Several pulmonary, hematological, or liver diseases are associated with telomeropathies. These diseases include pulmonary fibrosis as idiopathic pulmonary fibrosis (IPF) and myelodysplastic syndrome (MDS).

IPF manifests as bibasilar reticular abnormalities, bronchiectasis, honeycombing on high-resolution computed tomography, restrictive pulmonary function impairment, and decreased lung diffusion capacity for carbon monoxide. IPF is idiopathic interstitial pneumonia characterized by progressive fibrotic damage of lung parenchyma. MDS is a clonal hematopoietic tissue disorder manifesting as morphologic dysplasia in myeloid lineage and peripheral cytopenia [4].

Case report

A 69-year-old Caucasian male, a non-smoker, presented with a mild dry cough and mild shortness of breath after exercises. He was sent for suspected interstitial pulmonary fibrosis. The patient's family history was negative regarding pulmonary and malignant diseases. Until then he was only treated for hypertension. The patient was an old-age pensioner. He worked as an engineer (dust-free office work). Clinical assessment (including screening questionnaire, antibodies against specific antigens) was performed in order to exclude hypersensitivity pneumonitis or autoimmune disease. No exposure was found to cause exogenous allergic alveolitis. No causative antigens were found.

Physical examination revealed clubbing fingers and bilateral end-inspiratory crackles in the lower and middle lung areas. The posteroanterior chest-X ray showed bilateral reticular pulmonary infiltrates (Figure 1). High-resolution computed tomography (HRCT) of lungs identified reticular opacities, bronchiectasis, and honeycombing changes (Figures 2 and 3). Pulmonary function testing revealed no ventilation defect [forced vital capacity (FVC) = 3.54 L, 100% of the predicted value (p.v.); total lung capacity (TLC) = 5.13 L; 82%] and moderate decrease of diffuse lung capacity for carbon monoxide (DLco; 4.23 L; 53%p.v.). Arterial blood gas analysis was also normal. Bronchoscopy with bronchoalveolar lavage showed an increased number of neutrophilic granulocytes and lymphocytes (13%, 74%). Lymphocyte subtypes were investigated: CD3+CD4+ = 69.20%, CD3+CD8+ = 27.00%. The ratio CD4+/CD8+ was 2.5. The neutrophilic and lymphocytic alveolitis was caused by a previous lung infection in a patient immunocompromised by hematological disease. There was no yield of transbronchial lung biopsy. Due to the patient's condition and hematological disease, histological verification by transbronchial cryobiopsy was not indicated.

We considered other interstitial lung diseases (ILDs) including hypersensitivity pneumonitis (HP), but we did not find any exposure in either work or home. The HRCT finding was discussed with the Multidisciplinary Team (MDT). Other ILDs were excluded, autoantibodies were negative, and no exposure leading to hypersensitivity pneumonitis (HP) was found (negative questionnaires, specific IgG were negative). The diagnosis was concluded as usual interstitial pneumonia on HRCT of the thorax with honeycombing at dorsal basal regions. The patient had been treated with corticoids before he was referred to us. Radiological progression of lung fibrosis occurred during treatment. We gradually discontinued corticoids. The duration of this treatment was 6 months. We considered antifibrotic treatment, but we did not administer it, as the patient did not meet the indication criteria for antifibrotic therapy. At the same time, the patient developed thrombocytopenia (77 x 10^9/L) and macrocytic anemia (hemoglobin 108 g/L; mean red cell

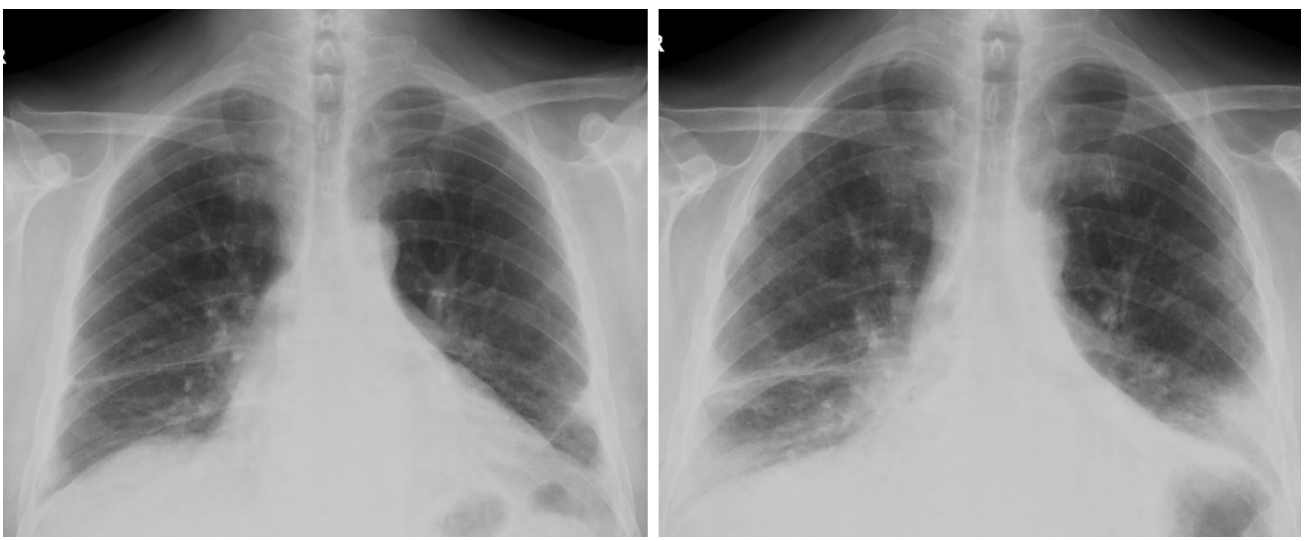

Figure 1. Chest X-ray before (left) and after COVID-19 infection (right). After COVID-19, new areas of bilateral decreased parenchyma transparency and consolidation are found.

volume 111 fL). Furthermore, high-risk MDS with blast excess (EB-2) was diagnosed (11.2% of myeloblasts in the bone marrow; deletion 5q in cytogenetics). Therapy with 5-azacytidine was initiated and the patient received 20 cycles of this treatment. Unfortunately, the patient was only temporarily stabilized by treatment and subsequently progressed into acute myeloid leukemia and died of severe COVID-19 pneumonia with respiratory failure.

Because of suspected inherited predisposition leading to IPF and MDS, genetic testing focused on whole exome sequencing (WES) was performed. The WES variants evaluation process was aimed at the analysis of single nucleotide variants (SNV) and short indels (indel) within virtual genes panel associated with myeloid malignancies and predispositions to both myeloid and pulmonary disorders (Supplementary Table 1). A germline heterozygous variant c.1360delG (NM_025099.5; g.8235132) encoding the p.Glu454Serfs*9 substitution in 8 exons of the *CTC1* gene was identified. The coverage of c.1360delG was 73 and variant allele frequency (VAF) was 47.95% in a patient. The sequencing result is shown in Figure 4. Deleting guanine at position 1360 creates a new reading frame, resulting in a premature stop codon at position 9. Variant c.1360delG is classified as pathogenic/likely pathogenic, according to the consensus guidelines by the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. The presence of variant c.1360delG was verified by Sanger sequencing. Shen *et al*. [5] reported a 31-years-old man with heterozygous c.1360delG variant in *CTC1* which was diagnosed with adult-onset severe idiopathic aplastic anemia (AA) and development of secondary paroxysmal nocturnal hemoglobinuria. In addition, a c.1049delC variant (VAF: 21.21%) in the *RUNX1* gene was identified and classified as a variant with uncertain significance (VUS).

Discussion

Telomeropathies are very heterogeneous diseases. Therefore, patients with the same mutation can present different manifestations. This report describes a rare case of coincidence of pulmonary fibrosis and hematological malignancy caused by a germline gene variant in *CTC1* (CST telomere maintenance complex component [1]. There is no similar case of the coincidence of these two diseases described in the medical literature. We did not find any articles describing the coincidence of the two diseases (aplastic anemia and pulmonary fibrosis).

The *CTC1* gene (OMIM #613129), located on chromosome 17p13.1, encodes a 1,217 amino acids nuclear protein Ctc1 which is a component of the conserved telomere maintenance CST complex along with the Stn1 and Ten1 proteins [3,6,7]. *CTC1* variants alter the function of the CST complex, which may result in the shortening of telomeres and DNA damage responses [8,9]. In that case, telomeres are recognized as damaged DNA that can result in cell-cycle arrest, cell apoptosis, or senescence. The CST complex was initially proposed to play a role in telomere length homeostasis by reducing access of telomerase to telomeres in order to prevent excessive telomere lengthening [10]. Subsequently, the CST complex was shown to promote telomere replication [6]. Therefore, the Ctc1 protein is involved in the maintenance of telomeres. Telomeropathies are very heterogeneous diseases depending on the gene mutated and the specific variants, their penetrance, and the existence of anticipation effects. Therefore, patients with the same variant can present different manifestations. Some patients present severe symptoms early, such as those of dyskeratosis congenita (DC) or the related Hoyeraal-Hreidarsson syndrome, Resvesz syndrome, and Coats plus syndrome. Moreover, diseases associated with telomeropathies may occur at a younger age than usual in sporadic forms: AA median age 20-30 years at diagnosis [11], idiopathic pulmonary fibrosis (IPF) median age 40-60 years at diagnosis [12,13]. A study by Arias-Salgado *et al*. describes genetic analyses of aplastic anemia and idiopathic pulmonary fibrosis patients with short telomeres caused by *CTC1* gene mutation but not as a coin-

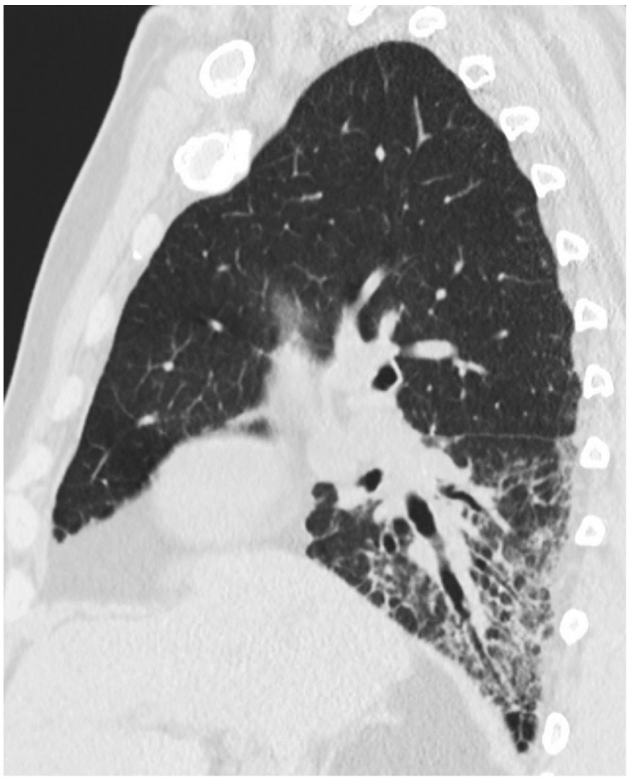

Figure 2. Our patient high-resolution computed tomography (HRCT) at diagnosis. Typical UIP HRCT pattern shown on sagittal view. Honeycombing, reticulation and peripheral bronchiectasis with basal and subpleural predominance are present.

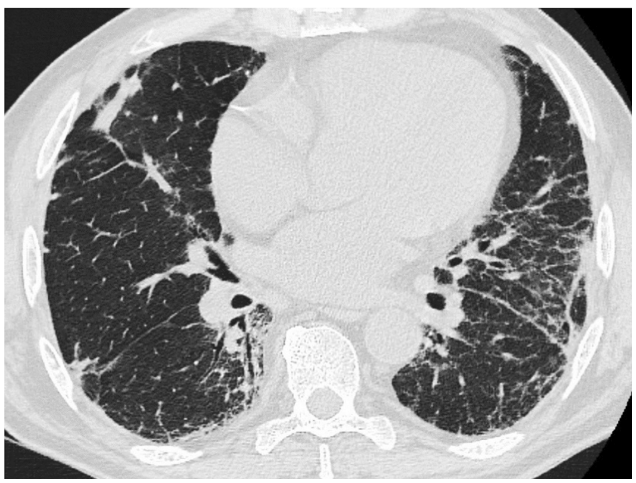

Figure 3. Our patient high-resolution computed tomography (HRCT) at diagnosis. Axial HRCT view through both lungs under tracheal bifurcation. Peripheral bronchiectasis on the right side in the paravertebral location and bilateral reticulation with subpleural predominance are present.

cidence of both diseases, but each disease separately. However, we did not find any articles describing the coincidence of the two diseases (aplastic anemia and pulmonary fibrosis) [13].

