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After 30 years, the annual recommendations of GINA proceeded to a major update in the stepwise therapeutic approach to asthma, affecting the way patients diagnosed with asthma are treated. More specifically, for Steps 1 and 2 treatment, the recommended use of SABA as a reliever therapy has been replaced by the use of low dose ICS-formoterol as a rescue medication. SABA inhalers can be entirely omitted for most patients with asthma, although GINA does not entirely eliminate their use as an add-on reliever therapy. Moreover, it is suggested the starting treatment to be directly with ICS-LABA even in patients with mild asthma, excluding the “step-up” process of ICS alone to ICS-LABA. In this way, most patients with asthma can be prescribed just one inhaler that can be used as both a maintenance (preventive) and rescue treatment: an inhaled corticosteroid-and-long-acting beta agonist, that is formoterol (ICS-LABA). All patients with asthma should receive at minimum an ICS-containing controller treatment either as needed or daily low dose (in mild asthma) for exacerbation prevention.

The explanation behind this change is based on a multiyear effort to provide evidence for new treatment strategies for as-needed asthma therapies, focusing on the use of a single inhaler. There is also evidence that frequent use of SABA-only increases the risk of exacerbations instead of protecting patients from them, despite of short-term relief of asthma symptoms, leading even to death. The combination of a fast-acting β₂-agonist and inhaled glucocorticoid on an as-needed basis — an anti-inflammatory reliever approach — has been proposed as a potential alternative strategy than SABA reliever alone. Several multicenter randomized trials aimed to show the effectiveness of combination products (ICS-SABA/LABA) compared with SABA treatment, both used as needed.

Papi et al found that symptom-driven rescue use of a combination of ICS-SABA in a single inhaler for 6 months is equivalent to regular treatment with inhaled beclomethasone in controlling mild persistent asthma, suggesting that mild persistent asthma may only require as-needed use of an inhaled corticosteroid and an inhaled bronchodilator, rather than regular treatment with inhaled corticosteroids.

Budesonide-formoterol as needed in mild asthma was investigated in two double-blind randomized studies, SYGMA 1 and 2, comparing budesonide-formoterol as needed with budesonide plus SABA and SABA alone. SYGMA 1 showed that as-needed budesonide-formoterol (ICS-LABA) provided
superior asthma symptom control to as-needed SABA terbutaline, but with a slight superiority (34.4% vs 31.1% of electronically recorded weeks, OR 1.14, p=0.046 within the statistical significance limits). However, as-needed budesonide-formoterol, it was inferior to budesonide maintenance therapy in asthma control (34.4% vs 44.4%, OR 0.64, 95% CI 0.57-0.73). Regarding exacerbations, budesonide-formoterol showed superiority to as-needed terbutaline, while it had similar exacerbation rates with budesonide maintenance group. SYGMA 2\(^9\) concluded that budesonide-formoterol as needed was non-inferior to twice daily budesonide with respect to the rate of severe asthma exacerbations but was inferior in symptom control. In the budesonide-formoterol as needed group patients had lower ICS exposure -approximately one quarter- than those in the budesonide maintenance group.

Another study, Novel START, complementary of SYGMA 1 and 2 tried to implement more real-life conditions and showed that in patients with mild asthma budesonide-formoterol as needed was superior to albuterol for the prevention of asthma exacerbations. However, regarding asthma control budesonide maintenance treatment group was superior to budesonide-formoterol as needed, a finding that favors this option in a patient whose asthma symptoms are the most bothersome\(^9\).

A following study (PRACTICAL), which is a 52-week open label multicenter superiority trial examined as a primary outcome the number of severe asthma exacerbations per patient per year in two treatment groups: ICS-LABA as needed vs ICS maintenance. Severe exacerbations per patient per year were lower with as-needed budesonide-formoterol than with budesonide maintenance plus terbutaline as-needed, although the authors concluded that the study provided “modest” evidence for the superiority of budesonide-formoterol to the reduction of exacerbation rates\(^\text{11}\).

When it comes to clinical practice, several factors such as patient preference, or the possibility of poor adherence should also be taken into consideration. It is common that patients are usually concerned about the adverse effects of ICS, even with low doses and the potential risks of treatment resulting in overreliance on SABAs and poor adherence to ICS maintenance treatment\(^\text{12,13}\). Even more common, an asthmatic with minor symptoms is vulnerable in stopping his regular treatment despite the doctor’s advice. In addition, although in mild asthma symptoms may be tolerable, airway inflammation usually exists and the risk for severe exacerbations still remains for these patients\(^\text{14}\). Another consideration is the treatment target: symptom control or reduction in the risk of exacerbations, an issue that poses again dilemmas about adherence and clinical status. The answer is to target both. Nevertheless, further studies are needed on this matter as all these studies still leave unanswered questions about the long-term impact of these strategies on airway inflammation, hyper-responsiveness, remodeling and asthma mortality compared with regular ICS usage\(^\text{15,16}\).

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CONFLICTS OF INTEREST
No conflicts of interest to declare.

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Family caregivers burden of patients with chronic diseases

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Key words:
- Family caregivers
- informal caregivers
- burden
- chronic illness
- burden identifiers
- aging population

Under the influence of the past decade's social, technological and economic developments Greece has been undergoing a period of important demographic changes. The birth deficit, immigration and the increasing life expectancy have changed the country's aging structure profile. The population pyramid is based on an aging population and the trend does not show any signs of reversal. At the same time, under the influence of medical technological developments and the changing lifestyle, a transformation of the disease model towards an increase of chronic diseases is taking place. Greece's health system is unable to cope with the increased nursing needs of chronic disease patients and as a result home caregivers have taken on more serious responsibilities on top of performing their daily duties.1,2

According to data of the Hellenic Statistical Authority one in two people, over the age of 15, has declared suffering from chronic illness.3 As Biegel has suitably asserted “given that no person lives in a vacuum all the consequences of a chronic illness are being borne directly or indirectly by his immediate environment meaning the family”.4 As stated by the Organization for Economic Co-operation and Development (OECD), at least one in ten adults is engaged in the informal unpaid care of friends or relatives saving up and underwriting the gaps of the national health system. The existing bibliography suggests that the role of the home caregiver is most frequently assumed by other family members (mostly spouses, children, siblings and grandchildren). To a lesser extent other relatives and friends also take the role of the home caregiver although they seldom take full care responsibilities. It is the social framework, religious beliefs and the cultural context that are usually putting the family in the role of the informal health carer.5,6

The main impact of informal home care- with only a few exceptions- has been to place emotional and physical burdens to the home caregivers but also social and financial ones. Serious consequences on mental health have also been observed such as depression, anxiety disorders, drugs and other substances abuse as well as in physical health with cardiovascular diseases, infections, malignant tumors and ultimately deaths. The literature also mentions some positive effects such as development of self-esteem, companionship, pride, and satisfaction. Patient features on the one hand, such as their age, functional level, as well as traits of their caregiver, such as gender, age, nationality, educational level, working status, income, care giving time, the existence of social support or the reciprocity of relation-
ships and their state of health, all seem to be involved in the manifestation of the burden. 7-10

In an attempt to record the burden of family caregivers of chronic patients hospitalized in the pulmonary clinic of the General Hospital of Serres, we performed a cross-sectional study involving 100 family caregivers of patients with one or more chronic diseases, of whom others were admitted to the Pulmonary Clinic and others went to regular outpatient clinics of the General Hospital of Serres. The Zarit Burden Interview questionnaire was used to measure the burden, while the Katz and Lawton questionnaires were used to rank patients’ functional level. At the same time, demographic data of patients and their caregivers were also recorded.11,12

Based on the sampled data, we observe that family caregivers of patients with chronic illnesses experience a moderate to severe burden. After applying a multivariate linear regression, it was found that caregivers with self-reported low personal incomes, lower self-reported overall health status, who care for a patient with reduced functional ability and older age are experiencing a greater burden degree.

The results highlighted the magnitude of the problem of the burden of family caregivers of patients with one or more chronic illnesses with or without dementia. The moderate to severe burden found in our study is confirmed by a number of studies in the literature.13-17

As the health system in Greece and other countries increasingly transfers responsibility to families of patients with chronic illnesses burdening them both financially and socially and psychologically, support actions are required. Health policies with the social network of health services need to organize strategies and interventions such as home care by professional caregivers who can at the same time teach skills and techniques to responsible relatives, handing out care allowances, and providing caregivers with periods of respite along with a transfer of accountability to official health structures or voluntary organizations at regular intervals to prevent or minimize the impact of the burden on this group of people and protect their quality of life.

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The Novel Measurements and Correlations for Pulmonary Function Tests (TNMC-PFT) in interstitial lung diseases (ILD) - Using technology to simplify patient care

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Key words:
- TNMC-PFT
- Metronome
- Single breath count
- Breath holding time
- FVC
- Six-minute walk distance

ABSTRACT
BACKGROUND Interstitial lung disease (ILD) patients often have difficulty in performing spirometry. Simple tests of pulmonary functions like the single breath count (SBC) and breath hold time (BHT) have been studied since years. At our institute (TNMC) we used these tests innovatively with modern technology in cases of ILD. The novel measurements and correlations for pulmonary function tests (TNMC-PFT) were compared with standard measures of PFT. MATERIAL AND METHODS A prospective study was conducted in adult ILD patients referred to the PFT laboratory of a tertiary care hospital. The diagnosis of interstitial lung disease was arrived at with multi-disciplinary discussion. Spirometry, SBC and BHT were recorded. SBC was timed to a metronome (downloaded from a free online App) set at 2 counts per second. Six minute walk test was done. The average of SBC and BHT were labelled as TNMC-PFT. Spearman’s Rho calculator was used to study correlation of TNMC-PFT with spirometry and six-minute walk distance (6MWD). RESULTS The study included 18 men and 47 women. They consisted of 21 hypersensitivity pneumonitis, 17 CTD-ILD, 7 sarcoidosis, 11 idiopathic pulmonary fibrosis, 5 idiopathic non-specific interstitial pneumonia, and 4 other ILD cases. Mean Age, FVC and 6MWD were 51.1 (14.9) years, 1.3 (0.5) L and 266.2 (75.5) m. SBC, BHT and their average (TNMC-PFT) correlated moderately with FVC (r=0.5, p<0.05) and 6MWD (r=0.5, p<0.05). CONCLUSION TNMC-PFT correlated well with FVC and six minute walk distance. TNMC-PFT can be a potential alternative to spirometry in ILD in severe disease and resource limited settings.

INTRODUCTION

Interstitial lung disease are a group of heterogenous disorders affecting the alveolo-capillary membrane. Pulmonary function tests (PFT) have a role in the management of these patients. However, ILD patients often have difficulty in performing simple spirometry and are often unable to perform other complex PFTs. Simple tests of pulmonary functions like the single breath count (SBC) and breath hold time (BHT) have been studied since years. At our institute (TNMC) we used these tests innovatively in cases of interstitial lung diseases (ILD). The novel measurements and correlations for pulmonary function tests (TNMC-PFT) were compared with standard measures of PFT like spirometry and six minute walk distance (6MWD).

