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PULMONARY EXACERBATIONS AS A RISK FACTOR FOR LUNG FUNCTION DECLINE - EXPERIENCES OF NATIONAL CYSTIC FIBROSIS CENTER

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Abstract

**Introduction/Aim:** Pulmonary exacerbations have negative impact on clinical course of cystic fibrosis (CF) lung disease being and are associated with a steeper decline in lung function, unfavorable prognosis and impaired quality of life.

Primary aim of this study was to determine whether increased number of exacerbations had influence on lung function in patients with CF. In addition, nutritional status, gender, presence of comorbid conditions and bacterial colonization of airways were evaluated as predictive factors for pulmonary exacerbations.

**Methods:** This retrospective cohort study included 83 pediatric and adult patients, treated from 2011-2015 in Mother and Child Health Institute of Serbia. The best result of forced expiratory volume in the first second (FEV₁) and forced vital capacity (FVC) on each year of follow-up was taken into account to calculate the five-year trend value of these indicators. The number of exacerbations per year of follow-up, and its impact on FEV₁ decline was evaluated.

**Results:** Mean annual decline of FEV₁ and FVC were 2.4% and 1.7% respectively. Malnourished patients had lower initial values of FEV₁ and FVC, and more frequent exacerbations in compare to normal weight and overweight patients.

The frequency of exacerbations was significantly higher in patients chronically colonized with Burkholderia cepacia ($p = 0.023$). Increased number of exacerbation was proved to be the most important factor in prediction of FEV₁ decline over time ($p = 0.013$).

**Conclusion:** Pulmonary exacerbations lead to more progressive lung function decline in patients with CF. Malnourishment and chronic airway colonization with Burkholderia cepacia results in more frequent pulmonary exacerbations.

**Key words:** cystic fibrosis, pulmonary exacerbations, lung function
Sažetak

Uvod/ Cilj:. Egzacerbacije plućne bolesti imaju negativan uticaj na klinički tok cistične fibroze (CF), a njihova veća učestalost povezuje se sa izraženijim sniženjem vrednosti funkcije pluća i lošijim kvalitetom života. Osnovni cilj ovog istraživanja bio je ispitivanje uticaja broja egzacerbacija na trend funkcije pluća kod oboljelih od CF. Pored toga, ispitivan je značaj stanja uhranjenosti, pola ispitanika, postojanja komorbidnih stanja i kolonizacije disajnih puteva patogennim bakterijama na trend funkcije pluća i učestalost egzacerbacija plućne bolesti.

Metode : Istraživanjem je obuhvaćeno 83 ispitanika, pedijatrijskog i adultnog uzrasta oboljelih od CF, koji su lečeni u periodu od 2011. do 2015. godine u Institutu za zdravstvenu zaštitu majke i deteta Srbije „Dr Vukan Čupić“. Najbolji rezultat forsiranog ekspirijumskog volumena u prvoj sekundi (FEV₁) i forsiranog vitalnog kapaciteta (FVC) svake godine praćenja uziman je u obzir pri računanju petogodišnjeg trenda vrednosti ovih pokazatelja. Evaluiran je broj egzacerbacija po godini praćenja i ukupan broj na kraju perioda praćenja.

Rezultati : Prosečno smanjenje vrednosti FEV₁ bilo je 2,4%, a FVC 1,7% godišnje. Neuhranjeni ispitanici su imali niže vrednosti FEV₁ i FVC i veći broj egzacerbacija u odnosu na normalno i prekomerno uhranjene (p=0,001). Učestalost egzacerbacija je statistički značajno veća kod ispitanika hronično kolonizovanih Burkholderiom cepaciom (p=0,023). Povećanje broja egzacerbacija predstavlja statistički najznačajniji prediktivni činilac pogoršanja FEV₁ u posmatranom periodu (p=0,013).


