

Chronic obstructive pulmonary disease – diagnosis and management of stable disease; a personalized approach to care, using the treatable traits concept based on clinical phenotypes. Position paper of the Czech Pneumological and Phthisiological Society

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This position paper has been drafted by experts from the Czech national board of diseases with bronchial obstruction, of the Czech Pneumological and Phthisiological Society. The statements and recommendations are based on both the results of randomized controlled trials and data from cross-sectional and prospective real-life studies to ensure they are as close as possible to the context of daily clinical practice and the current health care system of the Czech Republic. Chronic Obstructive Pulmonary Disease (COPD) is a preventable and treatable heterogeneous syndrome with a number of pulmonary and extrapulmonary clinical features and concomitant chronic diseases. The disease is associated with significant mortality, morbidity and reduced quality of life.

The main characteristics include persistent respiratory symptoms and only partially reversible airflow obstruction developing due to an abnormal inflammatory response of the lungs to noxious particles and gases. Oxidative stress, protease-antiprotease imbalance and increased numbers of pro-inflammatory cells (mainly neutrophils) are the main drivers of primarily non-infectious inflammation in COPD. Besides smoking, household air pollution, occupational exposure, low birth weight, frequent respiratory infections during childhood and also genetic factors are important risk factors of COPD development. Progressive airflow limitation and airway remodelling leads to air trapping, static and dynamic hyperinflation, gas exchange abnormalities and decreased exercise capacity. Various features of the disease are expressed unequally in individual patients, resulting in various types of disease presentation, emerging as the “clinical phenotypes” (for specific clinical characteristics) and “treatable traits” (for treatable characteristics) concept. The estimated prevalence of COPD in Czechia is around 6.7% with 3,200–3,500 deaths reported annually.

The elementary requirements for diagnosis of COPD are spirometric confirmation of post-bronchodilator airflow obstruction (post-BD FEV₁/VCmax <70%) and respiratory symptoms assessment (dyspnoea, exercise limitation, cough and/or sputum production). In order to establish definite COPD diagnosis, a five-step evaluation should be performed, including: 1/ inhalation risk assessment, 2/ symptoms evaluation, 3/ lung function tests, 4/ laboratory tests and 5/ imaging. At the same time, all alternative diagnoses should be excluded. For disease classification, this position paper uses both GOLD stages (1 to 4), GOLD groups (A to D) and evaluation of clinical phenotype(s). Prognosis assessment should be done in each patient. For this purpose, we recommend the use of the BODE or the CADOT index.

Six elementary clinical phenotypes are recognized, including chronic bronchitis, frequent exacerbator, emphysematous, asthma/COPD overlap (ACO), bronchiectases with COPD overlap (BCO) and pulmonary cachexia. In our concept, all of these clinical phenotypes are also considered independent treatable traits. For each treatable trait, specific pharmacological and non-pharmacological therapies are defined in this document. The coincidence of two or more clinical phenotypes (i.e., treatable traits) may occur in a single individual, giving the opportunity of fully individualized, phenotype-specific treatment.

Treatment of COPD should reflect the complexity and heterogeneity of the disease and be tailored to individual patients. Major goals of COPD treatment are symptom reduction and decreased exacerbation risk. Treatment strategy is divided into five strata: risk elimination, basic treatment, phenotype-specific treatment, treatment of respiratory failure and palliative care, and treatment of comorbidities.

Risk elimination includes interventions against tobacco smoking and environmental/occupational exposures. Basic treatment is based on bronchodilator therapy, pulmonary rehabilitation, vaccination, care for appropriate nutrition, inhalation training, education and psychosocial support. Adequate phenotype-specific treatment varies phenotype by phenotype, including more than ten different pharmacological and non-pharmacological strategies. If more than one clinical phenotype is present, treatment strategy should follow the expression of each phenotypic label separately. In such patients, multicomponental therapeutic regimens are needed, resulting in fully individualized care.

In the future, stronger measures against smoking, improvements in occupational and environmental health, early diagnosis strategies, as well as biomarker identification for patients responsive to specific treatments are warranted. New classes of treatment (inhaled PDE3/4 inhibitors, single molecule dual bronchodilators, anti-inflammatory drugs, gene editing molecules or new bronchoscopic procedures) are expected to enter the clinical practice in a very few years.

Key words: COPD; position paper; clinical phenotypes; treatable traits; bronchodilators; individualized care; personalized medicine

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1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) represents a serious disease or, more precisely, a heterogeneous syndrome, affecting hundreds of millions of people world-

wide¹. The disease is associated with significant mortality, morbidity and reduced quality of life.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) regularly (on a yearly basis) publishes a report dedicated to strategy of COPD management. This report is used by physicians worldwide as a basic strategy document, defining basic terms and concepts. However, several national or international COPD management guidelines or recommendations have been developed and published previously, that more precisely respect the scope, structure and individual characteristics of local healthcare systems¹⁻¹⁰. In contrast to other guidelines, this position paper is based on clinical phenotypes of COPD and employs the treatable traits concept for COPD treatment.

Experts from the Czech national board of diseases with bronchial obstruction have been commissioned by the Czech Pneumological and Phthisiological Society (CPPS) in order to draft an update on previous (2013) recommendations for diagnosis, management and treatment of stable COPD (ref.¹¹). The updated document has been discussed and revised at the Czech National Consensus Conferences in November 2018 (Hradec Kralove), April 2019 (Hradec Kralove), and June 2019 (Prague). After incorporation of the comments, the prefinal version of the document has been established. Final polishing of this official position paper has been performed by members of CPPS from January to August 2020 (during three expert meetings and several web based session).

The intention of the authors was to set this evidence-based position paper into the context of daily clinical practice and the current health care system of the Czech Republic. Currently, all treatment components are available in the Czech Republic; mandatory health insurance of all residents covers most of the treatment expenses including rehabilitation program, alpha-1 antitrypsin augmentation, lung transplantation, long-term oxygen treatment, and high-intensity non-invasive ventilation support. Above that, more than 90 % of care for patients with COPD is concentrated in the hands of respiratory specialists. This means, that literally almost every patient with COPD has unlimited access to lung CT scanning, advanced lung function assessment and full-scale phar-

macological and non-pharmacological treatment available in the Czech Republic¹¹. Special emphasis is placed on complex management of COPD and related comorbidities, personalized approach to care and on new scientific knowledge published since the previous Czech COPD management document¹¹.

2. DEFINITION AND PATHOPHYSIOLOGY

COPD is a preventable and treatable disorder that is characterized by persistent respiratory symptoms and airflow limitation that is due to lower airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles and/or gases. Besides these risk exposures, host factors (genetic factors, altered childhood lung growth, and accelerated premature aging) predispose individuals to develop COPD. The most common respiratory symptoms include breathlessness and chronic cough with or without sputum production. The above mentioned symptoms may be under-reported by COPD patients^{1,12-15}.

COPD is a heterogeneous condition with a number of pulmonary and extrapulmonary clinical features and concomitant chronic diseases. The pulmonary component of COPD is characterized by a partially reversible airflow limitation developing gradually due to prolonged abnormal inflammatory response and/or tissue abnormalities of the airways and lung parenchyma to noxious particles and gases^{1,16}. Oxidative stress, protease-antiprotease imbalance and increased numbers of pro-inflammatory cells (neutrophils, alveolar macrophages, T-lymphocytes and innate lymphoid cells) are the main drivers of primarily non-infectious inflammation in COPD (ref.¹⁷). A majority of patients with COPD have a predominantly neutrophilic type of inflammation, however, approximately every one of four/five patients presents with concurrent eosinophilic inflammation^{18,19}.

The chronic inflammation leads to accelerated and progressive breakdown of elastic fibers, peribronchial fibrosis, destruction of alveolar walls, microvessels and small airways, airway remodelling and mechanisms of chronic mucus hypersecretion^{17,21,22}. Progressive airflow limitation and airway remodelling leads to air trapping, static and dynamic hyperinflation, gas exchange abnormalities and to decreased exercise capacity and physical activity^{22,23}. The above listed mechanisms are expressed unequally and variably in individual patients, resulting in various types of clinical presentation. Nowadays, the “clinical phenotypes” concept is emerging, meaning “a single or combination of disease attributes that describe differences between individuals as they relate to clinically meaningful outcomes” to differentiate between various disease patterns and their clusters in specific subpopulations of COPD individuals^{3,11,24-26}.

Multiple systemic effects have been described in patients with COPD. Increased levels of circulating inflammatory mediators and acute-phase proteins are drivers or at least contributors to the development of comorbidities, including cardiovascular diseases, skeletal muscle dysfunction, osteoporosis, depression, cachexia, diabetes mellitus

or sleep apnoea syndrome²⁷⁻³². In consequence, persistent systemic inflammation is associated with higher risk of exacerbation and mortality³³. COPD is also considered a proven pre-cancerous condition^{27,34}.

Besides the already understood mechanisms, pulmonary cellular senescence is now considered a potent driver mechanism of COPD pathogenesis. Senescent cells secrete pro-inflammatory proteins and molecules, leading to chronic inflammation. Understanding the process of pulmonary cellular senescence may allow us to identify new therapeutic targets in the future³⁵.

3. RISK FACTORS

Tobacco smoking – including second-hand smoke and passive exposure – is considered the main cause of COPD. Besides smoking, other environmental exposures such as household air pollution, occupational particulates, ozone and ambient particulate matter were found important risk factors of COPD development³⁶.

There are also studies showing association between airflow limitation in childhood and greater risk of COPD and asthma-COPD overlap syndrome (ACOS) development in adulthood³⁷. The higher likelihood of developing COPD was also observed in low birth weight infants^{38,39}, childhood asthma^{40,41} and patients with frequent respiratory infections during childhood^{38,40}. Evidence also supports that tuberculosis^{42,43} and HIV patients are at higher risk of COPD development⁴⁴.

However, these factors are unlikely to be the only reason of developing COPD. In a small proportion of non-smokers, a genetic component to the disease or specific interactions between genetic and epigenetic factors and effects of the environment may play an important role⁴⁵. The most documented genetic risk factor of COPD is alpha-1 antitrypsin deficiency (AATD) (ref.^{46,47}). However, other genetic polymorphisms, including single genes encoding glutathione S-transferase, matrix metalloproteinases or superoxide dismutase, may also be associated with the pathogenesis of the disease⁴⁸⁻⁵⁰.

4. EPIDEMIOLOGY

Smoking epidemics in the developing countries, general aging of populations, and increased environmental exposure to air pollution are responsible for the increasing global incidence and prevalence of the disease^{51,52}. The latest worldwide prevalence was estimated at 11.7% (ref.⁵²). An estimated 12.4% of the EU population suffer from COPD (ref.⁵³). In the Czech Republic, the recently estimated prevalence is around 6.7%, i.e., around 710,000 patients per the 10,65 million population of the country⁵⁴.

According to the latest epidemiological data, COPD currently ranks fourth, however, by 2020, it was projected to become the third worldwide leading cause of death from non-communicable diseases^{1,51}. Current mortality data (for the year 2020) are yet not available. The disease claims around 3 million lives in the world annually⁵⁵. In

the EU, the mortality trend was linearly decreasing during the period between 1994 and 2010 (ref.⁵⁶). Following a period of notable increase since the 2000-10 decade, mortality from COPD in the Czech Republic was about stable between the years 2015 and 2018, with 3,200-3,500 deaths reported annually^{54,57}.

5. RISK ASSESSMENT

Prognostic assessment is one of the key issues regarding the disease management, offering the opportunity to identify high-risk patients requiring more assertive treatment approach. Traditionally, FEV₁ was the most widely used parameter for basic prognostic evaluation, reflecting the association between progressive lung function decline and increasing mortality risk⁵⁸.

In the last two decades, composite tools for long-term prognosis assessment have been constructed, including the ADO, BODE and related indices^{58,59}. The scoring system of the BODE and the score-specific four-year mortality risk are described in the article by Celli et al.⁵⁸. Recently, a new-generation multidimensional prognostic

instrument, the CADOT index, has been introduced. The CADOT showed slightly better prognostic properties compared to ADO and BODE indices and prevented the specific problems associated with the use of BODE (ref.⁶⁰). The CADOT incorporates also chronic heart failure that has strong linkage to mortality risk and also to functional impairment of the lungs⁶¹. As such, the CADOT instrument offers an alternative to the BODE index, if the 6-MWT (or an other component of the BODE) is not feasible. If calculation of BODE or CADOT score is not possible, a significantly higher risk of long-term mortality should be expected in group B patients with chronic hypoxemia (PaO₂ <7.3 kPa) and in group D patients, irrespective of hypoxemia⁶².