METHODOLOGY

A prospective observational study was conducted in adult ILD patients referred to the PFT laboratory of a tertiary care hospital with ethics committee permission from May 2018 to October 2018. The study was an independent analysis of ILD patients enrolled in a study on profile of ILD at our center. Consequent patients were enrolled in the study. As follow-up was not the objective of the study; the chronologically first PFT was only included in case of repeated follow-up of the same patient within the six-month study period. The diagnosis of ILD was arrived at with multi-disciplinary discussion and clinico-radiological correlation. Clinical history and examination were noted from patient’s clinic database. The radiographic features on chest X-Ray and high resolution computed tomography of thorax were documented. Spirometry was performed on an ATS/ERS 2005 compliant pulmonary function test machine (KOKO spirometer) first by a PFT technician. The variables of forced vital capacity (FVC), forced expiratory volume in first second (FEV1), the FEV1/FVC ratio and the peak expiratory flow (PEF) were measured. The SBC was recorded after 10 minutes of completion of spirometry. The patients were asked to take a deep breath and count as far as possible in their normal speaking voice without taking another breath. SBC was measured in cadence to a metronome (downloaded from a free online application) set at 2 counts per second. Figure 1 is the schematic representation of the metronome used in the study with arrow pointing to selection frequency of 120 beats per minute i.e 2 beats per second. Best of three attempts was noted. BHT was recorded after 10 minutes of SBC testing. The patients were asked to hold their breath after an effort inhalation until the breaking point and time duration was recorded in seconds. The best of three attempts was noted. Six minute walk test was done under supervision of a doctor as per ATS/ERS recommendation 10 minutes after BHT measurement. The 6MWD was recorded. All patients were offered bronchoscopy and transbronchial lung biopsy (TBLB).

Qualitative data was analysed with percentages and mean. The patients performed variably on the SBC and BHT manoeuvres, hence their average value was calculated. This parameter, “The Novel Measurement and Correlation of Pulmonary Function Test” was labelled as TNMC-PFT as it represented the abbreviated name for the purpose of the test as well as our institute too. Spearmen’s Rho calculator was used to study correlation of SBC, BHT and TNMC-PFT with FVC and six minute walk distance. P value of less than 0.05 was considered to be significant.

RESULTS

Total 81 patients of ILD presented to the PFT lab during the study period. Of them, 16 patients came for a repeat PFT. Their first PFT was only included. Thus the study included 65 patients finally. They consisted of 18 (27.7%) men and 47 (72.3%) women. The ILD subtype distribution was 21 (32.3%) hypersensitivity pneumonitis (HP), 17 (26.2%) connective tissue diseases associated ILD.
(CTD-ILD), 7 (10.8%) sarcoidosis, 11 (16.9%) idiopathic pulmonary fibrosis (IPF), 5 (7.7%) idiopathic non-specific interstitial pneumonia (iNSIP) and 4 (6.1%) others ILD (one cryptogenic organising pneumonia, one drug induced ILD, one Hermansky-Pudlak syndrome associated ILD & one Neurofibromatosis associated ILD). Mean age of the patients was 51.1 (14.9) years. The mean height and weight were 151.3 (9.7) cm and 55.4 (15.5) kg respectively. Seventeen of the eighteen men were smokers. None of the women smoked. All patients complained of cough and breathlessness. The severity varied. Thirty eight had comorbidities. Forty-three had Vitamin D deficiency. The clinical examination revealed crackles in all patients. The chest X-ray showed bilateral reticulonodular changes in all. HRCT thorax was consistent with changes of ILD and helped in the MDD.

The mean FVC was 1.3 (0.5) litres. The mean 6MWD was 266.2 (75.5) meters. The mean SBC was 20.5 (5.6) ranging from minimum count of 10 to maximum of 35. The mean BHT was 18.1 (5.5) ranging from 8 to 35 seconds. The mean TNMC-PFT was 19.1 (5.4) ranging from 9 to 32.5. The SBC correlated strongly with FVC (r = 0.46, p<0.05) and 6MWD (r = 0.48, p<0.05). The BHT correlated strongly with FVC (r = 0.54, p<0.05) and 6MWD (r = 0.48, p<0.05). The TNMC-PFT correlated strongly with FVC (r = 0.51, p<0.05) and 6MWD (r = 0.49, p<0.05). Fifty-seven patients had an FVC of more than one litre and 61 patients had a BHT of more than 10 seconds. Table 1 summarises the clinical characteristics of the various ILD.

In nine of total patients, bronchoscopy and TBLB was not done due to various reasons (unwillingness on part of patient-6, baseline desaturation - 2, resolution of ILD - 1). In the rest 56 patients; 29 (52%) had a positive yield, 17 (30%) had negative yield and in 10 (18%) records were not available for TBLB. Amongst the 21 HP patients; TBLB was consistent with diagnosis in 12 (57%), inconclusive in 5 (24%), records not available in 3 (14%) and not done in 1 (5%). Amongst the 17 CTD-ILD; TBLB was consistent with diagnosis in 8 (47%), inconclusive in 4 (23%), records not available in 2 (12%) and not done in 3 (18%). In Sarcoidosis, TBLB was consistent with diagnosis in 6 (86%), inconclusive in none and records not available in 1 (14%). In IPF, TBLB was consistent with diagnosis in 1 (9%), inconclusive in 5 (46%), records not available in 1 (9%) and not done in 4 (36%). Amongst the iNSIP, TBLB was consistent in 1 (20%), inconclusive in 2 (40%) and records not available in 2 (40%). TBLB was not done in COP (as disease had resolved), conclusive in HPS-ILD & NF-ILD and inconclusive in Drug induced ILD.

### DISCUSSION

ILD is a heterogenous disease with ongoing research in its multitude aspects. While the investigation aspect focuses on newer invasive procedures to prove the type of ILD; modification/simplification of the common PFTs

<table>
<thead>
<tr>
<th>Type of ILD</th>
<th>N</th>
<th>M/F</th>
<th>Mean Age</th>
<th>Mean Height</th>
<th>Mean Weight</th>
<th>Mean FVC</th>
<th>Mean 6MWD</th>
<th>Mean SBC</th>
<th>Mean BHT</th>
<th>Mean TNMC-PFT</th>
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<tbody>
<tr>
<td>HP</td>
<td>21</td>
<td>6/15</td>
<td>54.4 (12.1)</td>
<td>151.3 (10.1)</td>
<td>62.5 (16)</td>
<td>1.2 (0.5)</td>
<td>268.1 (64.5)</td>
<td>19.9 (4.3)</td>
<td>17.7 (3.9)</td>
<td>18.8 (3.7)</td>
</tr>
<tr>
<td>CTD-ILD</td>
<td>17</td>
<td>4/13</td>
<td>43.7 (13.8)</td>
<td>151.8 (10.8)</td>
<td>50.6 (14.5)</td>
<td>1.3 (0.6)</td>
<td>258.8 (80.8)</td>
<td>21.8 (6.5)</td>
<td>19.3 (6.3)</td>
<td>20.3 (6.5)</td>
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<tr>
<td>Sarcoidosis</td>
<td>7</td>
<td>1/6</td>
<td>42.9 (17.1)</td>
<td>151.9 (4.7)</td>
<td>52.7 (14.3)</td>
<td>1.6 (0.6)</td>
<td>314.3 (86.6)</td>
<td>21.4 (3)</td>
<td>17.9 (2.9)</td>
<td>19 (3.9)</td>
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<tr>
<td>IPF</td>
<td>11</td>
<td>5/6</td>
<td>63.3 (14.5)</td>
<td>152.6 (9.1)</td>
<td>50.4 (12.7)</td>
<td>1 (0.5)</td>
<td>246.4 (46.5)</td>
<td>15.7 (5.3)</td>
<td>14.7 (5.5)</td>
<td>15.2 (5)</td>
</tr>
<tr>
<td>iNSIP</td>
<td>5</td>
<td>2/3</td>
<td>49.8 (12.7)</td>
<td>150.4 (9.4)</td>
<td>57 (15.6)</td>
<td>1.4 (0.4)</td>
<td>274 (111.7)</td>
<td>26.4 (3.5)</td>
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<tr>
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<td>0/1</td>
<td>51</td>
<td>146</td>
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<td>1.8</td>
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<tr>
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<td>158</td>
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<td>1.8</td>
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<td>15</td>
<td>10</td>
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</table>

The smartphone downloadable free metronome obviates the need to carry a physical metronome along. Phones can install a wide range of metronome apps which may provide a click track to synchronize musicians. Smart applications, such as film scoring, a software metronome audio multitrack software packages. In recording studio computers and smartphones, or in music sequencing and metronomes run either as stand-alone applications on keyboards have built-in metronome functions. Software dial or buttons to control the tempo. Many electronic musicians use a metronome as a standard tempo reference. The various kinds of metronome are mechanical, electronic, software and apps. A mechanical metronome uses an adjustable weight on the end of an inverted pendulum rod to control tempo. The weight slides up the pendulum rod to decrease tempo, or down to increase tempo. The pendulum swings back and forth in tempo, while a mechanism inside the metronome produces a clicking sound with each oscillation. Mechanical metronomes don’t need a battery, but run from a spring-wound clockwork escapement. Most modern metronomes are electronic and use a quartz crystal to maintain accuracy, comparable to those used in wristwatches. The simplest electronic metronomes have a dial or buttons to control the tempo. Many electronic musical keyboards have built-in metronome functions. Software metronomes run either as stand-alone applications on computers and smartphones, or in music sequencing and audio multitrack software packages. In recording studio applications, such as film scoring, a software metronome may provide a click track to synchronize musicians. Smart phones can install a wide range of metronome apps which obviates the need to carry a physical metronome along. We used the smartphone downloadable free metronome app for this study.

In our study the SBC, BHT and their average TNMC-PFT correlated strongly with FVC and 6MWD. There are no previous documentation of the TNMC-PFT. We found that ILD patients performed variably with the SBC and BHT irrespective of the spirometry readings. Hence we took an average of both the readings to explore uneven details. The SBC and BHT have correlated with lung functions like PEF in healthy adults. The BHT was found to be gender independent. The SBC measurement with an mobile app has been documented once in literature in healthy individuals. As far as disease states were concerned, the SBC correlated with FEV1 and PEF in adult patients with obstructive airway diseases. The SBC correlated with lung functions both PEF and FVC in situations wherein spirometry is difficult to perform like children and neurological diseases. There is no mention of SBC or BHT in ILD as a large patient series. In a case study, SBC correlated with lung function post single lung transplant in an ILD patient.

As a by-product of this study also we discovered few new details. The change in the spectrum of ILD as compared to that reported earlier at our center was consistent with the changing trends as reported by the ILD India registry. We reported a predominant IPF disease earlier, now the cases of HP seemed to form the major group. This could be due to newer insight into the disease diagnostics and an slight investigator bias at the physician and radiology end post publication of the registry data. To avoid the bias we offered TBLB to all our patients. The yield of bronchoscopy guided TBLB in ILD was also studied. The good TBLB yield of 57% in HP was an interesting finding further reiterating the need for use of simpler invasive established procedures like TBLB in this disease which is an airway centred ILD. The poor yield in IPF is known, but with the MDD criteria in place there remains no need for any biopsy diagnosis in IPF. The small sub-groups of INSIP and the HP-inconclusive on TBLB could benefit from biopsies obtaining larger lung tissue for analysis like surgical lung biopsy or cryobiopsy. Analysis of a larger database would provide further validity to these.

