Chronic Obstructive Pulmonary Disease: Official diagnosis and treatment guidelines of the Czech Pneumological and Phthisiological Society; a novel phenotypic approach to COPD with patient-oriented care

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Background. COPD is a global concern. Currently, several sets of guidelines, statements and strategies to managing COPD exist around the world.
Methods. The Czech Pneumological and Phthisiological Society (CPPS) has commissioned an Expert group to draft recommended guidelines for the management of stable COPD. Subsequent revisions were further discussed at the National Consensus Conference (NCC). Reviewers' comments contributed to the establishment of the document's final version.
Diagnosis. The hallmark of the novel approach to COPD is the integrated evaluation of the patient's lung functions, symptoms, exacerbations and identifications of clinical phenotype(s). The CPPS defines 6 clinically relevant phenotypes: frequent exacerbator, COPD-asthma overlap, COPD-bronchiectasis overlap, emphysematic phenotype, bronchitic phenotype and pulmonary cachexia phenotype.
Treatment. Treatment recommendations can be divided into four steps. 1st step = Risk exposure elimination: reduction of smoking and environmental tobacco smoke (ETS), decrease of home and occupational exposure risks. 2nd step = Standard treatment: inhaled bronchodilators, regular physical activity, pulmonary rehabilitation, education, inhalation training, comorbidity treatment, vaccination. 3rd step = Phenotype-specific therapy: PDE4i, ICS+LABA, LVRS, BVR, AAT augmentation, physiotherapy, mucolytic, ABT. 4th step = Care for respiratory insufficiency and terminal COPD: LTOT, lung transplantation, high intensity-NIV and palliative care.
Conclusion. Optimal treatment of COPD patients requires an individualised, multidisciplinary approach to the patient's symptoms, clinical phenotypes, needs and wishes. The new Czech COPD guideline reflects and covers these requirements.

Key words: COPD, clinical phenotypes, individualized care, guideline, personalized medicine

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INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) represents a serious condition that is continuously spreading worldwide. Currently, multiple treatment guidelines exist around the world[1-5]. An Expert group has been commissioned by the Czech Pneumological and Phthisiological Society (CPPS) to suggest a draft recommendation guideline for the diagnosis and treatment of stable patients with COPD. The proposed document has been revised and further discussed at the National Consensus Conference (NCC). Revisions and NCC comments contributed to the establishment of the final version of the document. The authors aimed to place this entity into the context of the actual healthcare system and clinical practice in the Czech Republic: a) majority of COPD patients are in the care of pulmonologists with unlimited access to the lung function testing and chest CT, b) all treatment options are available, and c) a patient's health insurance covers most of the treatment expenses. The emphasis is placed on personalised care influencing the symptoms and phenotypes

of each patient, considering severe comorbidities and type of medication.

DEFINITION AND PATHOPHYSIOLOGY

COPD is a treatable and preventable clinically heterogeneous syndrome with dominant respiratory symptoms and various systemic consequences[6-8]. In general, it is a prolonged inflammatory reaction of a genetically predisposed subject to long-term inhalation exposure to air pollution, harmful particles and gases, which progresses in time. The pulmonary component is associated with expiratory airflow limitation, which is not fully reversible. The flow limitation in COPD develops gradually as a result of chronic, primarily non-infectious inflammation of the airways and lung parenchyma, to which a contributing factor is both the innate and acquired immunity[9-12]. The elastic properties of the lungs are responsible for resistance and potential collapse of peripheral airways. Residual volume (RV) is typically increased at rest in COPD patients and additionally dynamic hyperinflation occurs during physical activities, which is associated with increased expiratory effort[13,14]. Systemic consequences are often found in cardiovascular, musculoskeletal and other systems[15-18]. COPD can be considered a proven pre-cancerous condition[19].

EPIDEMIOLOGY

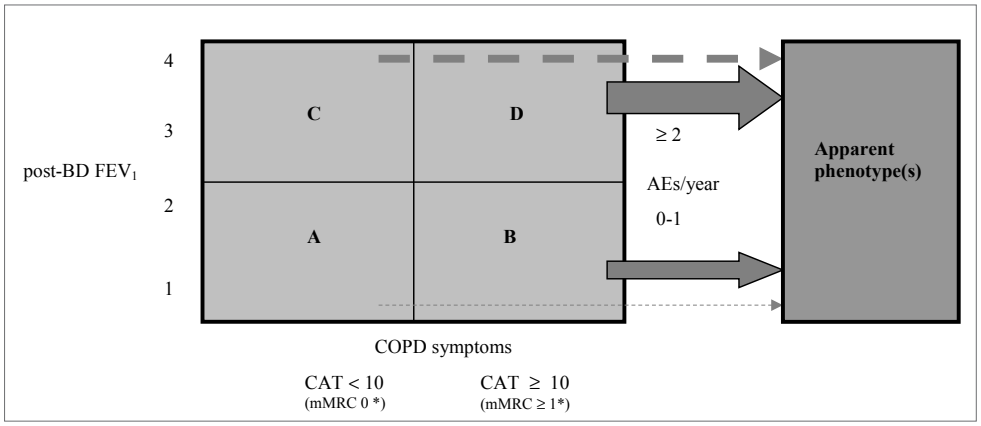
COPD is a frequent cause of mortality, increased morbidity and decreased quality of life[20,21]. Due to the aging of the population and deteriorating air pollution, the global incidence and prevalence of the disease is increasing. At least 4-6% of the population suffer from COPD in the EU (ref.[22-25]). In the Czech Republic, the recently estimated prevalence is 7-8%; approximately 16,000 patients are hospitalised each year as a result of COPD, and more than 2,500 die annually[26-28].

