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ΕΙΔΙΚΟ ΑΡΘΡΟ

Διακεκριμένοι Πνευμονολόγοι
N. Σιαφάκας
Vaping
Safer does not mean safe

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In recent years there has been a dramatic increase regarding the use of electronic nicotine delivery systems (eNDS). This increase was heavily based on the premise that eNDS are safer in comparison to combustible cigarettes. This comparison is problematic and misleading. Smoking is one of the deadliest addictions on earth. Comparing vaping to smoking may lead to a false sense of safety. First of all, safer does not mean safe, especially taking into consideration the enormous mortality and morbidity associated with smoking. Second the long term effects of vaping are largely unknown. It took decades to establish the detrimental effects of smoking. Claiming that vaping is safe is premature and irresponsible. Third, it is now well established that vaping can lead to potentially lethal acute lung injury known as e-cigarette associated lung injury (EVALI). The 2.290 reported cases of EVALI with 47 deaths prove that vaping is not a safe option. eNDS are an extremely profitable market with 11.3 billion dollars in the U.S. in 2018. Their sales are expected to surpass combustible cigarettes by 2023. Marketing of eNDS is quite aggressive and the increase in vaping is particularly disturbing among adolescents. In 2017, 11% of U.S. students in the 12th grade (age 17-18 years) reported vaping in the last month. The prevalence sky-rocketed to 20.9% in 2018 and 25.4% in 2019.

eNDS are devices of various designs consisting of 3 parts, the atomizer, the battery and the mouthpiece. The atomizer consists of the e-liquid reservoir, the wick and a metal coil that is wrapped around the wick. The wick is usually made of cotton or silica and is soaked in the e-liquid that contains propylene glycol, vegetable glycerin, nicotine and various flavoring agents. When the user presses a button, the electrical circuit is closed and electric current (supplied by the battery) runs through the coil resulting in high temperatures. This causes the aerosolization of the e-liquid that is inhaled through the mouthpiece. Thus, the term vaping is actually is misnomer. Vapor is a substance in the gas phase. People using eNDS do not inhale a vapor and actually they do not vape. eNDS users inhale a solution and specifically an aerosol, a suspension of tiny particles of liquid, solid, or both within a gas.

While, the long term effects of vaping are largely unknown there is increasing data proving that vaping can cause acute lung injury. In the U.S. 2.290 cases of EVALI have been reported and 47 deaths. EVALI is a serious complication of vaping as the vast majority of the cases (95%) were hos-
Hospitalized. Most of the EVALI cases were young patients, under 35 years old (77%), with a median age of 24 years and age range from 13 to 78 years. Common symptoms are cough, dyspnea or chest pain of acute or subacute onset. Fever and fatigue can also be seen. Some patients complain for nausea, vomiting, diarrhea or abdominal pain. According to CDC (Centers for Disease Control and Prevention) a confirmed case of EVALI requires: using an eNDS in 90 days prior to symptom onset, pulmonary infiltrates on chest X-ray or computed tomography (CT), and exclusion of alternative diagnoses (infection, cardiac, rheumatologic, or neoplastic process). Minimum criteria to exclude infection on initial work-up are: i) a negative respiratory viral panel, ii) a negative influenza PCR or rapid test and iii) other clinically indicated respiratory infectious disease testing (e.g., urine Antigen for Streptococcus pneumoniae and Legionella, sputum culture, if productive cough, BALF culture is done, blood culture, HIV-related opportunistic respiratory infections if appropriate) are negative. If infection is identified but the clinical team believes it is not the sole cause of the underlying lung injury or when the above mentioned tests to rule out pulmonary infection are not performed and the clinical team believes infection is not the sole cause of the underlying lung injury, the case is characterized as probable. These case definitions are not clinical guidelines but were designated for surveillance reasons.

From a pathological point of view, various patterns have been reported. Initially, it was thought that EVALI was a form of acute exogenous lipid pneumonia caused by the lipids within the inhaled aerosol. However, typical findings of exogenous lipid pneumonia are rarely reported. Furthermore, in computed tomography no areas of fat density (around -50 Hounsfield Units) are identified. Several forms of pathology patterns have been reported as diffuse alveolar damage (DAD), acute fibrinous pneumonitis (AFOP), organizing pneumonia (OP), giant cell interstitial pneumonia (GIP), and diffuse alveolar hemorrhage (DAH). Butt et al reviewed lung biopsies from 17 patients with EVALI (9 transbronchial biopsies, 1 cryobiopsy, and 7 surgical lung biopsies). There were no specific histological findings. Foamy macrophages and pneumocyte vacuolization were seen in all cases. Pigmented macrophages were never a dominant feature and granulomas were not seen. No cases of exogenous lipid pneumonia were identified in this series. Thus, a negative oil red O staining on BALF does not exclude the diagnosis of EVALI. The surgical lung biopsies and cryobiopsy cases allowed assessment of the distribution of disease that was predominantly centrilobular (75%). The wide variety of histology patterns is reflected on the imaging characteristics as well. Many radiological patterns have been described as ill-defined centrilobular nodules with upper lobe predominance, consolidation, ground glass opacities, septal thickening and an organizing pneumonia pattern with subpleural and peribular pattern. In every young patient with bilateral pulmonary infiltrates it is important to ask for any vaping history.

The actual causes of EVALI have not been determined yet. Both propylene glycol and vegetable glycerin have been designated by the FDA as “generally recognized as safe” (GRAS) for oral intake. Propylene glycol is extensively used as an antifreeze agent and in the food, plastics, perfume and pharmaceutical industries. However, it must be emphasized that safe to ingest does not mean safe to inhale. There is a paucity of data regarding the long term effects of inhaling heated glycol and vegetable glycerin.

Vitamin E is one such example. Vitamin E is found in many foods, including vegetable oils, cereals, meat, fruits, and vegetables. It is also available as a dietary supplement and in many cosmetic products, like skin creams. However, Vitamin E is used as a thickening agent in eNDS containing tetrahydrocannabinol (THC). Bronchoalveolar lavage fluid (BALF) from 29 patients with EVALI was tested by the CDC. All of the samples tested positive for Vitamin E. This was the first time that a chemical of concern was detected in biologic samples from patients with EVALI. In the above study, THC was identified in 82% of the samples representing another risk factor. In a case series from Illinois and Wisconsin 84% of the patients reported vaping THC products. Another characteristic example is diacetyl. Diacetyl is used as a buttery flavor agent in microwave popcorn and is designated as GRAS by the FDA. Nevertheless, when inhaled it can cause bronchiolitis obliterans, widely known as popcorn lung. Interestingly, diacetyl can be found in e-liquids. Finally, when heated, propylene glycol and glycerin can form acrolein and other toxic aldehydes. Public is strongly advised not to modify or add any substances to eNDS that are not intended by the manufacturer and are home-made, purchased illegally or through retail establishments.

There is also a misconception that eNDS are not related to second hand exposure. The 24 hour time weighted average (TWA) concentration of PM_{10} particles at a vaping convention was 12-fold increased above the regulation of the U.S. Environmental Protection Agency (150 μg/m³). Maximum concentration of PM_{10} exceeded 10,000 μg/m³ for more than 50% of the time during the vap-
Vaping is more than just inhaling vapor. It is actually an inhalation of several solid and liquid particles suspended in gas. Substances deemed to be safe for intake can have deleterious effects when inhaled. Furthermore, it is worth noting that the generated heat that is fundamental for the aerosolization of the e-liquid can lead to production of substances (as acrolein and other toxic aldehydes) that were not present initially. Finally, the eNDS give the opportunity of experimentation by adding various substances, adjusting coil resistance and thus the heat generated and so on. It took a lot of decades to finally realize the lethal results of smoking. Easy and premature conclusions regarding the safety of vaping can lead to detrimental results. The lungs were evolved through thousands of years based on the inspiration of atmospheric air. Inspiration of any other substance is potentially dangerous. As pneumonologists it is important to stand at the first line of defense raising awareness and passing on responsible information.

REFERENCES

Fatigue and Quality of Life after Pulmonary Rehabilitation Program

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- Chronic obstructive pulmonary disease
- Fatigue
- Pulmonary rehabilitation program
- Quality of life

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ABSTRACT
BACKGROUND. Fatigue and poor quality of life can play an important role in chronic obstructive disease and treatment outcomes. The aim of this study was to examine the levels of fatigue and quality of life (QoL) among chronic obstructive pulmonary disease patients before and after a pulmonary rehabilitation program. METHODS. In this experimental study, 31 chronic obstructive pulmonary disease patients at a large hospital of Athens were randomly followed a pulmonary rehabilitation program and completed two questionnaires pre- and post-intervention: the Fatigue Assessment Scale designed for measuring fatigue and the Missoula-Vitas Quality of Life Index-15 designed for measuring QoL. Statistical analysis of the data was performed via the Statistical Program SPSS version 19.0. The statistical significance was set up at 0.05. RESULTS. The results showed decreased levels of fatigue after the completion of the Pulmonary Rehabilitation Program compared to pre-intervention. Moreover, although QoL did not seem to change after the intervention, however the dimension “Transcendent” seemed to be increased for the majority of the participants. After the participation in the rehabilitation program a statistically significant and negative correlation was observed between mental fatigue and total score of quality of life (r= -0.436, p=0.014 <0.05) as well as between physical fatigue and the dimensions of “Interpersonal” (r= -0.470 p=0.008), “Well-Being” (r= -0.615, p=0.000), “Transcendent” (r= -0.636, p=0.000) and total score of QoL (r= -0.543, p=0.002). CONCLUSIONS. A pulmonary rehabilitation program seems to be a successful and innovative clinical prevention program leading to a lower level of fatigue for those patients who suffer from chronic obstructive pulmonary disease. Pneumon 2019, 32(3):72-80.

INTRODUCTION

Fatigue seems to be a main symptom among Chronic Obstructive Pulmonary Disease (COPD) patients which leads to restricted physical activity
and decreased exercise levels. Fatigue related to COPD seems to be acute, severe and more intense compared to fatigue which is only associated to aging for instance. More specifically, it influences individuals’ functionality in a daily basis.\textsuperscript{1} Therefore, fatigue contributes to a low Quality of Life (QoL) and may be the cause of high hospitalization levels or even death.\textsuperscript{2} According to a study that was conducted in Canada and recruited 2.4 million COPD patients from six sites which followed Pulmonary Rehabilitation Program (PRP) programs, fatigue seemed to be one of the most common symptoms along with dyspnea and pain with a prevalence of 77%, 93% and 74% respectively.\textsuperscript{3} In the same study fatigue seemed to be highly associated to a low QoL.

For people who suffer from COPD, fatigue seems to be associated to lung’s pathological changes that can result to lack of cardiovascular capacity. Moreover, the repetition of fatigue symptom followed by pain or dyspnea may affect individual’s perception and modify their ability regarding differentiation between harmful stimuli.\textsuperscript{3} Decreased physical activity is the result of dyspnea which by itself causes anxiety, panic and further aggravation of COPD symptoms. This repetitive process leads COPD patients towards a vicious cycle of refusal since they deny taking part in any exercise by also causing further deconditioning to their muscles and physical inactivity.\textsuperscript{4}

Overall, since COPD is estimated as an incurable disease, it also seems to affect patients’ QoL seriously. QoL can be severely worsened for individuals who suffer from COPD due to lung dysfunction as well as decrement on physical performance. COPD seems to decrease patients’ QoL through various ways, from being non-functional in a daily basis and experience difficulties in completing routine tasks, to postpone socializing and not being in mood and physical condition for enjoying time and activities with family and friends.\textsuperscript{5} Apart from the physical obstacles, patients who suffer from COPD may also face various psychological limitations including depression and anxiety.\textsuperscript{6} In a daily basis the majority of the patients referred fatigue, exhaustion, restriction and exclusion in basic daily living activities such as dressing, bathing, walking and eating. At the same time, they had difficulties in housework, leisure activities, and work-related activities as well as in their sexual life. Almost one third of the same study reported that it was affected to such an extent that it was forced to change a profession. Stopping an activity depends not only on the symptoms that are caused by the disease but also on the subjective importance and significance that patients show to these symptoms.\textsuperscript{7} Often patients do not realize that their activities have been reduced by assuming that this happens due to the fact that they “get older”.\textsuperscript{8}

**THE PULMONARY REHABILITATION PROGRAMS**

An effective and holistic treatment that would enhance patients’ QoL includes Pulmonary Rehabilitation Program (PRP). Pulmonary rehabilitation is focused on the prevention of COPD progression and on development regarding exercise and symptoms’ tolerance. There are various treatment programs and interventions for those patients who suffer from COPD including tobacco quit, ventilation maintenance, complementary oxygen, palliative support, pharmacological treatment or even surgical therapy when is needed.\textsuperscript{9} However, PRP seems to minimize COPD patient’s fatigue levels by also improving their QoL. According to the literature review and the existing international instructions and guidelines, PRP seems to hold a vital character in the COPD therapy. More specifically, according to a study\textsuperscript{10} among high and low fatigue groups, it was found that physical fatigue such as walking and physical exercise improved for both groups after the PRP. Dyspnea had also decreased until the end of the program and at one year later. In a study,\textsuperscript{11} patients showed significant improvement in their QoL and self-efficacy regarding their physical symptoms during a PRP. With a range between 0-100, patients scored 30% in their physical activity, 51.3% in their social functioning and 66.3% in their psychological functioning with an overall increment of 5.3% in their total QoL. More specifically, PRP provided by an interdisciplinary team includes pulmonologists, cardiologists, physiotherapists, nurses, ergophysiologists, psychologists and dieticians. Several studies\textsuperscript{12,13} have indicated that such an organized program tailored to the needs of each patient could improve functional ability to exercise, reduce symptoms of dyspnea and fatigue and improve COPD patients’ QoL at all stages of the disease.

The purpose of the current study was to examine whether fatigue and QoL are either improved or not after the completion of a PRP. Thus, it was expected that fatigue

**Abbreviations:**
- COPD: Chronic Pulmonary Obstructive Disease
- FAS: Fatigue Assessment Scale
- MVQoL-15: Missoula Vitas Quality of Life Index
- PRP: Pulmonary Rehabilitation Program
would be decreased and QoL would be improved after the PRP integration. The results of this research could shed more light on how a PRP could benefit patients who suffer from COPD as well as what seems essential in order to decrease their levels of fatigue. At the same time, little or no research has been conducted in the past in Greece regarding fatigue and QoL levels before and after a PRP. For this reason and since “Sotiria” Hospital offers a unique and distinct PRP intervention to the Greek population that is applied to each patient’s needs, it is very likely that the effects of PRP lead to decreased levels of fatigue.