There is an increasing number of inherited disorders in which excessive telomere shortening underlies the molecular defect, with dyskeratosis congenita (DC) being the archetypal short telomere syndrome. Excessive telomere shortening can affect almost any organ system, so the clinical manifestations are protean, including developmental delay, cerebellar hypoplasia, exudative retinopathy, AA, acute myeloid leukemia, IPF, idiopathic hepatic cirrhosis, head and neck cancer and dental abnormalities, and may be multisystemic [14]. Unfortunately, there are no "age-specific" telomere length standards, because their length is reflected in an incredible number of individual factors (age is only one of them) [15]. For this reason, it is still difficult to use telomere length for routine diagnosis. Diseases and conditions associated with pathogenic variants of *CTC1* include cerebroretinal microangiopathy with calcifications and cysts (CRMCC) and DC. The majority of *CTC1* pathogenic variants found in either CRMCC or DC are compound heterozygotes of a missense variant and a truncation variant, with a few exceptions of compound heterozygotes for two missense variants [16,17]. Blood cells from *CTC1* mutated patients were shown to exhibit shortened telomere lengths or telomere lengths at the lower range of normal [8,18]. However, one study reported no significant differences between the leukocyte telomere lengths of *CTC1* mutant patients and those of controls, raising the possibility that the disease mechanism of *CTC1* mutations may involve non-telomeric functions [19].

Short telomere syndromes associated with pulmonary diseases, particularly fibrosis, respond poorly to standard treatments, such as corticosteroids and bronchodilators. Androgen derivatives could be a potential therapeutic option able to re-elongate previously shortened telomeres. However clinical trials are needed to develop pharmacological agents aimed at correcting disease-causing genetic defects and determine if androgen therapy is effective for telomere-related interstitial lung diseases [20,21]. Lung transplantation may be required in end-stage disease. Higher rates of hematological, renal and infectious complications were seen, requiring reduced immunosuppressive regimens in all cases [14]. The prognosis of high-risk MDS is also poor. It is even worse in cases with a congenital predisposition. In our patient, there was only a temporary stabilization of the disease during 5-azacytidine therapy.

Conclusions

Telomeropathies are associated with a wide range of diseases and combinations of various pulmonary and extrapulmonary disorders. Lung diseases associated with short telomeres, such as pulmonary fibrosis, and also hematologic malignancies do not respond well to standard treatment. With our case, we want to draw attention to the fact that even apparently different diseases can have the same genetic basis in one patient.

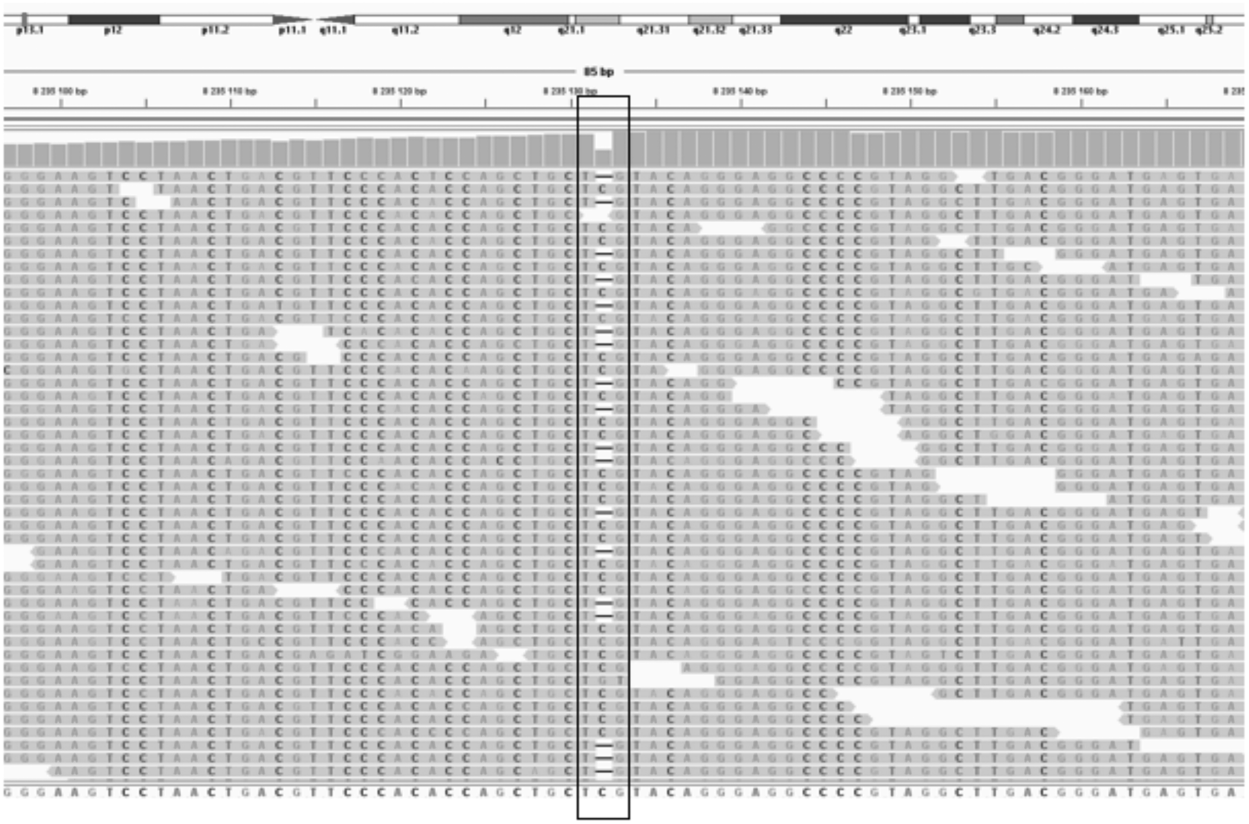

Figure 4. Visualization of c.1360delG variant (NM_025099.5; g.8235132) detected by whole exome sequencing using Integrative Genomics Viewer. Nucleotide deletion is marked by a black frame.

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Online supplementary material:

Methods - Whole exome sequencing (WES)

Table 1. Virtual genes panel associated with myeloid malignancies and predispositions to myeloid and pulmonary disorders.

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"Usabilità": parametro critico per la comparazione dei device inalatori

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RIASSUNTO

La scelta del device inalatorio rappresenta ancora un aspetto critico nella pratica clinica. Tutti i device inalatori ad oggi disponibili riconoscono peculiari fattori di criticità. Ne consegue che i pazienti non sono in grado di utilizzare tutti i device in modo egualmente efficace. La scelta del device dovrebbe pertanto tener conto di tutti i fattori in grado di condizionare l'efficacia e l'efficienza dei singoli device, non solo della soggettività del paziente.

L'"usabilità" è un parametro comprensivo e multidimensionale risultante dalla valutazione integrata e oggettiva dei fattori correlati alla tecnologia dei device, al vissuto del paziente, ai comportamenti educazionali ed organizzativi richiesti, e ai costi. Insospettabili differenze possono emergere in termini di usabilità anche fra device appartenenti alla stessa famiglia (MDI, DPI, SMI).

L'usabilità rappresenta un parametro chiave ai fini dell'ottimizzazione delle scelte nella pratica clinica, oltre che ai fini dello sviluppo futuro di nuovi e più performanti device.

Parole chiave

Device inalatori MDI, DPI, SMIs; Asma, BPCO, Usabilità.

INTRODUZIONE

Quella inalatoria è certamente la via da preferire per la somministrazione dei farmaci respiratori: essa consente infatti di raggiungere direttamente la struttura bersaglio, di utilizzare bassi dosaggi di principio attivo, una più rapida azione ed un migliore indice terapeutico [1-2].

Parallelamente allo sviluppo di nuove molecole, anche le tecnologie per l'inalazione hanno avuto uno sviluppo altrettanto importante, soprattutto orientate all'incremento della deposizione a livello polmonare dei principi attivi e alla semplificazione delle procedure per l'inalazione da parte del paziente, con conseguente miglioramento dell'aderenza e della compliance alla strategia terapeutica.

Tuttavia, la somministrazione per via inalatoria rappresenta tuttora un aspetto critico della terapia respiratoria, soprattutto per quanto attiene la gestione a lungo termine di asma bronchiale e bronco-pneumopatia cronica ostruttiva (BPCO). Di fatto, indipendentemente dalle molecole impiegate, l'efficacia della terapia inalatoria dipende in maniera determinante da diversi fattori, sia correlati al paziente che al sistema di erogazione utilizzato [3-6].

Le caratteristiche costruttive del device sono di per sé in grado di condizionare l'efficacia della terapia inalatoria prescelta. In particolare, la capacità del device di consentire una sufficiente frazione respirabile del farmaco (con un particolato di diametro ≤ 6 μ); di garantire una buona ripetibilità, precisione e stabilità delle dosi erogate, unitamente a una sufficiente facilità d'impiego da parte del paziente (specialmente nei pazienti anziani, in quelli fragili e/ con limiti cognitivi) sono punti cruciali in termini

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di management delle patologie ostruttive delle vie aeree [3-5; 7]. È stato infatti dimostrato come l'uso non corretto dell'inalatore possa condizionare in maniera significativa l'impatto di tali malattie: +47% di ospedalizzazioni; + 62% di accessi al pronto soccorso; +50% di cicli di antibiotici; + 54% di cicli di steroidi sistemici; +47% di giorni di assenteismo lavorativo o scolastico [8].

Sebbene il device ideale non esista ancora, è stato comunque stabilito che esso dovrebbe essere:

1. *efficace*: capace di consentire l'inalazione di una sufficiente quantità di farmaco con diametro del particolato ≤6 μ, indipendentemente dal flusso inspiratorio prodotto dal paziente;
2. *riproducibile*: in grado di garantire sempre la stessa quantità di farmaco inalatorio, anche in termini di frazione respirabile;
3. *preciso*: in grado di rendere sempre il paziente consapevole della quantità (o meglio, delle dosi) di farmaco ancora disponibile al suo interno [9];
4. *stabile*: capace di proteggere il farmaco dagli effetti delle variazioni di temperature e umidità;
5. *confortevole*: facile da usare in ogni circostanza, specie nelle situazioni critiche o di emergenza;
6. *conveniente*: in grado di contenere un numero di dosi sufficiente per un lungo periodo di tempo, e possibilmente di essere ricaricabile;
7. *versatile*: possibilmente utilizzabile per farmaci diversi;
8. *compatibile* dal punto di vista ambientale: privo di prodotti inquinanti;
9. *sostenibile* in termini di costi [2].

Due sono comunque gli assunti consolidati da tempo a tale riguardo:

1. pur per motivi diversi, tutti i device inalatori sono suscettibili di qualche criticità nel loro impiego [10];
2. i pazienti non sono in grado di inalare attraverso tutti i device in maniera egualmente corretta ed efficace [2;11].

Proprio su queste basi è imprescindibile la valutazione e la comparazione integrata di tutti i fattori sopra esposti, il cui valore finale determina la reale usabilità di ogni device inalatorio (Figura 1).

Ad oggi i device inalatori tascabili possono essere raggruppati in tre grandi categorie, ognuna con caratteristiche peculiari.

MDI

Rappresentano la più antica classe di device portatili e quella a più basso costo. L'emissione del farmaco dal device richiede la presenza di un propellente (il clorofluorocarbone in passato, l'idrofluoroalcano successivamente).