6. DIAGNOSIS OF COPD

The elementary requirements for diagnosis of COPD consist of spirometric confirmation of post-bronchodilator (post-BD) expiratory airflow limitation (bronchial obstruction) (Fig. 1). Spirometry should be done in all individuals with chronic respiratory symptoms (dyspnoea

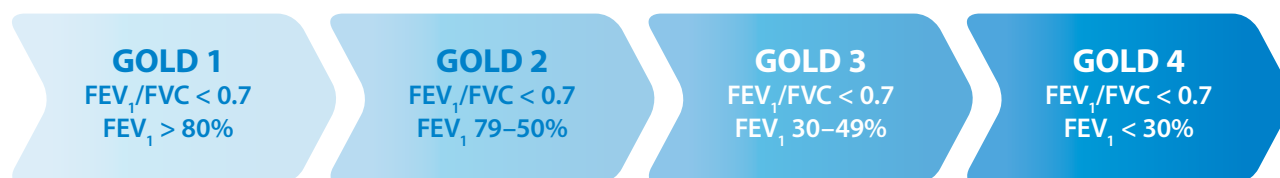


Fig. 1. GOLD stages (according to post-BD spirometry of COPD patients)

Table 1. Alternative diagnoses to COPD.

Alternative diagnosis	Clinical presentation similar to COPD (dominant symptom(s) in the bold)	Confirmation of alternative diagnosis (the most important options in the real-life practice)
Bronchial asthma [#]	Cough, dyspnoea, wheezing , sputum production	Normal TLco, periods without bronchial obstruction, normal chest HRCT
Bronchiolitis	Cough, dyspnoea	Chest HRCT inspiratory/expiratory (with mosaic pattern)
Bronchiectases ^{##}	Cough, sputum production , exacerbation	Chest HRCT (bronchiectases signs) (ref. ^{66, 67})
Cystic fibrosis	Cough, sputum production, dyspnoea	Sweat test (> 60 mmol/l) (ref. ⁶⁸)
Primary ciliary dyskinesia	Cough, sputum production , exacerbation	Nasal Nitric Oxide (< 105 ppb) (ref. ^{69, 70})
Extraesophageal reflux	Cough , especially after lying in supine position , sputum production, aspiration attack	Laryngoscopy/Gastroscopy, pH metry, esophageal impedance
Tracheobronchomalacia (intrathoracic collapse)	Cough, wheezing, dyspnoea	Bronchoscopy, dynamic chest HRCT during spirometry
Tracheal stenosis (fixed)	Cough, wheezing, dyspnoea	Bronchoscopy
Sarcoidosis	Cough, wheezing	Chest HRCT
Pulmonary embolism	Dyspnoea	Chest CT with contrast, D-dimers
Heart failure	Dyspnoea , cough	Heart ultrasound, chest X-ray, NTpro-BNP*

[#] Except for patients who have simultaneously present and balanced features of both diseases (asthma and COPD overlap – ACO)

^{##} Except for patients who have simultaneously present and balanced features of both diseases (bronchiectasis and COPD overlap – BCO)

* NTpro-BNP = N-terminal prohormone of brain natriuretic peptide

with exercise limitation and/or cough and/or sputum production), particularly in case of long-term risk exposure – see above⁶³. Expiratory airflow limitation was clearly defined by the European Respiratory Society as a decrease in FEV_1/VC below the lower limit of normal values (LLN) (ref.^{64,65}). Global Initiative for Chronic Obstructive Lung Disease (GOLD) simplifies the view on spirometric diagnosis of COPD to fit to the health care based on general practitioners. From the GOLD perspective, any person with post-BD $FEV_1/FVC < 0.7$ is considered a COPD case. In order to establish the definite COPD diagnosis, all alternative diagnoses associated with bronchial obstruction should be excluded – Table 1 (ref.¹).

COPD individuals exhibit gas trapping and increased lung hyperinflation from early stages of the disease. These important features can be documented by body-plethysmography. Measurement of transferfactor (TL_{CO}) for carbon monoxide provides additional information on the functional impact of emphysema and cardiovascular comorbidities in COPD subjects^{1,64}.

Worse lung function, more dyspnoea, higher comorbidity burden, and non-stable (exacerbated) course of COPD are associated with elevated overall health risks among COPD population. The above mentioned risk factors are useful for assessing the appropriate depth of the initial examination of a newly diagnosed case (Fig. 2).

7. INITIAL CLASSIFICATION OF A COPD CASE

This position paper uses combined classification including COPD stages (1 to 4), COPD groups (A to D) according to GOLD (ref.¹) and assessment of one or more clinical phenotype(s), if it is (they are) present.

At initial examination of COPD individuals, a comprehensive assessment of the patient using a history of worsening episodes called exacerbations and evaluation of respiratory symptoms (using the CAT questionnaire and/or the modified MRC dyspnoea scale) is recommended (Fig. 3).

The current GOLD 2020 strategy recommends that each patient be marked with the letter A-B-C-D, indicating a specific disease group. Health systems based on general practitioners propose initial pharmacological treatment according to A-D groups¹. In the conditions of different health care system in the Czech Republic, this is not necessary, however, we still find the A-D groups useful since they describe the extent of symptoms and exacerbations (Fig. 4).

Group A represents asymptomatic subjects in early stage of the disease, these patients can be successfully treated by general practitioners (GPs). In contrast, group B deserves particular attention as it consists of comorbidity-burdened patients with a less pronounced deterioration in lung function, though with a substantial mortality

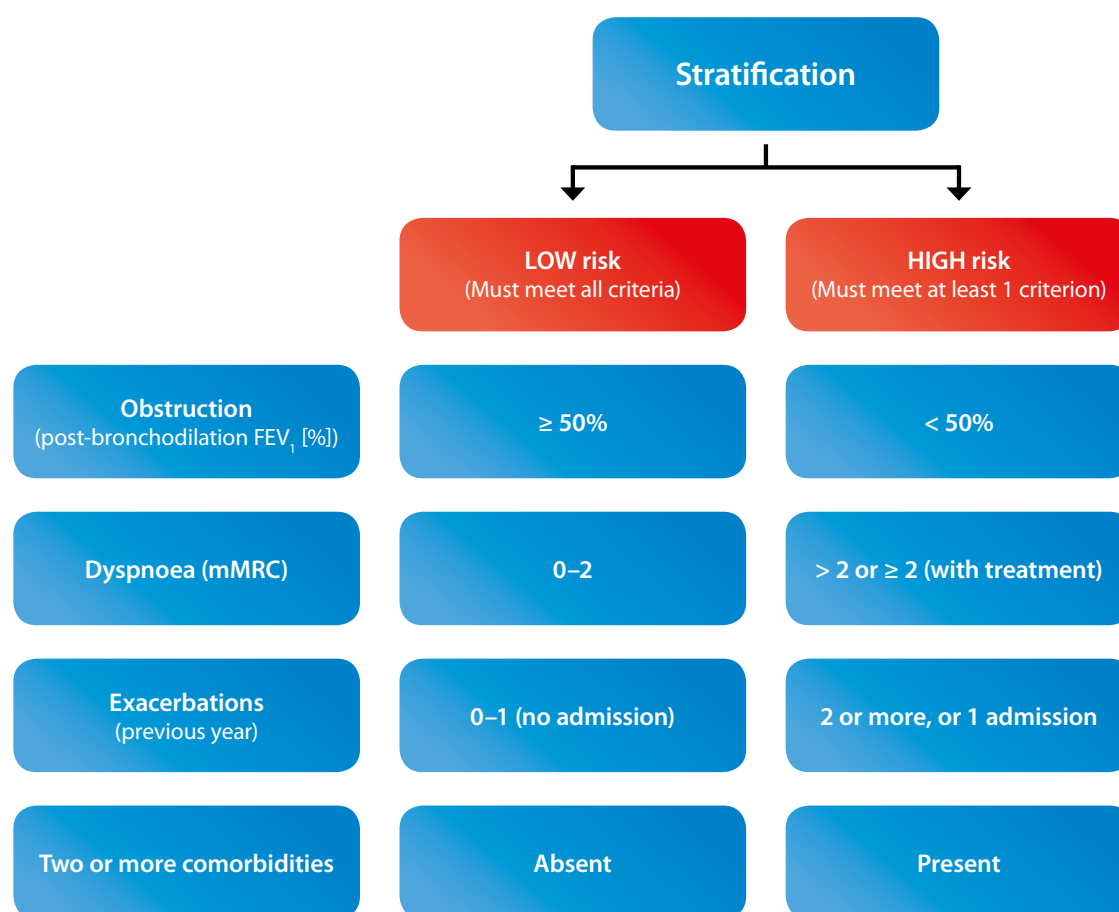


Fig. 2. Health risk assessment modified according to Miravittles et al. (ref. ³).

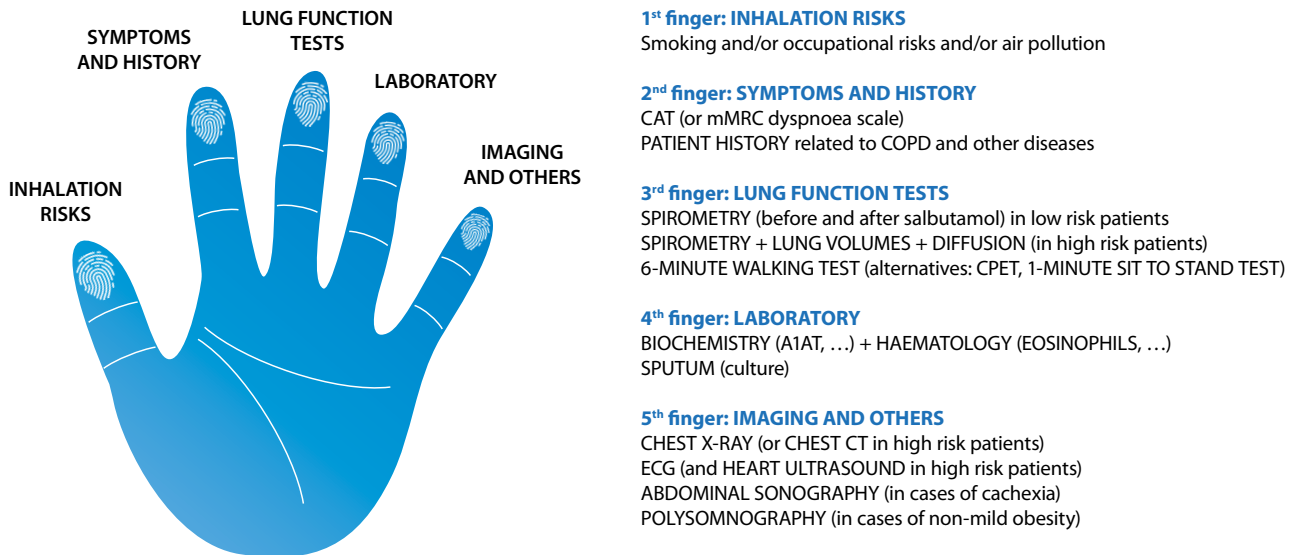


Fig. 3. Initial diagnostic procedures in new COPD cases.

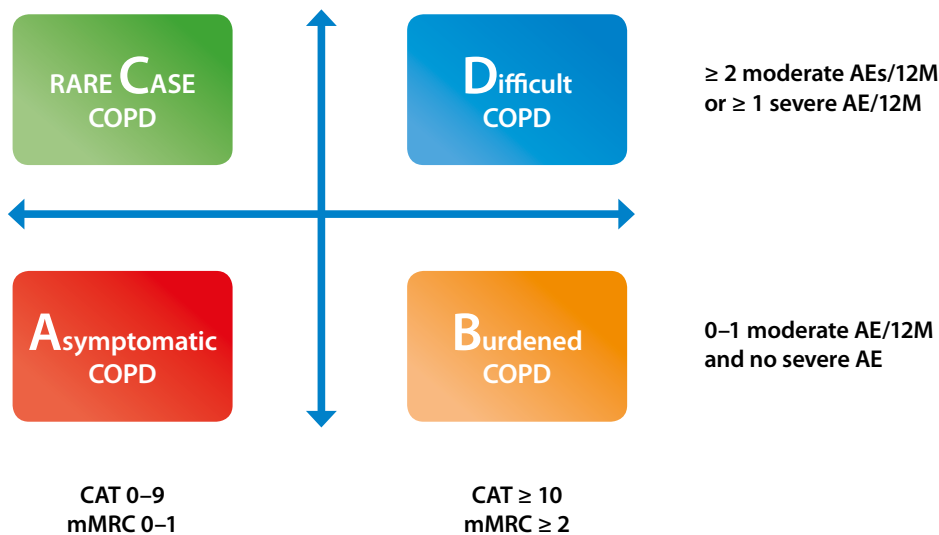


Fig. 4. GOLD groups according respiratory symptoms and number of exacerbations in the past 12 months.

risk⁶². Rare cases of oligo-symptomatic patients, comprising the small group C, can be usually found in the general population, but rarely in the pulmonologist’s care. The highest mortality risk is associated with group D (difficult). Subjects of this category 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.

A simple assessment of COPD severity with post-bronchodilator spirometry (stages 1 to 4) reflects the deterioration of lung function and the extent of bronchial obstruction. Despite the severity of bronchial obstruction has only weak correlation with symptoms and course of the disease, FEV₁ has a significant role in prognosis prediction and in some therapeutic decisions¹.