Ključne reči : cistična fibroza, plućna egzacerbacija, funkcija pluća
Introduction

Cystic fibrosis (CF) is the most frequent autosomal recessive disease in the Caucasians. In its typical form, CF is manifested by failure to thrive, repeated lung infections and impaired mucus clearance which leads to suppurative lung disease, characterized by decline in lung function during a lifetime, which gradually progresses to respiratory insufficiency (1). Recent data show that the mean life expectancy in the USA is 40 years and in Serbia is around 30 years (2). Many factors have contributed to significant life prolongation and improvements of quality of life. Among these factors, the major influence have early diagnosis, especially by introduction of neonatal screening programmes, hypercaloric diet and efficient treatment of pulmonary exacerbations (PE) (3).

Clinical stage of the disease can be expressed by several indicators (biomarkers) whose standardization enables an objective assessment of patient’s condition and final outcome. The most commonly used biomarker is the value of the forced expiratory volume in the first second (FEV$_1$), which is influenced by frequency and course of pulmonary exacerbations (4). Although there is no widely used standardized definition of pulmonary exacerbations, the ideal definition should cover objective clinical, biochemical and physiological factors. In clinical research settings hospitalization and intravenous use of antibiotics are listed as undeniable indicators (5). Pulmonary exacerbation is characterized by increased cough and sputum production, haemoptysis, fever, loss of appetite and weight loss, dyspnea, tachypnea, exercise intolerance and sinus discharge (6). It was showed that more frequent exacerbations led to a steeper lung function decline, poorer quality of life and earlier fatal outcome (4, 7).

In patients with CF, in ideal clinical course, the annual decrease of FEV$_1$ is about 2% (8). In most of the patients, PE is associated with a significant reduction in lung function, with gradual, but often not complete recovery thereafter. In 25% of cases lung function decline persists, despite aggressive systemic antimicrobial therapy (7). Favorable clinical response to treatment is FEV$_1$ recovery to ≥90% of the baseline value (9). Certain risk factors can contribute to unfavorable outcome and partial recovery besides
initially lower lung function. These risk factors are: female gender, impaired glucose tolerance, chronic colonization of respiratory tract with specific bacterial pathogens (e.g. Pseudomonas aeruginosa or Burkholderia cepacea) and initially lower FEV\textsubscript{1} values (9). Despite novel treatment modalities, the incidence of PE has not significantly decreased in the last two decades (8).

The aim of the study was to determine if increased number of exacerbations during the five years period had influence on lung function in our cohort of patients with CF. Additionally, we evaluated if nutritional status, presence of comorbid conditions and bacterial colonization of airways affect lung function decline, and if they can be used as a predictive factors for PE.

**Methods**

For the purpose of this retrospective cohort study, 110 pediatric and adult patients were screened. All patients were treated at the national CF center - Mother and Child Health Institute of Serbia “Dr Vukan Cupic”. Demographic data, current therapy, bacterial colonization of lower airways and lung function results were obtained from European CF registry and patient’s medical history files. Patients have performed regular physical therapy on daily basis during the study. The best annual values of FEV\textsubscript{1} and FVC were taken into account in calculating the five-year trend value of these indicators. The number of exacerbations per year and the total number at the end of the monitoring period were evaluated for each patient. Nutritional status was estimated according to Z score of body mass index (BMI). Patients were stratified into three groups: (underweight – BMI < 18.5 (or ≤ 1SD), normal weight – BMI 18.5-24.9 (−1 - +1 SD) and overweight – BMI > 24.9 (or ≥ 1SD).

The descriptive statistics, including mean and standard deviation of numerical variables, and frequencies and percentages of categorical variables were used to characterize the study sample. Differences between groups on numerical variables were analyzed by use of Kruskal-Wallis test, while the Fisher exact test or the Pearson chi-square test were used for categorical variables. Linear regression models were used to assess relationship between number of exacerbations or changes of FEV1, as a dependent variables, and independent
variables. The R environment for statistical computing (R Core Team, 2016) was used to conduct statistical analyses. Significance level (alpha level) was set at 0.05.