RISK FACTORS

Cigarette smoking remains the most important risk factor for COPD – COPD smokers tend to have more serious symptoms, increased mortality rate and faster deterioration of lung functions than in COPD non-smokers[29]. Apart from active smoking, which is responsible for 70-80% of cases of COPD onset, the following are also generally considered risk factors: environmental tobacco smoke – ETS, cannabis smoking, cigar, pipe or water pipe smoking; prolonged exposure to industrial pollution, long-term inhalation of vehicle exhaust, burnt fossil fuel and biomass fumes, low weight at birth and frequent infections during childhood[29,30]. The development of the disease is determined by the specific interaction between genetic and epigenetic factors, and effects of the environment[31,32].

DIAGNOSIS

The foundation of the modern approach in diagnosis of COPD lies within the evaluation of a patient's lung functions, symptoms, history of exacerbations and clinical phenotype. Validity of the diagnosis should be checked using a spirometry assessment. Spirometry should be performed in all symptomatic individuals (particularly in persons with a long-term risk) (ref.[1]). The essential requirement for COPD diagnosis is the presence of a post-bronchodilator (post-BD) expiratory airflow limitation,



Categories of COPD were adapted, with a minor modification (*), from the GOLD 2011 (ref.[2,34]). For a more accurate view it is recommended to classify COPD as a ratio: the severity of obstruction according to post-BD FEV_1 (1-4) / total disease category (AD). Incorporation of the degree of bronchial obstruction and GOLD 2011 category into the classification enables a more precise outlook on the patient.
For example, a patient with a moderate obstruction (post-BDT FEV_1 65%), significant symptoms (CAT 15) and repeated AEs (two per year) can be summarised as 2/D. Highly symptomatic patients with a very severe bronchial obstruction are described as 4/D, regardless of the number of AEs. A visible phenotype can be found especially in categories B and D (less so in category C and very rarely in category A).

Fig. 1. Classification of COPD.

which is defined, according to the ERS recommendations, as a decrease in the FEV_1/VC ratio below the lower limit of normal values (LLN) (ref.[30,33]).

CLASSIFICATION

When evaluating the complexity of COPD, it is recommended, in addition to the post-BD FEV_1 value detection, to monitor symptoms (using the CAT questionnaire and/or the modified MRC dyspnoea score) and the number of exacerbations. Using these parameters, it is possible to classify each patient into one of the four categories denoted A, B, C, D according to the GOLD 2011 (Fig. 1) (ref.[2,34,35]). Class A represents the early stages of the disease and can be sufficiently treated by general practitioners (GPs). In contrast, class B deserves particular attention as it consists of patients with a less pronounced deterioration in lung function, though with a substantial mortality risk – mainly due to cardiovascular and malignant causes or severity of lung emphysema that does not correspond to the FEV_1 value. Oligo-symptomatic patients, comprising class C, can be usually found in the general population, but rarely in the pulmonologist's care. The highest mortality risk is associated with class D. Subjects of this class are extremely threatened by high respiratory and cardiovascular morbidity and mortality rates. Hence the monitoring and treatment of such individuals has to be thorough and comprehensive in every aspect[36].

CLINICAL DISEASE COURSE AND PHENOTYPES

The most common clinical presentation of COPD is the sensation of breathing difficulties. Dyspnoea first occurs during high-intensity physical activities, subsequently during activities of daily living and later even at rest. Dyspnoea thus induces gradual exercise intolerance resulting in physical inactivity, lifestyle change and social isolation[37,38]. The majority of COPD patients are also affected by fatigue[39]. COPD patients commonly experience a cough, which is productive in about 2/3 of cases, defining the so-called bronchitic phenotype of COPD (ref.[40]). In contrast, patients with no chronic expectoration are often classified as emphysematous patients – predominantly with the co-occurrence of lung emphysema[6,7,41,42]. Some COPD patients simultaneously suffer from bronchiectasis, and this phenotype is known as COPD with bronchiectasis[43,44]. The relatively stable course of COPD is intermittently interrupted in some patients by attacks of acute deterioration, which exceed the regular day-to-day symptom variability. These attacks that last more than 2 days and require antibiotic treatment and/or systemic corticosteroids are called acute exacerbations (AEs). Subjects with 2 or more episodes of AE during the last year are termed frequent exacerbators[45-47]. A small pro-

Table 1. Summary of elementary COPD phenotypes.

COPD phenotypes	Basic features of COPD phenotypes
Bronchitic phenotype	The presence of productive cough (≥ 3 months/year in two or more consecutive years)
Emphysematic phenotype	Lifetime absence of productive cough and clinical signs of pulmonary emphysema*
Overlap COPD + asthma **	Major criteria: (a) strong BDT positivity (FEV_1 >15% and > 400 mL), (b) BCT positivity, (c) FENO ≥ 45-50 ppb and/or ↑eo (sputum) ≥ 3%, (d) history of asthma Minor criteria: (a) mild BDT positivity (FEV_1 > 12% and > 200 mL), (b) ↑ total IgE, (c) history of atopy - and definite COPD diagnosis
Overlap COPD + bronchiectasis	Accented, almost daily, purulent sputum expectoration, younger age, lower or no smoking burden, history of prolonged/recurrent respiratory infections, hemoptysis, HRCT confirmation of bronchiectasis - and definite COPD diagnosis
Frequent-exacerbation phenotype	Presence of frequent exacerbations (≥ 2/year) treated with ABT and/or corticosteroids
Pulmonary cachexia phenotype ***	BMI < 21 kg/m^2 – no other cause (FFMI < 16 kg/m^2 in males or < 15 kg/m^2 in females)

* It is useful (not necessary) to verify this by function assessment (TLCO, KCO < LLN, RV > ULN) for non-A patients and by chest HRCT if targeted therapy of emphysematous phenotype is planned