Limitations of study- Our study was disease centred and not population centred like most studies on PFT. As our focus was ILD patients we focused on the disease. The site of study being a tertiary care center, the selection bias and referral bias were unavoidable. We did not include a control arm as we wanted to set a background for future elaborate studies. We studied only the correlation aspect. Severity classification of the disease on lines with the FVC and six minute walk test criteria was not attempted. While
most patients could have performed DLCO manoeuvre as per ATS/ERS criteria, DLCO was not a part of the study protocol due to erratic gas supply.

To conclude, we used technology to simplify patient care. TNMC–PFT correlated well with FVC and six minute walk distance. In ILD patients unable to perform spirometry, TNMC- PFT can be a reasonable alternative to spirometry.

REFERENCES


Comparison of face-to-face Education of Caregivers and Hospitalized Elderlies with COPD and Its Impact on the Elderlies’ Self-care

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Key words:
- Elderly
- Carer
- Face-to-face Education
- Self-care
- Chronic Obstructive Pulmonary Disease

ABSTRACT

BACKGROUND: It is widely accepted that family members play a vital role in the health of patients with chronic diseases and promotion of healthy behaviors. This study aimed to compare face-to-face education to caregivers and elderlies with chronic obstructive pulmonary disease (COPD) and its impact on the self-care of the elderlies.

MATERIALS AND METHODS: This interventional study was carried out on 58 elderlies with COPD, who referred to a Hospital in Esfarayen, Iran from January 10, 2019 to August 30, 2019. The subjects were divided into two groups of elderly and caregiver education by random allocation. Self-care was taught to all participants individually by the researcher over four sessions. In addition, COOPDSC, CAT, and MNA questionnaires were completed by the subjects before the intervention, during discharge, and one month after the intervention.

RESULTS: In this study, comparison of mean self-care scores of the two groups revealed no significant difference before the intervention (P=0.06) and during discharge (P=0.12). However, there was a significant increase in the mean self-care score of the subjects in the group of education to the caregivers and elderlies, compared to the group of education to the elderlies (P=0.01).

CONCLUSION: According to the results, self-care education of elderlies and caregivers increased the level of self-care in patients. Therefore, it is recommended that the education provided by the health care providers be performed in the presence of the patient’s caregiver in order to improve the patients’ self-care.

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INTRODUCTION

Patients with Chronic Obstructive Pulmonary Disease (COPD) suffer from many problems, such as shortness of breath, intolerance, lack of proper air-
way clearance, lack of effective breathing patterns, cough and sputum, social isolation, and depression. Due to the debilitating nature of COPD, costs that directly caused by health care or indirectly imposed on family and society due to absence from work, causes a great socioeconomic burden on the individual and the healthcare system. The valuable and beneficial effects of patient education have been repeatedly stated in various studies. This will increase client satisfaction, improve quality of life, ensure continuity of care, alleviate patient anxiety, reduce the incidence of complications, increase participation in health care programs, and achieve client independence in daily living activities. Self-care is defined as activities individuals undertake with the intention of enhancing health, preventing disease, limiting illness, and restoring health. Lack of knowledge of self-care is the main cause of re-hospitalization of patients with chronic diseases such as COPD that can be avoided by training. In addition, education of self-care leads to increased quality of life, ensuring of continued care, decreased anxiety, less emergence of complications, increased cooperation in care programs, increased independence of patients in performing their daily activities and decreased costs. Self-care in chronic illnesses implies monitoring and controlling the symptoms of the disease, adherence to treatment, maintaining a healthy lifestyle, controlling the disease, daily functioning, emotions and social relationships. Many studies have been done on the methods of teaching the COPD patients. For example, Bourne and colleagues compared face-to-face versus online lung rehabilitation with six training sessions and found that the online method could be as effective as face-to-face in lung rehabilitation. Doğan and colleagues studied COPD patients' continuing health education by nurses and found that these trainings have had a significant improvement in PaO$_2$, PaCO$_2$, FEV$_1$, and SaO$_2$ patients.

Despite investigating the efficacy of multiple education methods on empowering COPD patients, there was no study found in searches, comparing face-to-face education of two groups of elderly patients and their caregivers, and its effect on elderly self-care. And considering the fact that most elderly people with COPD referred to Iranian hospital centers are illiterate, their self-care measures include medication adherence, avoidance of environmental contaminants and allergens, pulmonary rehabilitation therapies, needs more attention. Perhaps the caregivers' education, in addition to elders' education with a face to face method may improve patients' ability to self-care. Therefore, the present study aimed to compare of Face-to-face Education of Caregivers and Hospitalized Elderlies with COPD and Its Impact on the Elderlies' Self-care.

**MATERIALS AND METHODS**

**Design and participants**

This double-blind (patients-statistician) clinical trial was conducted on 58 elderlies who referred to Imam Khomeini Hospital in Esfaryen, Iran from January 10, 2019 to August 30, 2019. Inclusion criteria included: age above 60 years, diagnosis of COPD, lack of blindness or deafness, residing in Esfaryen, lack of severe chronic disease (any type of chronic disease, including CVA, paraplegia, epilepsy, and seizures), and no psychological diseases. Exclusion criteria were: lack of completing the post-test questionnaire, death during the study, and discharge from hospital in less than five days. Inclusion criteria of the caregivers was age of 18 years to take care of the elderly, being literate, and being responsible for the elderly most of the times. Exclusion criteria of these individuals included absence from two or more face-to-face training sessions and delivering elder care to another person. The CONSORT checklist was used for report of study.

**Intervention**

Due to a lack of similar research, 10 individuals were selected as a pilot group. The sample size was determined at 25. After receiving permissions from North Khorasan University of Medical Sciences, the permission letter was taken to Imam Khomeini Hospital from the head of the hospital. Participants were selected by convenience sampling based on inclusion and exclusion criteria and using the random allocation with permuted block method, according to sample size. 30 individual assigned to the group of education of the elderly and 30 individual assigned to the group of education of both elderly and caregivers. While 30 elderlies were selected for each group, two of the subjects died during the research, which resulted in a decrease in the number of samples to 29 in each group.

Research objectives and methodology were explained to all participants prior to the research. At first, followed by a pre-test including chronic obstructive pulmonary disease self-care behavior inventory (COPDSC), which was formerly validated by Abedi et al and its validity and reliability were confirmed. In the present research, the reliability of the mentioned tool was confirmed at the Cronbach's alpha of 0.72. The content of the educa-
RESULTS

Among the elderlies, 27 (46.6%) were male and 31 (53.4%) were female. The mean age of the intervention (Elderly and care giver education) and control group (Education to the Elderly) was 69.39±8.23 and 70.56±6.57 years, respectively. Other demographic characteristics of the subjects are shown in the related table based on the group. According to the results, no significant difference was observed between the groups in terms of gender, level of education, smoking status, disease duration, monthly income level, type of disease, allergen exposure, marital status, occupational status, place of residence, and drug consumption (P>0.05) (Table 1 and Figure 1).

On the other hand, statistical analysis results were indicative of a significant difference between the self-care scores of the elderly teaching group before the intervention, during discharge, and one month after the intervention (P<0.001). Given the significance of Friedman’s test, we used the post hoc tests with Bonferroni correction factor to evaluate the in-group differences of self-care status. In the elderly teaching group, a significant difference was detected between the times of before and during the intervention (P<0.001) and before and one month after the intervention (P<0.001). However, no significant difference was observed between during discharge and one month after the intervention (P>0.99) in this regard.

According to Table 2, while the mean score of the elderly education group was lower at all stages, no significant difference was observed in mean self-care score of both groups before the intervention (P=0.067) and during discharge (P=0.127). However, the mean self-care score significantly increased in the elderly and caregiver education groups one month after the intervention, compared to the elderly education group (P=0.015) (Table 2). The results also demonstrated a significant difference between self-care score in the elderly and caregiver education group before the intervention, during discharge and one month after the intervention (P<0.001). After the post hoc tests along with Bonferroni correction factor to assess the inner-group differences, there was a significant difference in the self-care status of the elderly and caregiver education group between the times of before the intervention and during discharge (P<0.001) and before and one month after the intervention (P<0.001). Nevertheless, no significant difference was observed between during discharge and one month after the intervention (P=0.637) (Table 2).
TABLE 1. Characteristics of the patients in the intervention (Elderly and care giver education) and control groups (Education to the Elderly)

<table>
<thead>
<tr>
<th>Variables</th>
<th>Intervention (n=29) (Elderly and care giver education)</th>
<th>Control (n=29) (Education to the Elderly)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Year)</td>
<td>Mean (SD) 69.39 (8.23)</td>
<td>Mean (SD) 70.56 (6.57)</td>
<td>0.863*</td>
</tr>
<tr>
<td>Gender</td>
<td>Male 17 (58.3%)</td>
<td>15 (51.7%)</td>
<td>0.559***</td>
</tr>
<tr>
<td></td>
<td>Female 12 (41.7%)</td>
<td>14 (48.3%)</td>
<td></td>
</tr>
<tr>
<td>Duration of illness</td>
<td>Less than 1 year 5 (21.2%)</td>
<td>11 (42.3%)</td>
<td>0.482***</td>
</tr>
<tr>
<td></td>
<td>1-2 years 12 (36.8%)</td>
<td>6 (15.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2-3 years 2 (10.5%)</td>
<td>4 (11.5%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>More than 3 years 10 (31.6)</td>
<td>8 (30.8%)</td>
<td></td>
</tr>
<tr>
<td>Level of education</td>
<td>Illiterate 12 (41.4%)</td>
<td>13 (44.8%)</td>
<td>0.661****</td>
</tr>
<tr>
<td></td>
<td>Under the diploma 13 (44.8%)</td>
<td>14 (48.3%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Above the diploma 3 (10.3%)</td>
<td>3 (10.3%)</td>
<td></td>
</tr>
<tr>
<td>Status of marriage</td>
<td>Married 16 (55.2%)</td>
<td>19 (65.5%)</td>
<td>0.42****</td>
</tr>
<tr>
<td></td>
<td>Divorced and deceased spouse 13 (44.8%)</td>
<td>10 (34.5%)</td>
<td></td>
</tr>
<tr>
<td>Cigarette Smoking</td>
<td>Yes 20 (69)</td>
<td>22 (75.9)</td>
<td>0.34***</td>
</tr>
<tr>
<td></td>
<td>No 9 (31)</td>
<td>7 (24.1)</td>
<td></td>
</tr>
<tr>
<td>Location</td>
<td>City 11 (31%)</td>
<td>9 (37%)</td>
<td>0.31***</td>
</tr>
<tr>
<td></td>
<td>Village 20 (69%)</td>
<td>18 (63%)</td>
<td></td>
</tr>
<tr>
<td>Job</td>
<td>Employee 2 (6.9%)</td>
<td>2 (6.9%)</td>
<td>0.44****</td>
</tr>
<tr>
<td></td>
<td>Housewife 14 (48.3%)</td>
<td>9 (31%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Free 13 (48.8%)</td>
<td>18 (62.1%)</td>
<td></td>
</tr>
<tr>
<td>Income</td>
<td>Low 19 (65.5%)</td>
<td>21 (73.5%)</td>
<td>0.6****</td>
</tr>
<tr>
<td></td>
<td>Medium 4 (13.8%)</td>
<td>5 (17.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>High 6 (20.7%)</td>
<td>3 (10.3%)</td>
<td></td>
</tr>
<tr>
<td>Exposure to allergens</td>
<td>Food, fruits, dust and pollen 15 (51.7%)</td>
<td>11 (37.09%)</td>
<td>0.56***</td>
</tr>
<tr>
<td></td>
<td>Tobacco smoke, pollutants, Bakersies smoke 6 (20.7%)</td>
<td>5 (17.2%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Washers 1 (3.4%)</td>
<td>1 (3.4%)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Animal wool and hair 7 (24.1%)</td>
<td>12 (41.4%)</td>
<td></td>
</tr>
<tr>
<td>Medication used</td>
<td>Yes 28 (96.6%)</td>
<td>23 (79.3%)</td>
<td>0.11****</td>
</tr>
<tr>
<td></td>
<td>No 1 (3.4%)</td>
<td>6 (20.7%)</td>
<td></td>
</tr>
</tbody>
</table>