Nonostante gli MDI siano ritenuti semplici da usare, il loro impiego corretto non è sempre garantito in quanto l'efficacia dell'inalazione dipende fortemente da numerosi fattori. Poiché l'emissione del farmaco dal device avviene a velocità di circa 80 km/h, ai fini di una corretta ed ef-

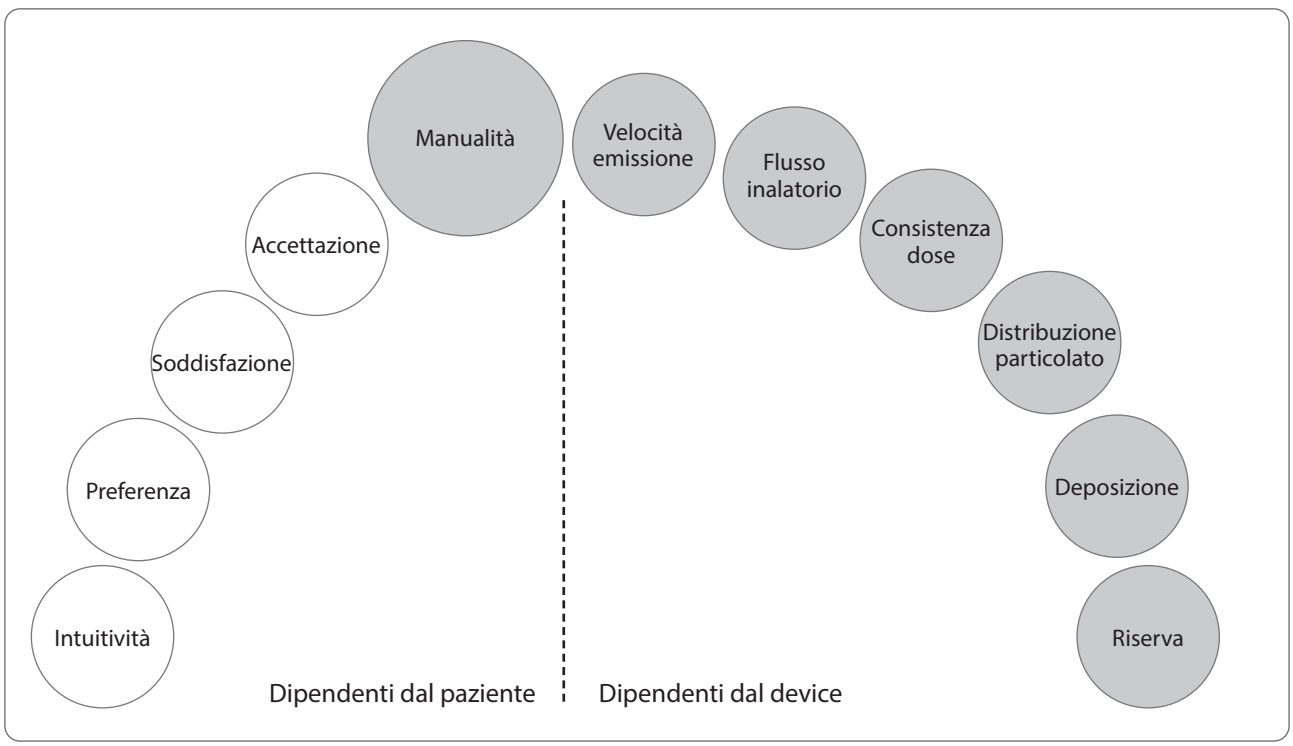

Figura 1 Fattori che possono condizionare l'Usabilità degli MDI (in grigio, i fattori critici).

ficace inalazione giocano infatti un ruolo determinante le condizioni fisiche del paziente, il suo stato cognitivo, la sua capacità di cooperazione [12]. Inoltre, con alcuni MDI la consistenza della dose emessa può variare di molto in base al livello di riempimento (o svuotamento) del device [13], evidentemente con esiti variabili e apparentemente ingiustificati.

Purtroppo, il paziente non può essere consapevole di tutte le criticità correlate all'inalazione mediante MDI e pertanto il suo grado di percezione e di giudizio ha solo un valore parziale. Paradossalmente, gran parte degli studi di comparazione fra diversi MDI si limitano a valutare esclusivamente il percepito del paziente. Ne consegue che il termine usabilità viene comunemente, ma erroneamente, impiegato come sinonimo di "facilità d'uso", "preferenza", "attrattività estetica", "intuitività" senza prendere in considerazione l'altra faccia del problema: il ruolo cioè di tutti gli altri fattori critici oggettivi (prevalentemente tecnologici) che non sono dipendenti dal paziente.

I fattori critici in grado di condizionare l'efficacia dell'inalazione mediante DPI sono riassunti nella Figura 1.

DPI

Pur se variabili nella forma e nell'aspetto, i DPI hanno rappresentato un sostanziale passo avanti nella tecnologia inalatoria. Hanno infatti eliminato l'impiego di propellenti; hanno semplificato le procedure inalatorie, hanno ridotto il livello di cooperazione richiesto al paziente, hanno migliorato l'aderenza alla terapia; hanno introdotto il contatore di dosi; hanno incrementato la deposizione polmonare del farmaco inalato; hanno ridotto la variabilità nella consistenza delle dosi erogate e hanno ridotto fortemente l'incidenza di effetti collaterali locali e sistemici [14-17].

Poiché i DPI non richiedono l'impiego di propellenti, sia la disaggregazione che l'aerosolizzazione delle polveri secche che devono essere inalate dipendono in massima parte dal flusso inspiratorio generato dal paziente attraverso il device e dalla conseguente variazione di pressione prodotta durante la manovra inalatoria [18-23].

Considerando le loro caratteristiche tecnologiche, i DPI possono essere differenziati in base al diverso livello di resistenza intrinseca al flusso aereo, alla differenza di pressione generata (e alla corrispondente variazione di flusso) e al grado di turbolenza prodotto all'interno del device [24-26]. Usualmente, sulla base del loro regime resistivo intrinseco (una caratteristica peculiare inalienabile in quanto frutto dei loro criteri di ingegnerizzazione) gli MDI vengono distinti in: a bassa resistenza (<5 Mbar 1/2 L/min –1; mid); a media resistenza (5-10 Mbar 1/2 L/min –1), ad alta resistenza (>10 Mbar 1/2 L/min –1) [18,25].

In altre parole, la disaggregazione della polvere secca del farmaco, il diametro del particolato da inalare, la consistenza e la variabilità della dose, nonché la deposizione polmonare dipendono in larga misura dal flusso inspiratorio generato dal paziente durante l'inalazione e dalla conseguente variazione di pressione e di turbolenza prodotta all'interno del device [1,18]. Ciò implica che un'inalazione efficace mediante DPI richiede al paziente un flusso espiratorio (FI) sufficientemente elevato per vincere la resistenza intrinseca (RI) del device. Se si considera il rapporto FI/RI, due sono le condizioni che conducono a un'inalazione inefficace del farmaco: 1) un FI insufficiente e 2) un valore molto basso di RI, rispettivamente il numeratore e il denominatore del rapporto. Infatti, quando la RI è troppo bassa (il denominatore del rapporto), il rapporto tende all'∞ e il FI richiesto per superare la RI risulta talmente elevato in questi casi che neppure i soggetti sani sono in molti casi in grado di raggiungere il valore soglia di FI necessario a effettuare un'inalazione efficace.

Ne consegue che il messaggio generalmente divulgato, e cioè che i DPI a bassa resistenza dovrebbero essere i preferiti perché più facilmente "usabili" dal paziente, è di fatto errato in termini di reale efficacia inalatoria e di vera "usabilità'" del device.

Per converso, quando la RI (il denominatore del rapporto) è troppo elevata, il rapporto tende a 0 anche se il FI richiesto è relativamente basso: in questi casi, la richiesta per vincere la resistenza intrinseca del device è talmente elevata che una parte non trascurabile di pazienti ostruttivi (quelli con marcata compromissione funzionale) non riescono a generare il FI richiesto a causa della meccanica polmonare compromessa [27].

Nella Tabella 1 sono riportati i DPI più comunemente usati e raggruppati per valore di RI e corrispondente FI richiesto per un'inalazione efficace. Nella stessa Tabella è anche riportato per ognuno in numero di manovre necessarie per la loro corretta attuazione.

I fattori critici in grado di condizionare l'efficacia dell'inalazione mediante DPI sono riassunti nella Figura 2.

SMI

La famiglia degli SMI di fatto è rappresentata da un unico device: il Respimat, disponible anche nella versione ricaricabile. Respimat non contiene propellenti: l'erogazione della dose è garantita da forze meccaniche che producono due sottili getti di soluzione del farmaco da erogare, i quali, convergendo e collidendo secondo un angolo prestabilito, generano l'emissione del tipico nebulizzato [28-31].

Sulla base del suo peculiare pattern di emissione, Respimat eroga il farmaco a bassa velocità (5-10 km/h) e consente al paziente una più facile ed efficace inalazione, riducendo il rischio di errori. Inoltre, la consistenza della dose si è dimostrata costante, indipendentemente dal livello di riempimento del device [13]. Tuttavia, in termini di manualità, anche Respimat richiede una certa dose

Tabella 1 Caratteristiche dei diversi DPI: n. delle manovre preparatorie richieste per l'inalazione, valore della resistenza intrinseca, flusso inspiratorio necessario per una inalazione efficace.

DPI	N. manovre	Resistenza intrinseca ($kPa^{0,5}$ L/min)	Flusso inspiratorio (L/min)
Breezhaler	7	0,017	111
Aerolizer	6	0,019	102
A bassa resistenza			
Accuhaler/Diskus	4	0,027	72
Novolizer	3	0,027	72
Ellipta	3	0,028	70
Genuair	3	0,028-0,031	64
A media resistenza			
Spiromax	3	0,031	62
Turbohaler	4	0,036-0,039	54
Nexthaler	3	0,036-0,042	54
Easyhaler	3	0,037-0,042	50
Clickhaler	3	0,039	50
Ad alta resistenza			
Handihaler	8	0,058	37

di collaborazione da parte del paziente, soprattutto per quanto attiene alle manovre di caricamento della dose.

I fattori critici in grado di condizionare l'efficacia dell'inalazione mediante DPI sono riassunti nella Figura 3.

USABILITÀ

Il concetto di usabilità origina dalla valutazione integrata di quanto riportato nelle Figure 1-3.

Risulta immediatamente evidente che la reale performance di ogni device, e quindi la sua effettiva usabilità, dipende da parametri di natura diversa e che quindi appartengono a differenti domini di giudizio.

Pertanto, la valutazione oggettiva dell' usabilità di un device non può che richiedere un approccio multi-fattoriale, basato sulla valutazione di tutti gli insiemi di fattori che possono fra loro interagire, e cioè: 1) di quelli principalmente dipendenti dagli aspetti legati al paziente (come comunemente già accade); 2) di quelli che hanno a che fare con la conoscenza delle peculiarità e delle limitazioni tecnologiche dei singoli device; 3) dell'entità e della qualità dell'educazione richieste per far sì che l'inalazione sia corretta ed efficace; 4) dello stato socio-economico del paziente; 5) del setting nel quale ci si trova a operare (domicilio, struttura ambulatoriale o ospedaliera), 6) del costo effettivo globale. Va però tenuto presente che quest'ultimo non corrisponde meramente al costo del farmaco come comunemente viene inteso, ma deve essere invece implementato dal costo delle risorse impiegate per il percorso educazionale del paziente (fino alla sua completa autonomia gestionale) e dal costo correlato agli esiti negativi della terapia casati dal non corretto uso del device (Figura 4).

In definitiva, l'usabilità è un parametro critico, ma molto più sfaccettato e complesso di quanto comunemente inteso. Ad esso concorrono diversi fattori paziente- e device-dipendenti, variamente fra loro intricati, che vanno attentamente valutati prima di esprimere un giudizio definitivo e oggettivo su un device inalatorio e sulla sua convenienza di impiego clinico.

Questo aspetto ha rappresentato il motivo primario per la definizione e la validazione del Global Usability Score (GUS), cioè del primo indicatore globale orientato alla misura quantitativa integrata di tutti i fattori che contribuiscono alla definizione della reale usabilità di un device inalatorio [32].