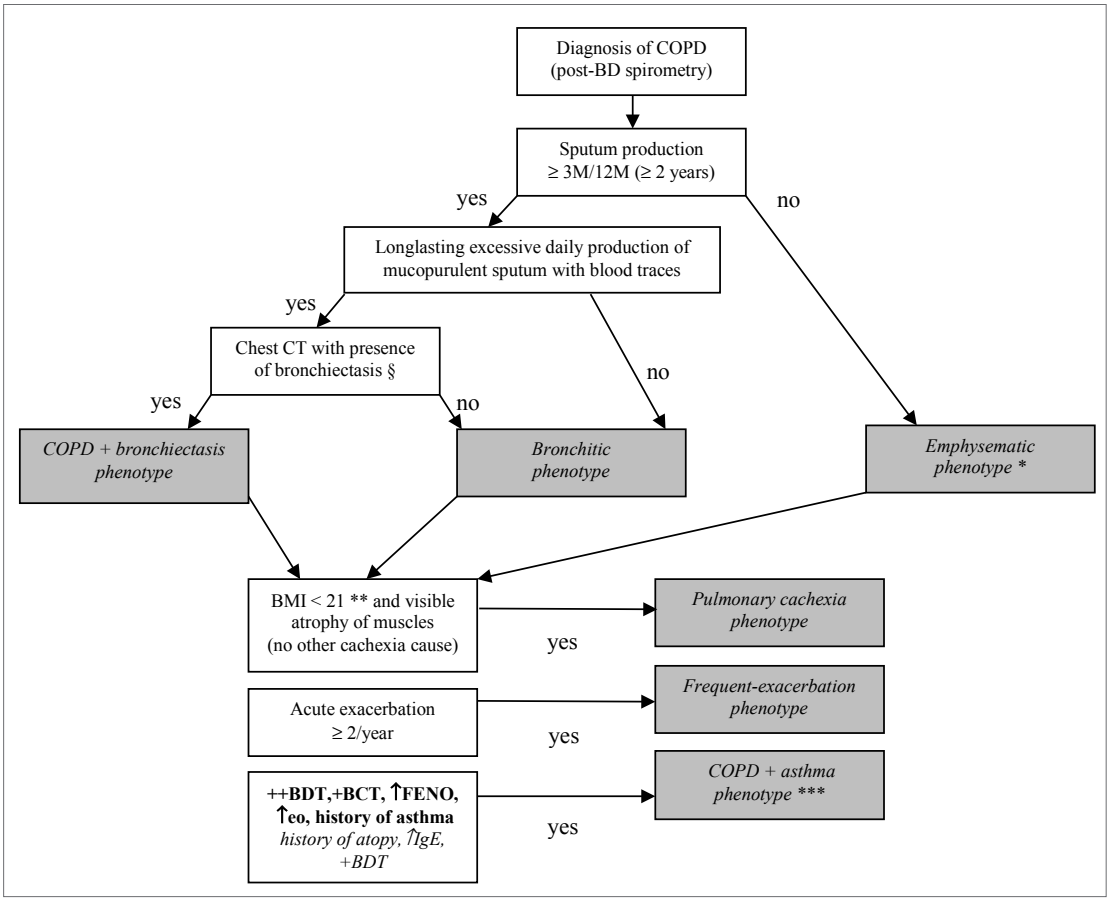
** COPD + asthma phenotype is confirmed by the presence of 2 major criteria or 1 major plus 2 minor criteria

*** FFMI can be measured by densitometry, antropometry or bioelectrical impedance analysis

portion of COPD patients display a tendency towards gradual decrease in body weight (BMI < 21), particularly in fat-free mass i.e. muscle tissue (decrease in fat-free mass index (FFMI) < 16 kg/m^2 in men, 15 kg/m^2 in women). These patients, excluding other causes of muscle tissue loss, define the COPD phenotype of pulmonary cachexia[17,41,48]. An important phenotype is COPD overlapping bronchial asthma that is characterised by the presence of either 2 major criteria, or 1 major and at least 2 minor criteria showing a persistent combination of clinical presentation that is typical for both conditions[3,8,42,49-51]. Table 1 gives an overview of those 6 basic COPD phenotypes, which occasionally might occur simultaneously in clinical practice (e.g. emphysematic phenotype and cachexia, or bronchitic phenotype and recurrent AE). Severe forms of COPD can lead, usually after many years, towards the development of chronic respiratory failure which is often associated with pulmonary hypertension leading towards an overload or failure of the right ventricle. Individuals in an advanced stage of the disease are referred to as having a terminal COPD. COPD is often accompanied by other diseases or comorbidities: lung cancer, ischemic heart disease, heart failure, depression, osteoporosis, anaemia, peptic ulcer and obstructive sleep apnoea[2,15,52,53].

PERSONALISED DESCRIPTION OF THE DISEASE

COPD is a syndrome with multiple clinical forms – phenotypes (Table 1). Each form represents a different approach to treatment. More accurate description of the disease increases the likelihood that effective treatment can be carried out[8,34-36]. Therefore, this document recommends classifying each COPD patient individually according to the bronchial obstruction (1. - 4.degree of the post-BD FEV_1) and disease category (A-D) (ref.[2,34]). An inclusion of the bronchial obstruction degree and disease category during diagnosis enables a more precise overview of each individual patient (Fig. 1). Patients should be classified into categories during the stable phase of the disease. As COPD progresses, the initial classification



* It is useful (not necessary) to verify this by function assessment (TLCO, KCO < LLN, RV > ULN) for all non-A patients and by chest CT if you plan the targeted therapy of emphysematous phenotype