*Mann–Whitney U test; **Degrees of freedom; ***Chi square test; ****Fisher exact test

DISCUSSION

The present research was performed to compare face-to-face education of caregivers and hospitalized elders with COPD and its impact on the elderly self-care. According to the results, there was a significant difference in the self-care score of the elderly education group before the intervention and during discharge and before and one
month after the intervention. However, no significant difference was observed in the self-care score of the elders during discharge and one month after the intervention. Therefore, it seems that self-care education was effective and stable after one month. In the elderly and caregiver education group, there was a significant difference in the self-care score of the subjects before the intervention and during discharge and before and one month after the intervention. However, no significant difference was observed during discharge and one month after discharge, which means that self-care education was effective and stable after one month. Despite the significant difference in the self-care score of the two groups, one month after the intervention, self-care score was more stable in the elderly and caregiver group. Moreover, the presence of a caregiver had an apparent effect on increased mean of

**FIGURE 1.** Study flow diagram.

**TABLE 2.** Comparison of mean and standard deviation of self-care in two groups before intervention, during discharge and one month after intervention

<table>
<thead>
<tr>
<th>Groups</th>
<th>Before intervention Mean (SD***</th>
<th>Discharge Mean (SD)</th>
<th>One month after intervention Mean (SD)</th>
<th>chi-square</th>
<th>P-value *</th>
</tr>
</thead>
<tbody>
<tr>
<td>Education to the Elderly</td>
<td>101.62 (16.08)</td>
<td>111.58 (17.62)</td>
<td>110.37 (16.11)</td>
<td>33.18</td>
<td>0.001</td>
</tr>
<tr>
<td>Elderly and care giver education</td>
<td>108.7 (13.89)</td>
<td>118.55 (13.56)</td>
<td>119.96 (12.77)</td>
<td>36.77</td>
<td>0.001</td>
</tr>
<tr>
<td>P-value**</td>
<td>0.067</td>
<td>0.127</td>
<td>0.015</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Friedman test was used; **Mann Whitney test was used; ***Standard deviation
self-care in the education process from discharge to one month after that period. In a research by Alhani et al (2013), there was a significant difference in mean score of adhering to self-care behaviors based on diagnosis of COPD, and 94% of patients had poor and moderate self-care. While the results of the mentioned study are in line with our findings, the majority of the patients had good self-care score and the process was improving until the end.

Results obtained by Etemadi Sanandaji et al, showed the higher effectiveness of face-to-face education, compared to the use of guidance booklets, for COPD patients. Therefore, it is suggested that nurses use this type of training for COPD patients to play a valuable role in the improvement of their respiratory self-efficacy and enhancement of their life quality. In fact, the results showed that face-to-face education can positively increase self-care ability in the elderly with COPD. Dalwand et al introduced family-centered approach as an effective method for children, parents, families and healthcare providers, one that improves healthcare services and increases the satisfaction of families with health-related facilities. In addition, Asgari reported an improvement in laboratory indices of patients with myocardial infarction following the use of family-centered educational model.

In a research by Abdi, self-care in most elderly was recognized as a depending need, and self-care ability was shown at a high level. In the current research, while there was an increase in self-care scores of both groups, the presence of a caregiver increased the stability of the intervention. Chaoyan Wang found a positive correlation between self-care behavior in patients and duration of care for the family member. In the current research, self-care score increased in the elderly in the group of elderly and caregiver at the end of the research, compared to before the intervention. However, the research groups were homogeneous in terms of the marital status of the participants, and 79.3% of the subjects’ caregivers were their children, which might be due to high age, illness, or death of spouse. In a research to describe family support, perception of self-efficacy, and self-care behavior in patients with COPD and to determine the relationship between the variables, Kara Kaşıkçı et al, reported a significant, positive relationship between family support and self-care behavior. The results of the aforementioned research are congruent with findings since evaluation of self-care scores revealed a higher increase in the scores of the subjects in the elderly and caregiver group, compared to the other group.

One of the major drawbacks of the research was the excessive dependency of some of the elderlies to their caregivers, which inhibited their use in the study. Another limitation was lack of entering all elderlies with COPD at the sampling time due to comorbidities such as pneumonia, which may have prolonged the sampling process. Also another limitation of present study was low sample size of study that lead to reduce the generalization of study results.

CONCLUSION

According to the results of the present research, self-care education to the elderly and caregivers increased self-care ability in the elderly with COPD. It could be expressed that increasing the knowledge of caregivers and elderlies with COPD improved the self-care ability in the latter. Our findings can be exploited by nurses, healthcare centers and the welfare organization to be implemented for caregivers and elderlies in order to improve the patients’ self-care.

ACKNOWLEDGMENTS

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CONFLICTS OF INTEREST

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Pneumothorax

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Key words:  
- Spontaneous  
- Traumatic  
- Pigtail  
- Bronchopleural fistula

ABSTRACT

Itardvin coined the term pneumothorax in the year 1803 and Laennec described its clinical features in 1819. It is defined as the presence of air or gas in the pleural cavity. Pneumothorax can be primary or secondary depending on underlying lung condition. This can be further classified as spontaneous, iatrogenic and traumatic. Primary spontaneous pneumothorax described by Kjaergard in 1932; occurs in people without underlying lung disease and in the absence of an inciting event. Secondary spontaneous pneumothorax (SSP) occurs in people with a wide variety of parenchymal lung diseases. Occasionally, the amount of air in the chest increases markedly when a one-way valve is formed by an area of damaged tissue leading to a tension pneumothorax and can present as a medical emergency. Symptoms are related to the amount of air present in the pleural cavity and underlying etiology. They typically include chest pain and shortness of breath. Diagnosis by physical examination alone can be difficult or inconclusive particularly in smaller pneumothoraces and X-ray chest or computed tomography (CT) scan is usually used to confirm its presence. Small spontaneous pneumothoraces typically resolve without treatment and require only monitoring. Larger pneumothoraces where patients are symptomatic needs intervention with simple needle aspiration, pigtail catheterization or intercostal drainage tubes. 


INTRODUCTION

The term pneumothorax was first coined by Itardvin, a student of Laennec in 1803 and its clinical features are described by Laennec in 1819. It is defined as the presence of air or gas in the pleural space. Symptoms are related to the quantity of pneumothorax and the underlying etiology. They typically include chest pain and shortness of breath. Diagnosis by physical examination alone can be difficult or inconclusive particularly in smaller pneumothoraces and X-ray chest (CXR) or computed tomography (CT) is usually used to confirm its presence. Small spontaneous pneumo-
thoraces typically resolve without treatment and require only monitoring. Larger pneumothoraces where patients are symptomatic need intervention with simple needle aspiration, pigtail catheterization or intercostal drainage tubes. Bronchopleural fistula can be considered a special case of complicated persistent pneumothorax, representing a challenging management problem associated with significant morbidity and even mortality.

TYPES OF PNEUMOTHORAX (Chart 1)

Air may leak from lung to pleural space in three situations: (1) arising spontaneously by alveolar rupture; (2) introduced following trauma; (3) generated by gas forming organisms. Accordingly pneumothorax can be spontaneous and non-spontaneous. Spontaneous pneumothoraces occur without any preceding trauma or obvious precipitating causes. It is classified as primary or secondary. Primary spontaneous pneumothorax described by Kjaergard in 1932; occurs in people without underlying lung disease and in the absence of any inciting event. Secondary spontaneous pneumothorax (SSP) occurs in patients with pre-existing lung diseases such as COPD, cystic fibrosis, or pneumocystis carinii pneumonia. Non-spontaneous pneumothoraces are also known as traumatic and are subdivided into non-iatrogenic and iatrogenic. Non-iatrogenic pneumothoraces can develop following direct or indirect trauma, such as penetrating or blunt trauma to the chest, with air entering the pleural space directly through the chest wall; visceral pleural penetration; or alveolar rupture due to sudden compression of the chest. Iatrogenic pneumothorax results from a complication of diagnostic or therapeutic intervention. Common causes of primary and secondary spontaneous pneumothorax are enumerated in Table 1.

SPONTANEOUS PNEUMOTHORAX

Spontaneous pneumothorax remains a significant health problem because the recurrence rate is estimated to be approximately 10%-20%, even after surgical management is performed. Spontaneous pneumothoraces, which occur in the absence of thoracic trauma, are classified as primary or secondary. A primary spontaneous pneumothorax (PSP) is a pneumothorax that occurs without a precipitating event in a person who does not have any known lung disease. The incidence of primary spontaneous pneumothorax (PSP) in men varies geographically, from 7.4 per 100,000 population per year in the United States to 37 per 100,000 population per year in the United Kingdom. The incidence is substantially less in women than in men, ranging from 1.2 per 100,000 population per year in the United States to 15.4 per 100,000 population per year in the United Kingdom. Primary spontaneous pneumothoraces usually occurs in tall, thin men between the ages of 20 and 30 years. Smoking increases a healthy male’s lifetime risk of developing a pneumothorax from 0.1 to 12%. Height is thought to be a risk factor because the pleural pressure gradient increases from the base to the apex of the lung. Consequently, apical alveoli in taller patients are subject to far greater distending pressures, which may precipitate subpleural cyst formation.
due to the underlying lung disease, they can present with compromised respiratory reserves and can be life threatening also. The diagnosis can usually be made on CXR, however CT is sometimes necessary to differentiate pneumothoraces from large thin-walled bullae.