METHODS

Design and sample

The study followed the convenience sampling. Among the 70 patients at the “Sotiria” hospital, 41 were eligible. Taking into account the inclusion criteria, all patients were adults and were diagnosed with COPD. Exclusion criteria were related to age (<18 and >65 years) and those patients who could suffer from severe diseases (heart or kidney or hepatic failure or other physical disabilities or mental illness) which could alienate the results. Another exclusion factor included language. Since the questionnaires were both translated in Greek, participants should also be native speakers or know the Greek language.

Finally, thirty-one (31) patients took part. Figure 1 shows the patients’ selection process. The rehabilitation program was conducted by the researchers who are health care professionals and have frequent contact with patients.

Ethics

Before the beginning of the research, license from the Scientific Council of the General Hospital of Athens (Greece) “Sotiria” was obtained. Participants were informed about the anonymity of their participation would, that the research is conducted for academic purposes, their participation is voluntary and that they could withdraw from participation anytime they wished, without having to give any explanations. In addition, if they desired, they could, also, get the results after the completion of the research project. Each participant was asked to read, and sign two copies of the consent form – one for him/her to keep and one for the researcher.

Stage I

After the patients’ selection process, the researchers distributed a form of demographic data and two questionnaires:

Demographic data form

The demographic form included the followings: age, gender, the first letter of his/her name, the first letter of his/her surname, educational level and marital status.

Fatigue Assessment Scale

For the purpose of the current study, the Fatigue Assessment Scale was applied. FAS is a 5-point Likert-type scale (1=Never, 2=Sometimes, 3=Regularly, 4=Often, 5=Always) consists of 10 items that refers on how patients usually feel regarding fatigue that is followed by relevant complaints. The score ranges from 10 (minimum) to 50 (maximum). FAS scores from 10-21 indicate no fatigue (normal), 22-34 fatigue and ≥35 indicate extreme fatigue. The Greek version of the FAS questionnaire was evaluated for its psychometric properties. At the same time, this scale is considered as a tool, which evaluates fatigue as a unidimensional experience. According to studies which were conducted for patients who were suffering from chronic illness and for renal disease patients who were receiving hemodialysis the Greek version of the FAS was found to be valid and reliable.

Missoula-Vitas Quality of Life Index-15 (MVQoLI-15)

Missoula-Vitas Quality of Life Index-15 (MVQoLI-15) is an evaluation tool that gathers information about patients’
QoL during an advanced disease. MVQoLI-15 is a 15-item questionnaire which consists of 5 dimensions of QoL, in particular, Symptoms (3 items), Function (3 items), Interpersonal (3 items), Well-Being (3 items) and Transcendent (3 items). A 5-point Likert-type scale (from Strongly Agree to Strongly Disagree) is employed to assess the range to which respondents believe that are related with the items or not. The questionnaire is specifically designed to evaluate each patient’s subjective experiences regarding QoL in each of these dimensions. It also seeks to describe each patient’s qualitative and subjective experience in a way that can be quickly interpreted by health professionals.17

For the purpose of the current study, the Greek version of the MVQoLI-15 questionnaire was used which was translated and evaluated for its psychometric properties.18

The Pulmonary Rehabilitation Program

After the first completion of the questionnaires, the PRP was carried out. The program was taking place at the Pulmonary Clinical Center for Research and Tobacco Control at “Sotiria” Hospital (Athens, Greece), every Monday, Wednesday and Friday from 01:00 P.M. to 03:00 between March-May 2018 through 36 sessions. The minimum number of sessions each patient could join was 20 but no less than that. Each session, and always according to each patient’s needs, included an application of the following: (i) individualized physical exercises (exercise on bicycle and exercises for strengthening the upper and lower limbs) with the supervision of an ergophysiologist (ii) Respiratory physiotherapy and relaxation techniques provided by a physiotherapist. Breathing physiotherapy aimed to educate COPD patients on the following: how to deal with dyspnea, how to breathe more effectively and with less dyspnea, how to synchronize their respiration with various stereotypical movements of everyday life, such as walking or climbing the ladder and finally how to eliminate their sputum through a more effective cough (iii) Nutritional support provided by a nutritionist aimed to increase muscle mass and control body weight either in the cases of weak and underweight patients or in the cases of obese patients (iv) Psychosocial support provided by a psychologist, aimed to eliminate anxiety, depression or any kind of phobia and/or panic attacks that may affect the patient negatively (v) Information and education on the nature and progression of the disease (anatomy, physiology, pathology, pharmacology, oxygen therapy, dyspnea) and the proper medication provided by physicians and nurses as well as training in long-term self-care (bronchial drainage techniques, relaxation, coping with dyspnea, addressing daily difficulties) and how to deal with exacerbations of the disease. Education aimed in making the patient aware of his/her current situation and teaches him/her new ways to control the disease.

Stage II

It took place after the completion of the rehabilitation program (3 months after the first completion of the questionnaires). The patients were given the questionnaires (FAS and MVQoL-15) for second time.

Data analysis

The mean values and standard deviations were used to describe the quantitative variables. Absolute (N) and relative (%) frequencies were used to describe the qualitative variables. A paired sample t-test was conducted in order to investigate the possible differences of fatigue and QoL before and after completing the PRP. To test the relationship of two quantitative variables, the correlation coefficients of Pearson (r) was used. The statistical significance was set at 0.05. The statistical program IBM SPSS 19.0 was used for the analysis.

RESULTS

The age range of participants was between 48-65 years old (M=58.61, SD=7.63). Most of them were males (n=21, 67.7%), married (n=22, 71%) and graduated from Secondary School (n=10, 32.3%).

Regarding the scores of FAS and MVQoLI-15 pre- and post- intervention, there was a significant difference in the scores before and after the PRP for physical fatigue (t(30)= 2.271, \(p=0.031\)), “Transcendence”, mental fatigue (t(30)= 2.979, \(p=0.006\)), total score of fatigue (t(30)= 3.276, \(p=0.003\)), “Transcendence” score (t(30)= -1.981, \(p=0.05\)). Table 1 shows the descriptive statistics for all the variables that were explored.

Table 2 shows the frequencies of participants who seemed to be fatigued, non-fatigued or extremely fatigued before and after the PRP.

Correlations

Before the participation in the rehabilitation program, a statistically significant and negative correlation was observed between mental fatigue and total score of MVQoLI-15 (\(r=-0.438, p=0.014 <0.05\)). Correlations of FAS score and MVQoLI-15 are presented in table 3.
TABLE 1. Descriptive Statistics and t-test results for physical fatigue, mental fatigue, total fatigue and quality of life (N=31)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Pre</th>
<th>Post</th>
<th>P*</th>
<th>95% CI for Mean Difference</th>
<th>t</th>
<th>df</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical fatigue</td>
<td>14.12</td>
<td>12.77</td>
<td>0.031</td>
<td>0.13, 2.57</td>
<td>2.27</td>
<td>30</td>
</tr>
<tr>
<td>Mental fatigue</td>
<td>9.80</td>
<td>8.12</td>
<td>0.006</td>
<td>0.52, 2.82</td>
<td>2.97</td>
<td>30</td>
</tr>
<tr>
<td>Total Fatigue</td>
<td>23.93</td>
<td>20.90</td>
<td>0.003</td>
<td>1.14, 4.92</td>
<td>3.27</td>
<td>30</td>
</tr>
<tr>
<td>Transcendent</td>
<td>9.58</td>
<td>14.74</td>
<td>0.05</td>
<td>-10.48, 0.15</td>
<td>-1.98</td>
<td>30</td>
</tr>
<tr>
<td>Symptoms</td>
<td>7.93</td>
<td>6.70</td>
<td>0.41</td>
<td>-1.82, 4.27</td>
<td>0.82</td>
<td>30</td>
</tr>
<tr>
<td>Function</td>
<td>1.51</td>
<td>-0.29</td>
<td>0.40</td>
<td>-2.54, 6.15</td>
<td>0.84</td>
<td>30</td>
</tr>
<tr>
<td>Interpersonal</td>
<td>15.90</td>
<td>19.09</td>
<td>0.12</td>
<td>-7.31, 0.92</td>
<td>-1.58</td>
<td>30</td>
</tr>
<tr>
<td>Well-being</td>
<td>-6.16</td>
<td>-0.80</td>
<td>0.19</td>
<td>-11.16, 0.45</td>
<td>-1.88</td>
<td>30</td>
</tr>
<tr>
<td>Total MVQoL-15 Score</td>
<td>35.15</td>
<td>41.18</td>
<td>0.19</td>
<td>-15.34, 3.28</td>
<td>-1.32</td>
<td>30</td>
</tr>
</tbody>
</table>

Notes: *Mean; **Standard Deviation; *p<0.05

TABLE 2. Descriptive characteristics of fatigue before and after the PRP (N=31)

<table>
<thead>
<tr>
<th></th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;22 non fatigued</td>
<td>8</td>
<td>17</td>
</tr>
<tr>
<td>Higher or equal to 22 fatigued</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td>Higher or equal to 35 extremely fatigued</td>
<td>0</td>
<td>1</td>
</tr>
</tbody>
</table>

After the participation in the rehabilitation program, a statistically significant and negative correlation was observed between mental fatigue and the dimensions of “Interpersonal” (r = -0.470, p = 0.008), “Well-Being” (r = -0.615, p = 0.000), “Transcendent” (r = -0.636, p = 0.000), and total score of MVQoL-15 (r = -0.543, p = 0.002). Statistically significant and positive correlation took place between physical fatigue and the dimension of “Function” (r = 0.461, p = 0.009 < 0.05), a statistically significant and negative correlation between total fatigue and the dimensions of “Interpersonal” (r = -0.444, p = 0.012), “Well-Being” (r = -0.550, p = 0.001), “Transcendent” (r = -0.568, p = 0.001), and total score of MVQoL-15 (r = -0.567, p = 0.001) (Table 4).

Regarding the differences between non fatigued (<22) and higher or equal to 22 fatigued patients before the participation in the rehabilitation program, the results showed that there was a statistically significant difference in QoL and specifically in the dimension of “Interpersonal” (M = 23.12 versus 13.39, p = 0.040).

Regarding the differences between non fatigued (<22), higher or equal to 22 fatigued patients and higher or equal to 35 extremely fatigued patients after the participation

TABLE 3. Correlations between dimensions of fatigue and QoL before the intervention

<table>
<thead>
<tr>
<th></th>
<th>Symptoms</th>
<th>Function</th>
<th>Interpersonal</th>
<th>Well-Being</th>
<th>Transcendent</th>
<th>Total QoL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical fatigue</td>
<td>r = .099</td>
<td>.117</td>
<td>-.046</td>
<td>-.087</td>
<td>-.305</td>
<td>-.007</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>.597</td>
<td>.530</td>
<td>.806</td>
<td>.643</td>
<td>.095</td>
</tr>
<tr>
<td>Mental fatigue</td>
<td>r = -.149</td>
<td>-.221</td>
<td>-.315</td>
<td>-.224</td>
<td>-.275</td>
<td>-.438*</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>.423</td>
<td>.231</td>
<td>.084</td>
<td>.227</td>
<td>.134</td>
</tr>
<tr>
<td>Total fatigue</td>
<td>r = -.021</td>
<td>-.049</td>
<td>-.197</td>
<td>-.171</td>
<td>-.329</td>
<td>-.239</td>
</tr>
<tr>
<td></td>
<td>p</td>
<td>.909</td>
<td>.793</td>
<td>.289</td>
<td>.357</td>
<td>.071</td>
</tr>
</tbody>
</table>

Notes: *p<0.05
in the rehabilitation program, the results showed that there was a statistically significant difference in quality of life and specifically in the dimension of “Transcendent” \((p=0.013)\) as well as the total score of MVQoL-15 \((p=0.046)\). Patients with no fatigue presented better QoL.

### DISCUSSION

The aim of this study was to compare the levels of fatigue and QoL (QoL) before and after the completion of a PRP in “Sotiria” public hospital. More specifically, the focus of this research was to examine whether these two variables could be affected and/or improved by COPD patients who were attending a PRP. It was hypothesized that PRP seems to be a successful and innovative clinical prevention program leading to lower levels of fatigue and a better QoL for those patients who suffer from COPD.

In order to examine the aforementioned hypothesis, a paired sample t-test was performed. Results showed that compared to the initial measurement, fatigue dimensions such as physical, mental as well as total fatigue scores were decreased in the second measurement that took place after the completion of the PRP. Similarly, QoL dimension such as transcendence seemed to be improved in the second and final measurement compared to the initial one. Therefore, lower levels of physical, mental and total fatigue but also higher levels of transcendence seem to confirm the hypothesis of the current research.

Thus, hypothesis was validated as the results showed that there is a significant difference between the two measurements regarding the levels of fatigue and Transcendence. Most of the patients reported lower levels of fatigue and a better transcendence dimension regarding QoL after the completion of the PRP. This is not a surprising finding. According to the literature, fatigue is the effect of a complicated interplay among individuals’ physical and behavioral characteristics. Various physical situations may lead to fatigue, thus, when an efficient therapy is applied, fatigue levels seem to decrease.\(^{19,20}\)

On the other hand, transcendence that could be related to the sanctuary and is defined as “a search for meaning, at times of pressure”\(^{21}\) seems to be as an internal belief system or a way out of which COPD patients could gain strength and consolation. According to the literature, whether transcendence is framed by the values of humanity, nature, or religion it also contributes to the individuals’ “ego” by providing them with strength and helping them to deal with increased anxiety.\(^{22}\)

According to a study\(^{23}\) that was conducted, regarding the relation of transcendence and physical activity for COPD patients, it was indicated that the practice of transcendence contributes to a statistically significant physical health. Another significant correlation was found between social functioning and transcendence practice. Therefore, each individual acquires a transcendent and spiritual dimension. According to a study that was conducted by Kayahan\(^{24}\) after the completion of a PRP, COPD patients who belonged to rehabilitation group seemed to show significant improvements in dyspnea, physical activity and their overall QoL compared to those patients who belonged to the control group.

Apart from the fact that the hypothesis was confirmed, another advantage of the current research is that this is the first time in Greece that a PRP uses these two instruments together in order to compare the possible differences in fatigue and QoL before and after the completion of the program.