8. CLINICAL PHENOTYPES OF COPD

COPD is not a rigid and uniform condition, it likely represents a continuum of different sub-diseases that may share biological mechanisms (i.e., endotypes), and present with similar clinical, functional, imaging and/or biological features (i.e., phenotypes or phenotypical labels) which may require specific treatment (i.e., constituting specific treatable traits) (ref.^{25,71,72}). In our concept, the six pre-defined clinical phenotypes are also considered independent treatable traits. For each treatable trait, specific pharmacological and non-pharmacological therapies are defined within this document.

Currently, there are two ways to delineate phenotypical features in each particular COPD case: the “Spanish approach” means that one COPD patient is described by one “clinical phenotype”. The Czech approach is that the COPD patient may be characterized by one or more phe-

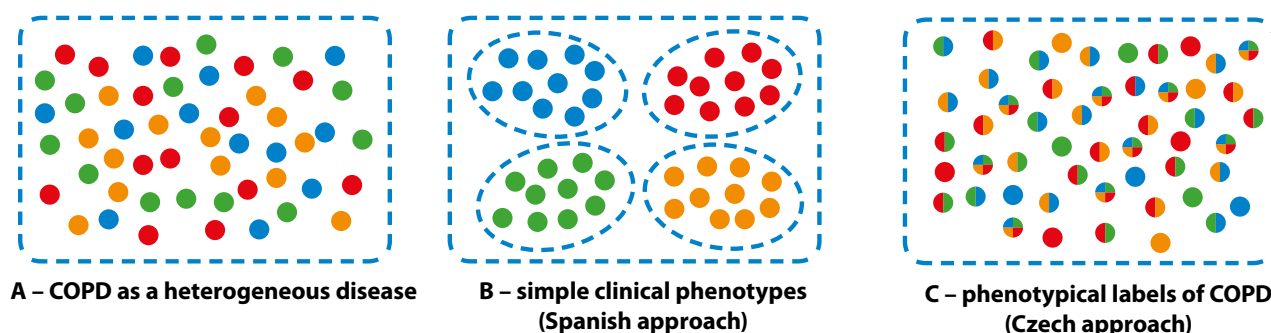


Fig. 5. Elementary concepts of COPD heterogeneity proposed by Agusti (ref. ⁷¹).

Table 2. Phenotypical labels in COPD – characteristics.

Methods / phenotypical labels or treatable traits	CB	EMPH	AE's w. INF	AE's w. eo	ACO	BCO	CACHEXIA
Subnormal BMI (and FFMI)		+					++
Daily sputum production	++					+	
Repeated infections of lower airways	+		++	+		+	
Repeated AE's			++	++			
History of AB < 40 years					++		
History of haemoptysis (any time)			+			+	
Bodyplethysmography		++					
Transferfactor (diffusion)		++					
Exercise and daily activity		+					+
↓ A1AT (blood)		++					
↑ Eosinophils (blood)				++	++		
Sputum culture is positive	+		+			+	
HRCT emphysema signs		++					
HRCT bronchiectases signs						++	
HRCT airway disease signs	+						

A1AT – alpha-1 antitrypsin

AB – bronchial asthma

ACO – asthma/COPD overlap

AE's w. eo – acute exacerbation (with eosinophilia)

AE's w. INF – acute exacerbation (with infection)

BCO – bronchiectases and COPD overlap

BMI – body mass index

CB – chronic bronchitis

HRCT – high resolution computed tomography

EMPH – emphysema

FFMI – fat free mass index

++ Essential meaning

+ Auxiliary meaning

notypes/phenotypical labels – one patient=one or more phenotypes^{3,11,62,73-75} (Fig. 5, Table 2).

Clinical phenotypes in individual patient may change over time, for example symptoms of chronic bronchitis or exacerbation rate can be improved after treatment. In these cases we prefer not to use the term “change of phenotype“ but rather “achievement of clinical control“ or “stabilisation of phenotype“. In case of new phenotype development (e.g., new bronchiectases or frequent exacerbations), treatment should be adjusted to the actual clinical disease presentation to maintain maximal control of COPD.

All patients with COPD independently of the presence of clinical phenotype(s):

The most common clinical presentation of COPD is limitation of daily living activities due to breathlessness sensation. Dyspnoea first occurs during high-intensity physical exercise, later during milder effort, finally at rest,

eventually resulting in physical inactivity, lifestyle change and social isolation^{1,76-78}. Chronic fatigue is a highly prevalent sign in the COPD population. Fatigue poorly correlates with the degree of airflow limitation, but perceived fatigue seems to be a key factor in the decreasing quality of life^{79,80}.

8.1. FREQUENT EXACERBATOR PHENOTYPE

The long-term stable course of COPD can be intermittently interrupted in some patients by sustained worsening which exceed the normal day-to-day symptom variations. These attacks of symptoms worsening that last ≥2 days and require change in medication and/or hospitalization are called acute exacerbations (AEs) (ref.^{81,82}). AEs have a significant and prolonged impact on health status and outcomes, and negative effects on pulmonary functions.

AEs with the need of antibiotic treatment and/or systemic corticosteroids' use are called moderate AEs. Those AEs resulting in hospitalization are considered severe AEs. The best threshold to distinguish "frequent exacerbators" and non-frequent exacerbators are two moderate-to-severe exacerbations per year. Therefore, the "frequent exacerbator" phenotype should be defined by at least two AEs treated in the past year. Frequent exacerbators have more pronounced airflow limitation, higher degree of symptoms and health-related quality of life impairment⁸³. A significant proportion of AEs are unreported and therefore left untreated, leading to a poorer prognosis compared to those treated adequately. COPD exacerbations are heterogeneous, and various phenotypes have been proposed which differ in biologic basis, prognosis, and response to therapy. Frequent exacerbations are the strongest predictor of future exacerbation frequency, suggesting a consistent phenotype⁸⁴⁻⁸⁷. Therefore, reduction of AEs has beneficial impact on patient outcomes and prognosis^{81,88}.

8.2. BRONCHITIC PHENOTYPE

COPD patients with the bronchitic phenotype commonly experience cough, which is productive (with long-term presence of phlegm) in about 60% of cases^{89,90}. CB subjects report worse respiratory symptoms (diurnal + nocturnal cough and phlegm) and experience higher risk of COPD exacerbations^{91,92}.

8.3. EMPHYSEMATOUS PHENOTYPE

Patients with pulmonary emphysema usually experience dyspnoea and have no chronic sputum expectoration (if there's no coincidence with bronchitic phenotype).

Emphysematous patients are clinically characterized by a more prevalent dyspnoea than any other COPD patients: A) early-morning and daytime dyspnoea in cases of mild emphysema, and B) diurnal + nocturnal dyspnoea in cases of severe emphysema. In most cases, chest high resolution computed tomography (HRCT) is necessary to confirm the presence of pulmonary emphysema. In addition, CT scans uncover the type of emphysema, its distribution and extent. Above that, CT scans help to exclude other lung diseases (tumours, lung fibrosis) and are also beneficial for bronchiectases detection⁹²⁻⁹⁵.

The Fleischner Society of radiologists proposed a statement that describes and defines the phenotypic abnormalities identifiable on visual and quantitative HRCT images in subjects with COPD. Emphysema is classified as centrilobular (subclassified as trace, mild, moderate, confluent, and advanced destructive emphysema), panlobular, and paraseptal (subclassified as mild or substantial). Additional important visual features include airway wall thickening, inflammatory small airways disease, tracheal abnormalities, interstitial lung abnormalities, pulmonary arterial enlargement, and bronchiectases⁹⁶⁻⁹⁸. Prior to CT scanning, clinical suspicion on emphysema should be

made in patients with a "barrel chest", with radiological signs of emphysema on a chest X-ray and/or with lung hyperinflation at pulmonary function tests.

8.4. ASTHMA-COPD OVERLAP (ACO)

ACO is characterized by persistent airflow limitation with several clinical features of bronchial asthma and several features typical for COPD. ACO may be a special phenotype of chronic obstructive airway diseases, in which asthma and COPD are located at the two opposite ends. The prevalence of ACO varies considerably due to variability of criteria for its diagnosis. Patients with ACO utilize a large proportion of medical resources because they experience more symptoms and AEs compared to those with asthma or COPD alone^{99,100}. Although definitions of ACO vary, a most typical presentation of ACO includes persistent bronchial obstruction in a COPD patient older than 40 years with either a previous history of asthma or large bronchodilator reversibility¹⁰¹. ACO includes two different conditions such as: a) asthma of smokers with airway remodeling and incomplete airflow reversibility, b) eosinophilic phenotype of COPD (ref.¹⁰²). Compared to their counterparts with asthma or COPD alone, patients with ACO have significantly worse respiratory symptoms, poorer respiratory quality of life, and increased exacerbations' and hospital admissions' risk¹⁰³.

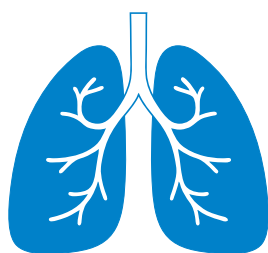
The simplified current Spanish Respiratory Society consensus defines ACO as: (a) the presence of chronic airflow limitation in a smoker or ex-smoker (more than 10 pack-years) patient ≥ 35 years old; (b) with current diagnosis of asthma; and/or (c) the presence of a strongly positive bronchodilator test ($\geq 15\%$ and ≥ 400 mL) or the presence of eosinophilia in peripheral blood (≥ 300 eosinophils/ μL) (ref.¹⁰³⁻¹⁰⁵).

The Czech Pneumological and Phthiseological Society proposed the persistent presence of either two major criteria, or one major and two minor criteria that are typical for coexistence of both conditions in ACO. These approach is slightly more restrictive than the Spanish one, in order to increased specificity of ACO phenotypical label (Fig. 6) (ref.^{75,106}).

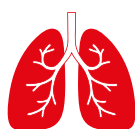
8.5. BRONCHIECTASES WITH COPD OVERLAP

Parallel to COPD, a minority of patients suffer from bronchiectases (defined as an abnormal dilatation of the bronchi, usually in two or more pulmonary lobes, without any other known cause). Above that, bronchiectases may also develop during long-term course of COPD. The prevalence of bronchiectases in COPD patients increases with higher stage of the disease (highest prevalence is present in COPD stage 4).

BCO is associated with increased lung inflammation and worse lung function^{107,108}. Bronchiectases should be considered in patients with COPD with greater severity of symptoms who often suffer from exacerbation or

**Major criteria:**

- a) strongly positive bronchodilator test (change FEV₁ ≥ 15% and ≥ 400 ml)
- b) history of bronchial asthma before 40 years established by physician
- c) presence of eosinophilia in peripheral blood (≥ 300 eosinophils/μl)
- d) sputum eosinophil count ≥ 3%
- e) positivity of metacholine bronchial challenge test
- f) increased FeNO (> 45–50 ppb) in the stable phase of COPD

**Minor criteria:**

- a) mild positivity of bronchodilator test (change FEV₁ ≥ 12% and ≥ 200 ml)
- b) history of atopy established by physician

Fig. 6. Asthma and COPD overlap (ACO) criteria.

repeated respiratory infections, especially in those who isolate *Pseudomonas aeruginosa* in sputum¹⁰⁹⁻¹¹².

8.6. PHENOTYPE OF PULMONARY CACHEXIA

Approximately 5-10% of COPD patients (especially those with severe bronchial obstruction) display a tendency towards gradual, slow, and unintentional decrease in body weight and altered body composition (simplified criterion BMI <21), particularly in fat-free mass i.e. muscle tissue (decrease in fat-free mass index (FFMI) <16 kg/m² in men, <15 kg/m² in women) (ref.^{62,113-118}). Pulmonary cachexia is associated with increased mortality risk among COPD patients¹¹⁹.

8.7. COINCIDENCE/CO-PRESENCE OF MORE PHENOTYPES

Coincidence of two specific phenotypes: chronic bronchitis + frequent exacerbator or BCO + frequent exacerbator are associated with a more negative influence of disease on patients quality of life and the course of the disease^{77,87}. The most severe COPD patients with clinically balanced triple mixture of emphysematous + chronic bronchitic + frequent exacerbation phenotypes suffer from severe symptoms, poorer quality of life, sleep disturbances, and highest levels of depression and anxiety⁹². Co-presence of emphysema, cachexia and frequent exacerbations is associated with poorest patients' prognosis¹²⁰.

Table 2 gives an overview of those six elementary COPD phenotypical labels/treatable traits, which occasionally might occur simultaneously in real-life practice (e.g., emphysematous COPD + pulmonary cachexia, or bronchitic COPD and frequent exacerbator). All the above mentioned forms of COPD can move, usually after many years, towards the development of chronic respiratory failure (hypoxemic, and/or hypercapnic) 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 terminal COPD.

COPD is often accompanied by other diseases or comorbidities: lung cancer, ischemic heart disease, lung fibrosis, pneumoconiosis, chronic heart failure, anxiety, depression, osteoporosis, anemia, peptic ulcer, gastroesophageal reflux disease and obstructive sleep apnoea^{1,121,122}.