**Results**

Data of 83 subjects among 110 screened were included in the analysis. Twenty seven subjects were excluded from the analysis due to incomplete medical records. The average age of the subjects at the beginning of the follow-up period was 17.1 ± 7.1 years, and the average age at the time of diagnosis was 3.7 ± 4.3 years, with similar sex distribution. Majority of study participants had normal weight, with an average Z score of BMI of -0.97 ± 1.4 SD.

During the five year of follow-up, subjects had an average of 0.6 exacerbations annually. Other demographic data are shown in Table 1.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender, n (%)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>42 (51)</td>
</tr>
<tr>
<td>Female</td>
<td>41 (49)</td>
</tr>
<tr>
<td>Age</td>
<td>17.1 ± 7.1</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>3.7 ± 4.3</td>
</tr>
<tr>
<td>BMI</td>
<td>18.1 ± 3.5</td>
</tr>
<tr>
<td>Z score BMI</td>
<td>-0.97± 1.4</td>
</tr>
<tr>
<td>Colonization with P.aeruginosa n (%)</td>
<td>53 (62)</td>
</tr>
<tr>
<td>Colonization with B.cepaica n (%)</td>
<td>10 (12)</td>
</tr>
</tbody>
</table>
Diabetes n (%) 12 (14)
Asthma n (%) 23 (27)
Liver disease n (%) 17 (20)

The average decrease of FEV$_1$ in the five-year period was 11.9% ± 14.5%, and annual decrease was 2.4% ± 2.9%. The average decrease of FVC was 8.6% ± 1.8%, and 1.7% ± 3.6% respectively. Annual decrease of FEV$_1$ and FVC was not different in regard to patient’s sex (p=0.2 and p=0.7 respectfully).

Underweight subjects had significantly lower values of FEV$_1$ in compare to normal and overweight patients (p=0.001). Similar difference was shown between the groups according to FVC values (p <0.001).

Furthermore, in underweight subjects exacerbations were more frequent over five years of follow-up compared to the other two groups (p= 0.02) (Table 2).

<table>
<thead>
<tr>
<th>Lung function and frequency of exacerbations according to nutritional status</th>
<th>Underweight (n=40)</th>
<th>Normal weight (n=38)</th>
<th>Overweight (n=4)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>FEV$_1$ (%)</td>
<td>64.0 ± 24.4</td>
<td>83.7± 24.4</td>
<td>91.5 ± 17.2</td>
<td>0.001</td>
</tr>
<tr>
<td>FVC (%)</td>
<td>71.2 ± 20</td>
<td>90.3 ± 19</td>
<td>98.3±12.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Average annual number of exacerbations during the study</td>
<td>0.8</td>
<td>0.5</td>
<td>0.0</td>
<td>0.02</td>
</tr>
</tbody>
</table>
It was showed that exacerbations were more frequent in patients chronically colonized with B. cepacia than in those colonized with P. aeruginosa or other pathogens (p=0.023) - Figure 1. Presence of diabetes mellitus (p= 0.796) and regular use of recombinant DNase (p= 0.282) and hypertonic saline (p= 0.791), were not proven to be risk factors for PE.

Fig. 1 Median of exacerbations in patients chronically colonized with B.cepacia

Univariant analysis with the number of exacerbations as a dependent variable showed that the presence of B. cepacia in underweight patients significantly increases the number of exacerbations (p = 0.018) (Table 3).
### Table 3

<table>
<thead>
<tr>
<th></th>
<th>B</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Burkholderia cepacia</td>
<td>0.90</td>
<td>0.018*</td>
</tr>
<tr>
<td>Pseudomonas aeruginosa</td>
<td>0.33</td>
<td>0.20</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.11</td>
<td>0.33</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>0.01</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Univariate linear regression had shown that the number of exacerbations (p = 0.002) and BMI Z-score (p = 0.028) were statistically significant predictors for FEV\(_1\) decline in five years of follow-up (dFEV\(_1\)). Both variables were entered into a multiple regression model with dFEV\(_1\) as a dependent variable. This analysis showed that there was a statistically significant association between the number of exacerbations and dFEV\(_1\). With an increase in the number of exacerbations, there was a tendency for greater deterioration of FEV\(_1\) in the observed period (p = 0.013) (Table 4).
Table 4

