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Advanced chronic obstructive pulmonary disease (COPD)

Abstract

Chronic obstructive pulmonary disease (COPD) is one of the most common chronic diseases and the fourth cause of death in the world. Its advanced forms (severe — in case of FEV_1 indicator below 50% of the norm and very severe — below 30%) usually lead to respiratory disability and premature death. The prognoses of those suffering from severe forms of COPD are no different from patients with lung cancer. The course of the disease is highly influenced by its exacerbation and co-morbidities, such as cardiovascular diseases, diabetes, lung cancer and peptic ulcer.

Treatment aims at stopping the progress of disease, preventing its exacerbation and relieving tiresome symptoms, mainly dyspnoea, chronic cough and decreasing tolerance of effort.

Key words: chronic obstructive pulmonary disease, dyspnoea, inflammatory condition

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The clinical picture of advanced COPD

The number of patients affected by chronic obstructive pulmonary disease (COPD) in Poland is estimated at 2 million with a considerable percentage suffering from severe (15%) or very severe (3%) disease. This means that the number of patients with advanced COPD in our country may be as high as 400,000.

Chronic obstructive pulmonary disease is defined as an illness with a progressive, poorly reversible airflow limitation in the respiratory tract resulting from inflammation triggered by noxious fumes and gases. Extrapulmonary consequences of COPD and comorbidities may adversely affect the course of the disease [2].

Spirometric manifestations of bronchial obstruction in the course of COPD include reduced FEV_1/FVC below 70% predicted and the lack of reversibility of bronchoconstriction following administration of a bronchodilator, while progression of the disease is manifested by an increasing FEV_1. Severe and very severe COPD is defined as FEV_1 reduction below 50% and 30% predicted, respectively [2].

The clinical picture of advanced COPD generally consists of:

— severe respiratory manifestations;
— systemic and extrapulmonary manifestations;
— comorbidities;
— recurrent exacerbations;
— mental status changes.

An additional element that is less frequently included in the descriptions of advanced COPD is the increasing family, professional and social isolation of patients and the need to provide support to the patient's family and those caring for the patient.

Respiratory manifestations

Most patients with advanced COPD suffer from dyspnoea often accompanied by severe cough and sputum production (especially in the morning). This

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is for the most part a result of chronic inflammation of the bronchial mucosa and the chest congestion caused by destruction of the respiratory epithelium. Replacement of respiratory by squamous epithelium (foci of metaplasia), reduced or absent ciliary response, impaired secretory function of the mucous glands of the respiratory tract and the impaired function of macrophages are just some of the mechanisms that lead to reduced airflow in the bronchi due to chest congestion. The bronchospasm results, as already mentioned, from chronic inflammation leading to bronchial wall remodelling but also from destruction of the parenchymal structure caused by emphysema. This leads to the formation of an air trap and eventually to hyperinflation manifested by increased total lung capacity (TLC) and residual volume (RV). The development of emphysema also damages the natural "scaffolding" of the pulmonary parenchyma that allows to preserve an appropriately wide bronchial lumen, especially during expiration. The loss of elastic elements of the parenchyma leads to bronchial "collapse" during the passive phase of expiration and forces the patient to use the auxiliary respiratory muscles. All this is manifested by increased pulmonary resistance, reduced closing volume (CV) and reduced maximal expiratory flows (MEF) in the so-called small calibre bronchi test (MEF75, MEF50 and MEF25) below 60% predicted. These changes are also responsible for the considerable reduction in exercise tolerance among patients with advanced COPD.

Systemic and extrapulmonary manifestations

Chronic obstructive pulmonary disease is accompanied by systemic inflammation, as evidenced by increased serum levels of C-reactive protein (CRP) and increased production of tumour necrosis factor alpha (TNFα) and other proinflammatory cytokines. Isolated studies have shown the presence of antibodies to elastin in the serum, which might demonstrate that COPD is a chronic autoimmune disease [3]. This hypothesis has not, however, been unequivocally confirmed.

Advanced COPD is often complicated by osteoporosis [4]. The reason for this phenomenon remains unclear, although it is hypothesised that proinflammatory cytokines that trigger processes accelerating bone degradation may play an important role in the pathomechanism of osteoporosis in COPD patients.

An important abnormality affecting the course of COPD is muscle weakness with the associated reduction in lean body mass. Many studies have demonstrated a reduced mass of large muscles, such as the femoral muscle [5]. Muscle weakness is one of the factors leading to wasting syndrome [6, 7]. In addition, it is believed that changes in the levels of TNF- and leptin observed during exacerbations of COPD may be related to poorer nutritional status and muscle weakness [8].