Di fatto, quando device inalatori (anche appartenenti alla stessa famiglia, ad esempio i DPI) vengono confrontati in termini di usabilità, possono emergere insospet-

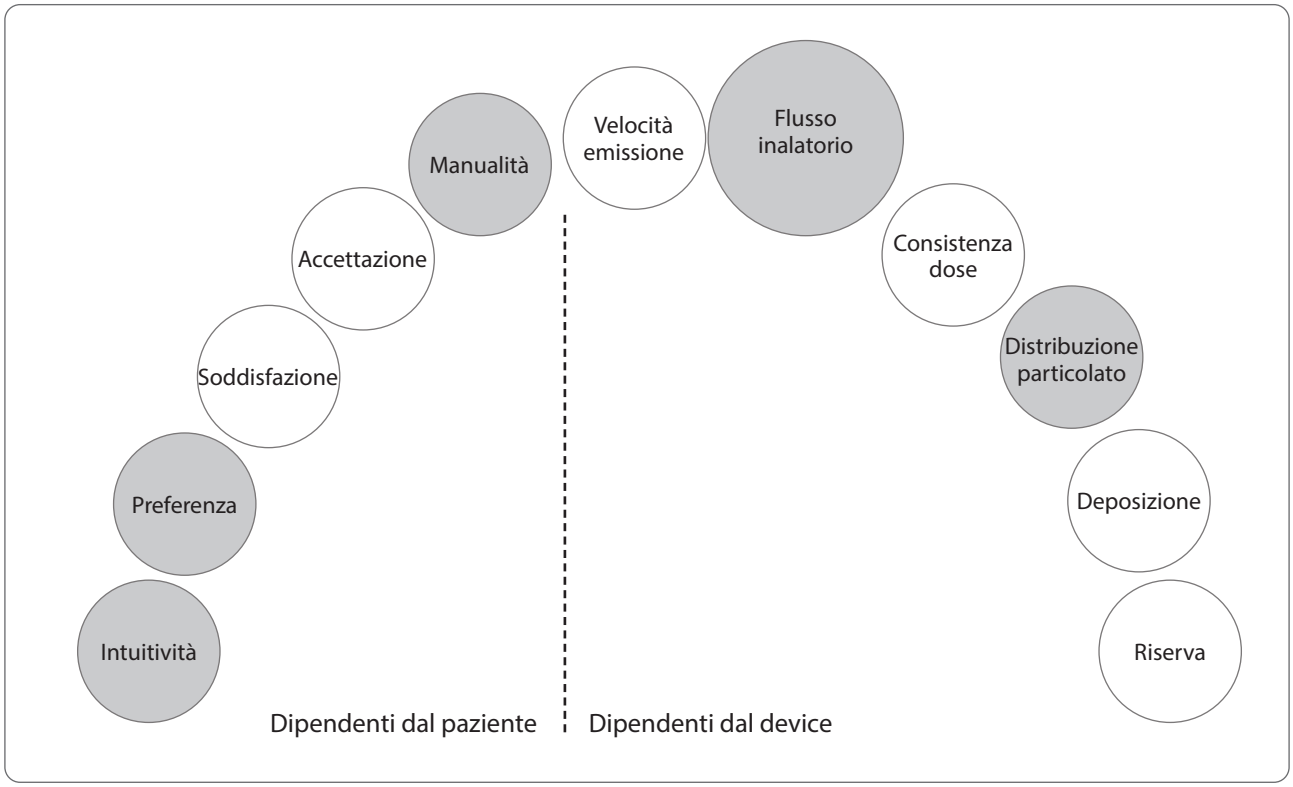

Figura 2 Fattori che possono condizionare l'usabilità dei DPI (in grigio, i fattori critici).

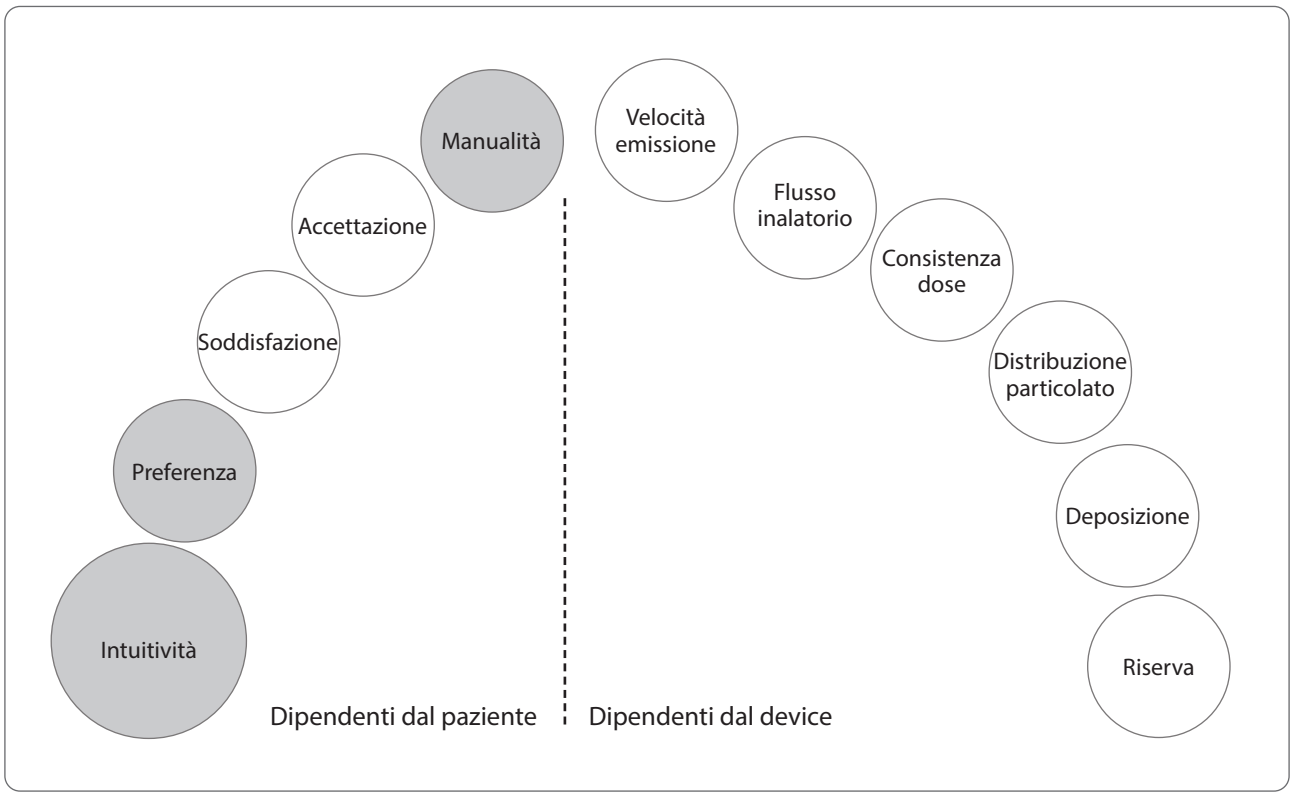

Figura 3 Fattori che possono condizionare l'usabilità degli SMI (in grigio, i fattori critici).

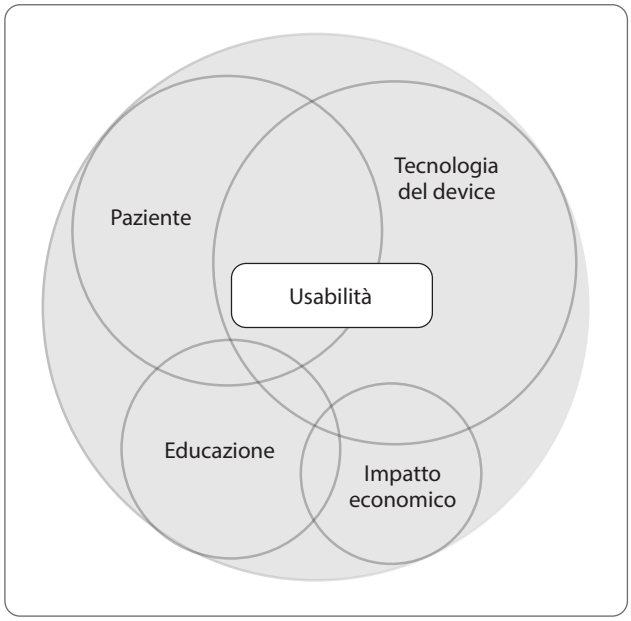

Figura 4 I diversi domini dei determinanti dell'usabilità.

tabili e significative differenze, tali anche da sovvertire i precedenti convincimenti [13, 33-35]. Ciò prevalentemente sulla base della valutazione delle peculiarità intrinseche dei device considerati, della qualità dell'educazione fornita al paziente e del costo globale effettivo.

In altre parole, si conferma la sostanziale discrepanza fra la reale usabilità e ciò che viene solitamente considerato sulla base di quanto il paziente è in grado di cogliere soggettivamente [34-35].

Purtroppo la scelta del device inalatorio è ancora troppo spesso guidata da grande empiria: la conoscenza delle caratteristiche tecnologiche dei diversi device inalatori (e quindi della loro potenziale performance) è tuttora gravemente lacunosa nella pratica clinica, risultando privilegiati i criteri decisionali basati sulla soggettività [36-45].

CONCLUSIONI

In conclusione, l'usabilità è un indice comprensivo e multidimensionale risultante dalla valutazione integrata e bilanciata dei fattori correlati alla tecnologia del device, al vissuto del paziente, ai comportamenti educazionali e organizzativi, e ai costi (Figura 4): tutti fattori imprescindibili per misurare e comparare in maniera oggettiva la convenienza delle scelte in tema di device inalatori. L'usabilità può infine rappresentare uno strumento chiave al fine di promuovere lo sviluppo di futuri e più performanti device inalatori.

Conflitto di interessi

L'autore dichiara di non avere conflitti di interessi. RWD è Associate Editor di *Multidisciplinary Respiratory Medicine*.

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Il sistema immunitario può essere efficace per prevenire le patologie respiratorie acute ricorrenti nei bambini?

INTRODUZIONE

Le infezioni respiratorie costituiscono un importante problema di salute pubblica riguardante prevalentemente le fasce estreme della popolazione, ovvero i bambini e gli anziani. Nel contempo, esse sono una delle principali cause di morte al mondo e la seconda causa di morte nei bambini sotto i 5 anni di età. L'incidenza delle infezioni respiratorie delle alte vie è inversamente proporzionale all'età: i bambini di media sono soggetti a 6-8 episodi l'anno, mentre gli adulti a 1-2. Uno studio di de Martino et al. ha infatti evidenziato che circa il 6% dei bambini italiani è affetto da infezioni respiratorie ricorrenti. Per risolvere questo tipo di infezioni respiratorie ricorrenti dei bambini e degli adulti la classe maggiormente usata di trattamento, per le peculiari caratteristiche e le evidenze di letteratura, è quella dei lisati batterici, composti costituiti dalla lisi e dalla processazione di vari antigeni batterici. Il lisato batterico più studiato a livello mondiale è l'OM-85, una molecola con proprietà immunomodulanti e immunostimolanti.

In particolare, per i bambini varie sono le teorie alla base dei meccanismi che causano le infezioni respiratorie ricorrenti in età pediatrica. Si ipotizza che esse siano determinate da un'associazione fra alterata immunità innata (deficit immunitari minori, fattori genetici con alterazioni del sistema immunitario innato, *noxae* in gravidanza, atopia, deficit di micronutrienti, obesità, ecc.) e ambiente esterno (fattori ambientali, infezioni persistenti, ecc.). Al momento possono essere rilevate solo le conseguenze di questo squilibrio, dato che non esistono esami immunologici specifici che le evidenzino.

Alla luce di queste evidenze e nell'ottica di ridurre anche il peso economico e sociale delle infezioni ricorrenti, la terapia immunostimolante nel corso degli anni è stata sempre più consigliata e somministrata a bambini soggetti a fattori di rischio per lo sviluppo di infezioni respiratorie ricorrenti e a bambini in precedenza affetti da infezioni respiratorie.

Studi clinici (vedi De Benedetto et al., Gutierrez-Tarango et al., Berber et al., Schaad et al.,) hanno dimostrato come la somministrazione di OM-85 abbia un effetto preventivo nei confronti delle infezioni respiratorie ricorrenti pediatriche, con una riduzione di incidenza del 35-40%. Con la riduzione delle infezioni respiratorie ricorrenti diminuisce anche l'uso di antibiotici, come è noto quindi con conseguente aumento delle resistenze batteriche e diminuzione dei costi sanitari. A questo proposito in un recente studio di Ravasio et al. è stato messo in luce come il trattamento con OM-85 abbia ridotto significativamente l'utilizzo di terapia antibiotica nei bambini trattati con conseguente riduzione della spesa sanitaria.