Some limitations of this research include the following: the total sample of 31 participants which does not seem to be large enough may decrease the power of the research and raise at the same time the margin of error by leading to a possible meaningless study. Another limitation is as-

---

**TABLE 4. Correlations between dimensions of fatigue and QoL after the intervention (N=31)**

<table>
<thead>
<tr>
<th></th>
<th>Symptoms</th>
<th>Function</th>
<th>Interpersonal</th>
<th>Well-being</th>
<th>Transcendent</th>
<th>Total QoL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical Fatigue</td>
<td>r</td>
<td>-.223</td>
<td>.461**</td>
<td>-.470**</td>
<td>-.615**</td>
<td>-.636**</td>
</tr>
<tr>
<td></td>
<td>(P)</td>
<td>.228</td>
<td>.009</td>
<td>.008</td>
<td>.000</td>
<td>.000</td>
</tr>
<tr>
<td>Mental Fatigue</td>
<td>r</td>
<td>-.209</td>
<td>.013</td>
<td>-.285</td>
<td>-.313</td>
<td>-.322</td>
</tr>
<tr>
<td></td>
<td>(P)</td>
<td>.258</td>
<td>.944</td>
<td>.120</td>
<td>.087</td>
<td>.077</td>
</tr>
<tr>
<td>Total Fatigue</td>
<td>r</td>
<td>-.248</td>
<td>.300</td>
<td>-.444*</td>
<td>-.550**</td>
<td>-.568**</td>
</tr>
<tr>
<td></td>
<td>(P)</td>
<td>.178</td>
<td>.101</td>
<td>.012</td>
<td>.001</td>
<td>.001</td>
</tr>
</tbody>
</table>

\* \(p<0.05\), ** \(p<0.01\)
sociated to the fact that the female participants were less than male participants, and more specifically they were only the one third of the total number that took place in the research. This factor cannot provide very accurate results regarding gender differences.

Moreover, the program’s limited time (3 months) could not guarantee an improved QoL with significant dimensions. In other words, a PRP that would last for more than three months could benefit the patients’ QoL by probably showing significant results regarding interpersonal relationships, wellbeing, symptoms, and/or function dimensions. Finally, future research should be performed regarding fatigue and QoL in pulmonary rehabilitation for COPD patients in order to investigate whether there are differences before and after the PRP. For instance, a research could be focused on the differences between fatigue and QoL before and after a six month to one year PRP.

CONCLUSION

Therefore, PR is an extensive intervention based on a patient’s meticulous assessment by providing exercise and education applied to each patient’s needs and by aiming to an individual’s behavioral change through a healthier lifestyle and a better QoL. PRP improves COPD patients’ physical and psychological state by offering long-term attachment to health-promoting behaviors.4

The results of the current study may aid health care professionals, COPD patients and academic community to enrich their knowledge about PR strengths and opportunities regarding the Greek population. More specifically, health care professionals may strengthen and support COPD patients to follow a routine, join constantly and complete the PRP in order to gain the program’s benefits by becoming more active and decrease their levels of fatigue. Since it seems to be the first time that the academic community may be benefited by such an innovative PRP that is applied in Greece, it seems that the program’s advantages could cause the spread of other new, sufficient and more efficient Pulmonary Programs that will be ready to serve the Greek population in the future.

COPD patients should be helped by doctors and health care professionals by applying the principles of PRP and face patients through a multidimensional way with special regard to their QoL. There should be a cooperation between professionals of the health care area and exploit every method towards this direction by taking seriously each patient’s particular problems in order to achieve relief from the chronic disease’s symptoms.

Furthermore, it seems to be essential to observe how the difference of fatigue and QoL levels could affect the results before and after the PRP measurement. Hence, future research should be conducted in order to develop strategies that they could diminish the fatigue in COPD patients and by improving at the same time their QoL. If, according to the literature, breath is related to the soul and mind is conceptually related to the soul,25 then doctor and specialized scientists in lung diseases should perform further research to the transcendent needs of COPD patients.

ACKNOWLEDGEMENTS

The authors would like to acknowledge patients who participated in this study.

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest

The authors declare that they have no conflict of interest.

Funding statement

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Ethical approval

Ethical approval was granted by the Scientific Council of General Hospital of Athens “Sotiria”. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Informed consent

Informed consent was obtained from all individual participants included in the study.
Εισαγωγή. Η κόπωση και η στενή ποιότητα ζωής μπορούν να διαδραματίσουν σημαντικό ρόλο στην χρόνια αποφρακτική ασθένεια και τα θεραπευτικά αποτελέσματα. Σκοπός αυτής της μελέτης ήταν η εξέταση των επιπέδων κόπωσης και ποιότητας της ζωής μεταξύ ασθενών με Χρόνια Αποφρακτική Πνευμοπάθεια πριν και μετά από πρόγραμμα πνευμονικής αποκατάστασης. Μέθοδος. Σε αυτή την πειραματική μελέτη, 31 τυχαία επιλεγμένα ασθενείς με Χρόνια Αποφρακτική Πνευμοπάθεια προέρχονται από Τριτοβάθμιο νοσοκομείο της Αθήνας συμπλήρωσαν, πριν και μετά από πρόγραμμα πνευμονικής αποκατάστασης, δύο ερωτηματολόγια: Την κλίμακα Fatigue Assessment Scale για τη μελέτη των επιπέδων κόπωσης και την κλίμακα Missoula-Vitas Quality of Life Index-15 για τη μελέτη της ποιότητας ζωής. Η στατιστική ανάλυση διεξήχθη μέσω του στατιστικού πακέτου SPSS 19.0. Το επίπεδο στατιστικής σημαντικότητας τέθηκε στο 0.05. Αποτελέσματα: Τα αποτελέσματα έδειξαν μειωμένα επίπεδα κόπωσης μετά την ολοκλήρωση του προγράμματος πνευμονικής αποκατάστασης σε σύγκριση με αυτά προ της παρέμβασης. Επιπλέον, αν και η ποιότητα ζωής δε φαίνεται να μεταβαλλεί μετά την παρέμβαση, η διάσταση «Πνευματικότητα» φαίνεται να αυξάνεται για την πλειονότητα των συμμετέχων. Μετά τη συμμετοχή στο πρόγραμμα αποκατάστασης παρατηρήθηκε σημαντική και αρνητική συσχέτιση μεταξύ της ψυχικής κόπωσης και της συνολικής βαθμολογίας της ποιότητας ζωής (r = -0.436, p = 0.014 <0,05), καθώς και μεταξύ της σωματικής κόπωσης και των διαστάσεων της ποιότητας ζωής «Διαπροσωπικές Σχέσεις» (r = -0.470, p=0,008), “Ευεξία” (r = -0.615, p=0,000), “Πνευματικότητα” (r = -0.636, p=0,000) και της συνολικής βαθμολογίας της ποιότητας ζωής (r = -0.543, p=0,002). Συμπέρασμα: Ένα πρόγραμμα πνευμονικής αποκατάστασης φαίνεται να αποτελεί ένα επιτυχές και καινοτόμο πρόγραμμα πρόληψης που οδηγεί σε χαμηλότερα επίπεδα κόπωσης σε ασθενείς με Χρόνια Αποφρακτική Πνευμοπάθεια.


Λέξεις - Κλειδιά: Χρόνια Αποφρακτική Πνευμοπάθεια, Κόπωση, Πρόγραμμα πνευμονικής αποκατάστασης, Ποιότητα ζωής

REFERENCES

Prognostic factors related with prolonged hospital stay in community-acquired pneumonia

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Key words:
- Community acquired pneumonia
- Length of hospital stay
- Outcomes
- Mortality

INTRODUCTION

Community-acquired pneumonia (CAP) is a common cause of patient hospitalization, and its burden on health care systems is increasing in...
Aging societies. Appropriate clinical management is important for reducing length of stay (LOS), health cost and mortality. Inpatient management is up to 20 times more expensive than outpatient care. Safely reducing the number of inpatient days is cost-effective and physicians are under increasing pressure from health insurance providers and their own institutions to discharge patients from the hospital as timely as possible. In the last two decades LOS in CAP patients has continuously been declining safely and maintaining the quality of care.

Clinical practice guidelines recommend discharging patients with CAP as soon as they are clinically stable, have no other active medical problems, and have a safe environment for continued care. Several studies have reported that pneumonia severity, comorbidities, and specific procedures (such as the use of mechanical ventilation) are associated with prolonged LOS in CAP patients. However, there are other factors that influence LOS such as clinicians characteristics and work efficacy, availability of beds, and social services that help patient support.

The aim of this study was to identify the factors independently associated with prolong LOS in hospitalized adult CAP patients during a 7-year period in a single hospital. We hypothesized that non-adherence to guidelines are significantly related with prolonged LOS in hospitalized patients with CAP.

**METHODS**

**Ethics statement**

For publication purposes, the study was approved by the Ethics Committee of our institution. Written informed consent was waived because of the non-interventional study design.

**Study design and patients**

This was a prospective observational study carry in an 800-bed university tertiary-care hospital in Athens, of consecutive adult (≥18 years old) patients with diagnosis of CAP admitted to the hospital from the emergency department between June 2011 and July 2018. The exclusion criteria were: a) severe immunosuppression (AIDS, chemotherapy, immunosuppressive drugs [e.g., oral corticosteroid ≥10 mg prednisone or equivalent per day for at least two weeks]), b) active tuberculosis, d) cases with a confirmed alternate diagnosis.

**Definitions**

Pneumonia was defined as a new pulmonary infiltrate found on the hospital admission chest radiograph, with symptoms and signs of lower respiratory tract infection. Severe CAP was defined according when at least one major or 3 minor criteria of the Infectious Disease Society of America/American Thoracic Society (IDSA/ATS) guidelines were present.

Prior antibiotic treatment was defined as the use of a previous antibiotic within at least 24 hours before the admission and given for the current episode of pneumonia. LOS was defined as the time (days) spent in hospital. The LOS was dichotomized using a cut-off point of 11 days considering that the mean LOS in the entire study population was 11.0 ±4.9 days.

The appropriateness of empirical antibiotic treatment was defined according to the IDSA/ATS guidelines for managing CAP. Pulmonary complications include pleural effusion, empyema, or radiological progression of pulmonary infiltrates at admission and during hospitalization. Overall mortality was defined as death from any cause during the hospitalization period.

**Data collection**

Demographic, epidemiological, and clinical information was systematically collected through patient interviews and medical chart abstraction. Other data were also recorded: history of cigarette smoking, alcohol abuse, asthma or chronic obstructive pulmonary disease, coronary artery disease, diabetes, dementia, hospitalization in the preceding year, and previous admissions for CAP. Initial clinical symptoms and physical signs noted were pleural pain, cough, expectoration, abrupt onset dyspnea, and the time-lapse (in days) from symptom onset. Laboratory analyses recorded leukocyte, haemoglobin, plasma urea (BUN), albumin, sodium, potassium and platelet levels and blood gas measurements (arterial oxygen tension (PaO2), arterial carbon dioxide tension, and pH) on admission.

Pneumonia severity upon hospital admission was estimated using the validated prediction rules: calculated according to the PSI and CURB65 score. During hospitalization, we recorded whether the patients had complications such as, pleural effusions, demonstrated radiographic progression of pneumonia, progressive respiratory failure, acute respiratory distress syndrome (ARDS), septic shock, or acute renal failure. Further details are reported elsewhere.

Microbiological data were obtained from medical
therapy, had higher PSI and CURB-65 risk, more frequently presented with confusion, dyspnea and higher CRP levels at admission.

Table 3 shows the mean LOS stratified by PSI risk class. The mean LOS increases steadily according to PSI risk class, starting from 7.8 (SD 4.5) days in patients belonging to PSI I class and reaching to 13.3 (SD 13.6) days in PSI V class patients. The mean LOS increases steadily according to PSI risk class (Figure 1).

Also patients in PLOS group presented with more tachypnea, acute respiratory failure, higher CRP level, multilobar affectation and pleural effusion. Their demographics and clinical characteristics at admission according to LOS are presented Table 1 & Table 2.

TABLE 1. Characteristics of the population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>PLOS N=286</th>
<th>SLOS N=644</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;65 years old</td>
<td>168 (33)</td>
<td>348 (67)</td>
<td>0.183</td>
</tr>
<tr>
<td>Gender, male</td>
<td>163 (57)</td>
<td>347 (54)</td>
<td>0.379</td>
</tr>
<tr>
<td>Aspiration</td>
<td>36 (13)</td>
<td>60 (9)</td>
<td>0.130</td>
</tr>
<tr>
<td>HCAP</td>
<td>64 (22)</td>
<td>96 (15)</td>
<td>0.006</td>
</tr>
<tr>
<td>Comorbidities</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Number com. ≥3</td>
<td>48 (17)</td>
<td>84 (13)</td>
<td>0.132</td>
</tr>
<tr>
<td>D.M.</td>
<td>55 (19)</td>
<td>132 (21)</td>
<td>0.657</td>
</tr>
<tr>
<td>COPD</td>
<td>80 (28)</td>
<td>165 (26)</td>
<td>0.435</td>
</tr>
<tr>
<td>Cardiovascular disease</td>
<td>101 (35)</td>
<td>202 (31)</td>
<td>0.236</td>
</tr>
<tr>
<td>Neurological dis</td>
<td>69 (24)</td>
<td>128 (20)</td>
<td>0.143</td>
</tr>
<tr>
<td>Smoking habit</td>
<td>135 (47)</td>
<td>267 (42)</td>
<td>0.101</td>
</tr>
<tr>
<td>Nonsmoker</td>
<td>117 (41)</td>
<td>278 (43)</td>
<td></td>
</tr>
<tr>
<td>Ex-smoker</td>
<td>34 (12)</td>
<td>97 (15)</td>
<td></td>
</tr>
<tr>
<td>Previous antibiotics</td>
<td>146 (53)</td>
<td>277 (44)</td>
<td>0.015</td>
</tr>
<tr>
<td>CURB65 ≥3</td>
<td>128 (45)</td>
<td>198 (31)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>PSI risk class</td>
<td>115 ± 39</td>
<td>98 ± 45</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Low risk</td>
<td>78 (28)</td>
<td>293 (46)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>High risk</td>
<td>205 (72)</td>
<td>342 (54)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are number of patients (%), mean (SD) or median (1st quartile-3rd quartile). Percentages calculated on non-missing data.

HCAP=Health Care Associated Pneumonia; DM=Diabetes mellitus; COPD=chronic obstructive pulmonary disease; CURB65-consciousness, urea, respiratory rate, blood pressure, 65 years old; ICU=intensive care unit; PSI=pneumonia severity index.
An etiologic diagnosis was obtained in 182 (20%) patients (PLOS 34% (98/285). The most frequent pathogen in both groups was S. pneumoniae (n=40, 22%). The pathogens identified most frequently in PLOS group were: Pseud. aeruginosa (n=12), Klebsiella pnem. (n=9) and Acinetobacter baum (n=9) and other Gram (-) s, whereas S. pneumoniae (n=22), atypicals (n= 8) and viruses (n=26) were more common in SLOS group.