Comorbidities

The frequent coexistence of COPD with other diseases, such as cardiovascular disease, diabetes mellitus, lung cancer and peptic ulcer disease, is increasingly drawing attention [9]. The factor that may significantly affect the occurrence of these conditions is smoking. Smoking results in local changes secondary to noxious effects of the toxic compounds present in cigarette smoke, on the one hand, leading to increased secretion of proinflammatory cytokines, such as TNF-α, on the other hand [10].

Repeated exacerbations

Most patients with advanced COPD demonstrate a constant progression of the disease that is interrupted by periodic exacerbations. Exacerbations may be:

— mild — characterised by an increased demand for medications although the patient can cope without additional medical assistance
— moderate — where the patient requires medical assistance in the outpatient setting in addition to the increased demand for medications;
— severe — generally defined as a sudden worsening of signs and symptoms that requires hospitalisation [11].

Patients with severe COPD suffer from an average of 2–3 exacerbations annually [12, 13], although it seems that exacerbations mainly affect patients with increased bronchial secretion [14]. Frequent exacerbations, especially those requiring hospitalisation, adversely affect the prognosis and are associated with increased mortality [15]. The most common causes of exacerbations (50–70% of the cases) include recurrent respiratory infections, cardiovascular events, acute exacerbation of congestive heart failure, exacerbation of the signs and symptoms of pulmonary heart disease [16]. Exacerbations may also be caused by pulmonary embolism. A systematic review of five papers, four of which were published between 2000 and 2007 and one in 1992, demonstrated that pulmonary embolism was a common cause of COPD exacerbation (being observed in nearly 20% of the patients) [17]. It should be

remembered that increased exposure to environmental factors or incorrect intake of medications may also precipitate exacerbations [18].

Mental status changes

The permanent reduction of exercise capacity and the persistent respiratory and systemic symptoms considerably decrease the quality of life [19, 20]. It seems that during exacerbations the quality of life additionally deteriorates, returning to baseline within at least two weeks following resolution of the incident [21]. Frequent exacerbations also permanently reduce the quality of life [22]. In most patients the severity of the disease leads to the feeling of social isolation [12]. The patient's unfavourable position often results in depression and anxiety, which in turn augment the perception of symptoms and worsen the quality of life, leading to a vicious circle. It has been demonstrated that anxiety and depression most commonly occur together [23], and the risk of depression in patients with severe COPD is 2.5-fold higher than that in healthy individuals. The American College of Chest Physicians (ACCP) points to the coexistence of anxiety and depression with such factors, as physical disability, comorbidities, home oxygen therapy, severe dyspnoea and reduced quality of life and with social factors, such as low social status and lonesomeness [24, 25]. Both anxiety and depression are more prevalent in women [23].

Prognosis

Prognosis in severe COPD is poor and comparable to that in advanced lung cancer. Five-year survival ranges from 50% to 26%, depending on the author [26, 27]. The prognosis is even worse in patients with hypercapnic respiratory failure. For example, over 29 months of follow-up the mortality rate in this group of patients was 32% [27]. In the group requiring mechanical ventilation for acute respiratory failure in the course of COPD exacerbation the mortality rate was 24% during hospitalisation and 75% over the next five years with a higher risk of death in the elderly and patients with a history of exacerbations requiring mechanical ventilation [28]. The mortality rate in patients over 65 years of age requiring hospitalisation for COPD exacerbation was slightly more than 7% during hospitalisation and 54% over the next five years. The factors that increased mortality included reduced FEV_1 values, increased CO_2 retention on admission, ischaemic heart disease, previous hospitalisations for COPD exacerbation and smoking [29].

Other factors that affect the prognosis include the severity of dyspnoea measured on the Medical Research Council (MRS) scale, body mass index (BMI), severity of obstruction as measured by FEV_1 and exercise capacity measured in the 6-minute walk test. These factors form the basis for the BODE index (**B**ody mass index, **O**bstruction, **D**yspnoea, **E**xercise capacity) [30], which assesses the risk of exacerbations requiring hospitalisation or leading to death [31]. It should be emphasised that the mortality rate in COPD patients depends on the number of exacerbations requiring hospitalisation [32].

Inflammation in the respiratory tract is an important element affecting the course of COPD [33], and the increased sputum neutrophil count is associated with FEV_1 reduction [34]. In addition, elevated serum CRP (an inflammation marker) considerably increases the risk of myocardial infarction [35]. It should, however, be noted that a recent study suggests a limited role of CRP in the assessment of prognosis in patients with moderate to severe COPD [36].