In aggiunta, lo studio dell'OM-85 per la prevenzione delle patologie respiratorie ha recentemente individuato il nuovo concetto di "allenamento immunitario", con cui si intende l'acquisizione di caratteristiche di memoria immunitaria da parte del sistema immunitario innato. Molto recentemente è stato dimostrato che la somministrazione di OM-85 genera meccanismi immunologici proprio dall'allenamento immunitario. La molecola ha inoltre capacità protettive nei confronti dello sviluppo di crisi di wheezing e di asma bronchiale, oltre che capacità immunostimolanti se assunto in concomitanza con la vaccinazione antinfluenzale. L'OM-85 infine pare abbia una funzione di regolazione negativa dei meccanismi necessari per l'infezione delle cellule epiteliali da parte del SARS-CoV-2.

Proponiamo qui di seguito una serie di interviste mirate su questa tematica di prevenzione delle infezioni respiratorie ricorrenti con 3 importanti esperti a livello internazionale, effettuate dalla testata PharmaStar durante l'ERS International Congress 2023 svoltosi a Milano nel settembre scorso*.

Parole chiave: Lisati batteri, OM-85, allenamento immunitario, infezioni respiratorie ricorrenti

*Trascrizione, elaborazione e traduzione delle interviste effettuate ai relatori (Prof. Susanna Esposito, Prof. Erika von Mutius, Prof. Manuel Soto-Martinez) durante l'ERS International Congress 2023 di Milano, 9-13 settembre 2023.

Il tavolo dei relatori (da sinistra il Prof. Manuel Soto-Martinez, la Prof.ssa Susanna Esposito e la Prof.ssa Erika von Mutius) durante il Simposio di approfondimento al Congresso ERS di Milano.

L'importanza dell'allenamento immunitario

Intervista realizzata alla Prof.ssa Susanna Esposito
Ospedale dei Bambini "Pietro Barilla", Pediatria, AO Università di Parma, Parma, Italia

Le infezioni respiratorie ricorrenti sono infezioni ripetute dell'apparato respiratorio che per definizione riguardano e si manifestano nell'età pediatrica. Oggi ci sono delle possibilità molto interessanti per la loro prevenzione utilizzando il cosiddetto "allenamento immunitario".

Prof.ssa Esposito, Lei da vera esperta della materia, ci può aiutare a fare un piccolo ripasso prima di entrare nell'argomento specifico. Cosa è esattamente il sistema immunitario innato e a cosa serve?

Tutti noi nasciamo con alcune cellule, che fanno parte appunto del nostro sistema delle difese, cellule che naturalmente con la crescita che è rappresentata dall'esposizione ad antigeni cioè a sostanze esterne che possono essere anche sostanze che determinano allergia, possono essere inquinanti, essere agenti infettivi, le stesse vaccinazioni sono un sistema che appunto permette di fare sì che le nostre difese si sviluppino. Quindi alla nascita ci troviamo in una condizione in cui abbiamo le cellule di difesa, ma queste cellule non sono ancora sufficientemente efficaci come quelle che si avranno e che diventeranno dopo i 5 anni d'età e comunque in età adulta.

Perciò, il sistema immunitario innato è rappresentato da tutto quell'insieme di difese che abbiamo dalla nascita e che si trova a fronteggiare le infezioni quando ancora non le ha conosciute.

Il sistema immunitario innato è composto ad esempio dai macrofagi e anche dalle importantissime cellule dendritiche che hanno un ruolo ponte con quella che è l'immunità adattativa, cioè che si sviluppa e che è già pronta all'uso in un certo senso quando vengono incontrati gli agenti infettivi.

Nel simposio tenutosi all'ERS di Milano, intitolato "Can the immune system be primed to prevent recurrent respiratory tract infections in children" a cui Lei ha partecipato come relatrice si è parlato molto dell'"allenamento immunitario". Può spiegare innanzitutto di cosa si tratta e poi il suo significato soprattutto in età pediatrica.

Tutti noi nasciamo con un'immunità innata, però come

sempre qualcuno ha l'immunità innata che è più pronta, altri hanno un'immunità innata che a fronte del fatto che non sia deficitaria è meno performante. E questi sono i bambini che si ammalano più frequentemente, i cosiddetti bambini con infezioni respiratorie ricorrenti. Non si tratta di bambini con immunodeficienza, essi si ammalano però più degli altri. Allora in questi bambini è importante che si riduca il rischio infettivo perché ogni infezione lascia poi uno strascico nella fase di convalescenza in cui c'è il rischio di acquisire una nuova infezione. Allora l'allenamento del sistema immunitario consiste nell'identificare la popolazione target, cioè i bambini che si ammalano più frequentemente degli altri e nell'intervenire allenando il sistema immunitario per fare sì che da una parte le infezioni durino meno e siano meno gravi, dall'altra che il bambino si ammali di per sé di meno.

Si è parlato di diversi farmaci che hanno questo scopo e di uno in particolare l'OM-85 che dispone di ampi dati in questo senso e agisce proprio migliorando l'allenamento immunitario, un farmaco che prende il nome di OM-85. Può parlare brevemente di che cosa si tratta e soprattutto della sua efficacia.

OM-85 è un lisato batterico che viene somministrato per via orale, con dei cicli di 10 giorni per 3 mesi consecutivi prima della stagione invernale e ha l'obiettivo proprio di stimolare l'immunità innata, determinando perciò un effetto che è immunostimolante, ma anche immunomodulante. Questo permette di ridurre il rischio infettivo e anche di abbreviare la durata degli episodi infettivi. È un prodotto noto da tantissimi anni, che comunque è stato studiato moltissimo anche per approfondire quelle aree di conoscenza minore che riguardano popolazioni selezionate. L'elemento chiave è appunto il bambino in generale con infezioni recidivanti e poi gli studi di oggi dimostrano sempre più la sua efficacia in condizioni come il broncospasmo ricorrente piuttosto che il bambino allergico che si ammala più degli altri. Possiamo dire che uno dei grossi vantaggi è innanzitutto il fatto che possa essere somministrato a partire già dai 6 mesi di vita. La maggior parte di questi bambini viene identificata comunque attorno ai 12 mesi di età e l'OM-85 è l'unico prodotto che può essere somministrato con dati di efficacia prima dei 3 anni d'età. Altro elemento importante è la palatabilità; infatti purtroppo sappiamo come nei bambini il gusto sia un punto importante e il fatto che l'OM-85 sia completamente insapore (ci sono delle bustine che si sciolgono in acqua o si può aprire anche la compressa e scioglierla in acqua) è un altro elemento importante per naturalmente favorire la somministrazione. In aggiunta, anche il costo è comunque molto contenuto.

L'allenamento immunitario dunque sta diventando un concetto cui dobbiamo abituarci e imparare a conoscere.

Assolutamente sì. Perché abbiamo conosciuto e stiamo leggendo ormai su tantissimi giornali per il grande pubblico il concetto dell'antibiotico resistenza. Sappiamo che purtroppo l'abuso di antibiotici sta creando una situazione molto complicata che è quella di far sì che abbiamo sempre meno prodotti disponibili. L'allenamento del sistema immunitario con questo sistema permette invece di evitare l'abuso di antibiotici e anche tutte quelle conseguenze che intaccano quella che è la nostra flora saprofita cioè la flora di cui siamo portatori, la diffusione di batteri resistenti e lo sviluppo di infezioni resistenti agli antibiotici.

Stimolare il sistema immunitario per prevenire le infezioni respiratorie ricorrenti

Intervista realizzata alla Prof.ssa Erika von Mutius
Allergologia pediatrica, Ospedale Pediatrico "Dr von Hauner", Università Ludwig-Maximilians, Monaco, Germania

Prof.ssa Von Mutius, nel simposio tenutosi all'ERS di Milano, intitolato "Can the immune system be primed to prevent recurrent respiratory tract infections in children" Lei ha concentrato l'attenzione del suo discorso su un farmaco in particolare, denominato OM-85. Qual è la composizione di questo farmaco?

OM-85 è un lisato batterico. Significa che contiene 21 ceppi che vengono "distrutti" da un processo chimico. In questo modo si ottengono piccoli componenti di questi batteri.

OM-85 imita quello che accade in natura, cioè "l'effetto fattoria" che Lei ha spiegato nella sua relazione?

Ciò che si sa di questi lisati batterici è che stimolano il sistema immunitario, in particolare stimolano quello innato. Dagli studi condotti nelle fattorie (farm studies), sappiamo che la stimolazione del sistema immunitario è importante per la prevenzione. Nelle fattorie sono presenti batteri leggermente diversi da quelli utilizzati nel prodotto, ma al momento sembra che l'effetto finale sia lo stesso.

Lei ha parlato anche di una sorta di training immunitario. Come funziona?
La teoria attuale è che i bambini che rischiano di sviluppare asma o respiro sibilante con infezioni delle basse vie respiratorie hanno un sistema immunitario innato che non è maturo, che non è stato sufficientemente allenato.

L'uso di questi lisati batterici può contribuire a far maturare il sistema immunitario in modo che possa combattere meglio le infezioni.

Questo metodo funziona?
Ci sono studi che dimostrano che funziona. È stata condotta una meta-analisi sugli studi più importanti e su quelli più robusti. Ci sono ancora alcune limitazioni, perché alcuni studi erano stati condotti con un basso numero di partecipanti, ma attualmente sono in corso tre studi molto ampi.

Il primo è in Europa, lo studio BEAR, un altro è EAGLE, negli Stati Uniti. Il loro scopo è proprio quello di trattare questi bambini e di valutare i risultati in termini di infezioni respiratorie e di sintomi associati, come la dispnea.

C'è un altro studio molto ampio negli Stati Uniti che esamina questi lisati come prevenzione primaria. Quindi su bambini che non hanno sintomi e sono in prevenzione primaria per lo sviluppo di sintomi asmatici.

Al momento, quale potrebbe essere il posto di OM-85 nelle terapie, quale potrebbe essere il paziente che più beneficerà del farmaco?
Credo che ne beneficeranno maggiormente i bambini piccoli, perché sono nella fase in cui avviene la formazione del sistema immunitario e in cui si manifestano molte infezioni respiratorie ed episodi di dispnea. Questi sono certamente i bambini in cui è necessario aiutare il sistema immunitario.

L'allenamento immunitario quindi funziona?
Lo speriamo. Desidero veramente molto che funzioni. I primi studi sono molto incoraggianti; tutti hanno mostrato efficacia, ma, come ho detto, ci sono alcune limitazioni e quindi abbiamo bisogno di studi di grandi dimensioni per riuscire a sapere davvero che funziona e come.

Meno infezioni respiratorie e minori episodi di respiro sibilante

Intervista realizzata al Prof. Manuel E. Soto-Martinez
Dipartimento di Pneumologia, Ospedale Pediatrico Nazionale "Dr. Carlos Sáenz Herrera", Caja Costarricense Seguro Social, San José, Costa Rica

Professor Soto-Martinez, innanzitutto, qual è l'importanza degli induttori di formazione immunitaria per contrastare il problema del respiro sibilante e come funzionano?
Prima di tutto, dobbiamo sapere che le infezioni delle vie respiratorie sono la causa principale di dispnea ricorrente nei bambini. Quindi i bambini, in particolare quelli più piccoli, di età compresa tra i 3 e i 5 anni, sono a maggior rischio di infezioni delle vie respiratorie perché hanno una risposta immunitaria immatura. Questo comporta il rischio di avere infezioni respiratorie ricorrenti.

Se miriamo ad allenare e a potenziare la risposta immunitaria, allora questi bambini potrebbero avere meno infezioni delle vie respiratorie e quindi meno episodi di respiro sibilante. L'intero carico che ne deriva sarà ridotto.

Come agiscono questi immunomodulatori?
Nel caso dei lisati batterici, gli studi hanno dimostrato che, stimolando il sistema immunitario intestinale, si ottiene una risposta sul sistema immunitario polmonare. Pertanto, questi bambini potrebbero avere meno infezioni, infezioni meno gravi, una minore durata di queste infezioni e migliori outcome.

Ci sono diversi studi in letteratura. In particolare, ci sono stati 3 studi, lo studio di Razi e altri studi successivi, che hanno dimostrato che nei bambini in età prescolare ad alto rischio di episodi ricorrenti, quando si somministrano lisati batterici come OM-85, questi pazienti hanno quasi il 40% di episodi di respiro sibilante in meno, meno infezioni e minor durata di questi episodi.