9. COPD SCREENING IN THE CZECH REPUBLIC

Targeted early detection of still undiagnosed COPD subjects in the high risk (smokers or exsmokers) and symptomatic (at least one respiratory symptom) population is extremely effective^{63,123-125}.

Early detection programmes of various diseases are part of the Czech national general health priorities previously declared in the strategy "Health 2020 - the national strategy for health support and protection and for disease prevention". The National council for implementation and steering of programmes for early detection of diseases is the consultation authority of the Ministry of Health of the Czech Republic in this field. The programme for early detection of chronic obstructive pulmonary disease (COPD) was among others nominated by the National council for realization and received the necessary financial support.

The target population for this pilot project are "healthy persons" with pre-defined risk of COPD development, that means: history of cigarettes smoking (10 and more pack/years) and/or other inhaled risks, aged 40 - 69 years and with symptoms of breathlessness during common daily physical activities (faster walking, stairs climbing). Basic detection of persons at risk are provided by general practitioners. Persons/smokers aged 40 - 69 years are actively contacted by their GP at any suitable occasion and are instructed and asked about their breathlessness. In case the patient fulfills the criteria of entering the program, he/she is referred to the cooperating pulmonologist. In the second step the pulmonologist instructs

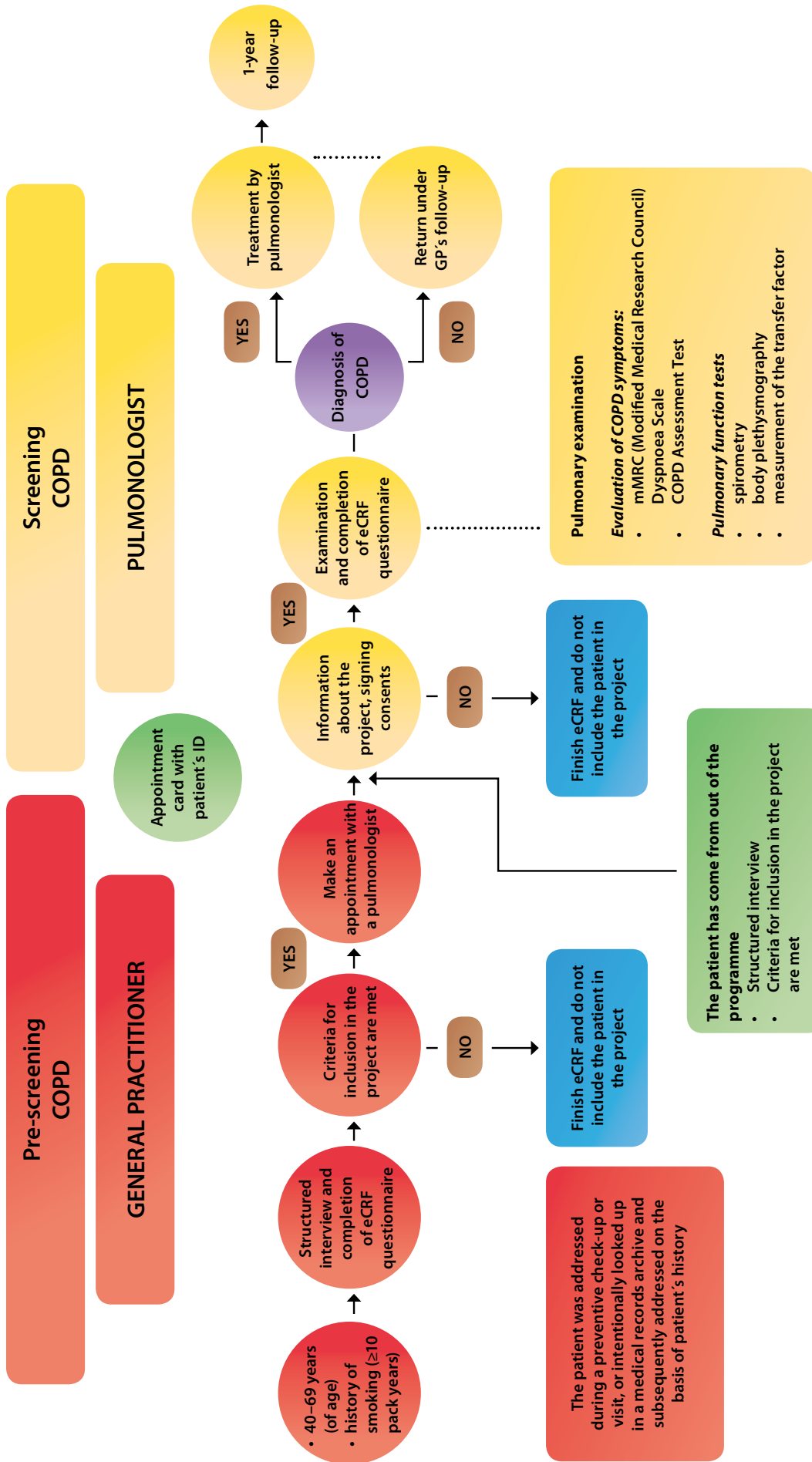


Fig. 7. The Czechia COPD screening programme in the high risk population – National Screening Centre.



Fig. 8. COPD management strategy.

the patient in detail, asks the patient for his/her written consent and evaluates the mMRC dyspnea scale and CAT questionnaire. Lung function tests are performed: post-bronchodilatory spirometry, bodyplethysmography and TL_{CO} assessment. As a result, a diagnosis of COPD can be established, together with deeper assessment of its impact on symptoms and lung function (Fig. 7).

10. TREATMENT

10.1. TREATMENT STRATEGY

Treatment of COPD should reflect the complexity and heterogeneity of the disease and be tailored to each individual patient²⁵. The aim of COPD treatment is to reduce symptoms, frequency and severity of exacerbations and improve exercise tolerance, prognosis and both short-term (disease control) and long-term outcomes (reduction in risk).

Treatment of COPD includes pharmacological and non-pharmacological therapy. According to the “five-finger concept“, the treatment strategy is divided into five areas/strata: (1) risk elimination, (2) basic treatment, (3) phenotype-specific treatment, (4) treatment of respiratory insufficiency and supportive care/end-of-life care, and (5) treatment of comorbidities (Fig. 8).

10.2. RISK ELIMINATION

Identification of risk factors and elimination/reduction of exposure is a fundamental part of COPD treatment. It is necessary for all patients with COPD, regardless of other therapy.

Smoking cessation

Current opinions: Smoking cessation remains the most effective intervention that reduces lung function decline, improves responses to bronchodilators and inhaled corticosteroids and reduces the incidence of acute exacerbations and bronchopulmonary infections. Therefore, effort toward smoking cessation or at least reduction of smoking exposure should be made as a first intervention in all patients with COPD. Importantly,

smokers with COPD are more nicotine dependent than smokers without COPD and also depression in smokers with COPD is more frequent when compared to smokers without COPD. Smokers with COPD usually experience low degree of smoking cessation self-efficacy and also are less motivated to quit than smokers without COPD; both factors are associated with low quitting rates¹²⁶. In a systematic review, average 12-months continuous abstinence rates for smokers with moderate-to-severe COPD were estimated at 1.4% after usual care, 2.6% after minimal counselling, 6.0% after intensive counselling and 12.3% after intensive counselling supported by pharmacotherapy¹²⁷. Individual counselling should be offered by each pulmonologist, intensive counselling plus pharmacotherapy can be provided by a pulmonologist or by experts in Nicotine Treatment Centres, constituting a network across Czech Republic. Pharmacotherapy available in the Czech Republic includes nicotine replacement therapy, bupropion and varenicline. The use of E-cigarettes to aid smoking cessation remains controversial¹. Further recommendations regarding smoking cessation are described in special guidelines¹²⁶.

Treatment recommendations of the expert group:

- Smoking cessation should be attempted in each patient.
- Psychosocial intervention should be supported by pharmacotherapy.

Environmental air pollution, occupational exposures

Current opinions: Urban air pollution contributes to the overall risk of COPD. Even more important is the role of urban air pollution as a trigger of exacerbations, particularly during seasonal worsening of urban and industrial air pollution. A specific case of environmental air pollution is passive exposure to tobacco smoke (“second hand smoking“), that may bring about respiratory symptoms and COPD exacerbation¹²⁸. Occupational exposures, including organic and anorganic dusts, chemical agents and fumes are associated with increased risk of COPD development¹. Elimination or reduction of exposure to occupational dusts and fumes, tobacco smoke and urban air pollutions are one of the first requirements of treatment regarding successful COPD treatment.

Treatment recommendation of the expert group:

- Elimination of all risk factors should be attempted in each COPD individual.

10.3. BASIC TREATMENT

Basic treatment of COPD is assigned for each patient with COPD as a fundamental treatment, regardless of their phenotype. Basic treatment should be started immediately after COPD is diagnosed. Basic treatment includes regular therapy by long-acting bronchodilators, symptoms-relieving treatment by short-acting bronchodilators, pulmonary rehabilitation, inhalation training, vaccination, appropriate nutrition and psychological and social support.

Long-acting bronchodilators

Current opinions: Long-acting bronchodilators should be used as the first pharmacologic step in the treatment of all patients with COPD with persistent symptoms and who require regular treatment. Long-acting bronchodilators can be divided in two groups: Long-Acting Beta₂-Agonists (LABA), i.e. drugs with beta₂ adrenergic effect (salmeterol, formoterol, olodaterol, vilanterol and indacaterol) and Long-Acting Muscarinic Antagonists (LAMA), i.e. drugs with anti-cholinergic effect (tiotropium, aclidinium, glycopyrronium, umeclidinium).

Most bronchodilators have a 12-hour duration of action and are administered twice daily, some have a 24-hour effect and can be administered once daily. Long-acting bronchodilators enable better control of symptoms, improve the quality of life, lung function and mortality and reduce the number of exacerbations and/or hospitalisations¹²⁹⁻¹³³.

Pharmacological intervention with bronchodilator therapy is beneficial from early stages of COPD (ref.^{131,132,134,135}). LAMA showed greater reduction of exacerbation rates than LABA (ref.^{136,137}). LAMA improve the effect of pulmonary rehabilitation on exercise tolerance¹³⁸. Combined treatment with LABA and LAMA has better effect on lung function, dyspnea and quality of life compared to monotherapy. Dual LABA and LAMA treatment can reduce number of exacerbations slightly better than LAMA alone^{134,135,139-141}. A number of different inhaler devices exist and the choice of inhaler device and dosage should be tailored to individual patient's needs and abilities. There are limited data regarding de-escalation from dual bronchodilators to monotherapy. The latest GOLD document suggested that if addition of a second long-acting bronchodilator does not improve symptoms, the treatment could be stepped down back to a single bronchodilator¹. Similarly, a step down to monotherapy can be considered if the new component of dual bronchodilators is poorly tolerated or if serious new side effects occur.

Treatment recommendations of the expert group:

- Monotherapy with only LAMA or only LABA should be used in patients with lower degree of dyspnoea with

mMRC 0-1 and less impaired lung function with FEV₁ >50%. If monotherapy is used, LAMA is preferred due to greater effect on reduction of exacerbation rates compared to LABA. One exception comes in patients with ACO where LABA is the preferable bronchodilator, usually combined with an inhaled corticosteroid (see below in Phenotype-specific treatment).

- Patients with more impaired lung function (FEV₁ ≤50%) and/or more symptomatic with mMRC ≥2 should be treated by dual bronchodilator therapy (LABA and LAMA). Combined treatment with LABA and LAMA can be administered using separate inhalers or by a single inhaler (fixed-dose LAMA/LABA). The choice of the optimal dual bronchodilator should depend on individual patient's needs and abilities.
- Patient on a LAMA or LABA monotherapy, with persistent dyspnoea or decline of lung function despite treatment, should step up to dual therapy. In case of dual therapy intolerance or if serious side effects occur, de-escalation to LAMA or LABA monotherapy can be considered. In such cases, a strict monitoring of patient is necessary and de-escalation is possible only if no worsening of symptoms, lung function decline and/or exacerbations occur.

Short-acting bronchodilators

Current opinions: Similarly to LABA and LAMA, short-acting bronchodilators include Short-Acting-Muscarinic Antagonists (SAMA) with an anti-cholinergic effect (ipratropium bromide), and Short-Acting Beta₂-Agonists (SABA): salbutamol, fenoterol and terbutaline. Both SAMA and SABA improve FEV₁, symptoms and exercise tolerance. Combined (fixed-dose) SAMA/SABA treatment is more effective in improving FEV₁ and symptoms compared to each monocomponent alone.

Treatment recommendations of the expert group:

- Short-acting bronchodilators should be used as an 'as-needed' treatment for occasional symptoms' relief. In most cases, they should not be used as regular treatment. SABA or/and SAMA can be added to basic treatment regardless of disease severity or COPD phenotype.
- Short-acting bronchodilators can be used as single therapy in patients without persistent symptoms, i.e., with FEV₁ ≥80%, mMRC 0 and CAT<10, who do not require regular treatment by long-acting bronchodilators.

