

The role of viral infections in COPD exacerbations

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Abstract

Aim: The role of viral infections in the exacerbations of chronic obstructive pulmonary disease (COPD) remains controversial. The rates of recent viral infections vary from 23 to 62%; moreover pathogens as *Chlamydomphila pneumoniae* are often detected in patients with COPD during an exacerbation. Investigating the impact of viral infections in COPD exacerbations, a study was conducted in an Athenian hospital of Greece.

Patients-Methods: All patients suffered from exacerbation of COPD (n=87), as well as from pneumonia and COPD (n=17). Seventy healthy volunteers were also assessed at the same time (comparison group). In all examinations we measured IgM blood antibodies for influenza A & B, RSV, parainfluenza viruses, *Mycoplasma pneumoniae* and *Chlamydomphila pneumoniae*. Sputum cultures and bacteria taken from all patients were evaluated if > 105cfu/ml.

Results: Sputum cultures revealed bacterial pathogens in a 40% of all patients but still only in three cases these were responsible for the presence of pneumonia. A comparison between patients with exacerbations of COPD and healthy volunteers revealed a statistical increase of IgM for influenza A virus and *Mycoplasma pneumoniae*. As far as patients with COPD exacerbations were concerned the difference was almost significant for RSV and influenza B but not significant for *Chlamydomphila pneumoniae*. Moreover, there was not detected such a difference between patients with pneumonia and COPD, and patients with COPD exacerbations.

Conclusions: The incidence of bacterial colonization in patients with COPD exacerbations attempts to draw the attention of the physician to the prudent use of antibiotics in patients with COPD.

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) is determined, following the GOLD (Global initiative on obstructive lung disease) criteria, as the non-reversible decrease in pulmonary airflow. The pathogenicity of COPD includes chronic inflammatory response to exogenous antigens (i.e. Toxic particulates and gases) [1,2,3]. Every patient with a history of smoking, chronic productive cough and dyspnoea has to be examined for COPD, which is currently a disease preventable and treatable. Diagnosis is established by spirometry (FEV1/FVC < 70%) [3,4]. COPD is a major cause of morbidity and mortality worldwide [2,3,4]. More than 23.000.000 people in the USA (14% of population) suffer from this disease with an annual rate of 119.000 attributed deaths. Overall the real incidence of COPD is underestimated [2,3]. COPD has increased more than 40% since 1982 being the 5th cause of death in the USA [3,4,5]. According to WHO in 2020, COPD is globally predicted to be the 3d more frequent cause of death [5,6].

COPD is characterized by exacerbations that promote the

gradual impairment of pulmonary function and the need for frequent hospitalizations bearing a significant devaluation in the patient's quality of life. Every episode of exacerbation deteriorates previous pulmonary condition and is classified as mild, moderate and severe and frequently requires hospitalization [7]. Bacterial and viral infections are considered as the major cause of COPD exacerbation especially in the initial phase of the disease. Viral infections are implicated in COPD exacerbations in 25-63% of cases [2,6,7].

It is also difficult to demonstrate the presence of an infectious agent during the COPD exacerbation for many reasons and mainly because the definition of COPD exacerbation is not always clear.

According to published data, COPD exacerbation is defined as the change in the quality and /or quantity of sputum production [7]. Moreover, microorganisms that belong to normal flora of the mouth and pharynx may be isolated in the sputum during COPD exacerbation in the absence of

clinical signs of infection. This is a confounding factor in the etiology of COPD exacerbation. [6,7]. In an attempt to contribute to the current knowledge on the role of viral infections in COPD exacerbations, this study was conducted in Sotiria Chest Hospital in Athens, Greece.

PATIENTS-METHODS

A prospective case-control study was undertaken. In the study included 104 adult patients (80 male, 24 female) with diagnosis of COPD who were hospitalized for COPD exacerbation or pneumonia in Sotiria Lung Hospital. During the same period at the same hospital, seventy healthy volunteers (30 male and 40 female) voluntarily participated in the control group. All participants were informed over the point of view of this study which was approved by the Ethics Committee of the Hospital.

Study definitions: The inflammatory process of the lung caused by an infective micro-organism was defined as pneumonia [8,9]. Only COPD patients with community-acquired pneumonia (CAP) took part in the study. Cases of hospital acquired pneumonia or ventilator-associated pneumonia were excluded.

Deterioration of dyspnoea, including the increased volume of sputum and the presence of pus, gave the definition of COPD exacerbation according to Anthonisen criteria [10]. Following these criteria, patients with COPD are classified in 3 groups: a) Group I is characterized by dyspnoea, increased sputum production and purulent sputum. b) Group II by 2 of the previous symptoms. c) Group III by only one of the previously described symptoms.

Quantitative sputum cultures detected bacteria possibly implicated in COPD exacerbations and pneumonia in all patients according to routine microbiological standard procedures. Only pathogens in a concentration of $> 10^5$ cfu/ml were evaluated.