<table>
<thead>
<tr>
<th>Regression models with dFEV1 as a dependent variable</th>
<th>Univariate regression models</th>
<th>Multiple regression models</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>B</td>
<td>p</td>
</tr>
<tr>
<td>Age at diagnosis</td>
<td>-0.21</td>
<td>0.587</td>
</tr>
<tr>
<td>Initial FEV1,% value</td>
<td>0.02</td>
<td>0.796</td>
</tr>
<tr>
<td>Number of exacerbations</td>
<td>-7.22</td>
<td>0.002*</td>
</tr>
<tr>
<td>Z score BMI</td>
<td>2.75</td>
<td>0.028*</td>
</tr>
<tr>
<td>Asthma</td>
<td>5.26</td>
<td>0.145</td>
</tr>
</tbody>
</table>

Discussion

Exacerbations of lung disease are significant factor of morbidity that affects decline of lung function in patients with CF. We showed that the most significant risk factor for exacerbation occurrence in our cohort of patients was chronic airway colonization with *Burkholderia cepacia*.

The natural course of CF lung disease is characterized by gradual deterioration with intermittent episodes of acute endobronchial infection (10). Lung function mostly has steeper decline in female patients from adolescence, which was not the case in our study. Exacerbations of pulmonary disease present a major burden for patients and their families with negative affection on quality of life. Due to inexistence of dedicated home care providers, all patients in Serbia are hospitalized for intravenous antibiotic therapy and intensive physical rehabilitation. The burden is even more significant for the health system, as antimicrobial therapy in hospital significantly increases medical expenses (8). In a large observational study, which involved more than 11000 patients, 42% of patients had exacerbation during a six-month of follow-up (11). In the etiology of exacerbation respiratory viruses play an important role by reactivation of chronic bacterial infection in the lower respiratory tract with common CF pathogens such as *Pseudomonas aeruginosa* or *Staphylococcus aureus*, which lead to prolongation of hospital stay (6,12).
Despite high prevalence of chronic Pseudomonas colonization in our cohort (62%), it has not been shown to be a significant predictor of appearance of PE. Patients with higher exacerbation score and shorter interval between it, had greater overall FEV₁ decline (4). Our research in relatively heterogeneous CF population confirmed that increased number of exacerbations correlate with more significant loss of lung function. The annual FEV₁ decline in our cohort was 2.4%, which was significantly higher compared to the results of other studies (1.8-2%) (8, 11). Although the treatment of patients with CF in our country is mostly performed without delay in a specialized center according to international guidelines, there are several reasons that may explain this negative trend. The most likely reasons are malnutrition and the high prevalence of chronic Burkholderia colonization, which is in accordance with previous studies (13, 14). Colonization with B.cepacia is associated with higher mortality and morbidity, including more frequent exacerbations, weight loss, and rapid lung function decline (15, 16). Patients colonized with B.cepacia in our cohort had higher exacerbation score. Association of chronic B.cepacia colonization with malnutrition, leads to even more frequent exacerbations compared to patients with normal weight. The results of large cohort study have shown that the nutritional status and pulmonary function are dependent variables in CF, which is in concordance with our results (17). More frequent PE and steeper decline in lung function in malnourished patients is directly related to poorer prognosis and unfavorable outcome.

**Conclusion**
Pulmonary exacerbations lead to a progressive lung function decline in patients with CF over time. Malnourishment and chronic airway colonization with Burkholderia cepacia results in more frequent pulmonary exacerbations. Objective assessment of the symptoms and signs of pulmonary exacerbation allows vigorous antimicrobial therapy. This usually leads to favorable clinical course with preservation of the lung function, which is an important indicator of respiratory health in patients with cystic fibrosis.
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