The causes of failure in the treatment of COPD exacerbations

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Abstract

Introduction. A significant proportion of patients with chronic obstructive pulmonary disease experience periodic exacerbations manifested by the increase of severity of symptoms and change in the character and volume of sputum. Exacerbations of COPD may lead to the occurrence or intensification of existing respiratory failure. There is a group of COPD patients that is more difficult to treat and requires longer hospitalization.

Purpose. The purpose of this work was to identify factors that could affect the effects of treatment or its elongation over time.

Discussion. Among the factors that may affect the failure of treatment of COPD exacerbations are incorrect diagnosis, wrong choices of treatment including inadequate antibiotics, or the delay of assisted breathing methods usage and oxygen therapy. Sometimes, the bad response to treatment may result from insufficient compliance. Coexistence of other diseases, like asthma, heart failure, cancer or connective tissue diseases can also lead to severe difficulties in treatment.

Summary. Effective treatment of an exacerbation may increase the time to occurrence of the next worsening and significantly decrease the risk of death.

Key words:

pulmonary disease, chronic obstructive; disease progression; respiratory insufficiency

Introduction

Chronic obstructive pulmonary disease (COPD) is defined as a frequent, treatable disease characterized by chronic respiratory symptoms resulting from pathology of airways and / or alveolar, associated with exposure to noxious gases or other suspended particles in the air. A significant proportion of patients experience periodic exacerbations manifested by the increase of severity of symptoms (shortness of breath and cough) and change in the character and volume of sputum. Exacerbations of COPD may lead to the occurrence or intensification of existing respiratory failure. According to the GOLD guidelines of 2017, prevention and treatment of exacerbations of this disease is an extremely important element of care for patients with COPD. [1]

It is estimated that about 2 million people suffer from chronic obstructive pulmonary disease in Poland, [2,3] and the diagnosis is often too late, that is, when the disease is already advanced or even after the first exacerbation requiring hospitalization.

After the diagnosis of the disease, all patients should be advised to stop smoking and to start and maintain physical activity, including respiratory rehabilitation. Vaccination against influenza virus is recommended for all COPD patients. Vaccination against pneumococci (PCV13 or PPSV23) should be used in patients over 65 years of age, while PPSV23 vaccination is also indicated in younger patients with multiple co-morbidities. [1,4] The effectiveness of protective vaccination in reducing the severity of COPD symptoms and the frequency of deaths has been proven. [5]

The treatment of exacerbation depends on its severity. Patients with mild to moderate exacerbations may be treated ambulatory. The necessity of admission to the hospital may occur in patients with moderate exacerbation, in which other co-morbidities coexist. The five most common conditions associated with COPD include diabetes mellitus, hypertension, atherosclerosis, dyslipidemia and osteoporosis. [6] In the case of severe exacerbations, medical help is needed in the hospital emergency department, and usually longer hospitalization is also necessary.

Among patients treated for exacerbation of chronic obstructive pulmonary disease, there is a group that is more difficult to treat and requires longer hospitalization. The purpose of this work was to identify factors that could affect the effects of treatment or its elongation over time.

Factors that may affect the failure of treatment of COPD exacerbations.

Incorrect diagnosis

In the face of therapeutic difficulties, it is worth making sure about the correctness of COPD diagnosis. It can not be excluded that a patient who visits a doctor due to an exacerbation of chronic respiratory disease, that has been treated for many years due to COPD, suffers from a different lung / respiratory disease. A properly conducted interview after the patient's admission to the Department may prompt the doctor to run additional tests. It is worth remembering that in the period of exacerbation, many diseases may take a similar clinical picture, accompanied by dyspnea, cough, respiratory failure and improvement after bronchodilator therapy and steroid therapy. Therefore, the change in the diagnosis during the exacerbation is not a correct procedure, however, deepening the diagnosis during the period of disease stabilization may bring unexpected results, change in the basic diagnosis and the associated change in treatment.