Blood gases analysis was performed in all patients at their hospital admission and their discharge. Inflammatory laboratory markers as CRP were measured in all patients.

Chest radiographs evaluated at hospital admission and on discharge. A computed lung tomography was performed in 4 cases: a) in order to exclude underlying malignancy b) for radiological diagnosis of pulmonary emphysema whenever x-ray was not diagnostic c) Diagnosis of bronchiectasis d) in every case that x-ray was not diagnostic.

The clinical condition (the onset of symptoms, fever $> 38^\circ\text{C}$,

dyspnoea, expectoration with sputum production –purulent or not-) on admission was assessed in all the participants in this study.

A history of prior hospitalizations (in wards and ICU) due to COPD exacerbation or pneumonia was also recorded.

Exclusion criteria: 1. Patients treated with systemic corticosteroids for more than one week last 3 months before study. 2. Patients with known malignancy 3. chronic renal failure (hemodilution). 4. Patients with Cirrhosis 5. Immunosuppressed patients. 6. A History of splenectomy.

Sputum samples were adequate for analysis epithelial cell were < 10 and polymorphonuclear leukocytes > 25 in direct microscopy. Gram staining was performed for bacteria related to pulmonary infections as Streptococcus pneumoniae, Staphylococcus spp Haemophilus Influenza, Enterobacteriaceae. Echo, Cocksackie, Respiratory Syncytial virus (RSV), adeno-viruses, Influenza A, B, parainfluenza, CMV as well as Chlamydia pneumoniae, Mycoplasma pneumoniae Legionella pneumophila were detected by serology tests looking for IgG and IgM titers.

Pulmonary infection was established by the following criteria: 1. Fever $> 38^\circ\text{C}$, purulent expectoration, leucocytosis and CRP elevation. 2. Blood gas indicating the presence or deterioration of hypoxemia ($\text{PO}_2 < 60$ mmHg), hypercapnia ($\text{PCO}_2 > 45$ mmHg), acidosis ($\text{pH} < 7.35$) both with bicarbonate blood levels. 3. Abnormal x-ray and CT demonstrating infection or bronchiectasis. 4. Microbiological diagnosis of infection based on sputum cultures. 5. High titer of IgM antibodies for all micro-organisms already mentioned in the text, presumed recent infection.

A statistical analysis was performed by chi-square test (Yates correction) with a level of statistical significance $< 5\%$.

RESULTS

One hundred four patients, 80 male (mean age 72.4 years, mean cigarette consumption 72.9 pack-years) and 24 female (mean age 72 years, mean cigarette consumption 16.8 pack-years) were included into the study. Healthy volunteers, 30 male (mean age 55 years, mean cigarette consumption 20 pack-years) and 40 female (mean age 53 years, mean cigarette consumption 12 pack years) were included as control group. According to Anthonisen criteria, 83.7% of patients presented with COPD exacerbation at admission. Among them 16.3% had a clinical and radiological diagnosis

of pneumonia and was not incorporated into the statistical analysis, being a separate group of patients. In 32.3% of cases of COPD exacerbation there were only changes in sputum production while in less than 50%, fever and leucocytosis were detected. Furthermore, all patients presented moderate or severe hypoxemia with either hypercapnia, or normocapnia, or hypocapnia. At discharge, hypoxemia was reconstituted in a significant level ($p < 0.0001$), both with normocapnia and normal blood pH ($p < 0.005$) (table 1).

Figure 1

Table 1: Blood gases analysis on admission and at hospital discharge.

Admission		Discharge	
	$\bar{x} \pm SD$	$\bar{x} \pm SD$	p
PO ₂ mm Hg	57.1 \pm 12.67	65.7 \pm 11.8	$p < 0.001$
PCO ₂ mm Hg	46 \pm 14.7	49.5 \pm 13.5	$p < 0.05$
pH	7.33 \pm 1.03	7.40 \pm 0.12	$p < 0.05$
HCO ₃ mEq/L	27.8 \pm 4.72	30.8 \pm 6.65	$p < 0.001$

Sputum sample was invaluable in 77 patients revealing normal flora in 61% of cases and only in 39% a pathogen in a concentration of 10^5 cfu. Pathogens detected were *Haemophilus* spp, n=7, *Pseudomonas* spp n=5, *Pseudomonas aeruginosa*, n=4 *S. pneumoniae*, n=2, *Klebsiella* spp, n=2 and miscellaneous pathogens as well. Among patients with pneumonia (n=17), positive sputum culture was detected in 3 cases by *Haemophilus* spp, *Pseudomonas* spp and *Acinetobacter* spp.

In cases of COPD exacerbations (n=87), 80.5% had a high titer of IgM antibodies in serology test for pathogens reported in materials and methods section. Overall, only 40% of healthy controls presented high titers of IgM (80.5% vs. 40%, $p < 0.0001$).