Treatment

The principal aims of treatment in COPD are to stop progression of the disease and counteract functional deterioration of the respiratory system as measured by FEV_1. Additional goals in advanced COPD are to relieve troublesome symptoms and prevent exacerbations.

Bronchodilators

Medications used on the as-needed basis include short-acting β_2-agonists, ipratropium or combinations thereof, such as fixed combinations of fenoterol and ipratropium. Although bronchodilators act peripherally, it is believed that their long-term use is more beneficial than periodic use [2].

Prolonged-action formulations, such as long-acting β_2-agonists, long-acting anticholinergic agents and prolonged-release theophylline formulations, are recommended in long-term treatment. Results of the UPLIFT study have recently been published. The study assessed the role of tiotropium for the treatment of COPD [37]. It was demonstrated that tiotropium improved pulmonary ventilation (although it did not prevent the FEV_1 decrease) and reduced the number of exacerbations and cardiovascular mortality. It should be empha-

sised that the effect persists during treatment and tiotropium has a good safety profile and may be used long-term [37]. In the majority of patients with advanced COPD combination treatment with two or three bronchodilators is used. This is well justified, as such a combination additionally improves pulmonary function and the patients' health [2]. This relationship has been confirmed by a recently published randomised study demonstrating that formoterol and tiotropium monotherapy for 24 weeks was less effective than the combination product [38].

Inhaled glucocorticosteroids

In patients with advanced COPD suffering from frequent exacerbations moderate-dose inhaled glucocorticosteroids may be considered [2]. The use of fixed combinations containing a glucocorticosteroid and a long-acting β_2-agonist in one container seems more effective than using the two agents as two separate formulations [39, 40]. The recently published randomised study to assess the anti-inflammatory efficacy of salmeterol/fluticasone, tiotropium/fluticasone and tiotropium demonstrated that the use of formulations containing fluticasone is associated with a significant reduction in the concentrations of interleukin 8 (IL-8) and matrix metalloproteinase 9 (MMP-9) at 3 months of treatment [41]. This effect may be associated with the improvement of COPD in patients with frequent exacerbations. On the other hand it should be emphasised that using the above drugs did not affect neutrophil or eosinophil counts in the sputum or CRP and pulmonary function parameters [41]. It should, however, be taken into account that the use of inhaled glucocorticosteroids does not reduce mortality but does increase the risk of pneumonia [42]. Systemic glucocorticosteroids are recommended in exacerbations of COPD, while there is no evidence to support the efficacy of long-term treatment with these agents, especially in view of the fact that adverse reactions, including steroid myopathy, may significantly worsen the course of the disease [43].

Home oxygen therapy

The principal aim of home oxygen therapy is to increase pO_2 above 60 mmHg (which roughly corresponds to oxygen saturation values exceeding 90%) with the view to ensuring appropriate tissue oxygenation. Eligibility for home oxygen therapy is therefore determined on the basis of arterial blood gas analysis values: $pO_2 < 55$ mm Hg, $SaO_2 < 90\%$ or $pO_2 < 60$ mm Hg with coexisting pulmonary hypertension, polycythaemia (haematocrit > 55%), radiological signs of pulmonary heart disease and/or signs of right ventricular hypertrophy.

Non-invasive ventilation

The benefits of non-invasive ventilation (NIV) in exacerbations of COPD are well documented [44]. In many patients with exacerbations accompanied by respiratory failure NIV offers the possibility to avoid the use of a ventilator [45, 46]. Recent studies have shown that in patients with severe COPD combination use of NIV and oxygen therapy is more effective than oxygen therapy alone in preventing the exertional oxygen saturation drop. Unfortunately, this benefit is largely diminished by the inconvenience resulting from the need of appropriate equipment [47]. NIV is also an alternative to mechanical ventilation in terminal patients and allows to reduce the "breathing exertion" and the subjective feeling of dyspnoea [48, 49]. The benefit of NIV in palliative care in patients with advanced COPD have not been established.

Surgical methods

Surgical methods are available only for few well-selected patients (bullectomy, lung volume reducing surgery, lung transplantation) or as part of clinical studies (intrabronchial stents) [50]. Lung volume reducing surgery is aimed to improve ventilation and, as a consequence, spirometry values. Previous reports suggested the possibility of increasing exercise capacity, reducing dyspnoea and improving the quality of life. Long-term results, however, vary greatly and depend on the type of surgery (unilateral versus bilateral) and the expertise of the medical centre. Results of the National Emphysema Treatment Trial suggest no advantage of lung volume reducing surgery in improving survival of patients with COPD and a slight advantage in the group of patients with emphysema of the superior pulmonary lobes and a low baseline exercise capacity [51]. At the same time an increased mortality and a lack of functional improvement in patients with emphysema of the remaining pulmonary lobes have been observed [51].