Penso quindi che questo sia un momento incoraggiante per noi pneumologi pediatrici, che vediamo i pazienti assumere questi lisati batterici e questo allenamento immunitario. Ci sono alcuni studi in arrivo che presto ci daranno ancora maggiori informazioni al riguardo.

L'ERS Congress di Milano conferma l'ampia partecipazione dell'era pre-COVID

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Conclusa l'edizione 2023 del Congresso Internazionale ERS (European Respiratory Society), che quest'anno ha avuto luogo a Milano dal 9 al 13 settembre, è tempo di bilanci. Per la seconda volta consecutiva l'annuale ERS Congress si è svolto in una modalità "ibrida", ovvero sia nella sede congressuale italiana che on line, in modo da consentire a tutti di seguire i lavori in presenza e non. La novità dell'online è stata necessaria negli anni passati durante la pandemia da COVID-19, ma superata questa emergenza e con l'ausilio delle tecnologie informatiche l'ERS ha scelto di offrire ai partecipanti l'iscrizione e la frequentazione in duplice modalità.

Nel complesso sono stati oltre 20.000, secondo le cifre fornite da ERS, i delegati che hanno seguito il variegato programma congressuale articolato in più di 400 sessioni su l'ampia gamma di argomenti scientifici e aggiornamenti relativi alla Medicina respiratoria.

Come di consueto, oltre alle sessioni scientifiche, ai simposi e agli approfondimenti, i partecipanti (così come la redazione di *Multidisciplinary Respiratory Medicine*) hanno avuto modo di aggiornarsi sugli sviluppi della ricerca nella Medicina respiratoria e nel contempo di visitare anche gli stand delle industrie operanti nel settore, sia del farmaco che degli apparecchi elettromedicali,

oltre agli stand delle tante Associazioni scientifiche provenienti da varie parti del mondo presenti nella sezione World Village del Congresso.

Tra i temi trattati quest'anno molta rilevanza hanno avuto anche quelli ambientali, con proposte e progetti per la protezione del clima, o prese di posizione dell'ERS a seguito del voto del Parlamento europeo per la revisione della direttiva "Ambient Air Quality" al fine di allinearsi con le line guida dell'Organizzazione Mondiale della Sanità entro il 2035, step importante nella direzione di una migliore qualità dell'aria per tutti. Altro tema connesso e portato avanti è stato quello indirizzato verso politiche per il controllo del tabacco e la riduzione del fumo (cfr. Tobacco 21 'endgame).

L'assemblea generale ERS ha designato come Presidente la Prof. Monika Gappa, che nel suo mandato intende proseguire importanti iniziative già avviate, quali global advocacy projects, l'International Respiratory Coalition, l'ERS Respiratory Channel e l'impegno di ERS per lo sviluppo sostenibile. Inoltre, la Prof. Gappa, pneumologa pediatrica, ha reso noto di voler contribuire con il proprio expertise ad approfondire lo studio sulle origini delle patologie respiratorie nell'infanzia, conoscenza utile per il trattamento delle malattie respiratorie nelle successive fasi della vita di tutti.

L'organigramma ERS per il periodo 2023–2024 include il Prof. Carlos Robalo Cordeiro, come Past President, la Prof. Silke Ryan quale Presidente Eletto e il Prof. Judith Garcia-Aymerich come Segretario Generale. Confermata come ERS Vice President la Prof. Joanna Chorostowska-Wynimko, che diventerà successivamente ERS President Elect nel 2024/25 e poi ERS President nel periodo 2025/26.

Il prossimo appuntamento con l'ERS Congress sarà a Vienna, dal 7 all'11 settembre 2024.

Peumomeeting 2.5: opinioni a confronto in Medicina respiratoria

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Il Dr. Guido Bertolaso insignito del Premio Pneumomeeting 2023 dai Chairmen del Congresso

Il tradizionale Congresso autunnale "Pneumomeeting" di Taormina ha avuto luogo dal 23 al 25 novembre scorsi, raggiungendo così la sua 16a edizione. Contrassegnata, come sempre da una vocazione clinica e interdisciplinare, oltre che da ottimo livello scientifico delle relazioni, generosa ospitalità dei Chairmen (Dr. Salvatore Bellofiore, Dr. Riccardo Giuliano, Dr. Salvatore Privitera, Dr. Mario Schisano e Prof. Carlo Vancheri) e perfetta organizzazione, l'edizione 2023 ha approfondito tematiche ed aspetti relativi alle patologie dell'apparato respiratorio. Tuttavia, non solo si è voluto fare il punto dopo l'emergenza del COVID-19 sugli assetti sanitari, sia ospedalieri che territoriali, cercando di favorire il confronto dialettico fra i professionisti sanitari, in particolare gli pneumologi, alla luce della loro esperienza scientifica e professionale, ma anche tentando di fornire spunti utili ai decisori politici al fine di migliorare la pianificazione e la gestione territoriale della Sanità.

Articolato su 3 percorsi diagnostico-terapeutici riguardanti rispettivamente le patologie oncologiche polmonari, le patologie polmonari ostruttive nella loro evoluzione e le patologie polmonari interstiziali, il programma scientifico ha presentato oltre ai classici Workshop, Letture e Simposi, anche la novità di 3 corsi di aggiornamento su tematiche pneumologiche specifiche, quali la ventilazione non invasiva, l'ecografia toracica e la riabilitazione respiratoria.

Ospite di eccezione è stato il Dr. Guido Bertolaso, Assessore al Welfare Regione Lombardia e già Capo della Protezione civile, che ha illustrato i risultati raggiunti nella lotta alla pandemia da Sars-COV2. A lui è stato conferito il Premio Pneumomeeting - Edizione 2023, insieme al Prof. Nicola Scichilone e al Dr. Giuseppe Failla.

Gli organizzatori hanno già fissato anche la data del prossimo appuntamento con Pneumomeeting, che si svolgerà sempre nell'affascinante cornice di Taormina dal 7 al 9 novembre 2024.

L'angolo della Cultura (non solo Medicina…)

a cura della Redazione

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Le tre baldracche di Schopenhauer

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Και το' με'ν οὖν σαφε'ς οὔτις
ανήρ ιδεν οὔδε'τις εσται ειδὼς.
"Nessun uomo ha mai saputo,
né saprà mai, nulla di certo".
Senofane, filosofo greco antico

"Una compagnia di ricci, in una fredda giornata d'inverno, si strinsero vicini, per proteggersi, col calore reciproco, dal rimanere assiderati. Ben presto, però, sentirono le spine reciproche; il dolore li costrinse ad allontanarsi di nuovo l'uno dall'altro. Quando poi il bisogno di scaldarsi li portò di nuovo a stare insieme, si ripeté quell'altro malanno; di modo che venivano sballottati avanti e indietro tra due mali, finché non ebbero trovato una moderata distanza reciproca, che rappresentava per loro la migliore posizione". Questa immagine fu descritta dal filosofo Arthur Schopenhauer nella sua ponderosa opera *Parerga e Paralipomena*. Sembra la descrizione perfetta di molte relazioni infelici. Si cerca l'altro per vincere la propria solitudine, ma quando si scoprono gli aculei lo si lascia, perché si cercava solo di vincere il freddo della propria solitudine. E ricomincia la ricerca, in un continuo illudersi e disilludersi che abbatte la speranza e infiacchisce la capacità di amare. Insomma, occorrerebbe trovare le giuste misure per amarsi, senza ferirsi troppo, perché in amore forse ferirsi è inevitabile…

Come si vede, Schopenhauer è decisamente pessimista e, in più, è sempre stato descritto come bizzarro, scontroso, misantropo, per nulla amico dei bambini. Ma alcuni ricordi di una vicina di casa modificano lo stereotipo: a Francoforte, la città dove visse dal 1833, il filosofo cambiò spesso casa e nell'ultimo anno traslocò in un appartamento sulla riva del Meno, al numero 16 della via Schöne Aussicht. Lì diventò inaspettatamente amico di una bambina di sette anni – Lucia Franz – e dei suoi due fratelli, nonostante i genitori le avessero imposto di evitare "quel signore che non aveva senso dell'umorismo, la cui conoscenza era una disgrazia perché quest'uomo, irascibile e violento, ha picchiato una donna, e prenderà a bastonate anche i nostri bambini". Ma le cose non andarono così perché il filosofo in realtà – considerato come un vero e proprio spauracchio, tanto che, al minimo segno di monelleria, il padre di Lucia gridava: "Chiamate Schopenhauer" – divenne, senza saperlo, il vero educatore dei bambini, più della loro istitutrice Miss Bethy.

Lucia andava a trovare il filosofo, come si fa con un nonno. Non che lui non fosse irascibile e insopportabile, e lei, come tutti, lo temeva, specie quando rientrava a casa dal pranzo quotidiano all'albergo Englisher Hof: imprecava e di colpo scaraventava i libri a terra. Lucia però aveva trovato una via per arrivare a lui, giocando con Atma, il cane che il filosofo amava e a cui aveva insegnato due giochi, entrambi mangerecci: il primo consisteva nell'afferrare a volo una salsiccia che Arthur strappava da un alberello sul tavolo vicino alla finestra e che veniva divorata seduta stante dal cane; il secondo, era quasi un gioco di prestigio che Schopenhauer faceva eseguire al cane, proprio per i bambini: metteva una zolletta di zuc-

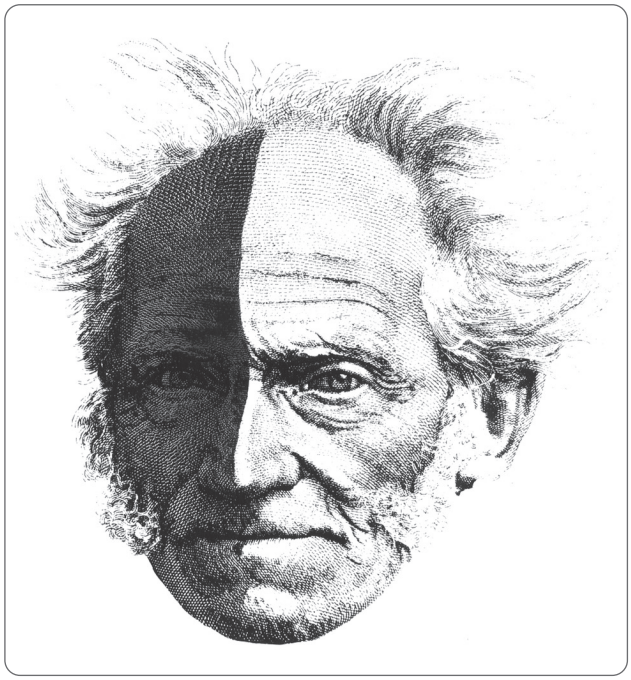

Figura 1 Arthur Schopenhauer 1788-1860.

chero sul naso di Atma, che ubbidientemente stava dritto di fronte a lui, poi iniziava lentamente a recitare l'alfabeto, mentre il cane rimaneva dritto e immobile, come un palo, guardando solo il suo padrone; arrivati alla lettera S (l'iniziale del cognome del filosofo!), Atma lanciava in aria la zolletta di zucchero e l'afferrava al volo, senza mai farla cadere a terra. Il tutto era Schopenhauer–specifico, nel senso che il "numero" veniva eseguito solo se la zolletta sul naso la metteva il filosofo; viceversa, se i bambini tentavano di mettere la zolletta di zucchero sul naso di Atma, il cane si rifiutava scuotendo la testa.

Il pensiero di Schopenhauer non viene certo scalfito da questi ricordi: la sua convinzione che "ogni vita è sofferenza", il fin troppo insistito "pessimismo" della sua filosofia. Ma è curioso come le visioni private, specialmente se gli occhi che guardano sono di bambini, introducano aspetti che sfuggono ai più, anche e soprattutto ai diretti interessati. Certo, Schopenhauer amico dei bambini! Chi l'avrebbe detto? Giovanissimo, nel 1813, aveva scritto: "È giusto, ma duro che, per aver gridato noi un paio d'anni, dobbiamo sentire gridare bambini per tutta la vita". Eppure sappiamo che, sempre nel suo ultimo anno di vita, egli ebbe affezioni quasi paterne per Julius Frank, un bambino di otto anni, che Schopenhauer aveva salvato dall'annegamento: lo stereotipo del filosofo bizzarro, scontroso, misantropo esce alquanto modificato. Quando la Franz – con cui il vecchio Arthur (che aveva descritto la vita umana come un continuo oscillare fra il dolore e la noia) giocava come un nonno qualsiasi – parla con affetto di lui, non possiamo fare a meno di sorridere e di pensare che il filosofo, malgrado avesse definito la maggior parte degli uomini merce di fabbrica della natura, veniva ricordato con affetto da uno di quei bambini divenuti adulti.