Pulmonary rehabilitation

Current opinions: Pulmonary rehabilitation is an important part of standard non-pharmacological treatment, which includes patient education, physiotherapy, occupational therapy (focused on activities of daily living - ADL), nutritional and psychosocial support (Fig. 9) (ref.^{142,143}). Physiotherapy consists of exercise training (endurance and strength) and techniques of respiratory physiotherapy. It is recommended that all patients with COPD

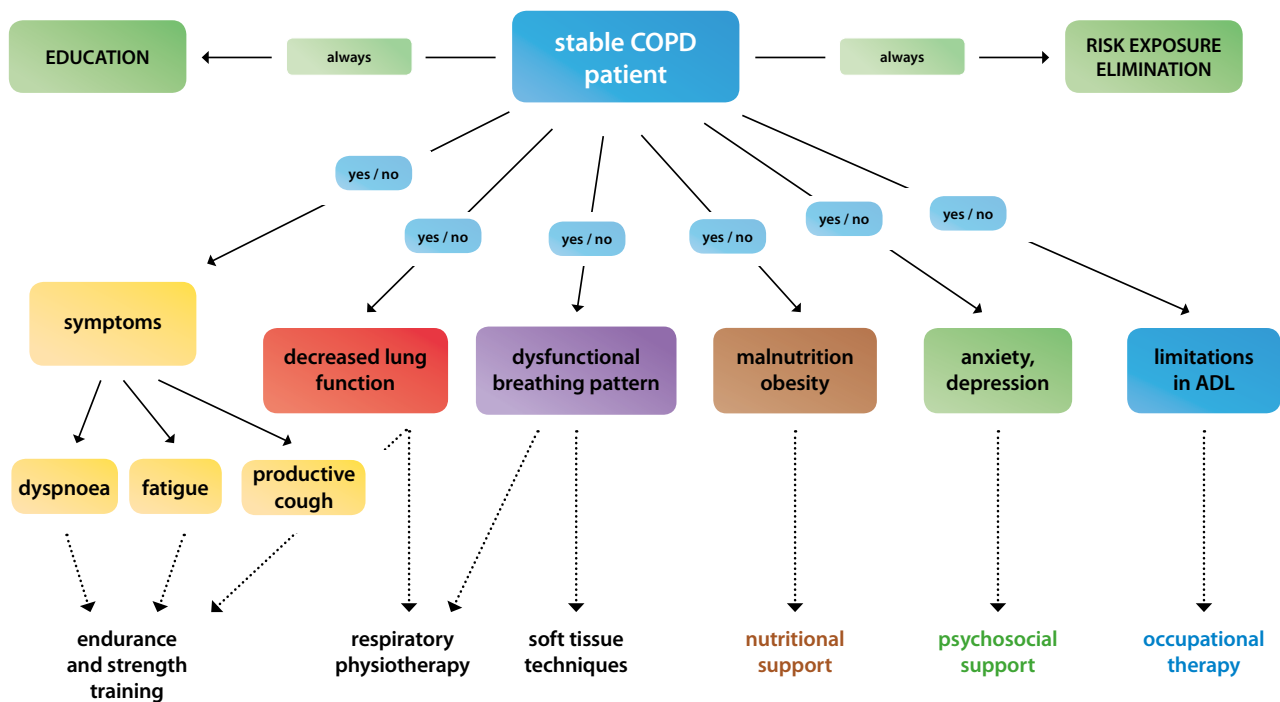


Fig. 9. Components of pulmonary rehabilitation in stable COPD.

who are symptomatic are involved in exercise training (3-5 times per week, 20-60 min, 6-8 weeks) regardless of lung function^{144,145}. Training sessions should be supervised by a physiotherapist at least twice a week and the training sessions (1-3 times per week) can be performed either at the patient's home or at a community rehabilitation centre⁶³. The respiratory physiotherapy techniques include reeducation of the breathing pattern, techniques of enhancing chest expansion, airway clearance techniques and ventilatory muscle training. It is very important to add other physiotherapeutic techniques to pulmonary rehabilitation treatment, if balance disorders, low back pain or stress incontinence is present (Fig. 10). These problems are more often present in patients with COPD compared to those who do not have this disease¹⁴⁶⁻¹⁴⁹.

Treatment recommendation of the expert group:

- Pulmonary rehabilitation should be considered in each patient with symptomatic COPD regardless of disease severity or COPD phenotype.

Inhalation training

Current opinions: Inhaled medications are the cornerstone of COPD pharmacotherapy. Several types of inhalers are currently authorized and used in the treatment of COPD in the Czech Republic. The group of pressurized metered dose inhalers (pMDI group) included three types of inhalers: traditional pMDIs (aerosol), Easi-Breathe and Respimat (soft mist inhaler, SMI). They require slow and deep breathing in for at least 4 seconds and they are the method of choice for patients with low inspiratory flow. The dry powder inhalers (DPI group) comprise several types of inhalers: Handihaler, Aerolizer, Breezhaler,

Diskus, Turbuhaler, Ellipta, Genuair, Twisthaler, Easyhaler or Spiromax¹⁵⁰⁻¹⁵².

Inhalator misuse is frequently observed among COPD individuals. The majority of COPD patients make mistakes, especially in the case of multiple inhalators in one patient. The inhaler technique should be checked (at least) annually by a pulmonary physician, physiotherapist, and/or respiratory nurse specialist.

Personalized training focused on all detected errors should be done subsequently by the same staff using the same instrument (Five Steps Assessment). Five Steps Assessment is available for free use at <https://www.fnhk.cz/plic/aplikace-inhalacnich-leku-edukacni-video/english-versions> (animated version for patients) and the version for health-care professionals in an article by Vytrisalova et al. (Table 3) (ref.¹⁵⁰).

Treatment recommendations of the expert group:

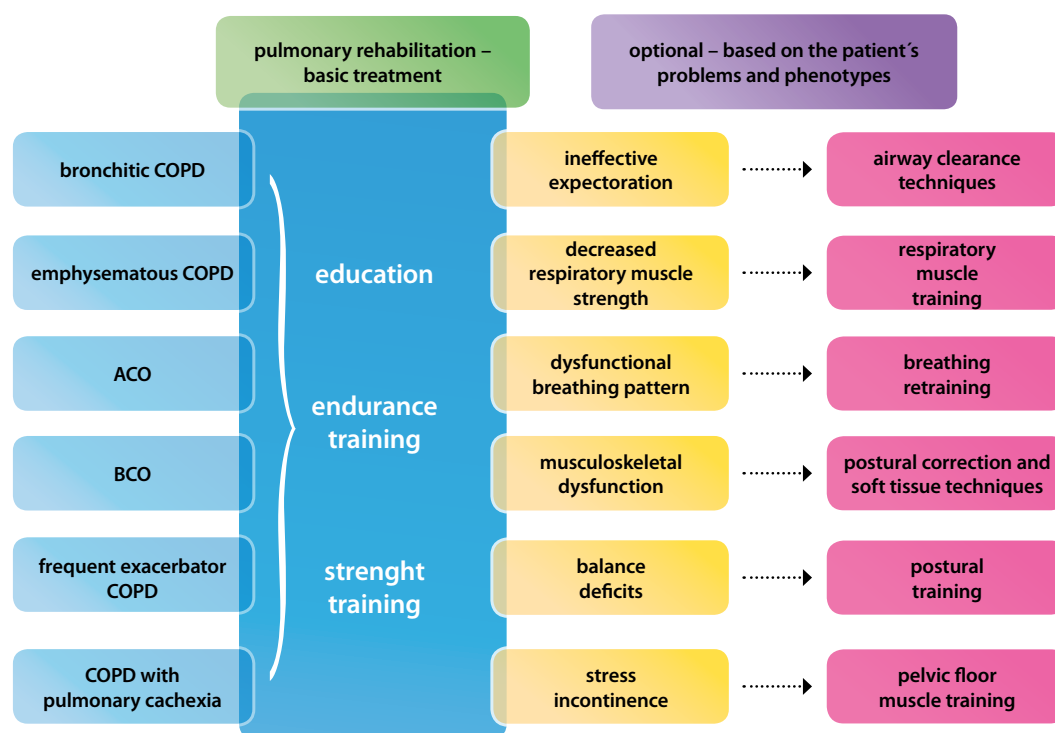
- We propose the use of a previously validated and published unique novel scoring instrument - Five Steps Assessment¹⁵⁰.

Vaccination

Current opinions: Influenza vaccination prevents influenza and reduces the risk of exacerbation and death in COPD patients. Pneumococcal vaccination is effective for prevention of community acquired pneumonia and invasive pneumococcal disease. Pertussis and diphtheria vaccine can also be considered.¹

Treatment recommendations of the expert group:

- Influenza and COVID-19 vaccination is recommended in patients with COPD, particularly in the elderly.



Legend: COPD – chronic obstructive pulmonary disease; ACO – asthma/COPD overlap; BCO – bronchiectases and COPD overlap

Fig. 10. Phenotypically targeted physiotherapy.

- Pneumococcal vaccination is recommended for all patients older than 65 years and for younger COPD patients with more impaired lung function and/or with comorbidities, especially cardiovascular diseases^{1,153}.

Appropriate nutrition

Current opinions: Malnutrition is an important and complex problem associated with COPD. The exact causal links between malnutrition and COPD are difficult to establish. Malnutrition can be the consequence of COPD severity, systemic inflammation, hypoxia and alterations of metabolism. On the other hand, malnutrition can result in respiratory muscle wasting and other features of COPD. Risk of malnutrition is estimated at 30-60% in hospitalized patients¹⁵⁴. Basic assessment of nutritional status can be provided by Body Mass Index (BMI) and Fat-Free Mass Index (FFMI) assessment. FFMI can be measured by skinfold calipers, densitometry or with the use of bioelectric impedance. Dual-energy X-ray absorptiometry (DEXA) is appropriate for combined screening of osteoporosis, fat-free mass (FFM) and fat mass. Patients with COPD and lower BMI have higher mortality risk than patients with slightly higher BMI. The prevalence of underweight in COPD increases with disease severity and is associated with the presence of emphysema. Low FFMI (less than 10%), irrespective of BMI and fat mass, is associated with higher mortality¹⁵⁵. Sarcopenia is characterised by low Skeletal Muscle Index (SMI) and leads to skeletal muscle weakness, particularly in older and/or overweight patients. Skeletal muscle index can be assessed by DEXA, magnetic resonance imaging and can

be estimated by anthropometry including skinfold calipers measurement^{156,157}.

Patients with COPD express various nutritional phenotypes associated with different clinical outcomes. Patients with obesity (BMI 30-35 kg/m²) have increased cardiovascular risk, patients with morbid obesity (BMI >35 kg/m²) and with sarcopenic obesity (BMI 30-35 kg/m² and SMI <2) furthermore have impaired physical performance. Patients with sarcopenia (SMI <2), cachexia (FFMI <16 kg/m² in males or FFMI <15 kg/m² in females) have impaired physical performance and increased mortality risk. Furthermore, malnutrition is associated with loss of mineral density, fat loss, muscle loss, or conversely with adiposity and obesity¹⁵⁵.

This position paper defines the specific „pulmonary cachexia phenotype“ of COPD, defined as cachexia in patients with advanced COPD inexplicable by other causes. Pulmonary cachexia phenotype incorporates patients with COPD and body mass loss, fat loss, muscle loss and/or loss of mineral density. Pulmonary cachexia phenotype is considered an independent risk factor of mortality in COPD patients¹⁵⁸.

Dietary management includes several therapeutic interventions. Patients with pulmonary cachexia should have nutritional supplementation. The diet should contain sufficient energetic value, be rich in proteins and be eaten in several small portions split throughout the whole day. The quality of fats should be considered. Oral nutritional supplements can be used if normal food and drink is insufficient for nutritional requirements. Counselling with a dietary specialist can be beneficial. Nutritional supple-

Table 3. Correct application technique (Five Steps Assessment system) used to initial education and regular check-up (ref. ¹⁵⁰).**5 easy universal steps to correct application technique include:**

1st step: remove the mouthpiece cover from inhaler (aerosol), turn the clear base until it clicks (soft mist inhaler) or another type of initial inhaler activation (more in video – see below)

2nd step: prepare dose of drug (for example insert a capsule into chamber, press the button, etc.) and hold device in the correct position (some of new inhalers have associated 1st step and 2nd step together)

3rd step: breath in and out and finally full and slow exhalation (exhale slowly all the air from the chest)

4th step: inhale the drug (slowly + smoothly during 4–5 seconds in case of pressurized metered dose inhaler or soft mist inhaler, quickly in dry powder inhalers)

5th step: take your inhaler device out of your mouth and hold your breath for several seconds and then breathe out slowly

Educational video available at: <https://www.fnhk.cz/plic/aplikace-inhalacnich-leku-edukacni-vidoa/english-versions>

mentation should be complemented by pulmonary rehabilitation programme including exercise training. Because of reported vitamin D deficiency and insufficient intake of vitamins with antioxidant capacity (vitamins A, C and E) in COPD, supplementation of vitamin D and other vitamins should be considered¹⁵⁵. A three-month intervention combining nutritional support, pulmonary rehabilitation and oral administration of testosterone in malnourished patients with chronic respiratory failure on LTOT has been reported previously¹⁵⁹. This multimodal intervention resulted in increased BMI and FFMI and was associated with better muscle functioning, higher quality of life and increased rate of 15-month survival¹⁵⁹.