**Empiric Antibiotic Therapy**

Data on empiric antibiotic treatment were available in 919 patients (Table 3). Antibiotic monotherapy had been administered to 244 patients (26%). The most frequent regimens were β-lactam plus either a macrolide (36%) or a respiratory fluoroquinolone (25%) (Table 4). PLOS patients more often received respiratory fluoroquinolones in combination (40%) compared with SLOS patients (19.5%). The empiric antibiotic treatment was inadequate in 162

**TABLE 2. Clinical Presentation of CAP according to LOS**

<table>
<thead>
<tr>
<th>Characteristics, n (%)</th>
<th>PLOS N=286</th>
<th>SLOS N=644</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Confusion</td>
<td>94 (33)</td>
<td>160 (25)</td>
<td>0.010</td>
</tr>
<tr>
<td>Respiratory Rate &gt;30/min, breaths/min</td>
<td>126 (44)</td>
<td>227 (35)</td>
<td>0.011</td>
</tr>
<tr>
<td>Insufficiency Respiratory (pO2 &lt;60mmHg)</td>
<td>193 (68)</td>
<td>386 (60)</td>
<td>0.025</td>
</tr>
<tr>
<td>CRP, mg/dL</td>
<td>18.3±13.7</td>
<td>15.5±11.6</td>
<td>0.018</td>
</tr>
<tr>
<td>Urea &gt;30mg/dl</td>
<td>199 (70)</td>
<td>403 (63)</td>
<td>0.045</td>
</tr>
<tr>
<td>PLT</td>
<td>282539±150441</td>
<td>258863±112387</td>
<td>0.019</td>
</tr>
<tr>
<td>Albumin mg/dL</td>
<td>3.14 ±0.6</td>
<td>3.32 ±0.6</td>
<td>0.004</td>
</tr>
<tr>
<td>Multilobar Involvement</td>
<td>155 (54)</td>
<td>252 (39)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pleural Effusion</td>
<td>119 (42)</td>
<td>112 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Shock</td>
<td>41 (14)</td>
<td>66 (10)</td>
<td>0.074</td>
</tr>
</tbody>
</table>

**TABLE 3. Duration of hospitalization in relation to initial antibiotic treatment**

<table>
<thead>
<tr>
<th>Antibiotic regimen, Number pts, %</th>
<th>LOS</th>
</tr>
</thead>
<tbody>
<tr>
<td>B-lactams monotherapy</td>
<td>104 (12)</td>
</tr>
<tr>
<td>Quinolone monotherapy</td>
<td>136 (15)</td>
</tr>
<tr>
<td>Combination Macrolide</td>
<td>340 (37)</td>
</tr>
<tr>
<td>Combination Quinolone</td>
<td>231 (25)</td>
</tr>
</tbody>
</table>

**TABLE 4. Therapy & Evolution of CAP according to LOS**

<table>
<thead>
<tr>
<th>Variable, n (%)</th>
<th>PLOS N=286</th>
<th>SLOS N=644</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diagnosis</td>
<td>98 (34)</td>
<td>84 (13)</td>
<td>0.001</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>55 (20)</td>
<td>189 (30)</td>
<td>0.001</td>
</tr>
<tr>
<td>Macrolides</td>
<td>80 (28)</td>
<td>260 (41)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Quinolone monotherapy</td>
<td>111 (17)</td>
<td>25 (9)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Combination macr + b-lactam</td>
<td>75 (27)</td>
<td>256 (40)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>quinol + b-lactam</td>
<td>113 (40)</td>
<td>118 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Guidelines Adherence</td>
<td>213 (76)</td>
<td>544 (85)</td>
<td>0.001</td>
</tr>
<tr>
<td>Cortis therapy</td>
<td>91 (32)</td>
<td>105 (16)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complications systemic</td>
<td>122 (43)</td>
<td>122 (19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Complications pulmonary</td>
<td>181 (64)</td>
<td>179 (28)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>ICU Admission</td>
<td>39 (14)</td>
<td>49 (8)</td>
<td>0.004</td>
</tr>
<tr>
<td>Mortality inhospital</td>
<td>23 (8)</td>
<td>56 (9)</td>
<td>0.74</td>
</tr>
<tr>
<td>LOS, mean days (SD)</td>
<td>20.4 ± 13</td>
<td>6.8 ± 3</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

Data are number of patients (%), mean (SD) or median (1st quartile-3rd quartile). Percentages calculated on non-missing data. CURB-65=consciousness, urea, respiratory rate, blood pressure, 65 years old. ICU=intensive care unit. PSI=pneumonia severity index.

* Patients could have more than one comorbidity. MV: mechanical ventilation. NIV: non-invasive ventilation.

$ Patients who received initially non-invasive ventilation but needed subsequently intubation were included in the invasive mechanical ventilation group.
of all cases (17%); most often in PLOS group 69 (25%) compared with SLOS 93 (15%) (p<0.001).

Predictors of PLOS

Among the variables associated with PLOS in the univariate analysis (Table 5), the previous antibiotic therapy, high level of CRP, hypoalbuminemia, PSI class ≥4, pulmonary and systemic complications, monotherapy, therapy with corticosteroids and non-adherence to guidelines remained significant independent associated with PLOS. In the multivariate analysis (Table 5), the factors independently related with a prolonged hospitalization was previous antibiotic therapy, hypoalbuminemia, PSI class ≥4, pulmonary complications, therapy with corticosteroids and non-adherence to guidelines. The most important variable associated with an increased LOS was the non-adherence to the guidelines (OR: 1.92).

Clinical outcomes

PLOS group had higher rate of ICU admission and needed of mechanical ventilation (invasive and non-invasive). Seventy-nine patients died giving a mortality rate of 8.5%. We did not find significant differences between groups regarding mortality (Table 4).

<table>
<thead>
<tr>
<th>FACTORS</th>
<th>Univariate analysis</th>
<th>Multivariate analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>OR 95% CI p-value</td>
<td>OR 95% CI p-value</td>
</tr>
<tr>
<td>Age, years (+1)</td>
<td>1.01 1.001-1.02 0.03</td>
<td>0.61 0.38-0.97 0.035</td>
</tr>
<tr>
<td>Previous antbs</td>
<td>0.7 0.53-0.73 0.015</td>
<td>0.52 0.32-0.84 0.008</td>
</tr>
<tr>
<td>PSI high class</td>
<td>0.44 0.33-0.6 &lt;0.001</td>
<td>0.57 0.357-0.908 0.018</td>
</tr>
<tr>
<td>CRP</td>
<td>1.02 1.003-1.035 0.020</td>
<td></td>
</tr>
<tr>
<td>Hypoalbuminemia</td>
<td>0.58 0.39-0.87 0.008</td>
<td></td>
</tr>
<tr>
<td>Multilobar involvement</td>
<td>0.55 0.411-0.722 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Pleural effusion</td>
<td>3.35 2.46-4.59 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Pulmonary complications</td>
<td>0.22 0.16-0.3 &lt;0.001</td>
<td>0.25 0.16-0.39 &lt;0.001</td>
</tr>
<tr>
<td>Systemic complications</td>
<td>0.32 0.24-0.43 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Guidelines adherence</td>
<td>1.9 1.34-2.7 &lt;0.001</td>
<td>1.92 1.12-3.3 0.018</td>
</tr>
<tr>
<td>Monotherapy</td>
<td>1.8 1.3-2.5 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Corticosteroids therapy</td>
<td>0.42 0.3-0.58 &lt;0.001</td>
<td>0.46 0.27-0.75 0.005</td>
</tr>
</tbody>
</table>

CI=confidence interval. CURB-65=consciousness. urea, respiratory rate, blood pressure, 65 years old. ICU= intensive care unit. OR=odds ratio. PSI=pneumonia severity index.

* Hosmer-Lemeshow goodness-of-fit test, p=0.32.
$ Patients who received initially non-invasive ventilation but needed subsequently intubation were included in the invasive mechanical ventilation group.

Note: CI = confidence interval; OR = odds ratio.

DISCUSSION

LOS is a major factor to consider when examining the relationship between patient severity and hospitalization costs because there is a high possibility that LOS acts both as an intermediate variable and an explanatory variable for costs. A multicenter study19, including 20 teaching and community hospitals in Canada, showed a wide variation in LOS and the management of CAP among hospitals. The causes of this variation are not well known.

In this study we identify predictors associated with prolonged hospital stay in patients with CAP as previous antibiotic therapy, high PSI score (≥4), hypoalbuminemia, corticosteroids therapy, guidelines non-adherence and pulmonary complications.

In our study previous antibiotic use for the current episode of pneumonia was associated with prolonged hospitalization. 46% of our cohort had received antibiotics prior to admission, mainly β-lactams (15%), macrolides (11%) and quinolones (8.5%). Previous studies showed that antibiotic treatment prior to hospitalization could contribute to a reduction of ICU admissions20, severity of pneumococcal pneumonia21 and systemic inflammation22. Specifically, Amaro et al20 reported that previous antibiotic use for pneumonia was associated with a lower incidence
of CAP caused by *S. pneumoniae* and higher incidence of atypical and *S. aureus* pneumonia.

Previously different predictors for LOS have been reported\(^{4,10,12,23}\). In line, with our results, authors encountered several factors that correlated (positively or negatively) with the LOS and which corresponded to the initial severity of the illness (PSI, or risk class of Fine), characteristics of the patients and initial antibiotic treatment. Our predictors at admission related with the severity of pneumonia (PSI >4) and patients’ acute disease condition, as hypoalbuminemia. The influence of the PSI score on this period was rather straightforward, with more seriously ill patients or those with more comorbidities taking longer to recover, for whom the factor of clinical stability may not be sensitive enough. Several studies have shown that albumin is a marker of nutritional status and is associated with mortality risk and recovery time of the patient. In the study of Menendez et al\(^4\), observed that in low-risk patients, LOS is determined mainly by the level of hypoxemia and pleural effusion, while in the higher risk classes, additional factors, such as multi-lobe involvement, diastolic blood pressure and the albumin concentration, also become significant\(^4\). They did not find an association between therapy and length of hospitalization, as we did.

Logistic regression identified that appropriate use of antibiotic, corticoids therapy and pulmonary complications as key independent predictors of LOS. We found that appropriate initial selection of antibiotics according to guidelines\(^7,24\) was associated with a shorter length of stay in univariate and multivariate analyses. These findings are similar to observations made by Capelastegui et al\(^6\) and Battleman et al\(^25\) and suggest that quality improvement targeted at antibiotic use may reduce LOS and save costs.

The influence of guideline compliant antibiotic treatment can be explained by the severity of pneumonia and the compliance of the clinicians of our hospital. Previous studies that analyzed the influence of treatment on the duration of hospitalization obtained discordant results\(^{4,10,26-28}\). Equally, the antibiotic therapy itself appears to be a cause for delayed discharge. Possible solutions may be improvements in the switch from intravenous to oral antibiotics or an increased use of outpatient parenteral antibiotic therapy for eligible patients.

With respect to the initial antibiotic regimen employed, univariate analysis indicated that there was a shorter LOS in those patients treated with quinolone monotherapy. However, this variable was not subsequently selected in the multivariate model.

The addition of corticosteroids in therapy of pneumonia resulted in prolonged hospitalization (15 days vs. 10 days, *p*<0.001) comparing to the other patients. In our population we don’t know exactly the date of start of corticosteroids, neither the reason for this therapy (complication, exacerbation, respiratory failure). It is for sure associated with the presence of COPD and asthma comorbidity.

On the contrary, studies had proved that adjunctive corticosteroids treatment for patients hospitalized with CAP can reduce time to clinical stability and LOS by approximately 1 day without a significant effect on overall mortality, according to a recent meta-analysis\(^{29,30}\). But it has to be determined, in which patients with pneumonia, what dose of corticosteroids and for how long?

Pulmonary complications are a cause of PLOS and an indicator of treatment failure in many studies\(^6,23,31,32\). Specifically, Menendez et al\(^11\) reported that complications appearing before 72 h were associated with prolonged hospitalization.

Furthermore, Suter-Widmer et al\(^23\) identified several factors on admission and during follow-up, which were independently associated with longer LOS in patients with CAP. Integrated them into a clinical prediction rule, accurately estimated LOS in CAP patients.

However, LOS is influenced by various other factors, such as clinicians’ practice style, availability of beds, and the availability of social services such as long-term care facilities for placement of those who can no longer care for themselves\(^12\). In another study, early mobilization of patients with CAP led to a reduction in LOS: 6.9 days for those who received the usual mobilization versus 5.8 days for those who received early mobilization\(^13\). The main strengths of the present study were the large sample size, the large number of variables collected from the clinical records. Our study has several limitations, also. First, the study was conducted in a single geographic area and thus may reflect a single standard of practice. However, “Sotiria” as a Chest diseases hospital is a reference hospital of central Greece. Second, time to first antibiotic dose and time to clinical stability was not assessed that which may influence LOS. So, we did not evaluate the relationships between initial variables and clinical stability and/or clinical response-to therapy separate from the LOS. Third, we don’t have data about the functional status of patients or the disability level (frailty) and the mobilization time of every patient to correlate it with LOS.

In our study we identify factors that increase LOS in patients with CAP and those factors that can be modified is an important responsibility for physicians as well as for administrators. Currently, several useful interventions can be suggested for shortening LOS: (i) Using Fine’s PSI
risk classes, the number of hospital admissions could be reduced by dealing with patients of class I and II in outpatient departments, (ii) the implementation of ATS or ERS guidelines advising rapid antibiotic initiation, an appropriate antibiotic selection and (iii) the addition of corticosteroids only in selected patients with high inflammatory response and severe pneumonia.29.

CONCLUSIONS

Within this study we identified different baseline and follow-up characteristics to be strong and independent predictors for LOS. A better understanding of the factors influencing hospital stay should lead to measures to reduce LOS.