§ CT scan only for patients with chronic excessive daily production of mucopurulent sputum with blood traces

** FFMI assessment is not available in routine clinical practice, so we recommend simple use of BMI

*** COPD + asthma phenotype can be confirmed by the presence of two major criteria (Bold) or *one major plus two minor criteria* (*Italic*)

Fig. 2. Schematic algorithm for recognition of COPD phenotypes intended for outpatient practice of pulmonologist.

might change, either due to effective treatment or deterioration of the disease. Furthermore, it is useful to include an accurate description of clinical phenotype(s) of the patient (Table 1, Fig.1 and 2) together with checking for the presence of respiratory failure including the list of detected risk factors and relevant comorbidities[2,52]. A patient can be considered being at a terminal stage when the life expectancy is less than 6 months, provided that the following condition also applies: dyspnoea at rest, which does not respond to pharmacotherapy resulting in a daily regime in bed + armchair; gradual clinical progression of the disease and permanent presence of hypoxemia[54,55]. If the patient's state closely approaches death (in weeks/days/hours), it is called end-of-life phase of the disease. The patient can be determined as being in the end-of-life phase: a) following a thorough consideration of all data available, b) following a consensus discussion of the disciplinary committee and c) following a discussion with the patient's family.

TREATMENT STRATEGY

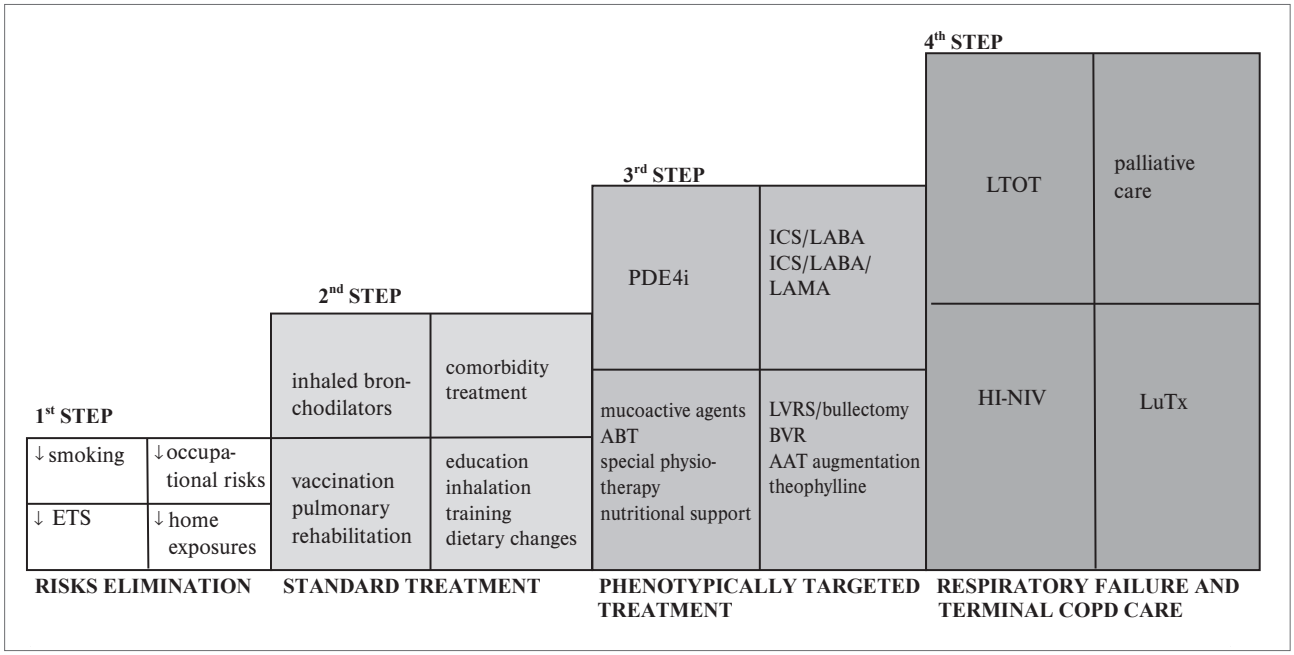
Main aims of COPD treatment are to reduce symptoms, avert the natural progression of the disease, improve quality of life, enhance physical activity, prevent complications and adverse consequences, and increase life expectancy[2]. The keystone of successful therapy is to eliminate the inhalation risks. Comprehensive therapeutic intervention in COPD patients comprises both pharmacological and non-pharmacological steps following current international recommendations and guidelines[1,2,4]. Treatment of COPD patients is thus generally determined by the functional impairment (1-4), disease category (A-D) and the phenotype(s) presence of the disease, while considering the presence of complications and comorbidities. Treatment recommendations can be divided into 4 steps (Fig. 3):

Elimination of risks (1st step): Smoking cessation significantly decelerates the declination in lung function[4,5,56,57]. In contrast, it has been clearly demonstrated that continuing exposure to smoke considerably accelerates disease progression, independently of its initial stage[12,57]. The effect of reduction of other risk factors has not been studied in detail; however, it is expected to be associated with a positive impact on the patient. Smoking cessation interventions have proved beneficial even in patients with severe COPD (ref.[56]).

Standard treatment (2nd step): Standard treatment is indicated for all COPD patients regardless of their phenotype. It includes both pharmacological (mainly inhalation drugs and vaccination) and non-pharmacological steps (physical activity, pulmonary rehabilitation, education and training of inhalation techniques). It has been shown that asymptomatic individuals with mild obstructive ventilatory impairment do not respond well to the therapy, therefore only elimination of risk factors is advisable in this case. The mandatory part of standard treatment are interventions targeted to influence serious comorbidities[2].