Treatment recommendations of the expert group:

- Not only lower BMI, but also sarcopenia and other features of malnutrition should be sought after.
- Nutritional supplementation combined with pulmonary rehabilitation and further modalities should be used in cachectic COPD patients.
- On the other hand, adiposity should be managed by controlled weight reduction, particularly if the adiposity has clinical relevance.

Education

Current opinions: Topics of education include smoking cessation, correct inhalation technique, early recognition of exacerbation, treatment adherence, nutrition, physical activity, correct decision-making and others^{1,160}. Education can be a component of pulmonary rehabilitation. Patients instructed about the nature of COPD and the implications of therapy can better understand, recognize, and treat the symptoms of their disease. Longer-lasting self-management strategies are recommended for clinical practice rather than brief interventions¹⁶¹.

Treatment recommendation of the expert group:

- All patients should receive adequate education to improve COPD self-management.

Psychological and social support

Current opinions: Severe COPD is a risk factor for the development of anxiety and depression. Patients with

depression are more likely smokers and find smoking cessation more difficult. On the other hand, smokers are more likely to be depressed, that may be the result of nicotinic acetylcholine receptors' activation¹⁶². Furthermore, patients with severe COPD and dyspnea often reduce their physical activity, leading to progressive decondition. Depression and decondition may result in decreased participation in social activities, often including sexual activity. Pulmonary rehabilitation improves depression and should be used as first-line treatment of depression.

Treatment recommendations of the expert group:

- If necessary, psychological counselling and/or psychological therapies and/or pharmacotherapy should be used.
- Psychological counselling can also be beneficial as part of smoking cessation efforts.

10.4. PHENOTYPE-SPECIFIC TREATMENT

Patients with an expressed clinical phenotype should receive adequate phenotype-specific treatment. Patient with COPD can have none, one or multiple concurrent clinical phenotypes, that can overlap. Clinical phenotypes in this concept can be understood as treatable traits. Phenotype-specific treatment is assigned to each clinical phenotype. Patients with an overlap of ≥ 2 clinical phenotypes should receive combined treatment targeted on all present phenotypic labels.

10.4.1. FREQUENT EXACERBATOR PHENOTYPE

Patients with frequent exacerbations (≥ 2 during last year) despite optimal bronchodilator treatment should receive inhaled corticosteroids, phosphodiesterase-4 inhibitors, mucoactive drugs, selected antibiotics or combination of these drug regimens.

Inhaled corticosteroids (ICS)

Current opinions: ICS monotherapy does not reduce mortality and has no effect on lung function decline^{132,163}.

ICS in combination with bronchodilators reduced the exacerbation rate, particularly in patients with previous history of exacerbations¹³². The effect of ICS on reducing exacerbations is higher in patients with higher blood eosinophil count and seems to be lower in patients with lower blood eosinophil count^{164,165}.

Chronic use of ICS in COPD can be associated with adverse effects, particularly pneumonia, but also oral candidiasis, dysphonia, hematomas, skin bruising and reduction in bone mineral density. Greater risk of pneumonia has been found in patients treated by fluticasone furoate and in current smokers, patients with lower BMI and previous history of pneumonia. Withdrawal of ICS in low risk COPD patients was not associated with increase in exacerbation rate¹⁶⁶.

Withdrawal of inhaled corticosteroids in COPD patients using triple therapy (ICS+LABA+LAMA) did not result in higher risk of exacerbations and led only to a small decrease in lung function, regardless of exacerbation history^{167,168}. However, patients without an exacerbation history and with a blood eosinophil count ≥ 300 cells/ μL experienced increased risk of exacerbations after ICS withdrawal¹⁶⁸. A recommendation regarding ICS withdrawal is described in a recent European Respiratory Society guideline¹⁶⁹.

Treatment recommendations of the expert group:

- ICS should be used in patients with frequent exacerbations and higher blood eosinophil count in the peripheral blood, either in stable phase or during COPD exacerbation.
- ICS should also be used in patients with frequent exacerbations and asthma-COPD overlap.
- ICS should be used in combination with long-acting bronchodilator therapy (i.e., added to basic treatment), usually as combination ICS+LABA or ICS+LABA+LAMA. ICS monotherapy is not recommended.
- ICS should be used with precaution and treatment should be reconsidered in patients with frequent exacerbations and lower blood eosinophil count, prior history of pneumonia and lower BMI, especially in patients with emphysematic and/or cachectic phenotype.
- In patients with low exacerbation rate (0-1 exacerbation/last year) with lower blood eosinophil count in peripheral blood, withdrawal of ICS may be considered.
- Cut-off value for high blood eosinophil count in peripheral blood is ≥ 300 cells/ μL , cut-off value for low blood eosinophil count is < 100 cells/ μL . Blood eosinophil count between 100 and 300 cells/ μL is considered grey zone; in these patients, blood eosinophil count assessment should be repeated and individual risks and benefits regarding ICS use should be considered.

Phosphodiesterase-4 inhibitors (PDE4 inhibitors)

Current opinions: Roflumilast is a once daily oral anti-inflammatory drug that reduces neutrophilic inflammation in the airways due to inhibition of intracellular

cAMP degradation and subsequent effect on inflammatory cytokines and mediators¹⁷⁰. Roflumilast reduces exacerbation rates in patients with severe and very severe COPD with chronic cough and sputum production, and with history of exacerbations¹⁷¹. Despite roflumilast has no direct bronchodilator activity, an add-on to LABA or LAMA improves lung function more than bronchodilators alone^{171,172}. Roflumilast reduces exacerbations also in patients with chronic bronchitis¹⁷³. Roflumilast can affect different types and isoforms of the PDE4 family of enzymes^{170,174}. Therefore, roflumilast has more adverse events¹⁷⁰, the most common including diarrhoea, nausea, weight loss, sleep disturbance, headache, loss of appetite or impairment of preexisting depression. Adverse events usually appear at roflumilast treatment initiation and may result in treatment discontinuation. On the other hand, adverse events can sometimes be prevented through intermittent administration of the drug at treatment initiation.

Treatment recommendations of the expert group:

- Roflumilast can be used in patients with frequent exacerbations and bronchitic phenotype. Particularly, roflumilast should be considered in patients with combination of these two phenotypes and severe airflow limitation and/or exacerbation history despite ICS+LABA treatment.
- Lower blood eosinophil count and/or higher neutrophilia can support the use of roflumilast in these patients, especially if a history of pneumonia is present.
- Roflumilast should not be used concurrently with theophylline and in patients with depression or pulmonary cachexia.
- In patients with adverse events, intermittent administration of the drug at treatment initiation can be considered.

Mucoactive drugs containing thiol group

Current opinions: Erdosteine and N-acetylcysteine are thiol-based mucoactive drugs. Both substances have muco-modulatory and antioxidant effect. Erdosteine reduces both the rate and duration of exacerbations in patients with COPD (ref.¹⁷⁵). The most pronounced effect of erdosteine on exacerbation rate and duration was observed in patients with milder airflow obstruction. Erdosteine's effects on exacerbations are not substantially influenced by blood eosinophil count¹⁷⁶. High doses of N-acetylcysteine reduced the number of COPD exacerbations per patient-year, but not the proportion of patients who remained exacerbation-free⁶. Mucolytics are well tolerated and safe drugs with rare adverse events.

Treatment recommendations of the expert group:

- Long-term treatment with thiol-based mucoactive drugs (erdosteine or N-acetylcysteine) should be used in patients with frequent exacerbations, BCO and bronchitic phenotype.
- Furthermore, they can be used as add-on therapy in patients with exacerbation phenotype without chronic

bronchitis, particularly in patients with early stages of COPD with less severe airway obstruction.

- Combination with other phenotype-specific drugs in frequent exacerbators (ICS, roflumilast) is possible and may be beneficial.

Long-term antibiotic treatment

Current opinions: Long-term azithromycin therapy significantly reduced the number of exacerbations¹⁷⁷, but was associated with increased bacterial resistance to macrolides and with adverse events, such as hearing loss and QT-interval prolongation¹⁷⁸. Similarly, intermittent treatment with fluoroquinolones (moxifloxacin 400 mg daily for 5 days every 2 months for 1 year) significantly reduced exacerbation rates in patients with purulent sputum production, but similarly was associated with bacterial resistance and with adverse events. The Spanish guidelines recommend long-term use of macrolides in patients with severe COPD and with at least 3 exacerbations in the previous year. The treatment should be administered in reference centers due to the need of strict monitoring of adverse effects and developments of antibiotic resistance³.

Treatment recommendations of the expert group:

- Long-term antibiotic treatment (macrolides, fluoroquinolones) is reserved as special treatment for severe or very severe COPD patients with frequent bacterial exacerbations despite all usual therapy.
- Long-term antibiotic treatment may also be considered in COPD patients with frequent exacerbations and bronchiectases.
- The treatment should be administered in tertiary care centers and with precaution to all possible adverse effects and microbial resistances development.

10.4.2. BRONCHITIC PHENOTYPE

Mucoactive drugs containing thiol group

Current opinions: Basic characteristics of erdosteine and N-acetylcysteine are listed in the section describing treatment of frequent exacerbation phenotype. Above that, erdosteine and other thiol-based mucoactive drugs have antioxidant and antiinflammatory effect that improves symptoms of chronic bronchitis¹⁷⁹. Chronic bronchitis phenotype is associated with higher risk of exacerbation and mortality¹⁸⁰. Therefore, reduction of exacerbations with thiol-based mucoactive drugs treatment is beneficial^{175,181}.

Treatment recommendations of the expert group:

- Long-term treatment with thiol-based mucoactive drugs should be used in patients with bronchitic phenotype, with or without history of exacerbation.
- Mucoactive drug therapy may be beneficial for patients with mild or moderate COPD as an early intervention approach¹⁸².
- The treatment can be adjusted to symptoms of chronic bronchitis (for example, erdostein twice daily during

marked sputum production, or in contrast, interruption of mucoactive treatment when there is no cough and sputum).

Phosphodiesterase-4 inhibitors (PDE4 inhibitors)

Current opinions: General characteristics of roflumilast are presented in the section describing the treatment of frequent exacerbation phenotype. Anti-inflammatory effect of roflumilast on neutrophilic inflammation in the airways and beneficial effect on lung function can be a rationale for roflumilast use in patients with bronchitic phenotype, especially if frequent bacterial exacerbations are present¹⁷².

Treatment recommendations of the expert group:

- Roflumilast can be used in patients with bronchitic phenotype of COPD, especially in patients with more severe stages of the disease, with a history of bacterial exacerbation or pneumonia.
- Higher neutrophils count (in airways and/or peripheral blood) supports the use of roflumilast.
- Roflumilast can be used in combination with thiol-based mucoactive drugs in patients with bronchitic phenotype.
- Roflumilast should be avoided in patients with pulmonary cachexia phenotype. Further limitations of roflumilast are presented in the section describing treatment of the frequent exacerbation phenotype.

Pulmonary rehabilitation

Current opinions: Airway clearance techniques improve mucus clearance and reduce airways inflammation.

Treatment recommendation of the expert group:

- Pulmonary rehabilitation and regular aerobic exercise should be routine part of treatment in patients with bronchitic phenotype as a tool to reduce symptoms and exacerbation rates.

10.4.3. EMPHYSEMATOUS PHENOTYPE

The main goals of therapy in patients with pulmonary emphysema are improvements of dyspnoea, respiratory mechanics, respiratory muscle strength, and reversal of macroscopic structural changes with the use of volume reduction procedures.

Methylxanthines

Current opinions: Theophylline is the only methylxanthine available for use in the Czech Republic. Theophylline improves dyspnea, especially when added to LABA (ref.^{183,184}). Theophylline has a modest bronchodilator effect, enhanced in combination with LABA (ref.^{184,185}). Theophylline is able to increase diaphragmatic muscle strength, reduce gas trapping and improve the mucociliary clearance¹⁸⁵. Although the role of theophylline in the general COPD population is considered controversial¹, the mentioned features of theophylline allow to

expect its benefit in management of patients with emphysema. The role of theophylline in prevention of exacerbations has not been documented¹⁸⁶. Theophylline has a narrow therapeutic range and frequent adverse effects. Theophylline is metabolized via cytochrome P450 1A2, therefore an interaction with other drugs may occur.

Treatment recommendations of the expert group:

- Theophylline should be used as phenotype-specific treatment in emphysematous phenotype of COPD.
- During long-term treatment, patient should be carefully monitored by a physician, including monitoring of adverse effects, plasma concentrations of theophylline and possible interactions with other drugs.

Pulmonary rehabilitation

Treatment recommendation of the expert group:

- Respiratory muscle training can improve the decreased respiratory muscle strength and should be used in patients with emphysematous phenotype.