ΠΕΡΙΛΗΨΗ

Προγνωστικοί παράγοντες που σχετίζονται με την παρατεταμένη διάρκεια νοσηλείας σε πνευμονία της κοινότητας

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Η πνευμονία της κοινότητας (ΠΚ) συνδέεται με υψηλή νοσηρότητα, θνησιμότητα και υψηλό κόστος. Το κόστος της ασθένειας αυξάνεται ανάλογα με τον τόπο φροντίδας (σπίτι, κλινική, ΜΕΘ) και τη διάρκεια της νοσηλείας (LOS). Η έγκαιρη αναγνώριση των προγνωστικών παραγόντων για παρατεταμένη παραμονή στο νοσοκομείο θα βοηθήσει στη μείωση του κόστους της ΠΚ. Σε δύο πνευμονολογικές κλινικές του νοσοκομείου Σωτηρία, διεξήχθη μια μελέτη παρατήρησης διαδοχικών ασθενών με ΠΚ από τον Ιούνιο 2011 έως τον Ιούλιο του 2018. Διαχωρίσαμε τον πληθυσμό σε δύο ομάδες: ομάδα παρατεταμένης νοσηλείας (PLOS) (νοσηλεία ίση ή μεγαλύτερη από τη μέση τιμή LOS) και (SLOS) (μικρότερη από τη μέση τιμή LOS). Αποτελέσματα: Από συνολικά 930 ασθενείς (55% άνδρες, 63,7 έτη (SD 18) με μέση διάρκεια διαμονής 11 ημέρων (SD 9, 6), 286 ασθενείς είχαν PLOS 20 ημερών (SD 13). Οι ασθενείς με PLOS ήταν μεγαλύτεροι (66 έτη έναντι 63 έτών, p = 0,023) και είχαν λάβει συχνότερα αντιβιοτικά πριν από την εισαγωγή τους (53% έναντι 44%, p = 0,015). Η πνευμονία τους κατά την εισαγωγή ήταν βαρύτερη με βάση το PSI skor και εμφάνιζαν συχνότερα συστηματικές επιπλοκές (43% έναντι 19%, p <0,001) και την ανάγκη για εισαγωγή στη ΜΕΘ (14% έναντι 6%, p <0,001). Παρόλα αυτά η θνητότητα δε διέφερε μεταξύ των δύο ομάδων. Προγνωστικοί παράγοντες παρατεταμένης νοσηλείας σε ασθενείς με ΠΚ αποτελούν η σοβαρότητα της πνευμονίας (PSI class >4), η λήψη αντιβιοτικών πριν νοσηλεία, η υποαλβουμιναιμία, η θεραπεία με κορτικοστεροειδή, οι πνευμονικές επιπλοκές και η μη τήρηση των θεραπευτικών οδηγιών.


Αναφορές - Κλειδιά: Πνευμονία της κοινότητας, Διάρκεια νοσηλείας, Θνησιμότητα

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New Antibiotics for Hospital-acquired pneumonia

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ABSTRACT

INTRODUCTION: Hospital-acquired pneumonia is the most common life-threatening hospital-acquired infection, and the majority of cases (80%) are associated with mechanical ventilation. Once pneumonia develops, the appropriateness of the initial antibiotic regimen is a vital determinant of outcome. AREAS COVERED: In this review we summarize the actual situation of new antibiotics for treatment of HAP and VAP. This article covers medical literature published in English language since 2000 until February 2019, on "hospital pneumonia", identified using PubMed and www.clinicaltrial.gov. The search terms used were "ventilator associated pneumonia", "resistance", "therapy" and "new antibiotics". EXPERT OPINION: Newer drugs approved for the combat of MDR pathogens for hospital pneumonia include cephalosporins active against MRSA and β-lactamases and as: ceftolozane combined with avibactam and ceftazidime with tazobactam. Other antibiotics active against ESBL are the combinations of carbapenems Cilastatin/imipenem/relebactam and meropenem/Vaborbactam, plazomicin a semisynthetic derivative of sisomycin, and a new cephalosporine cefiderocol.

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1. INTRODUCTION

Nosocomial pneumonia (NP) is a common nosocomial bacterial infection and is most prevalent in intensive care units (ICUs) 1 in individuals undergoing mechanical ventilation (MV) defined as ventilator associated pneumonia (VAP) but can also develop in nonventilated patients, named as hospital acquired pneumonia (HAP) 2. It accounts for 11% of Hospital acquired infections (HAIs) outside of ICUs and 26% of HAIs in the ICUs. 3-4 VAP represents a major clinical and economical problem in critically ill patients due to its associated morbidity, prolonged MV-days, and ICU length of stay (LOS), which translates to elevated health care costs. NP carries a crude mortality rate of 30% to 70% with an estimated attributable mortality rate to pneumonia between with an attributable mortality of 3-17% 5.

Key words:
- Hospital acquired pneumonia
- New antibiotics
- Resistance
- Telavancin
- Avibactam
- Cefiderocol

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2. MICROBIAL ETIOLOGY

The principal sources of pathogens in HAP cases are the health care environment and the patient’s own microbial flora. The microbial etiology of HAP in the ICU varies according to patient population, hospital ICU settings, the country, and the type of presentation (early- or late-onset).

A review of published studies of the causes of pneumonia in hospitalized patients and the results of the SENTRY Antimicrobial Surveillance Program in the United States concluded that six pathogens cause approximately 80% of HAP cases: Staphylococcus aureus, Pseudomonas aeruginosa, Klebsiella spp., Escherichia coli, Acinetobacter spp., and Enterobacter spp.

Gram-negative bacteria (GNB) are implicated in 50 to 80% of the cases of HAP in an ICU. Gram-positive pathogens account for 20 to 30% of HAP cases. The most common Gram-positive pathogens isolated from patients with HAP include S. aureus [methicillin-sensitive (MSSA) and methicillin-resistant (MRSA)], Streptococcus species, and Streptococcus pneumoniae.

The first global report on surveillance of antimicrobial resistance with data from 114 countries was published by World Health Organization (WHO) in 2014, this report confirm that antibiotic resistance is no longer a potential but a current major threat to global public health. The three pathogens with major concern about resistance were: E. coli (resistance to third-generation cephalosporins and fluoroquinolones), K. pneumoniae (resistance to third-generation cephalosporins and carbapenems), and S. aureus (resistance to methicillin) that are together with multi-drug resistant P. aeruginosa the principal pathogens involved in HAP infections.

Defining the frequency of MDR pathogens in each lactamase organisms, have contributed to the escalating rates of ICU is essential, since patients being treated in an ICU with more than 25% MDR pathogens have an increased risk of MDR VAP, regardless of other risk factors.

3. GUIDELINES THERAPY

When the clinical suspicion of HAP is high, it is essential to promptly start appropriate antimicrobial therapy as both delayed and inadequate treatment have been correlated with increased rate of morbidity and mortality. Previous studies reported a mortality rate associated with VAP of 30%-50% and even more when shock is present. In fact, in a large series involving patients with HAP, Alvarez Lerma et al revealed that patients who received adequate antibiotic treatment had lower mortality than did those who received inadequate therapy (16% vs 25%).

ATS/IDSA new guidelines for management of NP, published in 2016 in CID, first they define HAP as pneumonia in the non-ventilated patients and then they recommend selection of initial empirical treatment for HAP and VAP according to risk factors for MDR bacteria (underlying diseases and previous antibiotic prescription) and local susceptibilities.

According to the guidelines, the major risk factor for MDR HAP and for MDR Pseudomonas pneumonia and MRSA pneumonia also, was prior use of intravenous antibiotics.

1) Empirical therapy for VAP

In patients with suspected VAP, the recommendation including coverage for S. aureus, P. aeruginosa, and other GNB in all empiric regimens. The combination antibiotic therapy in VAP from P. aeruginosa suggested only in cases when: a) a risk factor for antimicrobial resistance exists, b) patients in units where >10% of gram-negative isolates are resistant to an agent being considered for monotherapy, and c) patients in an ICU where local antimicrobial susceptibility rates are not available.

Optimal combinations include meropenem or doripenem plus either levofloxacin or aztreonam or amikacin. Regarding MRSA coverage; guidelines recommend either linezolid or vancomycin.

2) Empirical therapy for HAP

For patients being treated empirically for HAP, we have to cover S. aureus. But, when the patient has risk factors for MRSA HAP (Table 1) vancomycin or linezolid is the recommended option.

Combination antibiotic therapy is recommended when we have suspicion for Pseudomonas or other gram-negative infection or a high risk for mortality (need for ventilator support due to HAP and septic shock).

At the moment, multidrug resistance in GNB is the

<table>
<thead>
<tr>
<th>TABLE 1. Risk factors for MRSA HAP</th>
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<tbody>
<tr>
<td>1. Prior intravenous antibiotic use within 90 days</td>
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<tr>
<td>2. Hospitalization in a unit where &gt;20% of S. aureus isolates are methicillin resistant</td>
</tr>
<tr>
<td>3. The prevalence of MRSA in the hospital is not known</td>
</tr>
<tr>
<td>4. Patient at high risk for mortality</td>
</tr>
</tbody>
</table>

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greater threat, with multidrug resistance rates more than 40% among GNB, because the rates of resistance of Enterobacteriaceae, particularly carbapenem-resistant enterobacteriaceae (CRE) is increasing rapidly worldwide. In the ICUs of US reported VAP isolates with third-generation cephalosporin resistance among Escherichia coli 67.5% and similarly 68.9% for K. pneumoniae; carbapenem resistance 42.7% among P. aeruginosa isolates and 66.3% among A. baumannii. Antimicrobial resistance increases on ICU through antibiotic use, patient to-patient transmission and medical procedures.

Facing the epidemic of MDR-GNB, antipseudomonal carbapenems (imipenem/cilastatin and meropenem) have become the most empirically prescribed β-lactams in European ICU for HAP/VAP.

Once the results of respiratory cultures become available, therapy can de-escalate, based on the identity of pathogens and their susceptibility to specific antibiotics, in order to avoid prolonged use of a broader spectrum of antibiotic therapy, preventing the development of more resistance. IDSA/ATS panel suggests using procalcitonin (PCT) levels plus clinical criteria to guide the discontinuation of antibiotic therapy.

4. CURRENTLY AVAILABLE OPTIONS

A few new therapeutic agents have been approved for clinical use the last decade for HAP and VAP; these include the antibiotics telavancin and ceftobiprole.

1) Telavancin

Telavancin (TLV), it is a lipoglycopeptide analogue of vancomycin, with a dual mechanism of action and potent in vitro activity against Gram(+) pathogens, including MRSA and isolates with reduced vancomycin susceptibility (VISA, hVISA). PK/PD analyses support the concentration-dependent activity and once-daily dosing regimen of TLV. TLV achieves a higher volume of distribution into tissues and penetrates the pulmonary epithelial lining fluid (ELF) and alveolar macrophages.

A worldwide evaluation of in vitro antimicrobial activity against 15 480 Gram(+) pathogens revealed that MICs of TLV are comparable or better than those for comparator antimicrobials. Specially, TLV has at least two-fold superior potency against staphylococci, including MRSA strains, compared with the other antibiotics. Data from the two prospective RCTs phase III, of 1503 patients with HAP (ATTAIN), were published by Rubinstein et al. indicating that TLV is noninferior to vancomycin (cure rates TLV was 58.9% compared with 59.5% with VAN) on the basis of clinical response in the treatment of HAP due to Gram(+) pathogens, mainly MRSA. In addition, at clinically attainable doses TLV inhibits Gram(-) isolates of antibiotic-resistant strains from biofilm models.

Renal function should be monitored in all patients receiving TLV, and dosage adjustments are required in patients whose CrCl is <50 mL/min. Owing to TLV’s renal toxicity, both European and US labels for the antimicrobial contain boxed precautions for its use. In the European label TLV is contraindicated in patients with pre-existing acute renal failure and those with severe renal impairment.

In Europe, EMA accepted TLV for the treatment for adults with NP and VAP known or suspected to be caused by MRSA, in patients without renal insufficiency. In 21/6/2013, FDA accepted it with the same indication as well.

2) Ceftobiprole

Ceftobiprole a novel, broad-spectrum, parenteral cephalosporin, with enhanced activity against Gram(-) pathogens, including Escherichia coli, Klebsiella pneumoniae, A. baumannii, P. aeruginosa and other Enterobacteriaceae, but inactive against bacteria expressing extended spectrum β-lactamases (ESBL). Similar to ceftaroline, ceftobiprole exhibits greater binding affinity than the other cephalosporins for PBP2a in MRSA.

In a large European antimicrobial resistance surveillance study, published in 2014, ceftobiprole showed activity against P. aeruginosa (64.6% susceptible by the EUCAST non-species-specific susceptibility breakpoint of 4μg/ml) that was lower than but similar to those of cefepime (78.6% susceptible) and ceftazidime (75.4% susceptible). Ceftobiprole was shown to be noninferior to ceftazidime plus linezolid for the treatment of HAP in a phase III RCT, including 781 patients (210 VAP), but the clinical cure rate in the population with VAP favored the linezolid/ceftazidime arm over the ceftobiprole arm, 56.7% versus 38.5%, respectively (p <0.05).

The standard dose of ceftobiprole is 500 mg every 8 h; dose adjustment of ceftobiprole is recommended in patients with moderate or severe renal impairment.

Ceftobiprole developed by Basilea ph.(Basel, Switzerland) is currently approved in 13 European countries and is the first cephalosporin monotherapy approved in the EU (October 2013) for the treatment of both CAP and HAP (excluding VAP).
In a review about ceftobiprole, reported that in patients with normal PK and non-VAP, ceftobiprole is effective for the treatment of HAP in the recommended doses, but it is unlikely to achieve the desired PD targets when PK parameters are altered in VAP (e.g., increased Vd and Cl).

5. NEW APPROVED ANTIBIOTIC CHOICES

Among the newer drugs in pipeline, five drugs have been approved by the FDA since May 2014, namely, ceftolozane/tazobactam, ceftazidime/avibactam, tedizolid phosphate, plazomicin (Table 2).

Clinical trials showed non-inferiority to comparators of both cephalosporin combinations when used in the treatment of complicated urinary tract infections (UTI) and complicated intra-abdominal infections (cIAI) (when used with metronidazole).

1. Ceftazidime–avibactam (C/A)

Ceftazidime-avibactam is combination of an established broad-spectrum cephalosporin (ceftazidime) and a novel β-lactamase inhibitor (avibactam) with activity against class A, class C, and some class D β-lactamases. Against Pseudomonas aeruginosa, the addition of avibactam also improves the activity of ceftazidime (~ fourfold MIC reduction). The role for C/A includes the treatment of suspected or documented infections caused by resistant GNB producing ESBL, KPCs and/or AmpC beta-lactamases.

A Phase III, RCT Comparative Study to Determine the Efficacy, Safety And Tolerability of C/A Versus Meropenem in the Treatment of NP/VAP showed 77.4% cure rate in the C/A group compared to 78.1% in the meropenem group, proving its noninferiority.