Ma chi era la donna picchiata da Schopenhauer e citata dal papà di Lucia? Il fatto si riferisce a un altro famoso episodio nella vita di Schopenhauer dove viene fuori che egli spesso si comportava come quei sapientoni che invitano a fare quel che dicono, ma non quel che fanno. Il teorico della compassione universale è infatti in difficoltà quando si tratta di compassione puramente locale, nel caso specifico la compassione che egli potrebbe manifestare nei confronti di una modesta sartina, Caroline Marquet; la quale, assieme a due compagne si era piazzata con i suoi attrezzi di lavoro nel corridoio del suo edificio, proprio mentre il filosofo, che insegnava sì l'eccellenza della castità e dell'astinenza sessuale, in quel momento stava attendendo la visita di una fanciulla di diciannove anni che collezionava più avventure amorose che ruoli nel teatro dove tirava a campare. Per dirla nei termini della filosofia schopenhaueriana: il falso saggio che vanta i meriti dell'estinzione della specie mediante l'esaltazione della castità aspetta l'occasione per godere dell'affermazione della volontà di vivere, mentre la sartina, inconsapevole discepola di Schopenhauer, che non ha letto, impedisce il manifestarsi della Volontà ostruendo il passaggio dell'incarnazione fenomenica della cosa in sé sessuale. In altre parole: la sartina intralcia un momento – diciamo così allegro – nella sua vita di meditazione.

Deponendo davanti alla polizia, Arthur fornisce la sua versione: tre donne ingombravano il corridoio senza averne diritto, lui chiese cortesemente di sloggiare, due obbedirono, la terza invece si rifiutò. Il filosofo la invitò ancora una volta cortesemente a sgomberare, e, bastone in mano, offrì il braccio per accompagnarla fuori; lei rifiutò, salì il tono, lui la portò fuori senza tanti riguardi, lei tornò col pretesto di recuperare un oggetto dimenticato, ma poi rifiutò nuovamente di uscire; allora lui la prese per la vita, la sollevò, la portò fuori, lei cadde per terra e perse la cuffia; a seguire invettive varie. Lui affermò di non averla trattata da "vecchia imbecille", ma riconobbe di aver detto una volta "vecchia baldracca", il che effettivamente cambia tutto. Caroline Marquet sostenne di essere stata picchiata col bastone, presa a pugni e calci; lui respinse questa versione. Un certificato medico attestò ecchimosi e una verruca strappata. Lui sostenne che la sartina si fosse fatta male da sola cadendo, ma affermò che, se avesse obbedito, avrebbe potuto evitare tutto ciò. In una lettera in cui raccontò la vicenda, Schopenhauer parlò delle "tre baldracche". Caroline Marquet sporse querela e amplificò la faccenda tornando in tribunale e spiegando che in seguito alle percosse aveva parzialmente perso l'uso di un braccio. Le indagini durarono

cinque anni. Si celebrò il processo. Il torto venne attribuito al filosofo, costretto a versare alla donna una pensione fino alla morte. La sarta, quasi per punirlo, visse ancora vent'anni e Schopenhauer, attaccato ai soldi, fece sempre fatica a digerire questo episodio che, come si vede, era ben noto al padre della piccola coinquilina del vecchio Arthur. Si leggeranno, pertanto, con un sorriso divertito le pagine del *Mondo come volontà e rappresentazione*, testo in cui Schopenhauer (tra l'altro, autore di mordaci battute contro il sesso femminile: "fra uomini esiste, per natura, solo indifferenza; ma fra donne, già per natura, vi è inimicizia anche solo incontrandosi per strada, si guardano a vicenda come i guelfi ed i ghibellini") vanta i meriti del saggio, libero dalla volontà di vivere, che perciò sopporta pazientemente l'affronto, manifesta una mitezza infinita, ricambia il male col bene, senza manifestare odio o collera, accoglie come una benedizione ogni offesa, ogni oltraggio e ogni danno, e, senza opporsi al torto che gli viene fatto, prende tutto col sorriso impassibile di Buddha. Purtroppo, le cose non erano andate così; com'è noto, gli uomini a parole sono tutti uguali, ma si differenziano nelle azioni. Tra il dire e il fare…

Meeting Calendar

WHEN	WHERE	WHAT	WHO TO CONTACT
		2024	
February 3-5	Dubai (UAE)	XV World Congress on Asthma, COPD & Respiratory Allergy	www.wipocis.org
February 13-14	Heidelberg (Germany)	Course: "EBUS training programme – part one"	www.ersnet.org
March 6-9	Belek (Turkey)	Lung Health Congress	www.uask2024.com
March 13-15	Paestum, SA (Italy)	Congresso Nazionale CHEST 2024	www.chest.it
March 18-20	Naples (Italy)	Skills course: paediatric bronchoscopy	www.ersnet.org
April 12-13	Matera (Italy)	Congress: "Basilicata 2024. Attualità e sfide future in Medicina Respiratoria: esperienze a confronto"	www.samacongressi.it
April 29-May 2	Kyrena (Cyprus)	27th Annual National Congress Turkish Thoracic Society	https://www.toraks.org.tr/
May 8-10	Tibilisi (Georgia)	IX European Congress on Asthma, COPD & Immunpathology	www.wipocis.org
May 17-22	San Diego, CA (USA)	ATS 2024 International Conference	https://conference.thoracic.org/
June 5-8	Marseille (France)	Skills course: Rigid bronchoscopy	www.ersnet.org
June 13-14	Bristol (UK)	Course: "Thoracic ultrasound training programme – part two"	www.ersnet.org
July 10-13	Santiago (Chile)	17° ALAT Congress	https://alatorax.org
September 7-11	Wien (Austria)	ERS Congress 2024	www.ersnet.org
September 30-October 2	Naples (Italy)	Skills course: paediatric bronchoscopy	www.ersnet.org
October 16-19	Marseille (France)	Skills course: Thoracoscopy and pleural techniques	www.ersnet.org
November 7-9	Taormina, ME (Italy)	Pneumomeeting 2024	www.pneumomeeting.it
November 16-18	Milan (Italy)	XXV Congresso Nazionale della Pneumologia	www.sip2024.it

Broncho Munal

ST 125-18
18.12.21

RIASSUNTO DELLE CARATTERISTICHE DEL PRODOTTO

1. DENOMINAZIONE DEL MEDICINALE
BRONCHO MUNAL Adulti 7 mg capsule rigide
BRONCHO MUNAL Bambini 3,5 mg capsule rigide
BRONCHO MUNAL Bambini 3,5 mg granulato in bustina

2. COMPOSIZIONE QUALITATIVA E QUANTITATIVA
BRONCHO MUNAL Adulti 7 mg capsule rigide
Una capsula rigida contiene:
OM-85 lisati batterici liofilizzati di Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae ssp. pneumoniae e ssp. ozaenae, Staphylococcus aureus, Streptococcus pyogenes e sanguinis, Moraxella (Branhamella) catarrhalis
7,00 mg

BRONCHO MUNAL Bambini 3,5 mg capsule rigide
Una capsula rigida contiene:
OM-85 lisati batterici liofilizzati di Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae ssp. pneumoniae e ssp. ozaenae, Staphylococcus aureus, Streptococcus pyogenes e sanguinis, Moraxella (Branhamella) catarrhalis
3,50 mg

BRONCHO MUNAL Bambini 3,5 mg granulato in bustina
Una bustina contiene:
OM-85 lisati batterici liofilizzati di Haemophilus influenzae, Streptococcus pneumoniae, Klebsiella pneumoniae ssp. pneumoniae e ssp. ozaenae, Staphylococcus aureus, Streptococcus pyogenes e sanguinis, Moraxella (Branhamella) catarrhalis
3,50 mg

Per l'elenco completo degli eccipienti, vedere paragrafo 6.1.

3. FORMA FARMACEUTICA

BRONCHO MUNAL Adulti 7 mg capsule rigide
Capsule rigide.
Capsule opache, con corpo e testa blu, contenenti una polvere da bianca a beige chiaro.
BRONCHO MUNAL Bambini 3,5 mg capsule rigide
Capsule rigide.
Capsule opache, con corpo bianco e testa blu, contenenti una polvere da bianca a beige chiaro.
BRONCHO MUNAL Bambini 3,5 mg granulato in bustina
Granulato in bustina.
Granulato beige chiaro.

4. INFORMAZIONI CLINICHE

4.1 Indicazioni terapeutiche

ADULTI:
Profilassi delle infezioni ricorrenti delle vie respiratorie (respiratory tract infections, RTI).

BAMBINI E ADOLESCENTI (età compresa tra 1 e 17 anni):
Profilassi delle infezioni ricorrenti delle vie aeree superiori (upper respiratory tract infections, URTI) nei bambini da 1 anno di età.

4.2 Posologia e modo di somministrazione

Posologia
ADULTI E ADOLESCENTI DI ETA' SUPERIORE AI 12 ANNI:
Il ciclo di trattamento profilattico per le infezioni ricorrenti delle vie respiratorie è:
Una capsula di BRONCHO MUNAL Adulti al giorno, da prendere a digiuno, per 10 giorni consecutivi al mese, per la durata di 3 mesi consecutivi.
Il ciclo di trattamento profilattico può essere ripetuto, se necessario.

BAMBINI FINO AI 12 ANNI DI ETA':
Stessa modalità di somministrazione degli adulti, poiché BRONCHO MUNAL Bambini contiene la metà della dose di BRONCHO MUNAL Adulti.

Modo di somministrazione
Uso orale.
Il contenuto della bustina va versato in una bevanda (acqua, succo di frutta, latte, ecc.) prima della somministrazione.
In pazienti che hanno difficoltà a deglutire la capsula, questa può essere aperta e il suo contenuto versato in una bevanda (acqua, succo di frutta, latte ecc.) prima della somministrazione, allo stesso modo della bustina.
La miscela si dissolve agitandola delicatamente. Si deve avvisare i pazienti di assumere tutta la miscela entro qualche minuto e di agitarla sempre appena prima di berla.

4.3 Controindicazioni
Ipersensibilità ai principi attivi o ad uno qualsiasi degli eccipienti elencati al paragrafo 6.1.
Bambini di età inferiore a 1 anno.
Malattie autoimmuni.
Infezioni intestinali acute.

4.4 Avvertenze speciali e precauzioni di impiego

Tracciabilità
Al fine di migliorare la tracciabilità dei medicinali biologici, il nome e il numero di lotto del medicinale somministrato devono essere chiaramente registrati.

Il trattamento deve essere sospeso in caso di febbre, in particolare all'inizio del trattamento.
Il paziente deve essere informato della possibilità, come evento indesiderato raro, di febbre elevata oltre i 39 °C, isolata e senza cause note, che deve essere differenziata dalla febbre che insorge a causa della patologia

originaria, sulla base delle condizioni laringee, nasali o otologiche; in caso di febbre elevata il trattamento deve essere sospeso e non ripreso.
Deve essere evitata l'assunzione concomitante di altri medicinali con attività immunomodulante aspecifica come quelli contenenti estratti batterici.
In alcuni casi è stata osservata l'insorgenza di attacchi d'asma in pazienti predisposti dopo l'assunzione di farmaci contenenti estratti batterici. In questo caso, BRONCHO MUNAL non deve essere assunto ulteriormente.
In caso di reazioni da ipersensibilità il trattamento deve essere interrotto immediatamente e non ripreso.
Non sono disponibili dati da studi clinici che dimostrano che l'uso di BRONCHO MUNAL possa prevenire la polmonite. Quindi la somministrazione di BRONCHO MUNAL per prevenire la polmonite non è raccomandata.

BRONCHO MUNAL non è indicato per il trattamento delle infezioni respiratorie acute ma esclusivamente per la prevenzione di recidive; non è tuttavia necessario sospendere la profilassi di recidive di infezioni respiratorie durante il trattamento di una infezione delle vie respiratorie in atto.