NON-SPONTANEOUS/TRAUMATIC PNEUMOTHORAX

They occur due to trauma which is either non-iatrogenic or iatrogenic in nature. A non-iatrogenic traumatic pneumothorax can result from either penetrating or non-penetrating chest trauma. With penetrating chest trauma; the wound allows air to enter the pleural space via the chest wall or via the visceral pleura from the tracheobronchial tree. With non-penetrating trauma, a pneumothorax may develop if the visceral pleura is lacerated secondary to a rib fracture or dislocation. In the majority of patients with pneumothorax secondary to non-penetrating trauma, however, there are no associated rib fractures. It is thought that the sudden chest compression abruptly increases the alveolar pressure, which may cause alveolar rupture. Air then enters the interstitial space and dissects toward either the visceral pleura or the mediastinum to produce mediastinal emphysema. A pneumothorax results when either the visceral or mediastinal pleura ruptures. The incidence of iatrogenic traumatic pneumothorax is also high. In a study of 3430 patients in 12 intensive care units in France, 3.0% developed a pneumothorax. The etiologies of the pneumothoraces in this study were mechanical ventilation in 42, central venous catheters in 28, thoracentesis in 21, and miscellaneous in 3. Currently, the leading cause of iatrogenic pneumothorax is transthoracic needle aspiration. The incidence of iatrogenic pneumothorax with this procedure is about 25%, and about 10% of the patients with pneumothorax receive tube thoracostomy. This procedure is more likely to result in a pneumothorax if the patient has COPD, if the lesion is deep within the lung, or if the angle of the needle route is wide.

Pneumothorax is also classified as closed, open, and valvular based on the pathology. In a closed pneumothorax the communication between the pleura and lung seals off as the lung collapses and does not reopen. Pleural pressures remain negative and air is gradually reabsorbed. An open pneumothorax has a persistent ‘air leak.’ Pleural pressures equal atmospheric pressure and

<table>
<thead>
<tr>
<th>Common causes of Pneumothorax</th>
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<tbody>
<tr>
<td><strong>Primary spontaneous</strong></td>
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<tr>
<td>Sub pleural Blebs</td>
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<tr>
<td><strong>Secondary spontaneous</strong></td>
</tr>
<tr>
<td>COPD</td>
</tr>
<tr>
<td>Cystic fibrosis</td>
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<tr>
<td>Status asthmaticus</td>
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<tr>
<td><strong>Infection</strong></td>
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<tr>
<td>Necrotising pneumonias</td>
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<tr>
<td>Granulomas</td>
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<tr>
<td><strong>Neoplastic diseases</strong></td>
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<tr>
<td>Carcinoma with ball valve obstruciton</td>
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<tr>
<td>Secondary to bronchial obstruciton</td>
</tr>
<tr>
<td>Tumor necrosis due to cytotoxic or radiation therapy</td>
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<tr>
<td><strong>Interstitial lung diseases</strong></td>
</tr>
<tr>
<td>Idiopathic pulmonary fibrosis</td>
</tr>
<tr>
<td>NSIP</td>
</tr>
<tr>
<td>Histiocytosis X</td>
</tr>
<tr>
<td>Lymphangiomyomatosis</td>
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<tr>
<td>Dube syndrome</td>
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<tr>
<td>Sarcomiosis</td>
</tr>
<tr>
<td>Pneumoconiosis</td>
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<tr>
<td><strong>Connective tissue disease</strong></td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
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<tr>
<td>Scleroderma</td>
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<tr>
<td>Ankylosing spondylitis</td>
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<tr>
<td>Marfan’s syndrome</td>
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<tr>
<td>Ehlers Danlos syndrome</td>
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<tr>
<td><strong>Iatrogenic</strong></td>
</tr>
<tr>
<td>Central venous catheterization</td>
</tr>
<tr>
<td>Thoracocentesis, pleural biopsy</td>
</tr>
<tr>
<td>Transthoracic, transbronchial biopsies</td>
</tr>
<tr>
<td>Intercostal block</td>
</tr>
<tr>
<td>Use of high PEEP</td>
</tr>
<tr>
<td><strong>Non iatrogenic</strong></td>
</tr>
<tr>
<td>Blunt and penetrating injuries such as</td>
</tr>
<tr>
<td>Rib fracture Rupture of bleb, Rupture of bronchus, lung tear</td>
</tr>
</tbody>
</table>

Male gender, tall stature, low body weight, and failure to stop smoking have been associated with an increased risk of recurrence. The risk of recurrence is reduced in patients who undergo chemical pleurodesis. Secondary spontaneous pneumothorax (SSP) occurs in patients with pre-existing lung disease such as chronic obstructive pulmonary disease (COPD), cystic fibrosis, or Pneumocystis carinii pneumonia. Due to the underlying lung disease, they can present with compromised respiratory reserves and can be life threatening also.
lung cannot re-expand. The term open is also applied to pneumothorax resulting from penetrating wound of the chest wall. A valvular pneumothorax occurs when the communication between the pleura and lung persists, but is small and act as a one-way valve, which allows air to enter during inspiration but prevents it from escaping during expiration. Tension pneumothorax usually results and pleural pressures are always positive.

Other types of pneumothorax described in literature are as follows. Tension pneumothorax is a pneumothorax complicated by cardio respiratory embarrassment due to decreased cardiac output. There will be mediastinal shift to opposite side. The intrapleural pressure exceeds atmospheric pressure throughout expiration and often during inspiration as well. Patients present with tachycardia, tachypnea, cyanosis, diaphoresis and marked hypoxemia with respiratory alkalosis or acidosis. A pneumothorax may be associated with a bronchopleural fistula. Bronchopleural fistulas (BPFs) are communications between the bronchial tree and the pleural space. They represent a challenging management problem and are associated with significant morbidity and even mortality. The term bronchopleural fistula is often used synonymously with open pneumothorax or ‘persistent air leak’ but constitutes a distinct clinical entity. A large bronchopleural fistula facilitates transmission of infection from air passages into the pleural space and empyema results. Some use terminologies as alveolar pleural fistula (APF) and bronchopleural fistula (BPF). APF (synonym: parenchymal-pleural fistulae), defined as persistent air leak for more than 24 hours after the development of an abnormal communication between the pulmonary parenchyma distal to a segmental bronchus and the pleural space. This is best distinguished from a BPF, which is a communication between the lobar or segmental bronchi and the pleural space, since aetiology and management are different. BPF presents with cough, copious purulent sputum and amorphic bronchial breath sounds on auscultation. Methylene blue injected in the pleural space is seen in the expectorated sputum (methylene blue test). CT with maximum intensity projection (MIP) images help to identify presence of BPF. The term complicated pneumothorax is suggested for pneumothorax with fluid (hydropneumothorax), pus (pyopneumothorax) or blood (hemopneumothorax). All these conditions require chest drainage as an initial management. A chronic pneumothorax results from formation of ‘pleural peel’ due to associated empyema and a persistent air leak. With increasing utilization of advanced radioimaging an entity called occult pneumothorax has been defined. It is a pneumothorax that was not suspected clinically nor was evident on the plain radiograph but rather identified on computed tomography scan.

### CLINICAL PRESENTATION

Pleuritic chest pain and dyspnoea are main symptoms. In patients with underlying lung disease, dyspnoea is severe and significant hypoxaemia can occur, even with a small pneumothorax. Arterial blood gas measurements typically show an increase in the alveolar–arterial oxygen gradient and acute respiratory alkalosis. Patients with a small pneumothorax (<15% of the hemithorax) often have a normal physical finding on examination. Tachycardia is the most common physical finding. In patients with a larger pneumothorax, examination shows decreased movement of the chest, a hyper-resonant percussion note, tracheal shift to opposite side, and decreased or absent breath sounds on the affected side. Coin test can be demonstrated. The physical findings are often subtle and may be masked by the underlying lung disease, particularly in patients with COPD. Pneumothorax may be associated with complications (Table 2). In case of a tension pneumothorax, there will be cardio respiratory embarrassment; BPF/large pneumothorax is associated with amorphic bronchial breath sounds on auscultation. A hydropneumothorax may have the signs denoted by 4S i.e. straight line dullness, shifting dullness, succussion splash and sound of coin percussion. Associated mediastinal emphysema (pneummediastinum) can cause subcutaneous emphysema, palpable crepitus and Hamman’s sign. It is characterized by precordial systolic crepitations and diminution of heart sounds.

<table>
<thead>
<tr>
<th>Complications of pneumothorax</th>
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<tr>
<td>Tension pneumothorax</td>
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<tr>
<td>Mediastinal emphysema</td>
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<tr>
<td>Bronchopleural fistula</td>
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<tr>
<td>Chronic pneumothorax</td>
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<tr>
<td>Loculated pneumothorax</td>
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<tr>
<td>Pyopneumothorax</td>
</tr>
<tr>
<td>Persistent air leak</td>
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<tr>
<td>Re-expansion pulmonary edema</td>
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</table>

*TABLE 2. Complications of pneumothorax*
RADIOLOGY

Various radiodiagnostic helps in diagnosis and management of pneumothorax. The diagnosis of pneumothorax can be confirmed in the majority of cases on an CXR – Postero-Anterior (PA) view (Figure 1) which also allows an estimation of the pneumothorax size. Air in the pleural space accumulates in the highest part of the thoracic cavity because air is less dense than the lung. A definitive radiologic diagnosis of pneumothorax can only be made when a visceral pleural line is evident as a faint but sharply defined line separating the lung parenchyma from the remainder of the thoracic cavity, which is clear and devoid of lung markings. An enlarged hemithorax, a depressed diaphragm, and a shifted mediastinum do not mean that a tension pneumothorax is present. In case of small pneumothoraces full expiratory film can be obtained in upright position. With full expiration the lung volume is reduced, and therefore the percentage of the hemithorax occupied by air increases, making identification of the visceral line much easier. Another option is to obtain lateral decubitus film with the side of the suspected pneumothorax superior. This increases the distance between the lung and the chest wall. Chronic lung conditions give rise to adhesions between parietal and visceral pleura restricting lung collapse. In such situations, a pneumothorax may be loculated and localized rather than spreading throughout the pleural space; thus altering the radiologic appearance of pneumothoraces (Figure 2). Both the BTS and ACCP guidelines divide pneumothoraces into small or large depending on the degree of lung collapse; however, they differ in their absolute definition. The BTS guidelines state that a 2 cm radiographic pneumothorax extending throughout the lung field on a CXR-PA occupies approximately 50% of the hemithorax. When the visible rim between the lung margin and the chest wall is less than 2 cm the pneumothorax is defined as small, and when the rim is greater than 2 cm it is termed large. The ACCP define a pneumothorax as small when the distance from apex to cupola is less than 3 cm, and large when the distance is greater than 3 cm.