Maintaining vigilance by the attending physician and prudent analysis of the results of laboratory tests, imaging examinations, including thoracic computed tomography or spirometry (apart from the period of exacerbation of the disease), may also lead to the diagnosis of an additional disease entity. The multitude of nonspecific symptoms in a patient with a definite diagnosis is undoubtedly a diagnostic challenge. The presence of pleural effusion, weight loss, night sweats or anemia should direct our attention to a thorough analysis of imaging tests to exclude the presence of cancer, not only lung cancer and pleural mesothelioma, but also other mediastinal tumors, head and neck tumors, as well as breast cancer, ovary cancer, lymphomas and leukemia. [7] The analysis of imaging and laboratory tests may also allow the diagnosis of other lung diseases or systemic diseases with a pulmonary manifestation, such as sarcoidosis,

pulmonary fibrosis, granulomatosis with polyangiitis or connective tissue systemic diseases.

In the case of doubts, the clinician has the possibility of additional diagnosis of asthma (ACO - asthma / COPD overlap). This diagnosis should be considered in the case of asthma-related history, past or childhood history of episodes of paroxysmal dyspnoea or paroxysmal cough, positive family history of allergic diseases or other allergic disease in the patient (urticaria, allergic rhinitis, sensitization to inhaled substances or food, the presence of nasal polyps).

Finding deviations in laboratory tests, such as absolute eosinophilia > 500/ul of peripheral blood or sputum eosinophilia may indicate the presence of a disease with an allergic mechanism, although it is not an indisputable confirmation. Eosinophilia described in cases of COPD is the indication for use of steroid therapy in inhaled treatment in these patients (GOLD assessment in this respect is ambiguous), however, it does not force the clinician to change the basic diagnosis. [8]

Insufficient compliance

Another, but equally important issue worth mentioning is the so-called compliance, i.e. the level at which patients adhere to the doctor's recommendations. The World Health Organization defines the compliance issue as a new problem in pharmacology. In the case of ineffectiveness of the applied therapy, the lack of proper cooperation with the patient should always be considered. The change in dosage, the change in the frequency of taking medication, the deliberate discontinuation of certain preparations by the patient are just examples of many errors that may occur during therapy. Most of these problems concern outpatients, but it can be assumed that such difficulties also apply to hospital treatment. [9]

Choice of medicines

The primary goal of therapy in COPD exacerbation is to reduce the severity of symptoms (dyspnoea, cough, presence of auscultatory phenomena, respiratory failure), shorten the duration of the exacerbation and reduce the risk of subsequent worsening. Drugs acting immediately are inhaled short-acting drugs from the group of β2-agonists (SABA) and cholinolytics (SAMA). [10] It should also be remembered that patients should initiate bronchodilator therapy with at least one long-acting drug before discharge from the ward, which allows the patient to get used to the new inhaler device and the appropriate technique of inhalation. It seems that the preferred group should be long-acting anticholinergics, due to a stronger reduction in the risk of further exacerbations, compared to long-acting B2-agonists.

The usage of systemic steroids in the treatment of severe exacerbations is not controversial. It has been proven that such treatment improves lung function, raises blood oxygen levels, shortens the recovery time and hospitalization time, as well as reduces the number of treatment failures. [10] ERS/ATS Guidelines (European Respiratory Society/American Thoracic Society) recommend the use of oral steroid therapy in the outpatient treatment of exacerbations for up to 14 days. The REDUCE study also argues that the restriction of taking oral steroids up to 6 days, compared to treatment for 14 days, is not associated with an increased risk of re-exacerbation (the follow-up was half a year). [11]

In a post-hoc analysis of over 17,000 patients with COPD (TIOSPIR study population), Calverley and colleagues demonstrated that in patients who received systemic glucocorticoid (GCs) therapy or GCs systemically in combination with an antibiotic, risk of repeated exacerbations and severe exacerbations requiring hospitalization and the risk of death was statistically significantly higher compared to patients receiving only antibiotics [12]. This study proves the need for accurate determination of indications for various types of COPD exacerbation therapy, especially the therapy with glucocorticoids.

Delay of oxygen therapy or assisted breathing methods

The standard procedure after admission to a hospital due to exacerbation of COPD is the determination of oxygen saturation or arterial blood gasometry. Depending on the results, passive oxygen therapy or noninvasive mechanical ventilation (NIV – noninvasive

ventilation) should be applied. The use of NIV should be considered in patients with symptoms of respiratory failure (e.g. tachypnea) and respiratory acidosis in gasometry (pH <7.35, pCO2 >45 mmHg). NIV shortens time to discharge from the hospital and reduces the risk of death associated with exacerbation of COPD. [13]. Delaying the use of assisted breathing methods may increase the duration of exacerbation and reduce the chance of effective treatment. In cases of advanced respiratory acidosis or the presence of contraindications for NIV use, it may be necessary to start invasive mechanical ventilation.