Standard pharmacological treatment

The foundations of standard pharmacological treatment in stable COPD patients are inhalation bronchodilators. The desired effect of treatment is a symptomatic



This procedure should be applied to all patients; in patients with a non-pronounced phenotype the intervention will initially be limited to risk elimination and standard treatment, while patients with a pronounced phenotype and the presence of respiratory insufficiency should be treated using all four treatment steps.

Fig. 3. Simplified four-step approach to management of stable COPD.

relief in dyspnoea, increased exercise tolerance and increased quality of life. Most bronchodilators have also been proved beneficial in reducing the occurrence of AE. It has not been clearly demonstrated that these drugs have a positive influence on deceleration of the lung function decline and disease progression or on increasing life expectancy, though it is likely[4,58-60]. Thorough education and repetitive checks of correct inhalation technique are required in all patients, as over 50% of patients use the drugs incorrectly[61].

Inhaled bronchodilators

A combination of both types of bronchodilators (beta2-agonists and muscarinic antagonists) has a more significant benefit than a dosage increase of a single type of agent[1,2,4,62,63]. Short-acting inhaled drugs (short-acting beta2-agonists (SABA) – salbutamol, terbutalin, fenoterol and short-acting inhaled muscarinic antagonist (SAMA) – ipratropium) constitute symptom-relieving treatment (it is not a preventative long-term treatment), or the main drug of choice for oligo-symptomatic patients. Available treatment guidelines describe the use of long-acting inhalation drugs (twice daily: long-acting muscarinic antagonist (LAMA) - aclidinium, long-acting beta2-adrenoreceptor agonist (LABA) - formoterol, salmeterol and once daily: ultra-long-acting muscarinic antagonist (U-LAMA) - tiotropium, glycopyrronium, umeclidinium and ultra-long-acting beta2-adrenoreceptor agonist (U-LABA) - indacaterol, olodaterol, vilanterol) in symptomatic patients with post-BD FEV_1 60-80% of the predicted value, and these are highly recommended in symptomatic patients with post-BD FEV_1 <60% of the predicted value[1]. The choice of specific agent depends on the physician, or patient's preference[1,2,4,58,59,64-73].

Additional components of the standard treatment

Pulmonary rehabilitation is an important part of standard non-pharmacological treatment, which includes patient's education, physiotherapy, occupational therapy (focused on activities of daily living – ADL), nutritional and psychosocial support[5,74]. Physiotherapy comprises exercise training (endurance and strength) and techniques of respiratory physiotherapy. It is recommended that all patients with COPD who are symptomatic are involved in exercise training (3-5 times per week, 20-60 min, 6-8 weeks) regardless of lung function[4]. However, exercise training becomes a mandatory part of standard treatment in patients with FEV_1 <50% of the predicted value (for less symptomatic cases of COPD, regular physical activity is often sufficient). Training sessions should be supervised by a physiotherapist at least twice a week and the remaining sessions (1-3 times per week) can be performed either at the patient's home or at a community rehabilitation centre[1]. The respiratory physiotherapy techniques include re-education of the breathing stereotype, techniques enhancing chest expansion, airway clearance techniques and ventilatory muscle training. The comprehensive pulmonary rehabilitation is further specified by a separate national guideline.

Vaccination: Vaccination is another component of standard treatment. Flu vaccination is essential for each COPD patient – every year from September to December before the regular onset of the annual pan-European epidemic. Although the effectiveness of pneumococcal vaccination remains controversial, the pneumococcal vaccine has recently been recommended for COPD patients aged over 65 years and for younger subjects with severe airflow limitation and/or significant comorbidity such as cardiac disease.

There is little evidence to show the effectiveness of other vaccinations (pertussis, heamophilus), these should therefore not be included in standard treatment[2,4,75-78].

Treatment of comorbidities: In addition to the treatment of COPD, it is necessary to consider reasonable and effective therapeutic interventions for all comorbidities[2].

Table 2. Overview of phenotypically targeted treatment.

COPD phenotypes	Phenotypically targeted treatment
Bronchitic phenotype	PDE4 inhibitor (roflumilast), mucoactive agents (NAC, erdosteine, carbocysteine), ABT (azithromycin, clarithromycin, moxifloxacin), chest physiotherapy (e.g. airway clearance techniques)
Emphysematic phenotype	LVRS (upper lobes emphysema), bullectomy (≥ 30% lung volume impairment), BVR (heterogeneous emphysema, without collateral ventilation), AAT augmentation (homogeneous and/or panlobular emphysema), theophylline
Overlap COPD + bronchiectasis	Mucoactive agents (NAC, erdosteine, carbocysteine, hypertonic saline), ABT (azithromycin, clarithromycin, moxifloxacin and other according microbiology results), chest physiotherapy (e.g. airway clearance techniques)
Overlap COPD + asthma	ICS + LABA, ICS + LABA + LAMA, antileukotrienes
Frequent-exacerbation phenotype	PDE4 inhibitor (roflumilast), ICS + LABA, ABT
Pulmonary cachexia phenotype	Pulmonary rehabilitation (with strength training) + nutritional support (anabolics only at a lower value of testosterone)

Phenotype-specific treatment (3rd step)

Phenotype-specific treatment should be considered, particularly in patients of B and D categories (Fig. 1), in addition to the standard treatment (Table 2). It is necessary to emphasise that the phenotypes described in Table 1 can interact or evolve over time. Phenotype description should include all phenotypes found in a specific patient and all of those phenotypes should be then influenced by therapy (Fig. 4). On the other hand, patients might lack a clearly distinctive phenotype, especially in the initial A-category of COPD, and the treatment will comprise only the first two steps in such patients.