Ultrasonography has been shown to have high sensitivity (95%), specificity (100%), and diagnostic effectiveness (98%) for pneumothorax when compared with CT as a standard. It is useful for detecting small collections not seen on plain films and the extent of the air collection can be estimated by tracking the presence of the ‘sliding lung sign’ over the chest wall. Experience in the use of ultrasound for this indication is required to be confident in its application. It is difficult or impossible to visualize pleural structures with ultrasound through surgical emphysema. A typical ‘comet tailing’ phenomenon of the movement of the lung tissue against the pleura during respiration can be seen in bullous disease, but is absent when the lung is collapsed as in pneumothorax.

CT thorax (Figure 3) is gold standard for confirmation of pneumothorax. The visible rim between the lung margin and the chest wall is less than 2 cm, indicating a small pneumothorax.

FIGURE 1. X-ray chest postero-anterior view showing pneumothorax.

FIGURE 2. X-ray chest postero-anterior view showing loculated pneumothorax.
of a pneumothorax. It also differentiates a pneumothorax from complex bullous lung disease; when aberrant chest tube placement is suspected. It allows definitive diagnosis of other pleural and lung pathologies and should be considered early when doubt exists. CT scanning is regarded as the best means of establishing the size of a pneumothorax. CT also help in distinction of pneumothorax from emphysematous bullae. The bullae of emphysema can be very large and, when situated in the periphery of the lung, can mimic a loculated pneumothorax. A chest drain inserted into a bulla in the mistaken belief that it is a pneumothorax is not uncommon. The lack of a lung edge, the round nature of the bulla, and the presence of multiple bullae elsewhere in the lung are all clues to the diagnosis. In difficult cases, CT is helpful in distinguishing between the two. The double wall sign is a valuable sign to help distinguish a pneumothorax from adjacent giant bulla (Figure 4). This sign occurs due to the air outlining both sides of the bulla wall parallel to the chest wall. Another classical differential diagnosis not to be missed is air-filled stomach or bowel in the chest secondary to diaphragmatic hernia. Ventilation scintigraphy can be used to localize the air leak in patients presenting with persistent air leak.

**MEASUREMENT OF PNEUMOTHORAX** (Figure 5a, b, c)

The size of a pneumothorax, in terms of volume is difficult to assess accurately from a chest radiograph which is a two dimensional image. In 1993 guidelines pneumothorax was classified into 3 groups: 1) Small: A small rim of air around the lung, 2) Moderate: Lung collapsed half way towards the heart border, 3) Complete: Airless lung, separate from the diaphragm. The volume of pneumothorax approximates to the ratio of the cube of the lung diameter to the hemithorax diameter. Thus, one can estimate the degree of collapse by measuring an average diameter of the lung and the hemithorax.
cubing these diameters, and finding the ratios. For example, a pneumothorax of 1 cm on CXR-PA film occupies about 27% of hemithorax volume; i.e. if the lung is 9 cm in diameter and the hemithorax 10 cm (10^3 - 9^3/10^3 = 27%). This is commonly used method for quantification of pneumothorax. Rhea and associates have described an alternate method for estimating the percentage of collapse. With their method, the average interpleural distance is calculated. This is the mean of the maximum apical interpleural distance and two measurements of interpleural distances in the mid points of the upper and lower halves of the lung. When this average interpleural distance is obtained, a scale is used to calculate the percentage of the lung that is collapsed.

**MANAGEMENT**

Treatment of pneumothorax (Chart 2) depends on the size, type of pneumothorax, presence of dyspnea, state of underlying lung, associated complications and recurrence. Various treatment modalities are simple

![Management of pneumothorax](chart2.png)

**CHART 2.** Management of pneumothorax.
needle aspiration, pigtail catheterization or intercostal drainage tubes, thoracoscopy or surgery (Table 3). A benign spontaneous pneumothorax that is small (less than 15%) can be treated with observation alone. The rate of absorption of air is about 1.25% of the total radiographic area per day, so that a 50% pneumothorax may take 4-6 weeks to resolve. Administrating large quantities of oxygen can decrease the rate of resolution. As the rate of absorption is very slow, for larger pneumothorax, simple aspiration with small canula or intercostal drainage tube should be used. The role of needle aspiration is limited to emergency treatment of tension pneumothorax to be followed as quickly as possible by intercostal tube drainage (ICD). Large spontaneous pneumothorax, SSP, traumatic pneumothorax, complicated and recurrent pneumothorax is drained by intercostal tube drainage. Precautions should be taken so that there is gradual withdrawal of air especially in longstanding larger pneumothoraces, to avoid re-perfusion pulmonary edema. Re-expansion pulmonary edema is due to increased permeability of the pulmonary vasculature which occurs following thoracocentesis or chest tube placement. For drainage of pneumothorax, ICD is usually inserted between the 4th and 7th intercostal spaces and between the mid and anterior axillary lines (The “Safe Triangle”). The tip of the tube should be directed upwards. It is a fallacy that drain must be put in a basal position to drain fluid and apical position to drain air. The anterior approach in the second interspace transfixed two major accessory respiratory muscles- the pectoralis major and minor. In case an apical drain is required for an apical loculation of air, the true apical approach above the scapula into the first interspace posteriorly should be preferred. BTS and ACCP have both published guidelines for the treatment of PSP; however they give contradictory recommendations for first-line treatment. The ACCP advises that simple aspiration is rarely appropriate in the treatment of PSP, while the BTS recommend simple aspiration as the first-line treatment in all PSP requiring intervention. A recent Cochrane report in 2007 systematically reviewed all published randomised control trials that compared simple aspiration versus intercostal tube drainage for spontaneous pneumothorax in adults. It concluded that there was no difference in the immediate success rate of the procedure, early failure rate, or one year success rate between the two groups. However, simple aspiration conferred a number of advantages including; lower percentage of patients hospitalised, decreased duration of stay, and the fact it is a relatively simple procedure to perform. There has been extensive debate regarding the optimal size of the intercostal drain. Evidence now suggests that small-bore pleural catheters are as effective as larger bore intercostal drains in the treatment of spontaneous pneumothorax. No significant correlation has been found between drain size and complication rate, recurrence rate, and length of hospital stay. However, small caliber catheters may not be suitable in the presence of pleural fluid (where they could block) or a large or persistent air leak (owing to inadequate re-expansion). ICD can be connected to a Heimlich valve, a chest drainage bag or an under-water seal drainage bottle (Figure 6).

![Figure 6. Intercostal Drainage with underwater seal.](image)

**TABLE 3.** Treatment modalities and approach in management of pneumothorax

<table>
<thead>
<tr>
<th></th>
<th>Primary</th>
<th>Secondary</th>
<th>Iatrogenic</th>
<th>Traumatic</th>
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</thead>
<tbody>
<tr>
<td>Observation</td>
<td>&lt;20%</td>
<td>-</td>
<td>&lt;30%</td>
<td>-</td>
</tr>
<tr>
<td>Tube thoracostomy</td>
<td>&gt;20%</td>
<td>All</td>
<td>&gt;60%</td>
<td>All</td>
</tr>
<tr>
<td>Small tube with one-way valve</td>
<td>Recurrence × 3</td>
<td>Recurrence × 2-3</td>
<td>20-60%</td>
<td>-</td>
</tr>
<tr>
<td>Pleurodesis</td>
<td></td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Surgical exploration and repair</td>
<td></td>
<td>Persisting (2 weeks)</td>
<td>Persisting</td>
<td>Persisting</td>
</tr>
</tbody>
</table>
drainage of urine is easily available and can be used as a pneumosac\textsuperscript{25,26} (Figure 7). They are effective and have the advantage of being less bulky, cheap and allow early mobility. Drains are removed after the lung has expanded fully and does not collapse on clamping and fluid drainage if any is less than 50cc of serous fluid in 24 hours. Patients with bronchopleural fistula needs prolonged drainage. In postoperative leaks, BPFs with small to moderate air leak requiring prolonged drainage or after accidental slipping or removal of ICDs, where pleuro-cutaneous fistula is formed; stoma bags with non-return valves can be used for drainage\textsuperscript{27} (Figure 8). It helps in reducing duration of hospital stay and chance of infection. The role of Asherman chest seals, sterile occlusive dressing for treating open pneumothorax and preventing tension pneumothorax in chest injuries from gun shots, stab wounds and other penetrating chest trauma is studied.\textsuperscript{28} This has a same principle as Helmlich valve except there is no intrathoracic component to this device and is just adherent to the chest wall. This could be successfully used in the management of a complicated post-operative leak. Drainable stoma bags also offer a non-return valve mechanism, do not have an intra-thoracic component and are just adherent to the chest wall. For selected patients with persistent air leak not amenable to surgical intervention, identification of air leak site with ventilation scintigraphy followed by targeted radiotherapy can be considered. This seals the leak via radiation induced fibrosis.\textsuperscript{29}

Associated BPF is essentially treated by tube drainage; closure of the BPF being the long term goal. Surgical therapy in the form of decortications and closure of BPF with a transposed muscle flap, the pericardial fat pad, or an omental pedicle flap, lobectomy, pleura pneumonectomy or the thoracoplasty are performed depending on patient’s condition and the surgeon’s skills. Bronchoscopic closure of smaller BPFs with tissue glue, fibrin glue, gel foam, lead plugs, balloon catheter or autologous blood patch can be attempted. The appropriate time for surgery is not known, and it is possible that lung expansion may occur after several weeks of tube drainage. Hence prolonged tube drainage is an alternative approach in selected cases. Patients with BPF requiring ventilator support should be put on high frequency jet ventilators to decrease flow through bronchopleural fistula.

**ROLE OF PLEURODESIS**

The aim of pleurodesis is to achieve symphysis between visceral and parietal pleural layers, in order to prevent accumulation of air in the pleural space in cases

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure7.png}
\caption{Urosac as a drainage bag (pneumosac).}
\end{figure}

\begin{figure}[h]
\centering
\includegraphics[width=0.8\textwidth]{figure8.png}
\caption{Stoma bag with non-return valve used for drainage of pneumothorax.}
\end{figure}
of recurrent pneumothorax or in patients with persistant air leaks following chest tube drainage. The complete removal of air from the pleural space is needed to keep the visceral and parietal pleural layers in close contact. In a prospective randomized study Almind et al.\(^{30}\) compared the recurrence of pneumothorax using drainage alone and drainage plus tetracycline or talc and found a rate of 36%, 13% and 8% respectively, after average follow up of 4.6 years. Alfageme et al.\(^{11}\) had 9% recurrence with tetracycline pleurodesis as compared to 35% in patients with drainage alone. Since 1935 more than 30 agents have been proposed as sclerosants to induce pleurodesis. In a study by Gyorik et al.\(^{32}\) the long-term success rate in preventing pneumothorax recurrence after a successful thorascopic talc pleurodesis was 95% at a median follow-up of 10 years. Commonly used agents for pleurodesis are: tetracycline, talc, doxycyclin, minocyclin, bleomycin, fibrin glue, autologous blood, povidone iodine, quinacrine. After injecting slurry made of sclerosant with xylocaine, ICD needs to be clamped for one hour and then released for allowing drainage of fluid formed due to inflammatory reaction. Once fluid quantity reduces to less than 50ml of serous fluid, ICD can be removed.