In addition, differences between patients and controls were illustrated in table 2

Figure 2

Table 2: Comparison of serology tests between patients with COPD exacerbations and controls(IgM positive)

Pathogen	Controls, n=70	Patients, n=87	p
RSV	10	25	0,03
Influenza A	2	26	<0,0001
Influenza B	2	14	0,007
Parainfluenza	12	14	0,8
C. pneumoniae	1	7	0,1
M. pneumoniae	1	14	0,001
Adeno-viruses	NA	12	NA

Influenza A virus and *Mycoplasma pneumoniae* are statistically significant in values of IgM > cut off between patients and controls. For the other studied pathogens (table 2) there is no significant difference between patients and controls. Patients with pneumonia have no difference from controls regarding IgM serology for investigated pathogens, other than bacteria (table 3).

Figure 3

Table 3: Comparison of serology tests between patients with pneumonia and patients with COPD exacerbations.

IgM (+)	Pneumonia	COPD exacerbations	p
RSV	6/17	18/87	0,2
Adenoviruses	2/17	7/87	0,6
Influenza A	4/17	22/87	1,0
Influenza B	2/17	12/87	1,0
Parainfluenza	2/17	13/87	1,0
M. pneumoniae	3/17	2/87	1,0
C. pneumoniae	3/17	7/87	0,2

DISCUSSION

Viral respiratory infections are a frequent cause of morbidity with high prevalence in patients with COPD [11]. The initial phase of COPD exacerbations could be attributed to viral infections with an incidence ranged from 25-63%, as it is already mentioned above. [6]. However, this hypothesis is not supported by other studies [12,13]. Perhaps, some authors reporting a 20%, rates of viral infections in COPD exacerbations underestimate the real incidence [12,13,14]. In the current analysis more than 80% of patients have a positive correlation between the episode of COPD exacerbation and the positive IgM values for H. influenza virus and M. pneumoniae. On the contrary, bacterial pathogens were absent in 50% while the incidence of detection did not predict the increase of COPD exacerbations [15]. Moreover, in intubated patients with COPD exacerbations, Fagon et al detected a microbial infection in 50% of cases [16]. According to published data, *Chlamydia* spp presented positive serology tests in 26% of the cases [17]. Smith et al, [18] reported a combined isolation of *S. pneumoniae* from sputum both with positive serology for H. influenza, but it is not clear if those pathogens have colonized the bronchial tree or are real pathogens

responsible for COPD exacerbations. Among 181 patients with COPD and 86 patients with COPD exacerbations, colonization with bacteria was more frequent (54%) in the exacerbation than in the COPD (29%) group. *Pseudomonas aeruginosa* and *Haemophilus influenza* were the most common isolates [19]. On the contrary Sethi et al did not find any difference in colonization profile between patients with COPD exacerbations and stable COPD patients [20]. This subject remains controversial despite published studies. In acute bronchitis, viral implication with positive serology tests was found in 30% of cases [12]. Soler et al reported a 15% of viral infections in patients with COPD exacerbation in need for mechanical ventilation and ICU hospitalization [17], while in 18% of cases *Chlamydia pneumoniae* was detected. Influenza viruses and RSV are also reported being involved in COPD exacerbations. However this is a finding that is not confirmed in our study for *Chlamydia* [21,22]. Edward et al [14] reported a 23% incidence of viral factor in COPD exacerbations, comparable to findings by Chastre and Fagon [21]. In an almost recent review, rhinoviruses, parainfluenza virus and RSV were more frequently associated with COPD exacerbations than adenoviruses [23].

In this study positive IgM antibodies were found for RSV (28.7%), influenza A virus (29.8%) while for Influenza B, parainfluenza, rates were less than 20%. Besides, only influenza A virus was statistically more prominent in patients than in controls, indicating a possible role of influenza in the pathogenesis of COPD exacerbations. The role of *Chlamydia pneumoniae* in COPD exacerbations is controversial: in some studies, a recent *Chlamydia* infection was documented in 75% of patients [24,25,26] while in others *Chlamydia* were involved only in 24-34% of cases [27,28].

In conclusion, the role of virus and atypical pathogens in COPD exacerbations remains obscure. *Mycoplasma* spp is a rare cause of exacerbations (not exceeding 14% of cases). *Legionella pneumophila* did not correlate with COPD exacerbations, unless of some geographic regions where the disease is endemic [30].

The main advantage of this study is the comparison of healthy volunteers in the same geographic region at the same season. Patients with pneumonia and patients with COPD exacerbations did not differ in terms of serology investigation while patients with exacerbations of COPD had a significant higher prevalence of positive serology for influenza and *Mycoplasma* than controls. This is an

indication that in the examined population, recent viral infection might be involved in the pathogenesis of COPD acute exacerbations.

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