In patients with high occurrence of exacerbations (especially if post-BD FEV_1 ≤60% of the predicted value) it is advisable to include a combination of LABA and inhaled corticosteroid (ICS) in the therapy[3,47,59,60,79]. Evidence for the effectiveness of LAMA + ICS is still lacking.

The clinical overlap of COPD and bronchial asthma is the second phenotype where the combination therapy (LABA + ICS) has proved to be beneficial: LABA + ICS are the first-choice treatment of this phenotype. A combination of ICS + LABA + LAMA represents another recommended therapy of this phenotype. Subsequently, the therapy can be complemented with antileukotrienes[3,80-82].

Roflumilast, a selective inhibitor of phosphodiesterase 4 (PDE4i), has been clearly demonstrated as beneficial in patients with a combination of the bronchitic phenotype and frequent exacerbation phenotype, who have post-BD FEV_1 <50% of the predicted value. Roflumilast also reduces the rate of moderate and severe AEs, and enhances functional parameters (due to its anti-inflammatory actions) – FEV_1 in particular[83,84].

Patients (≤50 years) suffering from emphysema phenotype (usually with a homogenous panlobular emphysema or predominantly lower lobe emphysema) should be screened for alpha1-antitrypsin (AAT) deficiency. AAT-deficient patients with FEV_1 between 30-60% of the predicted value, who are not active smokers, having a severe form of deficit (serum concentration <0.5 g/L) caused by a homozygous mutation in the protease inhibitor (Pi) gene encoding AAT, PiZZ (common deficiency allele encoding a G342K mutation) or Pinull (nil detectable), should be treated with a regular application of AAT augmentation therapy (once per 1-2 weeks intravenously) (ref.[85,86]).

Treatment of emphysematic patients with the presence of large bullae consists of resection of the bullae – so called bullectomy (especially if it occupies at least 1/3 of

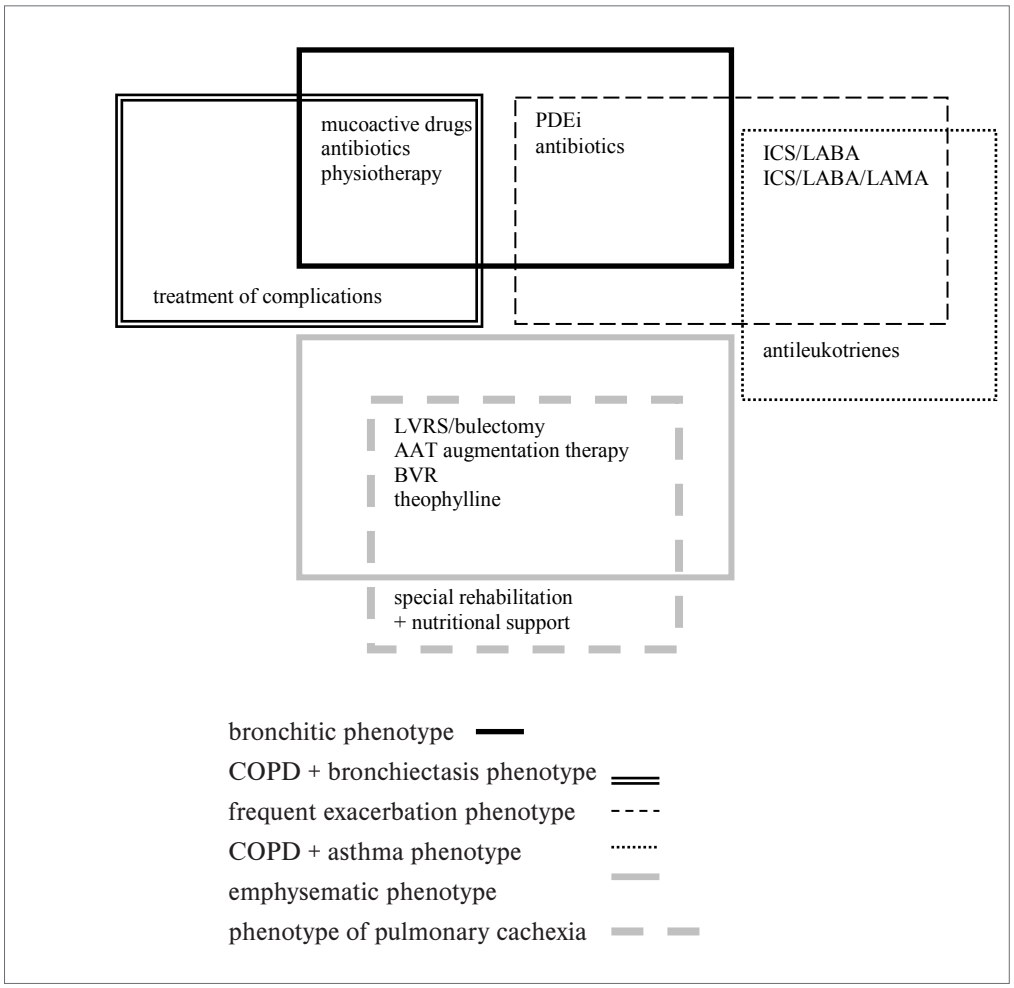


Fig. 4. Simplified diagram of phenotype-specific COPD treatment.

the hemithorax or behave expansively and deteriorate in symptoms) (ref.[87,88]).

Patients with a heterogeneous type of lung emphysema that is affecting apical parts of the lungs and with preferably low exercise tolerance should be considered for lung volume reduction surgery (LVRS), particularly in the presence of pulmonary hyperinflation RV ≥200% of the predicted value. Other inclusion criteria for LVRS indication are: mMRC dyspnoea score 3-4, absence of active smoking, emphysema phenotype with an upper lobes predominance, low exercise tolerance but not complete inactivity (pre-surgery 6MWD ≥140 m), FEV_1 20-45% of the predicted value, TLCO ≥20% of the predicted value, $PaCO_2$ ≤8 kPa, PaO_2 ≥6 kPa and BMI 16-31 kg/m^2 (ref.[88-90]). Patients, who cannot and/or are not willing to undergo the surgical treatment method (LVRS), can be offered bronchoscopic volume-reduction (BVR) method, preferably as part of a clinical trial[91,92].