**ROLE OF THORACOSCOPY**

Thoracoscopy allows simple observation and talc poudrage. Video assisted thoracotomy (VATS) permits procedures like mechanical pleurodesis, pleurectomy and bullectomy. The accepted surgical indications for pneumothorax include persistent air leak, recurrence, radiologically demonstrated huge bulla, spontaneous hemo-pneumothorax, incomplete expansion of the lung, tension pneumothorax, bilateral involvement and SP in a high-risk occupation such as pilot or scuba divers.\(^{33}\) A recent consensus from the American College of Chest Physicians recommended the observation of air leaks for 4 days prior to surgical intervention.\(^{17}\)

Patients in good clinical condition, patients with prolonged air leak longer than 5 days due to inadequate lung expansion, and patients with bullae on chest computed tomography are benefitted by VATS procedures.\(^{34}\) VATS allows stapling of blebs and small bullae through the use of an endostapler, laser ablation, or electrocoagulation. Repeated talc pleurodesis would make subsequent video-assisted thoracoscopic surgery to succeed in controlling a persistent air leak due to likely formation of patchy adhesions. Pleurodesis can be done chemically with talc in sufflations or mechanically with pleural abrasion or partial pleurectomy. Fluorescence-enhanced autoflourescence thoracoscopy is a new technique; which identify lesions not visible at routine thoracoscopy.

**REFERENCES**


Ambroxol … more than an expectorant
The benefit of using ambroxol in chronic respiratory diseases?

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Key words:
- Chronic bronchitis
- Chronic obstructive lung disease
- COPD
- CRD
- Ambroxol
- Anti-inflammatory therapy
- Bronchiectasis
- Mucoactive
- Antibiotics
- Common cold

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ABSTRACT
Chronic respiratory diseases comprise of chronic obstructive pulmonary disease (COPD), asthma, occupational lung diseases and bronchiectasis, amongst others. Most of these long-term diseases are not curable and cause an enormous economic burden. Mucoregulators such as ambroxol have been used for decades as a treatment for pulmonary diseases, in order to reduce the burden of the disease and improve quality of life by promoting mucus clearance. Effects of ambroxol include the increase of surfactant production, cytokine reduction and counteracting of oxidative stress in the lungs. Positive effects of ambroxol have been described in vitro and in clinical studies for COPD, chronic bronchitis as well as in acute respiratory infections. In addition, antiviral, antibacterial and antifungal properties have been demonstrated. Ambroxol has a good safety profile. In this short review article, the current clinical knowledge on Ambroxol is summarized.


Chronic respiratory diseases (CRDs) are mainly diseases of the airways and lung parenchyma and are responsible for high individual and economic costs. Some of the most common are chronic obstructive pulmonary disease (COPD), asthma, occupational lung diseases and bronchiectasis. In addition to tobacco smoke, other risk factors include air pollution, occupational chemicals and dusts, and frequent lower respiratory infections during childhood. Most CRDs are not curable, however, various forms of treatment that help dilate major air passages and improve shortness of breath help in the control of symptoms, reduce the toll of morbidity, disability and premature mortality, reduce frequent infections known as exacerbations of the disease and improve the quality of life of patients. In advanced countries such as Greece COPD is due by 90% to smoking. The main symptoms of the disease are cough, sputum expectoration and dyspnea.

Oxidative stress is a consequence of inability of resident antioxidant mechanisms to neutralize pro-oxidant factors generated endo- or exog-
enously. As a consequence, the oxidants predominate and oxidative stress occurs. Reactive oxygen and nitrogen species (ROS and RNS) are the most prominent products in oxidative stress. Cigarette smoke contains more than 1017 oxidant/free radical molecules per puff and more than 4700 chemicals.

A variety of oxidants and free radicals provoke an imbalance between oxidants/antioxidants in lung epithelium and systemic circulation of smokers and COPD patients. Thus, therapeutic strategies targeting oxidative stress with pharmacological antioxidant agents or boosting the endogenous levels of antioxidants is likely to be beneficial as an adjunctive tool in the treatment of COPD patients.

Mucoregulators such as ambroxol are used in the treatment of respiratory diseases characterized by impaired mucus clearance and have been shown to possess antioxidative activity in vitro as well as in vivo. This review article focuses on the position of ambroxol as an additional treatment of these diseases. Ambroxol [trans-4-(2-amino-3,5-dibromobenzylamino)-cyclohexane hydrochloride] stimulates synthesis and secretion of surfactant by type II pneumocytes and inhibits sodium absorption by airway epithelial cells.

The pharmacological effects of ambroxol cover a wide range, including mucus regulation on gland cells, increased production of pulmonary surfactant, neutralization of oxidative and nitrosative stress, suppression of respiratory virus replication, reduction of proinflammatory cytokines, chemotaxis, respiratory burst of inflammatory cells, tissue lipid peroxidation, and local anaesthetic effects.

Ambroxol is an active metabolite of bromhexine and has been established for decades in the treatment of acute (e.g., bronchitis) and chronic respiratory diseases (e.g., COPD). Pharmacological and clinical studies showed the mucoregulatory and secretagogue properties of ambroxol. The scientific conclusion of the European Medicines Agency (EMA), on ambroxol has been summarized as relevant for treatment of bronchopulmonary diseases thus potentially contributing to the positive benefit-risk profile of the compound.

Anti-inflammatory properties of ambroxol on granulocytes and mast cells have been shown in vitro in a mouse model in the context of asthma therapy. In two controlled clinical studies ambroxol was used as an adjuvant in COPD therapy. In both studies the authors describe positive effects on the prevention or treatment of exacerbations. Even though the study design of these trials does not allow to draw safe conclusion (due to the lack of placebo controls), they confirm findings of previous investigations. According to The Global Initiative for Chronic Obstructive Lung Disease (GOLD) anti-inflammatory therapy in stable COPD includes mucolytics as they reduce the risk of exacerbations in selected populations.

A 6-month double-blind, randomized study with 75 mg ambroxol sustained release/day was conducted versus placebo in 214 patients with chronic bronchitis in the winter months. 45.5% in the treated group and 14.4% in the placebo group remained exacerbation-free (p<0.01). In addition to this highly significant difference, the number of severe exacerbations with fever and the number of sick days (p<0.01) differed significantly in favor of the ambroxol-treated group. These results were substantially confirmed by an open-label study including 5,635 patients. In the AMETHIST trial in 242 patients with COPD, Patients received long-term treatment with 75 mg ambroxol sustained release b.i.d. for 1 year, or placebo. A total of 38% of placebo-treated patients in a subset of 45 patients with more severe baseline symptoms, were exacerbation-free during the study. In contrast, in the same subgroup, 63% of Ambroxol-treated patients were exacerbation-free (p=0.038). The longest lasting study with 75 mg ambroxol sustained release/day was conducted by Ceglain 180 patients with chronic bronchitis present for more than 5 years. This was a randomized, double-blind placebo-controlled study in 22 centers over 2 years. With a small drop-out rate of 13% it was shown that, compared with the placebo group:

- symptoms such as dyspnea, expectoration and cough were markedly reduced,
- lung function parameters such as vital capacity (VC), forced expiratory volume in 1 second (FEV1) and peak expiratory flow (PEF) were significantly improved,
- there was a reduction in adjuvant medications such as antibiotics and corticosteroids,

The highly significant reduction in sick days compared with the placebo group is particularly important (p<0.01) considering the individual patient’s quality of life.

Poole and Black pointed out in a systematic analysis conducted for a Cochrane Review that therapy with secretolytic substances is also of socio-economic significance. Mucocactives are also considered good practice in patients with bronchiectasis, a condition characterized by increased mucus production.

A pilot study in elderly adults showed effects of ambroxol on the prevention of acute respiratory infections,
such as common cold and influenza, compared to an active control (carbocysteine and rebamipide)\textsuperscript{22}. A further clinical trial in children with acute pneumonia describes a higher effective rate (sum score of different symptoms) in the group with concomitant ambroxol inhalation, compared to standard care alone\textsuperscript{23}.

Besides the effect of ambroxol on mucus clearance, further antiviral, antibacterial and antifungal properties have been recently described and published. Different working groups conclude direct and indirect anti-infectious properties such as increasing bioavailability of antibiotics by ambroxol\textsuperscript{24-35}. Therefore, the available data suggest that the efficacy of ambroxol in COPD and acute bronchitis might at least partly be mediated by these pharmacological properties. It is worth to mention that there is a special interest for ambroxol in the scientific community as an adjuvant in the treatment of infections with biofilm-producing pathogens such as Pseudomonas aeruginosa and Candida albicans\textsuperscript{24,25,29}. The first studies in animal models provide preliminary evidence for an improved penetration of anti-infectives such as vancomycin and voriconazole in the presence of ambroxol through the biofilm-barriers of these pathogens\textsuperscript{26,33} and even a direct inhibition of biofilm formation by ambroxol was shown in a pneumonia rat model\textsuperscript{29}.

Further studies were published regarding the prevention of pulmonary complications in severely ill patients by ambroxol\textsuperscript{36-42}. It is worth to mention one trial in lung cancer patients undergoing lobectomy. In this study, short-term perioperative treatment with ambroxol reduced both, the rate of postoperative pulmonary complications and the duration of postoperative hospital stay\textsuperscript{37}.

A new potential treatment area for ambroxol, as suggested by the rising number of publications in this field, is the treatment of lysosomal storage disorders such as Morbus Gaucher\textsuperscript{43-50}. In an uncontrolled pilot study, the symptoms of Morbus Gaucher patients did not worsen under ambroxol treatment for 6 months\textsuperscript{51}. Further studies are needed to confirm these preliminary findings.

Ambroxol has been available in the EU market since 1978 and is currently used in more than 50 countries worldwide\textsuperscript{52,53}. According to a 2008 update report, the safety of ambroxol is well-established, since it is based on its use in more than 15,000 patients in more than 100 studies, with a total patient exposure estimated at 4,789,563 patient-years\textsuperscript{54}. According to the PRAC 2015 report, the worldwide patient exposure is even higher, estimated to be 31,881,769 patient-years for ambroxol-containing products indicated in secretolytic therapy, but also in the treatment of infant respiratory distress syndrome and in the prophylaxis of postoperative complications.

According to the seven randomized, placebo-controlled trials presented in a latest review\textsuperscript{6}, ambroxol was well-tolerated during short-term and long-term treatments (up to two years), showing no differences with respect to adverse events compared to the placebo groups. This finding falls in line with the results of the 2015 meta-analysis of 34 randomized, placebo controlled clinical trials that compared oral mucolytic therapy versus placebo administered regularly for at least two months in adults with chronic bronchitis or COPD. In a total of 21 studies lasting from 2 to 36 months, 608 adverse events were reported in 3,170 subjects treated with mucolytics versus 669 adverse events in 3,176 placebo-treated subjects, with all adverse events being mild and self-limited (odds ratio, 0.88; 95% confidence interval, 0.78 to 1.00). Hence, this large systematic review of randomized, controlled trials indicates that there is probably no difference between mucolytic and placebo treatments in terms of the total numbers of adverse effects that they cause\textsuperscript{54}.