Inadequate antibacterial treatment

Antibiotic therapy should be used in patients who are experiencing an increase of dyspnoea, increased sputum volume and change of its character to purulent. An indication for the administration of antibiotic is also the need for usage of mechanical ventilation, both invasive and non-invasive methods. The recommended duration of antibiotic use is ideally 5-7 days, and the preferred route is the oral route. Stolbrink et al. proved that the antibiotic treatment time above 6 days was not associated with greater eradication of pathogens, but with the occurrence of more side effects. [14] In patients initially requiring high blood antibiotic levels, i.e. administered intravenously, it is recommended to use sequential therapy, i.e. after a few days of treatment, when the patient's condition has stabilized and the body temperature has remained physiological within 24 hours, replace the intravenous antibiotic with its oral form in an equivalent dose. The most frequent pathogens include *H. influenzae*, *M. catarrhalis* and *S. pneumoniae*, therefore, in the majority of patients with COPD, the first line antibiotics are aminopenicillins with clavulanic acid, macrolides (preferred in atypical pathogens) or cefuroxime (in the case of isolation of β-lactamase-producing microorganisms). In patients with frequent exacerbations or requiring mechanical ventilation, gram negative bacteria, such as *P. aeruginosa* may be expected, which is why it is important to perform sputum cultures and determine antibiotic resistance. Finding the presence of pathogens in the sputum is not always the same as determining the infectious agent. Bacterial colonization is a common phenomenon, especially in the COPD group. It results from changes in the epithelium of the upper and lower respiratory tract and the presence of bronchiectasis, conducive to retention of sputum in the airways. The retained secretion, undergoing superinfection, causes the formation of local inflammatory conditions, transmitting to the surrounding pulmonary parenchyma, which may lead to irreversible changes, e.g. fibrosis. Despite the high risk of colonization of the airways of patients with COPD, in patients with initial sputum cultures positive for *H. influenzae*, *M. catarrhalis*, *S. pneumoniae* or *P. aeruginosa*, after applying molecular typing techniques during the exacerbation period, new strains of these bacteria were usually detected in the sputum. [15].

Clinical symptoms suggesting the efficacy of antibiotic therapy are a reduction in the patient's dyspnoea and purulent content in the sputum [1]. The use of inappropriate antibiotic therapy may also be a factor affecting the time and effects of COPD exacerbations.

Coexistence of other diseases

The complications in treatment of COPD exacerbations may also result from other, sometimes undiagnosed, diseases, an example of which can be heart failure.

According to various estimates, chronic heart failure coexists in patients with COPD in 20-70% of cases. [16] It is worth noting that unrecognized heart failure can mimic the symptoms of COPD. [1] Guidelines for treatment in this group of patients do not differ from the general recommendations. It is recommended to use β1-blockers, which prolong the survival of patients with COPD and heart failure. These drugs, despite the presence of indications, are often not prescribed to patients with COPD due to their mechanism of action, that may seem opposite to β2-agonists. Scientific evidence indicates, however, that the use of selective β1-blockers in this group of patients is safe and beneficial. [17] It should be emphasized that the coexistence of COPD with heart failure is often underestimated due to the similarity of symptoms, and the treatment of only one of these diseases is sometimes insufficient and causes therapeutic failure.

Summary

The element that guarantees the effectiveness of treatment of exacerbations in COPD is the correct diagnosis of this disease, the classification of the severity of the disease and the implementation of appropriate treatment, consistent with the currently applicable guidelines in this area. In difficult and unusual cases, a thorough analysis of the test results may bring a solution in the form of a change in the diagnosis or confirmation of coexistence of COPD with other diseases, including cardiovascular diseases, cancer or other respiratory diseases. An important element of therapy is also proper communication with the patient, ensuring compliance of the treatment with recommendations issued by the doctor. Effective treatment of an exacerbation may increase the time to occurrence of the next one and significantly decrease the risk of death.

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