Bullectomy offers the greatest benefit to patients with single or multiple bullae located at least the upper third of the lung with shifting and compression of the healthy pulmonary parenchyma and rapidly deteriorating dyspnoea [52]. Bullectomy generally leads to a brief improvement of restrictive signs and symptoms and increases lung ca-

pacity, exercise capacity and the quality of life, and in some cases improves hypoxaemia, hypercapnia and dyspnoea. The beneficial effects of bullectomy are maintained for at least 5 years in 33–50% of the patients. The procedure, however, is associated with a high perioperative mortality rate of up to 22% [52].

The data regarding long-term outcomes of more extensive procedures in the remaining portion of the pulmonary parenchyma are inconclusive.

According to the United Network for Organ Sharing (UNOS), COPD is the most common indication for lung transplantation [53]. Single-lung transplantation increases FEV_1 and FVC by about 50% predicted and 70% predicted, respectively, while double-lung transplantation results in an increase in FEV_1 and FVC of up to 85% predicted and 92% predicted, respectively [54]. Exercise capacity increases proportionately in both methods. The quality of life is improved considerably but only a few patients can resume full-time employment. The 1-year and 5-year survival rates are 82% and 43%, respectively [53]. The most common cause of death is transplant rejection (up to 70%) [55].

Non-pharmacologic treatment

The American Thoracic Society (ATS) has recently published recommendations on palliative care for patients with respiratory diseases [56]. In severe chronic dyspnoea general and respiratory rehabilitation treatment including muscle exercises, respiratory physiotherapy, patient education (including dietary education) and psychological support are recommended in addition to the pharmacologic treatment typical of COPD. A systematic review of randomised studies have shown that rehabilitation allows to reduce dyspnoea and the feeling of exhaustion and to improve the patient's emotional condition and disease control [57] in patients with and without respiratory failure [58, 59]. Of note is the fact that even patients with very advanced disease requiring chronic mechanical ventilation improve their activity as a result of general training and respiratory rehabilitation [60].

Opioids

The GOLD guidelines clearly point out that if severe dyspnoea persists despite optimal treatment administration of opioids should be considered [2]. It seems, however, that the use of opioids in everyday practice is largely restricted by the lack of knowledge regarding their proper use among general practitioners and respiratory medicine specialists and by the belief that they are associated with a high risk of life-threatening respiratory depression. Experience from the treatment of dyspnoea in lung cancer patients seems to question these concerns [61]. There is no consensus as to the posology of morphine for dyspnoea in patients with advanced COPD. As is the case with lung cancer patients, treatment should be started from immediate-release formulations and regularly administered doses of up to 2.5 mg. Careful dose titration allows to establish individual requirement for each patient. In cases of sudden exacerbation of dyspnoea the "rescue" dose should be 1/12 to 1/6 of the daily dose [62]. In patients with insufficient response midazolam may be added [63].

Supportive treatment

In each form of COPD, including advanced COPD, prevention of respiratory tract infection plays an important role, especially in the elderly. Influenza immunisations are recommended in all age groups with additional pneumococcal immunisations in patients over 65 years of age [2]. The justifiability of chronic treatment with mucolytic agents, including antioxidant formulations, such as N-acetylcysteine, is still being debated. It seems that there is insufficient evidence to support the effectiveness of such treatment [2, 64], although it seems justified to use this drug class in exacerbations, especially in exacerbations accompanied by impaired bronchial secretion.

Preventive or chronic use of antibiotics is not recommended.

At any stage of the disease, however, including very advanced disease, treatment of tobacco dependence is recommended. There is convincing evidence of improved pulmonary function and survival in patients who have ceased to smoke [65, 66]. An absolute prohibition to use home oxygen therapy in chronic smokers is also an important aspect.

It should be noted that in some patients with advanced COPD an improved oxygenation of blood may be achieved with almitrine, although this is not considered a standard [67].

Summary

Advanced COPD carries a very poor prognosis and patients experience severe respiratory and systemic manifestations that may persist despite ap-

propriate treatment. Everyday experience shows that many patients are not effectively assisted. It therefore seems necessary to develop national recommendations on palliative care for patients with advanced COPD.

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