Nutritional support should be given to patients with the pulmonary cachexia phenotype, preferably in combination with a rehabilitation programme. Nutritional specialists choose the type and content of the nutritional therapy based on the assessment of energy requirements of the patient, residual oral intake, and the possibility of oral or enteral food intake, which are always preferred over parenteral intake[93,94].

Antibiotic therapy (ABT) may have a positive effect during stable disease in selected phenotypes: in patients with an increased production of phlegm – bronchitic phenotype; in patients with frequent exacerbations; and also in the COPD with bronchiectasis. Some positive effects were observed, particularly with macrolides, most prominently azithromycin, but also with the respiratory fluoroquinolone moxifloxacin[3,95-103].

Long-term application of muco-active agents (erdosteine, carbocysteine, N-acetylcysteine) may be considered for symptomatic persons with the bronchitic phenotype and COPD patients with bronchiectasis[3,104,105]. A complete recommendation regarding the phenotype-specific treatment is given in Table 2 and Fig. 4.

Treatment of respiratory insufficiency and palliative care in COPD (4th step)

Modern personalised medicine provides many effective approaches to treatment of patients with chronic hypoxemia or hypoxemia + hypercapnia (i.e. oxygen therapy, home non-invasive ventilation and lung transplantation). Specific therapeutic guidelines exist even in the case of further progression of the disease into terminal COPD (palliative care) (Fig. 3).

Oxygen therapy should reflect the stage of the disease, and is mainly indicated in the following cases:

1. Oxygen is most often supplied to patients as a long-term home-based oxygen therapy (LTOT; ≥16 h per day) in patients with chronic respiratory failure, provided they satisfy the relevant indication criteria. LTOT is one of the methods which improve the survival rate of hypoxemic patients. Among the principal indication criteria for LTOT are the results of arterial blood gases (in addition to the absence of active smoking, good compliance, and the presence of the standard therapy reflecting the category and phenotype of disease). The main criterion is PaO_2 below 7.3 kPa with no signs of hypercapnia deterioration. If PaO_2 is 7.3-8.0 kPa, LTOT is considered when other clinical findings are confirmed (ECG, radiological and/or echocardiographic signs of pulmonary hypertension, a secondary polyglobulia, and/or substantial desaturations during sleep or exercise). The topic of LTOT has been recently updated in the Czech Republic in the form of a national guideline[106].

2. Oxygen therapy during pulmonary rehabilitation regardless of the presence of exercise-induced hypoxemia. There is no noticeable effect on survival rate, however a reduction in dynamic hyperinflation and enhancement in ventilation response to exercise have been demonstrated, enabling a greater level of aerobic activity[107].

3. Oxygen supplementation during airflight is another indication of therapeutic use of oxygen in patients with a stable phase of COPD. Oxygen therapy should be considered in all individuals with either SpO_2 <92% at rest or SpO_2 <84% during 6MWT (ref.[108]).

The use of long-term home-based non-invasive ventilation (NIV) is the method of choice in stable COPD patients with chronic hypercapnic respiratory failure, i.e. most frequently in patients classed es 4/D. The use of high inspiratory pressures, so-called high-intensity NIV (HI-NIV), has shown clinical benefits. The aim of HI-NIV is to reach adequate nearly alveolar ventilation through the use of high inspiratory pressures (up to 25-30 cm H_2O) at the respiratory rate that approaches the spontaneous rate of the patient (usually around 20-25 breaths per min). Patients who are indicated for HI-NIV have a symptomatic daily hypercapnia (>55 mmHg) and at least 2 episodes of hypercapnic respiratory failure per year with the need of NIV support, or patients who have hypoventilation during sleep regardless of oxygen-therapy. It has been demonstrated that HI-NIV improves $PaCO_2$, slows down the accelerated decline in lung functions, enhances one's ability to exercise, improves quality of life and decreases the rate of hospital admissions due to the exacerbation of hypercapnic respiratory failure[109-111].

Lung transplantation is advised for non-smoking patients with high BODE score. Patients with BODE 5 should be monitored, whereas patients with BODE 7-10 are prompted to have transplantation provided that they satisfy one or more of the following criteria: FEV_1 ≤20% and/or TLCO ≤20% of the predicted value, chronic hypoxemia, history of a severe acute exacerbation with hypercapnia ($PaCO_2$ >6.6 kPa) and pulmonary hypertension with failing right ventricle[87,88].

Palliative care in COPD

Terminal phase of COPD is characterised by recurrent attacks of acute deterioration of chronic respiratory failure, right ventricle failure, presence of lung infection and the decompensation of other severe comorbidities. Patients in terminal COPD can be similarly identified as patients who are indicated for transplantation (BODE 7-10). Therefore, they constitute a similar group – the main difference is represented by contraindications for

lung transplantation in the group of patients who are indicated for palliative therapy. These situations often lead to a point where treatment boundaries (described below) for the patient need to be defined. Decision on the boundary establishment is carried out during the multidisciplinary team meeting and agreed with the consent of the patient's family and patient, providing he/she is fully conscious and capable of making a decision.