Non-pharmacological treatment

Current opinions: Non-pharmacological therapeutic interventions in patients with advanced pulmonary emphysema include bronchoscopic lung volume reduction (BLVR) and lung volume reduction surgery (LVRS).

BLVR procedures include endobronchial valves (EBV) and coils placement. Both valves and coils can be used in patients with severe hyperinflation, severe emphysema and absent airway disease (asthma, chronic bronchitis, bronchiectases) (Table 4) (ref.¹⁸⁷).

Targeted implantation of endobronchial one-way valves into the airways of an isolated emphysematous lobe appears to be one of the most promising innovations¹⁸⁸⁻¹⁹⁰. After a valve placement, FEV₁ and walking distance (6MWT) should improve. The efficacy of valve placement depends on the presence of interlobar collateral ventilation. Major complications following a valve placement include COPD exacerbations, hemoptysis, valve migration, and pneumothorax^{187,191}.

Endobronchial coils can be used in patients with heterogeneous as well as homogeneous emphysema, independently on interlobar collateral ventilation¹⁸⁷. The implantation of coils is usually permanent, only one or two coils can be removed. After a coil treatment, FEV₁ and walking distance (6MWT) should improve. Reported complications of the coil procedure include COPD exacerbations, hemoptysis, transient chest pain, pneumonia, pneumothorax, and noninfectious coil-associated opacities¹⁸⁷.

Further endoscopic lung volume reduction procedures include bronchoscopic thermal vapour ablation, biologi-

Table 4. Eligibility criteria for EBV, LVRS or bullectomy.

	EBV	LVRS	BULLECTOMY
Clinical characteristic	Dyspnoea (mMRC score ≥ 2)	Dyspnoea (mMRC score ≥ 2) Low fitness	Dyspnoea (mMRC score ≥ 2)
	Stable prior to procedure	Stable prior to procedure	Stable prior to procedure
Chest HRCT	Heterogeneous emphysema (upper or lower lobe predominance)	Heterogeneous emphysema (upper lobe predominance)	Impairment of $> 1/3$ of affected hemithorax
	No collateral ventilation in the targeted lobe		Radiographic evidence of compressed lung
RV	$> 175\%$ of predicted value	$> 175\%$ of predicted value	
FEV ₁	15–50% of predicted value	15–50% of predicted value	
TLco (DLco)	> 15 –20% of predicted value	$> 20\%$ of predicted value	
PaCO ₂	No hypercapnia	No hypercapnia	No hypercapnia
History	No severe pulmonary comorbidity	No severe pulmonary comorbidity	No severe pulmonary comorbidity
	Able to undergo sedation or general anesthesia	Able to undergo general anesthesia	Able to undergo general anesthesia
Smoking	Smoking cessation	Smoking cessation	Smoking cessation

(ref. ^{187-190, 194, 196-199}).

Abbreviations: EBV – endobronchial valve, FEV₁ – forced expiratory volume in 1 second, HRCT – high resolution computer tomography, LVRS – lung volume reduction surgery, RV – residual volume, TLco – transfer factor.

cal lung volume reduction (using the lung sealant system), or airway bypass stent^{187,191-193}.

Surgical methods (LVRS or bullectomy) are less frequently used compared to BLVR. LVRS should be considered in patients with upper-lobe predominant distribution of emphysema. LVRS in well-selected patients improved symptoms, dynamic hyperinflation, cardiopulmonary mechanics, exercise capacity, exacerbation rate and mortality^{191,194-196}.

Plasmatic levels of alpha-1 antitrypsin should be examined in each patient with COPD, especially with emphysematous phenotype in order to identify patients with severe forms of alpha-1 antitrypsin deficiency⁴⁷.

Treatment recommendations of the expert group:

- In patients with the large bullous type of emphysema, endoscopic or surgical volume reduction procedures should be considered in specialized tertiary care centers.
- Targeted implantation of endobronchial one-way valves (EBV) should be considered in patients with isolated emphysematous lobes.
- LVRS or bullectomy should be considered in patients with predominant upper-lobe distribution of emphysema, and low pre-procedure exercise capacity.
- Patients with alpha-1 antitrypsin deficiency should be referred to the specialized Center for treatment of alpha-1 antitrypsin deficiency (Thomayer Hospital, Prague) to consider alpha-1 antitrypsin augmentation therapy.

10.4.4. ASTHMA-COPD OVERLAP (ACO)

Patients with overlap of COPD and asthma (ACO) usually have a combination of symptoms of both diseases and some degree of eosinophilic inflammation in airways. Therefore, treatment of all patients with ACO phenotype should include inhaled corticosteroid, as phenotypical-specific treatment added to basic treatment with bronchodilators.

Inhaled corticosteroids(ICS) in combination with bronchodilators

Current opinions: The first option of phenotype-specific treatment of ACO is combination ICS+LABA. Similarly to asthma strategies, the dose of ICS should be set to the minimum dose necessary for disease control maintenance. Triple therapy ICS+LABA+LAMA should be used, if dual combination LABA+LAMA as basic treatment is necessary and ICS as phenotype-specific treatment is added-on or if ICS+LABA as phenotype-specific treatment is insufficient to achieve satisfactory disease control.

Treatment recommendations of the expert group:

- Combination of ICS+LABA should be used in patients with ACO.
- Triple therapy ICS+LABA+LAMA should be used if dual combination LABA+LAMA as basic treatment is necessary or if only ICS+LABA combination is insufficient to achieve satisfactory disease control.

Leukotriene receptor antagonists (antileukotrienes)

Current opinions: There is no evidence supporting the use of antileukotrienes in COPD. Antileukotrienes had no effect on lung function decline in a non-selected COPD population²⁰⁰. However, during long-term montelukast treatment in moderate-to-severe COPD patients, significant improvement of disease symptoms, reduction in ICS and inhaled bronchodilators' need as well as reduction in emergency department referrals and hospitalizations was observed, though no changes in FEV₁ were recorded²⁰¹. These data can be a rationale for antileukotrienes' use in selected patients with ACO.

Treatment recommendation of the expert group:

- Leukotriene receptor antagonists can be considered in patients with ACO phenotype if allergic feature of asthmatic component is present and ICS+bronchodilator combination is not sufficient to achieve satisfactory control of the disease.

10.4.5. BRONCHIECTASES WITH COPD OVERLAP (BCO)

Mucoactive drugs containing thiol group

Current opinions: Basic characteristics of thiol-based mucoactive drugs are presented in the section describing the treatment of frequent exacerbation phenotype. Importantly, erdosteine has an antibacterial effect due to inhibition of bacterial adhesiveness. Erdosteine also increases antibiotic concentrations in the airway mucus²⁰². Mucoactive drugs are recommended in patients with bronchiectasis and difficult expectoration²⁰³.

Treatment recommendation of the expert group:

- Long-term erdosteine or other mucoactive drug (N-acetylcysteine) treatment should be used in patients with bronchiectases and COPD overlap phenotype.

Phosphodiesterase-4 inhibitors (PDE4 inhibitors)

Current opinions: General characteristics of roflumilast are presented in the section describing the treatment of frequent exacerbation phenotype. Data regarding effect of roflumilast in patients with bronchiectases or BCO are lacking. However, roflumilast inhibits neutrophilic airway inflammation in COPD and prevents exacerbations in COPD with chronic bronchitis. Neutrophils are the prominent cell type involved in pathogenesis of both bronchiectases and COPD (ref.²⁰⁴). This could be a rationale for roflumilast use in patients with COPD and bronchiectases.

Treatment recommendations of the expert group:

- Treatment with roflumilast can be considered as complementary treatment in patients with BCO, especially if excessive sputum production and/or frequent exacerbations are present.
- The effect of roflumilast treatment should be evaluated and treatment with roflumilast should be continued only if it's beneficial.
- Limitations of roflumilast treatment are presented in the section describing the treatment of frequent exacerbation phenotype.

Antibiotics

Current opinions: Recent European guidelines recommend long-term treatment by inhaled antibiotics (colistin or gentamicin) as first-line treatment in patients with bronchiectases experiencing exacerbations and/or chronic *Pseudomonas aeruginosa* airway colonisation. The same guidelines support chronic macrolide therapy as a second-line treatment in selected patients with bronchiectases^{203,204}.

Treatment recommendation of the expert group:

- Chronic antibiotic treatment (or inhaled antibiotics) should follow the bronchiectases treatment guidelines, as mentioned above.

Pulmonary rehabilitation

Current opinions: Pulmonary rehabilitation improves exercise capacity and reduces exacerbation rates in patients with bronchiectases. Airway clearance techniques improve mucus clearance and airways inflammation. The ERS guidelines recommend pulmonary rehabilitation programme and regular aerobic exercise as tools to reduce exacerbation rates.

Treatment recommendation of the expert group:

- Pulmonary rehabilitation and airway clearance techniques should be routine part of treatment in patients with BCO.

Other treatments

Current opinions: There is interest in immunostimulating agents. These drugs consist of antigens of several bacterial strains and are designed to stimulate the immune response (for example Broncho-Vaxom). These agents reduced exacerbation rates in COPD patients. Novel treatments are under investigation, for example neutrophil elastase inhibitors or CXC chemokine receptor 2 antagonist CXCR2 (ref.²⁰⁵).

Treatment recommendation of the expert group:

- Immunostimulating agents can be considered as complementary treatment in patients with BCO.

10.4.6. PHENOTYPE OF PULMONARY CACHEXIA

COPD patients with pulmonary cachexia should receive rigorous nutritional support, pulmonary rehabilitation and psychosocial support²⁰⁶. Since pulmonary cachexia more frequently occurs with advanced-stage COPD, treatment of respiratory insufficiency and supportive treatment may be necessary. If patients with pulmonary cachexia experience frequent bacterial exacerbations and/or bronchiectases, long-term antibiotic treatment should be considered. Roflumilast treatment should be avoided.

Treatment recommendations of the expert group:

- Nutritional support, complex pulmonary rehabilitation and supportive care should be used to revert poor prognosis of cachectic patients.
- Long-term antibiotic treatment is recommended if frequent bacterial exacerbations and/or bronchiectases are co-present with cachexia.

10.4.7. MULTIPLE PHENOTYPES' CO-PRESENCE

If more than one clinical phenotype is present, treatment strategy should follow the expression of each clinical phenotype separately. In such patients, multicomponental therapeutic regimens are required, often resulting in a fully individualized care.

10.5. TREATMENT OF RESPIRATORY FAILURE, LUNG TRANSPLANTATION AND PALLIATIVE CARE (END-OF LIFE CARE)**Long-term oxygen therapy**

Current opinions: Long-term oxygen therapy (LTOT) for patients with COPD and chronic respiratory failure improves symptoms, exercise capacity, cognitive function, quality of life and hospitalisation rates. The effect of LTOT on mortality risk remains controversial^{207,208}. Criteria for LTOT in the Czech Republic are: respiratory failure with resting $p_aO_2 < 7.3$ kPa, or p_aO_2 between 7.3 and 8.0 kPa and at least one of four further criteria, i.e., pulmonary hypertension or secondary polyglobulia or arterial oxygen desaturation less than 90% during at least 30% time of sleep or exercise-induced arterial oxygen desaturation. Smoking abstinence is necessary. Possible sources of oxygen for LTOT include oxygen concentrator, portable oxygen concentrator or liquid oxygen. Oxygen should be administered for ≥ 16 h daily. Further indications for oxygen supplementation in COPD include nocturnal hypoxemia, oxygen administration during exercise or during airflight. If hypoxemia with hypercapnia is present, non-invasive ventilation should be considered²⁰⁹.

Treatment recommendation of the expert group:

- LTOT should be considered in severe chronic hypoxemia ($p_aO_2 < 7.3$ kPa) or in moderate hypoxemia coinciding with pulmonary hypertension, polyglobulia,

oxygen desaturation <90% during at least 30% time of sleep or exercise-induced arterial oxygen desaturation.

Domiciliary non-invasive ventilation

Current opinions: The use of long-term domiciliary non-invasive ventilation therapy (dNIV) is the method of choice in stable COPD patients with chronic hypercapnic respiratory failure (indication criteria are listed in Table 5), most frequently in patients with COPD stage/group 4/D. In many cases, there is need to combine dNIV and long-term oxygen therapy (LTOT).

Best clinical outcomes were observed with dNIV preset to achieve the physiological goal of maximal PaCO₂ reduction^{210,211}. This dNIV concept, the so-called high-intensity NIV (HINIV), commonly uses high inspiratory pressures (20-40 mbar, according to patient's tolerance) at the respiratory rate that approaches the spontaneous rate of the patient. Expiratory pressure is usually preset low (3-6 mbar), unless there is need to compensate obstructive sleep apnea (OSA) (ref.^{212,213}). OSA is a common condition and increases mortality in COPD patients²¹⁴. We therefore recommend polygraphy prior to dNIV initiation²¹⁴.