Clinical studies documented that CAZ-AVI, 2000 mg/500 mg every 8 hours, is the optimal dose regimen to achieve the PK/PD target attainment in patients with HAP.

It has been approved by FDA in February 2015 for the treatment of cIAI in combination with metronidazole and cUTI. Afterwards, on April 2016 EMA approved the antibiotic Zavicefta, intended for the treatment of UTI, IAI, HAP and infections due to aerobic GNB where treatment options are limited.

2. Ceftolozane–tazobactam (C/T)

Ceftolozane/tazobactam (brand name Zerbaxa), a novel cephalosporin in combination with an established β-lactamase inhibitor, is approved by FDA in December

| TABLE 2. New Antibiotics for HAP/VAP |
|-------------------------------|-------------------------------|-----------------------------|---------------------------------|---------------------------------|
| Drug (Company)                | Company                       | Antibiotic class            | Activity spectrum/MDR targeted | Phase and Potential indications |
| Plazomicin (Zemdri)           | Achaogen                      | Aminoglycoside              | Gram(-) including CRE           | Phase III for IAI and HAP/VAP caused by CRE |
| Tedizolid phosphate (Sivextro)| Cubist Pharmaceuticals/       | Oxazolidinone               | Gram(+), including MRSA and linezolid-resistant MRSA | Approved for ABSSI, in phase III for HAP/VAP |
|                               | Merck Sharp & Dohme           |                             |                                 |                                  |
| Ceftolozane+ tazobactam (Zerbaxa)| Cubist Pharmaceuticals/       | Cephalosporin + BLI         | Gram(-), including carbapenem, piperacillin + tazobactam and ceftazidime-resistant Pseudomonas aeruginosa, ESBL-producing strains | Approved for cUTI and cIAI/ in phase III for VAP and phase I for paediatric use |
|                               | Merck Sharp & Dohme           |                             |                                 |                                  |
| Ceftazidime+ avibactam (Avycaz)| AstraZeneca/Actavis           | Cephalosporin + new BLI     | Gram-, including MDR P. aeruginosa, ESBL-producing strains and KPC | FDA Approved 2015 for cIAI, f cUTI, in phase III for cIAI and HAP/VAP |
| Meropenem+Vaborbactam (Carbavance or Vabomere)| Medicines Company | Carbapenem + BLI            | MDR Gram(-), including CRE      | Phase III cUTI, cIAI, HAP |
| Cilastatin/relebactam/imipenem (Recarbrio)| Merck Sharp & Dohme | Carbapenem + BLI            | MDR Gram(-), including CRE      | FDA approved for cIAI cUTI, Phase III Bacterial infections; Pneumonia |

BLI: β-lactamase inhibitors; cUTI: complicated urinary tract; cIAI: complicated intra-abdominal infections
2014, for the treatment of cIAIs and cUTIs caused by ESBL-producing *Enterobacteriaceae* species, drug-resistant *P. aeruginosa*, and some *Streptococcus* species.

Ceftolozane is a new cephalosporin based on the ceftazidime with the exception of a modified side-chain at the 3-position of the cephem nucleus, which confers potent antipseudomonal activity. The combination with tazobactam, in a ratio 2:1, increases its benefit against *enterobacteriaceae* with ESBL production, such as *E. coli* and *K. pneumoniae*. It did not demonstrate activity against serine group of carbapenamases, ie, KPC and metallo-β-lactamases. C/T also demonstrated superior *in vitro* activity against ceftazidime-resistant *Escherichia coli* and *K. pneumoniae* when compared with ceftriaxone, cefepime, and piperacillin/tazobactam.

Its antipseudomonal activity is attributed to its ability to evade the multitude of resistance mechanisms employed by *P. aeruginosa*, including efflux pumps, reduced uptake through porins and modification of PBPs.

In the single-dose studies, ceftolozane had a mean plasma half-life (t1/2) of 2.6 hours (range, 2.43–2.64) and a volume of distribution at steady state (Vss) of 5.1 L/h (ceftolozane alone) and 12.3 L/h (C/T). The clearance of ceftolozane, alone and with tazobactam, was shown to occur exclusively via renal elimination.

C/T is approved in a dosage of 1 g/0.5 g administered every 8 hours by intravenous infusion over 1 hour for the treatment of cIAI in combination with metronidazole for 4-14 days and cUTI for 7 days.

A RCT, phase III (ASPECT-NP) of C/T compared with meropenem for 726 patients with VAP completed its recruitment recently and results are pending.

C/T is not currently approved for pneumonia but seems promising in this indication due to its specific action in severe infections caused by MDR and extensively drug resistant *P. aeruginosa*, the high cure rates displayed in patients with pulmonary exacerbation of cystic fibrosis, and for the good profile of tolerability.

### 3. Tedizolid Phosphate

Tedizolid (formal name Sivextro) was the third antibiotic approved by the FDA for ABSTI in 2014 and has also been recommended for approval by EMA’s CHMP. Tedizolid is an oxazolidinone derivate and is available in oral and intravenous forms. It demonstrates antimicrobial activity across a broad range of Gram (+) pathogens and greater potency than linezolid against wild-type and MDR pathogens, including linezolid-resistant *Staphylococcus aureus* strains.

Tedizolid is active against MRSA that possess the *cfr* gene and VRE. The higher intrinsic activity shown with lower MIC values when tested in protein-free media may be partly offset in vivo by a high protein binding of about 90%. Tedizolid was 2- to 8-fold more potent than vancomycin against *staphylococci*, 4-fold more potent than linezolid against *enterococci* and *streptococci*, and up to 4-fold more potent than linezolid against anaerobic species, in a large survey of 1063 isolates. Livermore and colleagues observed that tedizolid was 4-fold more potent than linezolid, with MIC values tightly clustered around 0.5 μg/mL vs 2.0 μg/mL for linezolid. The current FDA approved clinical breakpoint for tedizolid susceptibility is ≤0.5 mg/L.

With its half-life of approximately 12 h, tedizolid is dosed once daily. It demonstrates linear pharmacokinetics, has a high oral bioavailability of approximately 90%, and is primarily excreted by the liver as an inactive, non-circulating sulphate conjugate. Tedizolid does not require dosage adjustment in patients with any degree of renal dysfunction or hepatic dysfunction. Data from the two completed Phase III clinical trials demonstrated that the studied tedizolid regimen (200 mg twice daily for 6 days) had significantly less impact on hematologic parameters as well as significantly less gastrointestinal treatment-emergent adverse effects than its comparator linezolid.

A RCT, phase III, with primary objective is to determine the noninferiority (NI) in all-cause mortality (ACM) within 28 days after randomization of tedizolid (200 mg daily for 7 days) compared with i.v. linezolid (600 mg twice daily for 10 days) in ventilated participants with VAP has completed its recruitment.

Although much of the role of tedizolid in HAP/VAP remains to be defined by expanding clinical experience, tedizolid is likely a welcomed addition to the mere handful of agents available for the treatment of multidrug-resistant Gram-positive infections.

### 4. Plazomicin

It is an aminoglycoside derivative of sisomicin; the first of the new generation aminoglycoside, known as neoglycoside; inhibits bacterial protein synthesis and exhibits dose-dependent bactericidal activity. It has enhanced activity against many MDR GNB as *K. pneumoniae*, *E. coli* and *Enterobacter* species with MIC<sub>90</sub> of 1 and 2 μg/mL respectively. Plazomicin was also found to have lower MIC for *Acinetobacter baumanii* when compared with the licensed aminoglycosides.
Interestingly, it has shown potent activity against Gram-positive bacteria such as MRSA, including aminoglycoside-resistant isolates64. The compound is now being studied in a global phase III trial enrolling patients with bloodstream infections or NP due to carbapenem-resistant Enterobacteriaceae.

Significantly improved activity has been observed in OXA-producing A. baumannii compared with other aminoglycosides. In a study of Salguero et al.63 have found that plazomicin has the potential to be useful for the treatment of carbapenem-resistant A. baumannii isolates combined with different antibiotics, primarily carbapenems.

It exhibits synergy with daptomycin and ceftobiprole against MRSA and also against Pseudomonas when combined with cefepime, doripenem, and piperacillin-tazobactam65. In similar assays with 25 isolates of P. aeruginosa, plazomicin was synergistic with piperacillin/tazobactam, cefepime, doripenem, and imipenem in 92%, 80%, 80%, and 68% of the isolates66.

Intravenous dosing of plazomicin of 15 mg/kg yielded a maximum concentration of 113 μg/ml, the half-life was 3 hours and the steady-state volume of distribution was 0.24 l/kg. The lung penetration is poor with the ratio ELF/plasma AUC being 13%, similar to amikacin (14%). Trials on healthy volunteers have shown no evidence of ototoxicity or nephrotoxicity67.

The phase III CARE study (ClinicalTrials.gov Identifier NCT01970371) evaluated the efficacy and safety of plazomicin versus colistin as part of a definitive combination regimen for the treatment of serious infections (bloodstream infections or NP or cUTI) due to CRE and has been recently completed68. Plazomicin showed reduced all cause mortality of 11.8% at day 28 compared with 40% of colistin. A lower rate of mortality or serious disease-related complications was observed for plazomicin compared with colistin (23.5 versus 50.0%, respectively; 90% CI: 0.7, 51.2%). Furthermore, plazomicin was also associated with a lower incidence of nephrotoxicity than colistin.

However, small sample sizes (68 patients) limit the interpretation of the findings in the CARE trial.

While initial data with plazomicin appear promising, broad use of this medication may be limited by clinicians’ underlying hesitancy to use aminoglycosides given the adverse effects of nephrotoxicity or ototoxicity associated with older agents in this class. Additionally, it has variable activity against P. aeruginosa and no activity against A. baumannii, S. maltophilia, streptococci, enterococci, and anaerobic organisms69.

Plazomicin (ZEMDRI) is approved by the FDA for adults with complicated urinary tract infections (cUTI), including pyelonephritis, caused by Escherichia coli, Klebsiella pneumoniae, Proteus mirabilis, or Enterobacter cloacae, in patients who have limited or no alternative treatment options70.

5. Meropenem/Vaborbactam (M/V)

Meropenem/Vaborbactam (M/V) (brand name Vaborbactam), is a combination of meropenem with a beta-lactamase inhibitor, vaborbactam that is being developed for the treatment of gram-negative infections, such as cUTIs, HAP including those due to carbapenem-resistant Enterobacteriaceae (CRE)71. The combination has no in vitro activity against Class B metallo-β-lactamases and OXA-48-β-lactamases72. The combination achieved greater kill of KPC-producing Enterobacteriaceae compared with meropenem alone. Both agents are able to reach the ELF in appreciable amounts in healthy adult volunteers, with an unbound ELF/plasma ratio of 0.65 for meropenem and 0.79 for vaborbactam73.

It can be administered as a fixed combination by i.v. infusion.

The FDA has approved its use for cUTI (August 2017) on the basis of the double-blind, double-dummy RCT TANGO-I (NCT02166476), in which the primary efficacy endpoint (clinical cure or improvement and microbiological clearance at the end of intravenous therapy) was observed in 188 patients receiving M/V (98.4%) vs. 171 patients receiving piperacillin/tazobactam (94.0%), meeting superiority criteria74.

Another TANGO study, a Phase III RCT75, including 150 patients with serious infections (including cUTIs, cIAIs, bactereemia, or HAP/VAP) due to Antibiotic carbapenem-resistant enterobacteriaceae has demonstrated success against a wide range of KPC-positive Enterobacteriaceae, as a viable option against MDR GNBs.

6. Upcoming new antimicrobials

1. Imipenem /Cilastatin + Relebactam (IMI/REL)

Another combination of imipenem/cilastatin with relebactam (brand name Recarbrio) a class A and C beta-lactamase inhibitor, is designed to restore imipenem activity against certain imipenem-resistant GNB, including Pseudomonas aeruginosa and KPCs76. In a collection of a total of 2,778 isolates of E. coli were
gathered during the 3-month surveillance study the combination of imipenem with relebactam demonstrated activity against KPC-producing Enterobacteriaceae and multidrug-resistant \textit{P. aeruginosa}. However, IMI/REL is not active against imipenem-resistant Enterobacteriaceae expressing IMPs, VIMs or NDM MBLs, \textit{A. baumannii}, or IMP-or-VIM- producing \textit{P. aeruginosa}. The addition of relebactam did not improve the activity of imipenem against \textit{A. baumannii}, however\textsuperscript{77}.

Two comparative studies for IMI/REL has completed:

\textbf{a)} The RCT study (NCT02493764) aims to compare treatment with IMI/REL to piperacillin/tazobactam (PIP/TAZ) in patients with HAP/VAP\textsuperscript{78} and

\textbf{b)} The RESTORE-IMI 1 study (NCT02452047) comparing IMI/REL to colistimethate sodium in combination with imipenem/cilastatin for the treatment of imipenem-resistant bacterial infections, including those caused by \textit{P. aeruginosa} and KPC-producing organisms, in patients with HAP/VAP, c UTI and cIAI\textsuperscript{79,80}. It demonstrated a higher clinical response (71.4% vs. 40%) and lower all-cause mortality (9.5% vs. 30%) when compared with cilastatin/colistimethase sodium.

On July 2019, FDA has approved Recarbrio (imipenem, cilastatin and relebactam), to treat adults with cUTI and - cIAI\textsuperscript{81}

\section{2. Cefiderocol}

Cefiderocol is a siderophore cephalosporin based on the mechanism of bacterial cell entry binding to ferric iron.

It has recently been developed to combat a variety of bacterial pathogens, including β-lactam- and carbapenem-resistant organisms, as carbapenem-resistant Enterobacteriaceae (CRE) and meropenem (MER)-resistant \textit{P. aeruginosa}, \textit{Stenotrophomonas maltophilia}, and \textit{A. baumannii}. Furthermore, cefiderocol showed activity against classes A, B, and D carbapenemase-producing isolates, comprising metallo-β-lactamase (MBL)– producing Enterobacteriaceae\textsuperscript{82}.

In one surveillance study including 282 meropenem-nonsusceptible isolates collected from Greek hospitals, cefiderocol produced the lowest MIC values among 10 comparators against \textit{P. aeruginosa}, \textit{A. baumannii}, \textit{K. pneumoniae}, and \textit{Providencia stuartii}\textsuperscript{83}. In a larger surveillance study including isolates collected from both North America and Europe, cefiderocol MICs were ≤4 μg/mL for 6,078 (99.9%) Enterobacteriaceae isolates, including 164 (97%) meropenem-nonsusceptible strains (88). Results were similar for \textit{P. aeruginosa}, with 353 (100%) meropenem-nonsusceptible strains exhibiting MIC≤4 μg/ mL\textsuperscript{84}. Additionally, activity against \textit{A. baumannii} (n=839) was reported (MIC\textsubscript{90}/\textsubscript{50} 1/0.12 μg/mL).