The treatment boundaries are designated as: **DNR/DNI** – do not resuscitate and/or intubate, *NIV max* – non-invasive ventilation is defined as the last means of support, **Withholding** – is stopping the treatment going any further (e.g. no further transfusions, no further catecholamine support, no use of elimination methods, the absence of surgical interventions) **De-escalation or withdrawal** of currently supplied care – for example the discontinuation of oxygen substitution (i.e. decrease of FiO_2 to 21%), discontinuation of catecholamine support, weaning from the ventilation support[54,55].

An important part of palliative care is the administration of opioids (orally, transdermally or parenterally), first justified in discussion with the patient's family or the patient himself/herself. The main rationale for the use of opioids in this situation is sedation and inhibition of pain (e.g. from compressive spinal fractures), and otherwise unmanageable sensation of dyspnoea. Monitored administration of benzodiazepines is also effective at this stage of the disease. Very severe dyspnoea treatment can be supported with inhalation of furosemide and several other non-pharmacological methods – e.g. by cooling the face[54,55,112-114].

LIMITATIONS

This document has several limitations. In terms of methodology, we analysed the data in published literature without further evaluation of the quality and relevance of the data source.

Experience and opinions of the Expert group, together with the actual possibilities and resources of the healthcare system in the Czech Republic constituted an important criterion for the establishment of this guideline. Furthermore, we did not form or add other clinical entities of COPD into the basic phenotype schedule, because of the lack of information about the patients' clinical and phenotypic relevancies (e.g. combination of pulmonary fibrosis and emphysema, COPD-obstructive sleep apnoea overlap or rapid decliners). Finally, it should be noted that the majority of our recommendations need to be validated in future clinical trials. However, we hope that these limitations do not affect our basic phenotypically targeted and personalised recommendations.

CONCLUSION

Optimal treatment of patients with COPD requires a tailored and multidisciplinary approach focused on the patient's symptoms, risks, needs and wishes. The treatment should consider the personal, social and cultural factors of each patient (called personalised medicine). It should cover all aspects of this multi-organ syndrome, simultaneously its systemic consequences and associated comorbidities. It is essential that the treatment includes participation of the patient and the attending pulmonologist, but also involves the patient's family members and other healthcare professionals such as general practitioners, physiotherapists, psychologists and nutritionists[115]. Educational interventions are needed to improve the implementation of guideline-based management. The main components of therapy include the elimination of risk factors, standard treatment focused on reducing the symptoms and impact of the disease, together with an intervention of clinically relevant comorbidities and phenotype-specific treatment with potential therapy of respiratory failure. A necessary assumption is the interaction between the patient and physician, and patient's continual education and training. If the disease develops as far as the terminal stage, it is advisable to further expand the relationship and to determine the future treatment care boundaries in time[55,61,115].

ABBREVIATIONS

AAT, Alpha-1 antitrypsin; ADL, Activity of daily living; AE, Acute exacerbation; ABT Antibiotic therapy; BCT, Bronchial challenge test; BDT, Bronchodilator test; BMI, Body mass index; BODE, Index of body composition, bronchial obstruction, dyspnoea and exercise capacity; BVR, Bronchoscopic lung volume reduction; CAT, COPD Assessment Test; COPD, Chronic obstructive pulmonary disease; CPPS, Czech Pneumological and Phthisiological Society; CT, Computer tomography; DNR/DNI, Do not resuscitate/intubate; ECG, Electrocardiograph; Eo, Eosinophil; ETS, Environmental tobacco smoke; FEV_1, forced expiratory volume in 1 second; FENO, Fractional exhaled nitric oxide; FFMI, Fat-free mass index; FiO_2, Fraction of inspired oxygen; GPs, General practitioners; HI-NIV, High-intensity non-invasive ventilation; ICS, Inhaled corticosteroid; IgE, Immunoglobulin E; KCO, Carbon monoxide uptake rate; LABA, Long-acting beta2-agonist; LAMA, Long-acting muscarinic antagonist; LLN, Lower limit of normality; LTOT, Long-term oxygen therapy; LuTx, Lung transplantation; LVRS, Lung volume reduction surgery; M, Month; mMRC, Modified Medical Research Council dyspnoea scale; NAC, N-acetylcysteine; NCC, National Consensus Conference; $PaCO_2$, Partial arterial pressure of carbon dioxide; PaO_2, Partial arterial pressure of oxygen; PDE4i, Phosphodiesterase 4 inhibitor; RV, Residual volume; SABA, Short-acting beta2-agonist; SAMA, Short-acting muscarinic antagonists; SpO_2, Oxygen saturation; TLCO, Transfer factor of the lung for carbon monoxide; ULN, Upper limit of normality; VC, Vital capacity; 6MWD, Six minute walking distance; 6MWT, Six minute walking test; ↑, Rise; +, Light positivity; ++, Strong positivity;

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AUTHORS' CONTRIBUTION

VK, JCH and VZ suggested a draft guideline. VK, JCH, VZ, KN, JK and VS revised and edited the proposed document. VK, JCH, KN and VS organized the National Consensus Conference. VK, JCH, VZ, JZ1, JZ2, JZ3, KN and SP established the final version. VK, KN, JZ1 and JZ2 prepared the paper for submission. KH and VK prepared validation of these recommendations.

CONFLICT OF INTEREST STATEMENT

Author's conflict of interest disclosure: The authors stated that there are no conflicts of interest regarding the publication of this article. VK, JCH, VZ, KN, JK, JZ3 and VS have been involved in advisory board committee and/or performed as a keynote speaker and/or have attended further postgradual education on one or more occasions during last 3 years that was sponsored either by AstraZeneca, Boehriger Ingelheim, GlaxoSmithKline, Nycomed-Takeda, Novartis, Pfiser or Respironics. JZ1, KH, SP and JZ2 state that no sponsorship donation has been received, and declare that no other, real or perceived, conflict of interests exists in relation to the manuscript.

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