In summary, ambroxol is still investigated in both preclinical and clinical trials by research groups worldwide. Recent findings suggest relevant pharmacological and clinical effects particularly in the treatment of infections with biofilm-producing pathogens and the protection from pulmonary complications after surgery or in the intensive care. Further trials are needed to prove the encouraging findings in patients with lysosomal storage disorders.

In conclusion, the multiple effects - secretolytic, secretomotor, mucociliary clearance-promoting, anti-inflammatory and oxidative stress-reducing - of ambroxol in combination with the excellent safety profile even in long-term use, raises the interest of its clinical usefulness and drives the need for new studies to elucidate its precise role in the management of chronic respiratory diseases.

**AUTHOR CONTRIBUTIONS**

CB wrote the manuscript. RN, KM, LS and BP were involved in the data analysis or interpretation of the data and have critically revised the article. All authors have approved the final version of the manuscript. All authors are accountable for accuracy and integrity of the work.
CONFLICTS OF INTEREST

CB is an employee of Sanofi. RN, and BP have received payments for lectures from Sanofi Greece. KM, LS and BP have received payment for advisory boards from Sanofi Greece.

ΠΕΡΙΛΗΨΗ

Αμβροξόλη ... περισσότερο από ένα αποχρεμπτικό. Το όφελος της χρήσης της αμβροξόλης σε χρόνιες αναπνευστικές παθήσεις;

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Οι χρόνιες αναπνευστικές παθήσεις περιλαμβάνουν την χρόνια αποφρακτική πνευμονοπάθεια (COPD), το άσθμα, επαγγελματικές πνευμονοπάθεις και βρογχεκτασίες, μεταξύ άλλων. Οι περισσότερες από αυτές τις μακροχρόνιες ασθένειες δεν είναι ιάσιμες και προκαλούν τεράστια οικονομική επιβάρυνση. Τα βλεννορυθμιστικά όπως η αμβροξόλη έχουν χρησιμοποιηθεί εδώ και δεκαετίες ως θεραπεία σε νόσους των πνεύμων, για να μειώσουν τη βαρύτητα τους και να βελτιώσουν την ποιότητα ζωής, προωθώντας την κάθαρση της βλέννας. Οι επιδράσεις της αμβροξόλης περιλαμβάνουν την αύξηση της παραγωγής του επιφανειοδραστικού παράγοντα, τη μείωση των κυτταροκινών και την εξουδετέρωση του οξειδωτικού στρες στους πνεύμονες. Οι θετικές επιδράσεις της αμβροξόλης έχουν περιγραφεί in vitro και σε κλινικές μελέτες για τη ΧΑΠ, τη χρόνια βρογχίτιδα καθώς και τις οξείες αναπνευστικές λοιμώξεις. Επιπλέον, έχουν περιγραφεί αντιβιοτικές και αντιμυκητισιακές ιδιότητες. Η αμβροξόλη έχει καλό προφίλ ασφάλεια.


Lέξεις - Κλειδιά: Χρόνια βρογχίτιδα, Χρόνια αποφρακτική πνευμονοπάθεια, χρόνιες αναπνευστικές παθήσεις, Αμβροξόλη, Αντιφλεγμονώδης θεραπεία, Βρογχεκτασία, Βλεννοκινητικά, Αντιβιοτικά, Κοινό κρυολόγημα

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Achalasia with megaesophagus and aspiration pneumonia in an elderly man

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Achalasia is one of the most common causes of dysphagia. Achalasia is caused by a loss of ganglion cells in the myenteric plexus, which causes the muscles of the esophagus to fail to properly propel food and liquid from the mouth into the stomach1. Food stuck in the flaccid esophagus, where it may be regurgitated, or inhaled into the lungs leading to aspiration pneumonia2. Typical symptoms include difficulties in controlling the swallowing process, regurgitation, retention of food, weight loss, chest pain and aspiration pneumonia.

Megaesophagus a disorder of the esophagus whereby the esophagus becomes abnormally enlarged, is the end-stage of achalasia cardiae. Megaesophagus may occur secondary to diseases such as achalasia or Chagas disease.

FIGURE 1. CT scans of chest of a 70 years male showing massive dilation of the esophagus (megaesophagus) with a consecutive slip-shaped narrowing of the trachea and right lower lobe aspiration pneumonia.

REFERENCE

Mucoviscidosis and pulmonary tuberculosis

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Key words:
- AFB
- Cystic fibrosis
- Genotyping
- GeneXpert MTB/RIF assay
- MTB

A nineteen-year-old caucasian male, chronic smoker (>20 cig/day), diagnosed with mucoviscidosis at the age of 4 years old, was admitted with a two week history of fevers, night sweats, coughing up blood, severe chest pain, worsening cough and 10 kilograms weight loss. Acid fast bacilli cultures revealed no growth and sputum cultures had grown Pseudomonas aeruginosa. His forced vital capacity and forced expiratory volume had dropped to 55% and 40% of predicted volumes. Vital signs revealed Oxygen saturation 78%, a pulse rate of 100 beats per minute, high temperature (over 39 degrees celsius) and a respiratory rate of 26 breaths per minute. On clinical examination: yellow teeth, an ill-appearing thin male with increased work of breathing and bilateral coarse rhonchorous breath sounds. Laboratory results showed leukocytosis (14,000/mm$^3$), hepatic cytolysis (slightly aminotranferases increase) and C-reactive protein concentrations were elevated (≥10 mg/L). Admission chest radiograph (Figure 1) and computed tomography chest (Figure 2) revealed severe chronic lung disease with a generalized irregular thickening of linear markings throughout the lungs, invariable hyperinflation, bronchiectasis, multiple bilateral cavitary lesions, multiple small cysts superimposed on diffuse, coarse, reticular pattern. Initially the patient received oxygen therapy, symptomatic treatment and broad spectrum antibiotics without significant clinical improvement even after one month of treatment. By that time, the subsequent cultures grew mycobacterium tuberculosis, which was sensitive to all first line tuberculosis drugs. Due to recent development and based on the national protocol¹, the patient was initiated on a weight-based dosing of 4 drug antituberculous regimen: isoniazid, rifampicin, ethambutol and pyrazinamide. Human immunodeficiency virus status negative. After 2 weeks the patient had clinical improvement with resolution of his hemoptysis, chronic cough and febrile episodes. After daily-use of hypertonic saline (sterilized, extra-salty water) he has shown better mucus clearance along with an increase in his weight, forced vital capacity and forced expiratory volume had improved to 80% and 68% of predicted volumes, respectively. After he was cured of tuberculosis, he was referred to a specialized center in cystic fibrosis.

REFERENCE:
Multidrug resistant tuberculosis associated with human immunodeficiency virus

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A 30 year old male with the antibodies to human immunodeficiency virus infection detected in July 2016 was registered in the Mures County Center for acquired immune deficiency syndrome. He refused antiretroviral therapy. The infection was associated with intravenous drug use for three years. Diagnosis was as follows: human immunodeficiency virus infection late stage (4 B), the progression phase in the absence of antiretroviral therapy. On admission he complained of high fever (40 degrees celsius), chest pain, cough, weakness, and weight loss. Clinical findings: submandibular and cervical lymph nodes were enlarged (0.7 cm), painless and dense. Frequency of respiratory movements was 20 per minute. During auscultation, wheezing was present. Heart sounds were rhythmical. Laboratory tests: erythrocytes - 6.6×10¹²/l, hemoglobin - 129 g/l, leukocytes - 4.45×10⁹/l, hematocrit - 38.9%, lymphocytes - 7%, basophils - 1%, platelets - 90×10⁹/l, monocytes - 7.9%, neutrophils - 79.4%, eosinophils - 0.9%, cholesterol - 3.02 mmol/l, creatinine - 80 μmol/l, glucose - 3.99 mmol/l, albumin - 34.9 g/l, normal iver enzymes, total bilirubin - 5 μmol/l, total protein - 79.8 g/l, urea - 5 mmol/l, polymerase chain reaction number of human immunodeficiency virus ribonucleic acid copies: 2390000 copies/ml, cluster of differentiation 3-39%, cluster of differentiation 3-8%, negative results for hepatitis B infection, blood culture was also negative. Results of sputum smear: mycobacterium tuberculosis was detected and resistant to isoniazid, streptomycin, rifampicin, capreomycin and kanamycin. Sputum cultures were all negative. Tests and scans were carried out by an ophthalmic and otorhinolaryngology scientists. He received treatment according to national guidelines: intravenous standard regime (pyrazinamide, ethambutol, amikacin, levofloxacin, para-aminosalicylic acid and cycloserine). The male patient refused again antiretroviral therapy treatment. Died one month later from pulmonary complications.

FIGURE 1. Chest X-ray of a 30 year old immunodeficiency virus positive male. Note in the left the peribronchial thickening. In the right hand film is a blown up image showing the peribronchial thickening more clearly (watch the arrow). The high resolution computed tomography (in the middle) render bronchiectasis, centrilobular nodularity (tree-in-bud) and mosaic attenuation in the same patient.

REFERENCE
Primary intestinal tuberculosis

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A twenty year old male patient without known comorbidities, who works every day in a cow farm, deep into the mountains. He was grumbling of persistent abdominal pain for around one month in the right iliac fossa, followed by motion sickness, repeated vomit, infrequent dry cough, fatigue, constant night sweats and a total of seven kilograms in weight loss. On inspection, it was observed a slightly expanded abdomen and painful at palpation in the right iliac fossa, related with the presence of a palpable lump in that specific region. Blood test results within normal range. Chest radiography normal. Abdominal radiography displayed increased air in the small bowel. Abdominal computed tomography unveiled a five centimeters in circumference mass, in the terminal portion of the ileum. The male patient was referred to a gastroenterology department, an immediate colonoscopy was made and histopathological samples where taken. The histopathological analysis of biopsies revealed positive ziel neelsen tuberculous granulomas with central caseation. Human immunodeficiency virus test negative. Ophthalmology and Otolaryngology consultants did clinical examination on the young male and revealed normal test results. Based on the regimen proposed by the national guidelines1, successful antituberculous treatment was initiated for a period of six months. It is very crucial for doctors to be aware that intestinal tuberculosis may be considered as differential diagnosis of intestinal diseases, even in immunocompetent patients who present vague abdominal symptoms and relevant physical findings, especially in cases with centered pain and palpable mass in the right lower quadrant of the abdomen, in areas where tuberculosis is endemic like in subregions of Eastern Europe.

REFERENCE


FIGURE 1. Colonoscopy revealed lumen reduction, diffused ulcerated lesions coated by fibrin and an inflammatory enlarged lesion in the cecum and ileocecal orifice, that are occluding the intestinal flow to the end of the ileum.
INSTRUCTIONS FOR AUTHORS

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Table 1. Suggested Maximum Length Requirements for Submitted Manuscripts (November 2008)

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The rationale for the study should be summarized and relevant background material outlined. The Introduction should not contain findings, methods used or conclusions.

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Acknowledgements

Acknowledge the persons who provided a true contribution and who endorse the data and conclusions. Acknowledge any funding sources.

References

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