The suggested dosage is 2 g every 8 hours with a 3 hour infusion. In case of renal impairment, the dosage has to be adjusted. Concerning safety, the adverse events are mild and well tolerated in healthy volunteers\textsuperscript{85}.

A multicenter Phase III trial, including 150 patients, comparing cefiderocol i.v. to best available therapy against serious infections caused by carbapenem-resistant pathogens (CREDIBLE) completed on April 2019 (NCT02714595).

Another RCT phase III has recently completed, involving 300 patients, will investigate cefiderocol versus meropenem, both groups in combination with linezolid, for the treatment of NP (HCAP, HAP, VAP) caused by GNB (APEKS-NP, NCT03032380).

Considering its profile, cefiderocol is a promising cephalosporin with an important potential for the treatment of pneumonia due to carbapenem-resistant GNB, including CRE, MDR \textit{P. aeruginosa}, and \textit{A. baumannii}.

\section{3. Murepavadin}

Murepavadin, is a peptidomimetic that acts on LptD protein involved in transport of the lipopolysaccharide component of the outer cytoplasmic membrane of \textit{P. aeruginosa}\textsuperscript{86}. It belongs to a novel class of antibiotics called the Outer Membrane Protein Targeting Antibiotics (OMTAs).

Key features of murepavadin include strong activity against \textit{P. aeruginosa} among over 1500 worldwide isolates (MIC\textsubscript{90} ≤0.25 μg/mL) and proven efficacy in animal infection models with evidence of ample penetration into lung epithelial lining fluid (ELF)\textsuperscript{87}.

The results of two Phase II trials in patients with VAP and non-cystic fibrosis bronchiectasis, though abbreviated findings are summarized on the company website. Of note, clinical cure rate at test-of-cure (7±2 days after end-of-treatment) was 91% in 12 patients with confirmed VAP caused by \textit{P. aeruginosa}, including 9 patients with confirmed MDR pathogens. Murepavadin was administered for 10–14 days in this study at a dose of 2.5 mg/kg as a 2-hour IV infusion three times\textsuperscript{88}.

Nephrotoxicity, however, remains a concern associated with the use of murepavadin and requires further investigation.

In contrast to commonly used broad-spectrum antibiotics, murepavadin is a precision medicine and as such it supports the growing practice known as “antibiotic stewardship”, which seeks to reduce the excessive use of broad-spectrum products to avoid the buildup of resistance and to preserve the microbiome of the patients.
6. INHALED ANTIBIOTICS

During the last decade, inhaled antibiotics, especially colistin, has been widely used worldwide as a therapeutic option, supplementary to conventional intravenous antibiotics, for the treatment of MDR Gram-negative HAP and VAP. The use of inhaled antibiotics achieves high drug concentrations at the site of infection and may help reduce prolonged systemic antibiotic use by eradicating MDR Gram-negatives more rapidly and effectively than systemic therapy alone.

The IDSA/ATS recommends inhaled antibiotics for VAP due to GNB that are susceptible to only aminoglycosides or polymyxins (colistin or polymyxin B) and includes both inhaled and systemic antibiotics. The antibiotics can be used for inhalation are colistin, levofloxacin, liposomal amikacin, Fosfomycin/tobramycin and aztreonam lysine. The Society of Infectious Diseases Pharmacists recommends that the typical dose for tobramycin is 300 mg every 12 h and colistin 150 mg every 12 h, and for colistin a dose of 150 mg every 12 h.

Effective treatment of VAP caused by MDR organisms such as P. aeruginosa and Acinetobacter baumannii has been reported with high dose nebulized colistin, even achieving airway eradication. In a meta-analysis found that nebulized antibiotics might be associated with higher rates of clinical cure, but there were no differences regarding the other secondary outcomes, including microbiological cure, mortality or renal toxicity. Their use is currently restricted by technical issues, as a lack of specifically formulated solutions for inhalation and a limited number of devices designed for the nebulization of antibiotics. Ongoing, prospective, RCTs with aerosolized antibiotics appear to be promising, such as a combination amikacin– fosfomycin solution delivered via a PARI eFlow inline system, and the Amikacin Inhale, an integrated drug–device combination for the delivery of specially formulated Amikacin Inhalation Solution through a Pulmonary Drug Delivery System.

7. CONCLUSION

Considering the dramatic increase in rates of MDR VAP, clinicians must be aware of current MDR pathogens and appropriate management. Optimal treatment of MRSA pneumonia involves vancomycin, linezolid and the new agents telavancin and ceftobiprole. In the targeted GNB area, there are 3 new drugs ceftazidime-avibactam, ceftolozane-tazobactam, plazomicin and two carbapenem's combinations (meropenem/Vaborbactam and Cilastatin/imipenem/relebactam). Interestingly, Murepavadin is a pathogen specific antibiotic, has been granted Qualified Infectious Disease Product (QIDP) and fast track designation from the FDA for the treatment of VABP due to Pseudomonas aeruginosa. Inhalation has been used as an adjuvant to systemic therapy in VAP caused by MDR GNBs in combination with systemic antibiotics.

Although more responsible antibiotic prescribing may help optimizing the management of NP research needs to continue to try and identify new antibiotics and adjunctive therapies.

Finally, with few new antibiotics in the pipeline, the emphasis is still on prevention and control of the spread of MDR GNBs. Effective infection control practices, surveillance measures, antimicrobial stewardship programs have been implemented to attempt to reduce the occurrence of nosocomial GNB infections.

ΠΕΡΙΛΗΨΗ

Νέα αντιβιοτικά για τη νοσοκομειακή πνευμονία

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Η νοσοκομειακή πνευμονία (ΝΠ) είναι μία κοινή νοσοκομειακή λοίμωξη και συνδέεται με αυξημένη θνησιμότητα και αυξημένο κόστος νοσηλείας. Στην θνητότητα συμβάλλουν τα ανθεκτικά μικρόβια [κυρίως Gram(-)] που είναι συχνοί αιτιολογικοί παράγοντες ιδίως της πνευμονίας του αναπνευστήρα (ΠΑ). Μελέτες αναφέρουν ποσοστό θνησιμότητας που οχητίζεται με το ΠΑ 30%-50% και ακόμη υψηλότερο σε σηπτικό σκο. Όταν η κλινική επιφάνεια της ΝΠ είναι υψηλή, είναι απαραίτητη η έναρξη έγκαιρης και κατάλληλης αντιμικροβιακής θεραπείας για τη καθυστέρηση και αποτελέσματα έχουν συνεισενέγκει με αυξημένη νοσηρότητα και θνητότητα. Για να αντιμετωπίσουμε την απειλή της μικροφικτικής αντοχής, ειδικά στη
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Co-existence of endobronchial lipoma and lung adenocarcinoma

ABSTRACT

Endobronchial lipoma is an infrequent benign tumor originating from adipose tissue, most commonly seen in middle-aged men, with a peak incidence between the fifth and sixth decades of life. Usually, the tumor is found in central airways, in lobar or segmental bronchi, mainly located in the right lung and easily detected during bronchoscopy. The lesion may lead to chronic lung destruction due to bronchial obstruction. Bronchoscopic resection with biopsy forceps is both diagnostic and therapeutic method of choice. Lung cancer is the leading cause of mortality worldwide and is diagnosed in advanced stage, due to lack of specific symptoms. Non-small cell lung cancer (NSCLC) accounts for 80-85% of all cases, with adenocarcinoma being the most common histologic subtype. In this article, we present a rare case of co-existence of endobronchial lipoma located in the right lung and adenocarcinoma located in left lung in a 61-year old smoker, without any symptoms.

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Endobronchial lipoma is an infrequent benign tumor originating from adipose tissue, most commonly seen in middle-aged men, with a peak incidence between the fifth and sixth decades of life. Usually, the tumor is found in central airways, in lobar or segmental bronchi, mainly located in the right lung and easily detected during bronchoscopy. The lesion may lead to chronic lung destruction due to bronchial obstruction. Bronchoscopic resection with biopsy forceps is both diagnostic and therapeutic method of choice. Lung cancer is the leading cause of mortality worldwide and is diagnosed in advanced stage, due to lack of specific symptoms. Non-small cell lung cancer (NSCLC) accounts for 80-85% of all cases, with adenocarcinoma being the most common histologic subtype. In this article, we present a rare case of co-existence of endobronchial lipoma located in the right lung and adenocarcinoma located in left lung in a 61-year old smoker, without any symptoms.
INTRODUCTION:

Endobronchial lipomas are infrequent benign tumors originating from the adipose tissue, with incidence ranging from only 0.1 to 0.5% of all lung tumors. They consist of mature adipose tissue, fibrous components, and normal bronchial epithelium (figure 3). The tumors are commonly found in the central airways, in lobar or segmental bronchi of the endobronchial tree, mainly located in the right lung, and are easily detected during bronchoscopy, with only a small percentage being located in the periphery of the lung. Smoking and obesity are significant risk factors for the development of endobronchial lipomas. Macroscopically, all the lesions are seen as wellcircumscribed, soft, yellow masses ranging in size from 1 to 3 cm in the greatest diameter, with a smooth round surface.

Lung cancer is the most frequent cause of cancer-related deaths worldwide. Every year, 1.8 million people are diagnosed with lung cancer, and 1.6 million people die as a result of the disease. Non-small cell lung cancer is the predominant form of the disease, accounting for approximately 85% of cases. Smoking is well acknowledged as the main risk factor for lung cancer, and is estimated to be responsible for 90% of cases in males and 80% of cases in females. However, over recent decades several changes have taken place in lung cancer epidemiology. Adenocarcinoma, replacing squamous cell cancer, has become the most common morphological type of lung cancer. In addition to smoking, several other risk factors, e.g. second-hand smoke, air pollution, cooking fumes, exposure to indoor radon and comorbidities such as chronic obstructive pulmonary disease (COPD) or previous tuberculosis, have become more widely recognized.

Surgery is the recommended treatment for patients with stage I–II non-small-cell lung cancer (NSCLC). 5-year survival is 77–92% for clinical stage IA, 68% for stage IB, 60% for stage IIA, and 53% for stage IIB. Most patients present with advanced disease at the time of diagnosis and have a poor prognosis, with the vast majority surviving less than 5 years. Although new therapies have been introduced in recent years that target molecular disease drivers present in a subset of patients, there is a significant need for treatments able to improve response and extend survival while minimizing effects on quality of life.

CASE

A 61-year old man, current smoker presented with a shadow pointed out in left upper lobe in chest X-Ray, as an incidental finding. A contrast enhanced chest computed tomography (CT) revealed a low-density tumor mass of 3.5 cm in maximum diameter, located in the segments 1+2 of left upper lobe, peripherally, in touch with the pleura (Figure 1). Flexible bronchoscopy revealed no endobronchial lesion in left upper lobe as showed in chest CT; however, segment 8 of basal group of right lower lobe was completely occluded by a sub yellow mass, finding that was not revealed in CT scan. The tumor had a round, smooth, shiny surface as found out during the exclusion. The lesion was almost fully resected using needle biopsy (Figure 2). Pathologic examination confirmed endobron-
Endobronchial lipoma and no evidence of malignancy. The mass was formed by well differentiated adipose tissue. The patient underwent fine needle biopsy (FNB) by chest CT navigation of the lesion in left upper lobe, the histopathology of which revealed lung adenocarcinoma of low differentiation (Figure 3).

DISCUSSION

Endobronchial lipoma is most commonly seen in middle-aged men, with a peak incidence between the fifth and sixth decades of life. Fever, progressive dyspnea, persistent cough, sputum production, hemoptysis, wheezing, stridor, recurrent pneumonia, due to partial or total bronchial obstruction and secondary lung parenchyma destruction caused by the tumor, are common clinical features of presentation. The slow tumoral growth is the reason for late manifestation of symptoms, ranging from a few months to several years before diagnosis. Due to lack of specific symptoms, endobronchial lipomas can be misdiagnosed as asthma, chronic bronchitis or chronic obstructive pulmonary disease.

Chest X-Ray shows hilar enlargement, atelectasis or pneumonia. Thoracic CT may reveal a low density mass located in main bronchus. The definite diagnosis is only obtained after biopsy performance during fiberoptic bronchoscopy, which is needed to exclude or confirm the presence of other pathology findings that would point to alternative diagnoses (e.g. liposarcoma, hamartoma).

The treatment options in endobronchial lipoma include bronchoscopic resection of the tumor, bronchotomy, lobectomy or pneumonectomy. The choice of approach depends on tumor size, location of the tumor and the degree of lung damage caused by the lesion. Recurrence rates are low. Surgical resection of the tumor is indicated when there is a possible co-existence of malignant neoplasm, or technical difficulties during bronchoscopic procedure. Ablative techniques can be used concomitantly with bronchoscopy and include yttrium aluminum garnet (YAG) laser, argon plasma coagulation of the base, cryotherapy, or ethanol ejection in the base.

CONCLUSION

Endobronchial lipoma is a rare, benign tumor, located in central airways, affecting middle-aged smokers, with male predominance. The co-existence with lung adenocarcinoma is infrequent.

It is noteworthy that detailed bronchoscopic evaluation is crucial, as we have observed lesions during bronchoscopy in different sites than those revealed in CT scan.

The bronchoscopic resection of endobronchial lipoma is the treatment of choice, because it is both diagnostic and therapeutic and is associated with less morbidity compared to surgical approach. Furthermore, bronchoscopy in not only less invasive method, but also preserves lung tissue, achieves good symptomatic control and local control and prevents from permanent lung damage.
ΠΕΡΙΛΗΨΗ
Συνύπαρξη ενδοβρογχικού λιπώματος και αδενοκαρκινώματος πνεύμονα

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Το ενδοβρογχικό λίπωμα είναι ένας σπάνιος καλοήθης όγκος με προέλευση από τον λιπώδη ιστό. Εμφανίζεται πυκνότερα σε ανδρείς καπνιστές μέσης ηλικίας, με υψηλή θετικότητα στην 5η και 6η δεκαετία της ζωής. Συχνά, ο όγκος εντοπίζεται σε κεντρικούς αεραγωγούς, σε λοβαίους ή τμηματικούς βρόγχους, κυρίως στο δεξιό πνεύμονα και αναδεικνύεται εύκολα κατά τη βρογχοσκόπηση. Η βλάβη μπορεί να οδηγήσει σε χρόνια καταστροφή του πνευμονικού παρέγχυμα, λόγω βρογχικής απόφραξης. Η βρογχοσκοπική εκτομή με λαβίδα ηλεκτροκαυτηρίας (snare) αποτελεί συχνά διαγνωστική και θεραπευτική μέθοδο εκλογής. Ο καρκίνος πνεύμονα είναι η κύρια αιτία θανάτου παγκόσμια και διαγνώσκεται σε στάδια, λόγω απουσίας ειδικών συμπτωμάτων. Ο μη μικροκυτταρικός καρκίνος πνεύμονα ευθύνεται για το 80-85% των περιπτώσεων, με το αδενοκαρκίνωμα να αποτελεί το πιο κοινό ιστολογικό τύπο. Σε αυτό το άρθρο παρουσιάζουμε μια σπάνια περίπτωση συνύπαρξης ενδοβρογχικού λιπώματος στο δεξιό πνεύμονα και αδενοκαρκινώματος στον αριστερό πνεύμονα σε 61χρονο άνδρα καπνιστή, χωρίς συμπτωματολογία.