Eccipienti con effetti noti
Questo medicinale contiene meno di 1 mmol (23 mg) di sodio per capsula rigida / bustina, cioè essenzialmente 'senza sodio'.

4.5 Interazioni con altri medicinali ed altre forme di interazione

Non sono stati effettuati studi d'interazione con altri farmaci né con vaccini.
La risposta immunitaria può essere inibita nei soggetti con immunodeficienza congenita o acquisita, in terapia immunosoppressiva o con corticosteroidi.

4.6 Fertilità, gravidanza e allattamento
Gravidanza
I dati relativi all'uso di BRONCHO MUNAL in donne in gravidanza sono in numero limitato. Gli studi sugli animali non indicano effetti dannosi diretti o indiretti di tossicità riproduttiva.
A scopo precauzionale, è preferibile evitare l'uso di BRONCHO MUNAL durante la gravidanza.
Allattamento
Non essendo stati eseguiti studi specifici e non essendoci dati disponibili, come misura precauzionale è preferibile evitare l'uso del prodotto durante l'allattamento.
Fertilità
Gli studi sugli animali non mostrano effetti di BRONCHO MUNAL sull'indice di fertilità.

4.7 Effetti sulla capacità di guidare veicoli e sull`uso di macchinari
BRONCHO MUNAL non altera o altera in modo trascurabile la capacità di guidare veicoli e di usare macchinari.

4.8 Effetti indesiderati
Le reazioni avverse per BRONCHO MUNAL sono elencate in base alla classificazione MedDRA per sistemi e organi.
All'interno della classificazione per sistemi e organi, le reazioni avverse sono riportate in ordine di frequenza:

Molto comune:	≥1/10,
Comune:	≥1/100, <1/10,
Non comune:	≥1/1.000, <1/100,
Raro:	≥ 1/10.000, <1/1.000,
Molto raro:	<1/10.000,
Frequenza non nota:	non può essere definita sulla base dei dati disponibili.

MedDRA Classificazione Sistemica Organica / Frequenza	Reazione Avversa
Disturbi del sistema immunitario	
Non comune	reazioni di ipersensibilità (eruzione eritematosa, eruzione generalizzata, eritema, edema, edema palpebrale, edema del viso, edema periferico, gonfiore, gonfiore del viso, prurito, prurito generalizzato, dispnea)
Non nota	angioedema
Patologie del sistema nervoso	
Comune	cefalea
Patologie respiratorie, toraciche e mediastiniche	
Comune	tosse
Patologie gastrointestinali	
Comune	diarrea, dolore addominale
Non nota	vomito, nausea
Patologie della cute e del tessuto sottocutaneo	
Comune	eruzione cutanea
Non comune	orticaria
Patologie sistemiche e condizioni relative alla sede di somministrazione	
Non comune	affaticamento
Raro	piressia

In caso di disturbi gastrointestinali o disturbi respiratori di lunga durata, il trattamento deve essere interrotto.
In caso di reazioni cutanee, il trattamento deve essere interrotto poiché può trattarsi di reazioni allergiche.

Segnalazione delle reazioni avverse sospette
La segnalazione delle reazioni avverse sospette che si verificano dopo l'autorizzazione del medicinale è importante, in quanto permette un monitoraggio continuo del rapporto beneficio/rischio del medicinale. Agli operatori sanitari è richiesto di segnalare qualsiasi reazione avversa sospetta tramite il sistema nazionale di segnalazione al sito https://www.aifa.gov.it/content/segnalazioni-reazioni-avverse.

4.9 Sovradosaggio

Non sono noti casi di sovradosaggio.

5. PROPRIETA' FARMACOLOGICHE

5.1 Proprietà farmacodinamiche
Categoria farmacoterapeutica: vaccino batterico; agente immunostimolante.
Codice ATC: J07AX.
Meccanismo d'azione
BRONCHO MUNAL ha mostrato proprietà immunomodulanti in vitro e in vivo nel corso di studi preclinici e clinici. Gli estratti batterici contenuti in BRONCHO MUNAL favoriscono una risposta antinfettiva aspecifica

(intensificazione della fagocitosi) mediata da risposte cellulari e umorali. E' stata osservata una risposta cellulare legata alla stimolazione dei linfociti B e T nonché l'induzione della produzione di citochine da parte di diversi tipi di leucociti e una risposta immunitaria umorale rappresentata dalla produzione di anticorpi di tipo IgA e IgG.

Effetti farmacodinamici

In alcuni studi, in seguito a trattamento con BRONCHO MUNAL, è stata osservata l'induzione di meccanismi di difesa immunitaria innati e/o adattativi; in dettaglio è stato osservato un aumento dell'IFN γ serico e del livello di immunoglobuline (IgA e IgG) circolanti.

In uno studio in aperto non controllato, condotto su 9 bambini affetti da deficit selettivo di IgA, è stato osservato un ripristino delle proprietà dei marcatori di membrana dei linfociti T e un aumento della risposta linfocitaria aspecifica.

In uno studio in doppio cieco, controllato con placebo, condotto sul lavaggio broncoalveolare di 20 soggetti affetti da bronchite cronica, è stato osservato un aumento dell'attività dei macrofagi alveolari (aumento della migrazione e della motilità, aumentato rilascio di O_2 in condizioni basali e dopo stimolazione).

Efficacia e sicurezza clinica

Adulti

In alcuni studi, in seguito all'associazione di BRONCHO MUNAL alla terapia di base, è stata osservata una minore frequenza di infezioni delle vie respiratorie (RTI) e di esacerbazioni della patologia di base in pazienti affetti da COPD/CB lieve o moderata, rinosinusite cronica o asma ricorrenti e di esacerbazioni delle infezioni in pazienti con condizioni respiratorie croniche di base, come COPD/CB lieve o moderata, rinosinusite cronica e asma.

In alcuni studi è stata osservata anche una riduzione del consumo di antibiotici o di altre terapie concomitanti.

Popolazione pediatrica

Il trattamento con BRONCHO MUNAL è stato associato ad una riduzione della frequenza di infezioni respiratorie acute in pazienti pediatrici con infezioni ricorrenti delle alte vie respiratorie o a rischio di URTI. In pazienti pediatrici con condizioni respiratorie croniche di base, il trattamento con BRONCHO MUNAL è stato associato ad una ridotta frequenza di esacerbazioni di rinosinusite cronica o tonsillite cronica e di manifestazioni respiratorie quali asma/sibilo.

In alcuni studi, il trattamento con BRONCHO MUNAL è stato associato ad una riduzione dell'utilizzo di trattamenti concomitanti, come antibiotici, antisettici locali o prodotti anti- infettivi, sedativi della tosse e mucolitici.

5.2 Proprietà farmacocinetiche

In base alla natura del prodotto, non può essere condotto uno studio farmacocinetico convenzionale, essenzialmente a causa della presenza di più componenti e dell'assenza di un metodo analitico idoneo.

Non ci sono dati disponibili relativamente ad assorbimento, distribuzione, biotrasformazione, eliminazione, linearità / non linearità, relazione(i) farmacocinetica(che) / farmacodinamica(che).

5.3 Dati preclinici di sicurezza

Tossicità a dose singola

La singola somministrazione endovenosa di OM-85 fino a 2,000 mg/kg nel topo e a 1,400 mg/kg nei ratti non ha provocato segni di tossicità.

Tossicità a dosi ripetute
La somministrazione orale ripetuta di OM-85 per 26 settimane nei ratti a dosi fino a 2,000 mg/kg/die e per 3 mesi nei cani a dosi fino a 100 mg/kg/die non ha rivelato effetti tossici.

Carcinogenicità
Non sono disponibili dati sulla possibile azione carcinogena di BRONCHO MUNAL dopo assunzione orale. L'esperienza clinica non fa supporre un effetto in tal senso.

Mutagenicità
I possibili effetti genotossici di OM-85 liofilizzato sono stati esaminati in una serie di saggi di tossicità genetica, costituiti da test di retromutazione batterica in vitro (test di Ames, che utilizza *S. typhimurium* ed *E. coli*), test dei micronuclei in vivo e test delle aberrazioni cromosomiche. OM-85 non ha indotto mutazioni nei saggi in vitro e in vivo.

Disturbi della fertilità
La somministrazione orale di OM-85 liofilizzato fino a una dose massima di 1.600 mg/kg/die a ratti maschi e femmine non ha mostrato alcun effetto sulla fertilità e sulla riproduzione. Il trattamento è stato ben tollerato e non ha influenzato le prestazioni di accoppiamento, i tassi di impianto e di aborto spontaneo, il numero di cuccioli per animale, il rapporto maschi/femmine e il peso del feto. Il comportamento riproduttivo e la fertilità della prima generazione erano normali e anche la prole della seconda generazione non ha mostrato anormalità.
In ratti femmina trattati durante la gestazione fino a 21 giorni dopo il parto con una dose massima di 1.600 mg/kg/die di OM-85, il comportamento, il parto e l'allattamento erano comparabili con quelli dei gruppi di controllo.

Teratogenicità
La somministrazione orale a ratti e conigli in gestazione fino a una dose massima di 1.600 mg/kg/die di OM-85 è stata ben tollerata e non ha causato effetti tossici significativi su embrioni o feti rispetto ai controlli.

6. INFORMAZIONI FARMACEUTICHE

6.1 Elenco degli eccipienti
Capsule rigide:
Amido di mais (pregelatinizzato), mannitolo, propile gallato anidro (E310), sodio glutammato anidro, magnesio stearato.
Composizione dell'opercolo della capsula: gelatina; titanio diossido (E171), indigotina (E132).
Granulato in bustina
Amido di mais pregelatinizzato, mannitolo, magnesio silicato, propile gallato anidro (E310), sodio glutammato anidro, magnesio stearato.

6.2 Incompatibilità
Non pertinente.

6.3 Periodo di validità
3 anni.

6.4 Precauzioni particolari per la conservazione
Questo medicinale non richiede alcuna condizione particolare di conservazione.

Conservare nella confezione originale per proteggere il medicinale dalla luce.

6.5 Natura e contenuto del contenitore
BRONCHO MUNAL Adulti 7 mg/Bambini 3,5 mg capsule rigide:
confezioni da 10 capsule rigide e 30 capsule rigide.
Le capsule sono confezionate in blister, con un lato di PVC/PVDC e l'altro di alluminio/PVDC.
BRONCHO MUNAL Bambini 3,5 mg granulato in bustina:
Confezione da 10 bustine.
Confezione da 30 bustine.
Bustine in accoppiato carta/alluminio/polietilene.
È possibile che non tutte le confezioni siano commercializzate.

6.6 Precauzioni particolari per lo smaltimento e la manipolazione
Nessuna istruzione particolare per lo smaltimento.
Il medicinale non utilizzato ed i rifiuti derivati da tale medicinale devono essere smaltiti in conformità alla normativa locale vigente.

7. TITOLARE DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO
ABIOGEN PHARMA S.p.A.
Via Meucci 36 – Ospedaletto - PISA

8. NUMERI DELL'AUTORIZZAZIONE ALL'IMMISSIONE IN COMMERCIO

BRONCHO MUNAL Adulti 7 mg capsule rigide - 30 capsule	A.I.C. n. 026609026
BRONCHO MUNAL Adulti 7 mg capsule rigide - 10 capsule	A.I.C. n. 026609014
BRONCHO MUNAL Bambini 3,5 mg capsule rigide - 30 capsule	A.I.C. n. 026609040
BRONCHO MUNAL Bambini 3,5 mg capsule rigide - 10 capsule	A.I.C. n. 026609038
BRONCHO MUNAL Bambini 3,5 mg granulato in bustina – 30 bustine	A.I.C. n. 026609053
BRONCHO MUNAL Bambini 3,5 mg granulato in bustina – 10 bustine	A.I.C. n. 026609065

9. DATA DELLA PRIMA AUTORIZZAZIONE/RINNOVO DELL'AUTORIZZAZIONE
Data del rinnovo più recente: Gennaio 2008

10. DATA DI REVISIONE DEL TESTO
Dicembre 2021

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E.C.M.

Il corso sarà inserito nella lista degli eventi definitivi ECM del programma formativo 2024 del Provider accreditato DYNAMICOM EDUCATION (cod. ID 181).

Chairmen

Francesco de Blasio

Mino Pelaia

LOCATION

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