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Λέξεις - Κλειδιά: Βρογχοσκόπηση, Μάζα, Ενδοβρογχικό λίπωμα, Βιοψία, Αδενοκαρκινώματα πνεύμονα

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A rare radiological finding

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A 74-year-old female was referred to our clinic for evaluation of intermittent chest pain of 1-month duration. She had no known comorbid illness or prior surgeries. Chest X-ray showed a large opaque lesion occupying half of the left hemithorax. Computed tomography of the chest revealed a thin-walled, non-enhancing low-attenuation mass (12.5×7.2×9.6 cm) compressing over the left pulmonary artery and collateral pleural effusion. The patient underwent a thoracotomy with removal of the mass. A uniloculated, serum-filled cyst was resected. Results of cytological testing were negative for malignancy and histopathologic evaluation was consistent with a pericardial cyst.

Pericardial cysts represent approximately 5% of thoracic cysts and usually present as asymptomatic masses, detected incidentally on imaging usually located at the right cardiophrenic angle. They usually appear as thin-walled, non-contrast-enhancing bodies excluding continuity with the vascular space. CT scanning reliably depicts the size, shape, location, and thin-walled nature of pericardial cysts and the absence of other masses within the chest. Pericardial cysts are usually clinically silent but occasionally can lead to complications including cardiac tamponade, congestive heart failure, atrial fibrillation and pericarditis.

REFERENCES
Post-tuberculosis lung herniation
An unusual case

Ioannis Kokkonouzis,
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A 71-years old, dentist, non-smoker, was examined due to acute onset dyspnea, after the surgical repair of abdominal hernia. It was already known that she had a history of tuberculosis pleurisy, more than four decades ago, which was treated with multiple thoracocentics at that time, but was without any symptoms whatsoever until nowadays. Pre-surgical pulmonary evaluation revealed a moderate restrictive syndrome on lung functional test. On acute basis a CT pulmonary angiography performed. This demonstrated a considerable enlargement of right lung, due to compensatory hyperinflation, which was herniated to the left hemothorax though the middle mediastinum. The latter was sifted left wise causing a marked displacement of the heart, the great vessels and the left hemidiaphragm (Figure).

The commonest cause for non-traumatic lung herniation is pneumonectomy after malignant diseases.1 Benign diseases, pronominally tuberculosis, can be also the underling pathology.2 Nowadays this is the fact especially when the disease had occurred in the pre-medication era. As a result only few old patients in the westerner world have such a dramatic radiological appearance. On the other hand under the occurrence of more refugees waves from low income countries with poor health status, such images would be re-emerged.

REFERENCES


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Treatment outcome in allergic bronchopulmonary aspergillosis complicating asthma

Petru Emil Muntean, MD

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A 37 year old man, working in a bakery, presented with a two week history of wheeze, asthenia, fatigue, persistent low-grade fever, productive cough and shortness of breath. His symptoms initiated following a single exposure to clouds of flour dust inside the factory. The cough and wheeze were worst at night and early in the morning. The patient had no precedent history of respiratory or even an atopic disease. On inspection there was diffused audible expiratory wheeze. Spirometry test, revealed a reversible airway obstruction with a change in forced expiratory volume in the first second of over 22 percent and a change in volume of 300 milliliters, peak expiratory flow 60 percent of predicted value. Based on epidemiological data in the area, specific blood tests showed high total immunoglobulin E levels of 1532 kilo units per litre, elevated eosinophil count of 1.45×10⁹ per litre and strongly positive aspergillus fumigatus specific immunoglobulin E 39.9 kilo units per litre. Sputum culture grew aspergillus fumigatus. Using a bronchoscope, cytological examination of bronchoalveolar lavage fluid showed characteristic branching of fungal hyphae. Based on the protocol, the male patient received specific asthma treatment, an inhaler containing the active substance called beclometasone dipropionate 250 micrograms once daily, but for long-term-use. Also, because of the confirmed diagnosis of allergic bronchopulmonary aspergillosis, an immediate treatment¹ was started with daily oral Prednisolone 20 milligrams + Itraconazole 200 milligrams. In a few weeks, his general symptoms resolved rapidly with improvement in lung function and total immunoglobulin E substantially decreased. Due to the fact that the diagnosis of allergic bronchopulmonary aspergillosis was quickly discovered and the treatment was immediately administered, after six months of therapy, a follow-up computed chest tomography showed almost complete resolution of the abnormalities.

REFERENCE

FIGURE 1. Chest radiography showed mucoid impaction with the classic finger in glove pattern.

FIGURE 2. High resolution computed chest tomography, mucoid impaction and shows the classic presentation of central bronchiectasis.
Pathophysiology in laryngeal granulomatous disease

Petru Emil Muntean, MD

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A 35 year old male presented to our Pneumology Department with a one month history of persistent fever, moderate weight loss (7 kilograms in a week), night sweats, dysphagia, cough and a history of tobacco and alcohol use. Had notable hoarseness of voice and no history of recent tuberculosis contact. No cervical lymphadenopathy. Laboratory tests within normal range. By laryngoscopic biopsy, histopathological examination showed necrotising granulomatous inflammation without marks of malignancy. Ziehl Neelsen staining of the tissue and sputum sample revealed both acid fast bacilli and grew mycobacterium tuberculosis on culture. Based on national protocol¹, he started right away a 4 drug antituberculous therapy and had within a week a good clinical improvement.

FIGURE 1. The Otorhinolaryngologist performed a fiberoptic laryngoscopy which unveiled oedema and diminished mobility of the right true vocal cord, enlargement of the arytenoids, along with predictable granulomatous harshness of true vocal cords bilaterally, upraising suspicions of laryngeal carcinoma.

FIGURE 2. Chest radiography displayed granulomas in the left middle lung, consolidation of the right upper lung zone with numerous cavitary lesions in the right infrahilar region.

REFERENCE:

Mounier-Kuhn syndrome

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Campeni City, Alba County,
Romania

A 65 year old male, nonsmoker was admitted into the Pneumology Department with the complaints of productive cough, dyspnea, chest pain and fatigue. He is a known patient, under treatment for chronic obstructive pulmonary disease. Over the years he had multiple lower respiratory tract infections. Physical examination showed bilateral inspiratory crackles and turgid jugular veins. Purulent sputum was analyzed and Pseudomonas aeruginosa was isolated. Blood analysis came normal. Spirometry test showed forced expiratory volume in the first second 35%, forced vital capacity 44% and tiffeneau index of 79. Arterial blood gases showed hypoxemia and hypercapnia with respiratory acidosis. The patient received nasal oxygen at 1.5 liters/minute, bronchodilators, antibiotics associated with mucolytic treatment and physical rehabilitation therapy. Pneumococcal + flu vaccination, regular follow-up visits were suggested. After 14 days, the patient was discharged and has been doing well since.

FIGURE 1. Chest radiography postero-anterior view revealed right paratracheal lucency, reticular dense areas and cystic lesions mostly in the right middle and lower zones and ill defined opaque regions.

FIGURE 2. Bronchoscopy revealed diverticulum vents on the tracheal wall.

FIGURE 3. Chest computed tomography, axial view revealing bilateral cystic bronchiectasis presenting mainly in the right middle and lower lobe and also dilated trachea (>4 centimeters) and bilateral main stem bronchi diverticula emerging from the intrathoracic trachea.

REFERENCE:
Διακεκριμένοι Πνευμονολόγοι

Νίκος Σιαφάκας, MD, PhD

Ομότιμος Καθηγητής Πνευμονολογίας, Πανεπιστήμιο Κρήτης
Ωμότιμος Καθηγητής Πνευμονολογίας Πανεπιστημίου Θεσσαλίας.

Το πρόσφατο άρθρο του καθηγητή Ι. Ιωαννίδη του Πανεπιστημίου του Stanford με τίτλο "A standardized citation metrics author database annotated for scientific fields" έγινε δεκτό με ευνοϊκά σχόλια από την παγκόσμια επιστημονική κοινότητα 1.

Η μελέτη του Καθ. Ιωαννίδη και των συνεργατών του ανάλυσε τα βιβλιομετρικά δεδομένα 7 εκατομμύριων επιστημόνων από όλο τον κόσμο, όλων των επιστημονικών πεδίων, και παρουσίασε διεξοδικά τα στοιχεία των 100.000 καλύτερων 1. Η ανάλυση αυτή (ranking) βασίστηκε στον αριθμό των δημοσιεύσεων, στις αναφορές (citations) αλλά και άλλους γνωστούς βιβλιομετρικούς δείκτες εκτίμησης του επιστημονικού έργου, όπως ο h-index 1.

Στην αξιολόγηση αυτή αναφέρονται 1031 διακεκριμένοι Πνευμονολόγοι από όλο τον κόσμο (Respiratory System). Στην πλέον τιμητική θέση (4η) βρίσκεται ο καθηγητής P. Barnes (UK), πρώτος όχι μόνο μεταξύ των Πνευμονολόγων αλλά και μεταξύ όλων των κλινικών επιστημόνων του πλανήτη!

Ακόμη, στις δέκα πρώτες θέσεις των Πνευμονολόγων παρουσιάζονται επίσης τα ονόματα των S. Holgate (UK), D. Strachan (UK), M. Kollef (USA), Chung Kiam Fan (UK), M. Matthay (USA), R. Boucher (USA), W. Mac Nee (UK), S. Suissa (CAN), and B. Celli (USA).

Υπολογίζοντας τους διακεκριμένους Πνευμονολόγους ανά χώρα, διαπιστώνουμε ότι οι περισσότεροι εργάζονται σε ΗΠΑ (501), Αγγλία (138), Καναδά (90), Γερμανία (46), Αυστραλία (36), Γαλλία (32), Ιταλία (23), Ολλανδία (19), Ισπανία (17), Σουηδία (15) και Βέλγιο (14). Ευρωπαϊκές χώρες με μονοψήφιο αριθμό διακεκριμένων Πνευμονολόγων είναι η Δανία (6), η Φιλανδία (5), η Ιρλανδία (4), η Δανία (3) μαζί με τη Νορβηγία (3), τη Πορτογαλία (2) και η Πολωνία (1).

Προφανώς τα παραπάνω μεγέθη δεν είναι απολύτως συγκρίσιμα, αναλογιστείς τις τεράστιες πληθυσμιακές διαφορές μεταξύ των χώρων, καθώς και τις διαφορές στο ποσοστό του ΑΕΠ που διαθέτει κάθε χώρα για την έρευνα.

Επίσης, στον κατάλογο (ranking) αυτό αναφέρονται τα ονόματα 249 Ελλήνων επιστημόνων όλων των επιστημονικών πεδίων. Πρώτος, και με μεγάλη διαφορά, είναι ο Καθ. Γεώργιος Χρούσος του Πανεπιστημίου της Αθήνας. Ο Καθ. Χρούσος βρίσκεται στην πολύ τιμητική θέση 164ος (από τις 100.000) δηλαδή εξαιρετικά υψηλά παγκοσμίως.

Από τους 300 Ελλήνες επιστήμονες που εργάζονται στη χώρα μας οι 94 (32%) ανήκουν στην Κλινική Ιατρική με εξειδικεύσεις στον τομέα της Ογκολογίας (23), στο Καρδιαγγειακό Σύστημα (22), στην Ενδοκρινολογία (7), τη
Γαστρεντερολογία (6), τη Ρευματολογία (5). Είναι προφανές ότι η Πνευμονολογία με μόνο τρεις υψηλού κύρους επιστήμονες, υπολείπεται των άλλων κλινικών ειδικοτήτων στη χώρα μας.

Από τα παραπάνω, αβίαστα βγαίνει το συμπέρασμα ότι αν και η Πνευμονολογία διαπρέπει στα διεθνή επιστημονικά δρώμενα, στην Ελλάδα υπολείπεται ακόμα.

Κατά τη γνώμη μου, είναι επείγουσα ανάγκη να αυξηθεί η πνευμονολογική ερευνητική δραστηριότητα και νομίζω ότι, είναι καθήκον και προτεραιότητα των νεοτέρων ακαδημαϊκών πνευμονολόγων να το πράξουν. Σημαντικό ρόλο προς αυτή την κατεύθυνση θα πρέπει να παίξουν τα πανεπιστημιακά πνευμονολογικά τμήματα, τα μεγάλα πνευμονολογικά κέντρα (“Η Σωτηρία”, “Γ. Παπανικολάου”) και οι επιστημονικές εταιρείες του χώρου (ΕΠΕ, ΕΝΘΕ).

Με καλώς εννοούμενο επιστημονικό ανταγωνισμό μεταξύ των ακαδημαϊκών κέντρων, αλλά και μεταξύ των άλλων ειδικοτήτων, η Ελληνική Πνευμονολογία θα πρέπει να συνεχίσει την ανοδική πορεία της τόσο στη χώρα μας αλλά και στη διεθνή επιστημονική κοινότητα.

Ελπίζω και εύχομαι, στην επόμενη μελέτη του καθηγητή Ιωαννίδη τα ονόματα των Ελλήνων πνευμονολόγων να έχουν τουλάχιστον διπλασιαστεί!!!

REFERENCE

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PNEUMON is an open access, single blind peer reviewed, published quarterly in English as the official scientific journal of the Hellenic Thoracic Society, both in print and online. The Journal publishes original papers of international interest on laboratory and clinical research that are pertinent to lung biology and disease. Clinical and experimental work dealing with the whole field of respiratory medicine, including allied health, cell and molecular biology, epidermiology, immunology, pathology, pharmacology, physiology, intensive and critical care, pediatric respiratory medicine and thoracic surgery will be considered for publication.

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

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