In stable hypercapnic COPD patients HINIV treatment resulted in lower mortality risk, improvement in blood gases, lung function and quality of life (QoL) and enhanced effect of pulmonary rehabilitation^{210,212,215-217}. While dNIV has no proven benefit in patients after acute hypercapnic COPD exacerbation when hypercapnia resolves²¹⁸, dNIV added to LTOT reduced risk of readmission or death when hypercapnia (PaCO₂ >7.0 kPa) persisted for at least 14 days after resolution of acute respiratory acidosis²¹⁹.

Treatment recommendation of the expert group:

- dNIV should be considered in hypercapnic COPD individuals; exact indications are summarized in Table 5.

Lung transplantation

Current opinions: COPD is one of the most frequent reasons for lung transplantation. Lung transplantation improves health status and functional capacity¹. The majority of lung transplants in patients with COPD are bilateral

lung transplantations. Of 19,135 lung transplantations for COPD performed worldwide between January 1992 and June 2017, the median survival was 7 years in patients receiving bilateral lung transplant and 5 years in patients receiving single lung transplant, respectively²²⁰.

Lung transplantation should be considered in patients with very severe COPD with failing conservative treatment. In the Czech Republic, patients with COPD should be referred to the Czech Lung Transplantation Center once fulfilling these criteria: (1) progression of COPD despite maximal treatment including pharmacotherapy, pulmonary rehabilitation and LTOT, (2) BODE score ≥ 5 , (3) PaCO₂ >6.6 kPa and/or PaO₂ <8 kPa, (4) FEV₁ <25% of predicted values.

Contraindications for lung transplantation include history of malignancy in the last 5 years, poorly controlled disease/dysfunction of another major organ system (e.g. heart, liver, kidney, brain), ischemic heart disease not amenable to revascularization, acute instability (including but not limited to acute sepsis, myocardial infarction or liver failure), uncorrectable bleeding disorder, poorly controlled chronic infection by virulent and/or resistant microbe, active tuberculosis, significant chest wall or spinal deformity, obesity with BMI >35 kg/m², psychiatric disorders, patient's non-adherence to treatment, patient's inadequate social support, functional limitation with inability to participate in a rehabilitation program, a history of drug abuse or dependence (e.g., alcohol, tobacco, marijuana, or other illicit substances) (ref.^{221,222}).

Eligible patients are placed on the lung transplant waiting list once fulfilling at least one of the following criteria: (1) BODE score ≥ 7 , (2) FEV₁ <15-20% of predicted values, (3) history of ≥ 3 severe exacerbations during last year, (4) history of at least one severe exacerbation with hypercapnic respiratory failure, (5) moderate to severe pulmonary hypertension. LVRS can be performed in selected patients prior to lung transplantation.

Treatment recommendation of the expert group:

- Patients with very severe COPD eligible for a lung transplant (criteria see above) should be referred to the Czech Lung Transplantation Center, University Hospital Motol, Prague.

Table 5. Indication for use of domiciliary non-invasive ventilation in COPD patients.

dNIV is indicated for stable COPD patients in presence of at least one of the following criteria:

Symptomatic daytime hypercapnia (PaCO₂ ≥ 6.5 kPa)

Nocturnal hypercapnia (PaCO₂ ≥ 7.3 kPa)*

Mild daytime hypercapnia (PaCO₂ 6.0–6.5 kPa) with nocturnal increase ≥ 1.3 kPa*

Persistent hypercapnia (PaCO₂ > 7.0 kPa) for at least 14 days after finishing acute ventilation therapy for acute respiratory acidosis

Hypercapnia increase ≥ 1.0 kPa after oxygen inhalation and concurrently exceeding PaCO₂ ≥ 6.0 kPa[#]

Legend:

PaCO₂ – partial pressure of carbon dioxide in arterial blood

kPa – kiloPascal

* measured by transcutaneous capnometry (or blood gases analysis at awakening)

[#] i.e., hypercapnia increase contraindicating LTOT indication

Palliative and end-of-life care

Current opinions: Patients with advanced-stage (end-stage) COPD should receive palliative care, that should prevent and relieve their suffering. Adequate communication or/and psychological care for patients and their families may be necessary. However, mortality risk prediction may be challenging in patients with severe COPD, since the gradual slow lung functions deterioration can be modified by acute exacerbations, often very frequent and with variable effect on both short-term and long-term outcome.

The main goal of best supportive care is achievement of sustainable quality of life for the patient and his/her family. End-of-life care should be provided to patients in final stage of the disease. Palliative and end-of-life care include various interventions, i.e., pharmacological therapy of COPD symptoms, pain, rehabilitation, oxygen therapy, non-invasive ventilation, administration of opioids, pharmacological sedation or treatment of depression and anxiety. The uncertainty regarding prognosis may play a significant role in discussions with patients and their families and can be a reason why patients with COPD are less likely to receive hospice care services^{223,224}.

Treatment recommendation of the expert group:

- Palliative and end-of-life care including pharmacological therapy of COPD symptoms, pain, rehabilitation, oxygen therapy, non-invasive ventilation, administration of opioids, pharmacological sedation or treatment of depression and anxiety should be offered to patients in final stage of the disease, with treatment choice depending on actual clinical problems.

10.6. TREATMENT OF COMORBIDITIES

All relevant comorbidities should be identified and adequately treated. In general, comorbidities should be treated in usual way, regardless of coincidence with COPD. There are several comorbidities, that deserve special attention since they may strongly influence the natural course of COPD. Some comorbidities are present in COPD patients very frequently and as such, can be perceived as treatable traits of COPD. Coincidence of COPD and multiple prevalent comorbidities can also be viewed as “comorbid phenotype”.

Cardiovascular diseases

Current opinions: Cardiovascular diseases (CVD) coexist with COPD very frequently due to high prevalence of both disease categories in adult and senior populations. As stated above, increased levels of circulating inflammatory mediators and acute-phase proteins are drivers not only by COPD pathogenesis, but also contributors to the development of comorbidities, including CVD, skeletal muscle dysfunction, osteoporosis, depression, cachexia, diabetes mellitus or sleep apnoea syndrome²⁷⁻³².

The coexistence of COPD and CVD has a negative impact on prognosis⁶⁰. CVD as a comorbidity of COPD includes chronic heart failure (CHF), ischemic heart

disease, arrhythmias, atherosclerotic peripheral vascular disease and systemic hypertension. Acute worsening/decompensation of CVD, especially (but not limited to) CHF, ischemic heart disease or arrhythmias, may mimic or accomplish acute exacerbation of COPD and differential diagnosis can be very difficult. Furthermore, exacerbation of COPD may result in decompensation of CVD and *vice versa*. Treatment by oral selective beta₁-blockers and by inhaled selective beta₂-agonists can be used in patients with coexisting CVD and COPD (ref.¹).

Treatment recommendation of the expert group:

- CVDs are main drivers of mortality in COPD patients; therefore, careful management of these comorbidities is warranted.

Gastroesophageal reflux disease (GERD)

Current opinions: Estimated prevalence of GERD among patients with COPD ranges from 17% to 54% (ref.²²⁵). Presence of GERD is associated with greater risk of acute COPD exacerbation²²⁵. It is speculated that GERD may be a driver of certain subtype of COPD exacerbations.

Treatment recommendation of the expert group:

- In patients with frequent exacerbations phenotype, GERD should be treated adequately once diagnosed.

Obstructive sleep apnea (OSA)

Current opinions: OSA is a relatively common comorbidity of COPD with similar physiological and molecular consequences, including hypoxia, systemic inflammation, CVD, pulmonary arterial hypertension and other comorbidities. OSA is rarely present in patients with emphysematous phenotype of COPD (usually associated with low BMI). In contrast, chronic bronchitic phenotype is characterized by peripheral airway mucosal edema, bronchial hypersecretion and increased BMI, and these conditions promote easier development of OSA. Patients with overlap of COPD and OSA have worse prognosis compared to both COPD or OSA alone²²⁶.

Treatment recommendation of the expert group:

- Especially in COPD patients with bronchitic phenotype and overweight, OSA should be considered, eventually raising need for dNIV therapy.

Other comorbidities

Osteoporosis is frequently present with emphysematous phenotype and low BMI. Treatment of osteoporosis should correspond to usual guidelines.

Depression and anxiety are important comorbidities associated with poorer prognosis. Therefore, psychological treatment (or even psychiatric care) and social support should be part of the basic treatment in COPD as mentioned above.

As already mentioned, lung cancer is often associated with COPD, and patients with larger degree of cigarette smoke exposure, with emphysematous phenotype or a

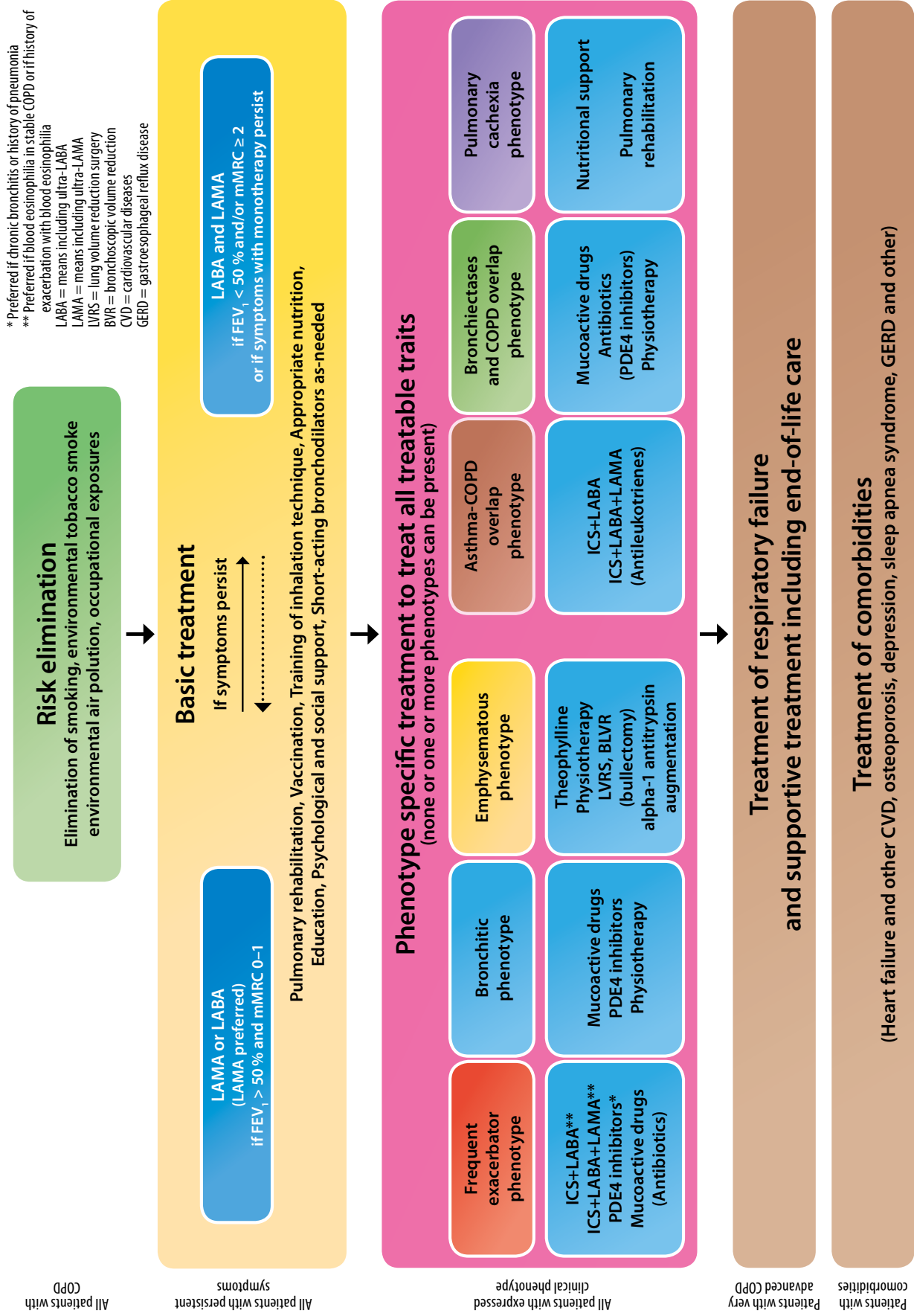


Fig. 11. Flow chart of stable COPD management (Details to each therapeutic modality see in text).

combination of emphysematous and bronchitic phenotypes express higher risk of lung cancer development^{27,34}.

11. FLOW CHART OF MANAGEMENT OF STABLE COPD

After COPD is diagnosed, maximal effort to eliminate risk factors should be made and basic treatment should be started. Clinical phenotype assessment should be done as soon as possible. If at least one phenotype/treatable trait is expressed, phenotype-specific treatment should be started in accordance with each patient's individual needs.

New phenotypes can develop in each individual patient and the present phenotypes may dynamically change over time. Therefore, treatment should be re-evaluated in about one-year periods and eventually adjusted to the actual clinical appearance and circumstances. Not only therapeutic adds-on, but also treatment reduction should be considered in case the current treatment is ineffective or obsolete or when long-term control of phenotype-specific symptoms has been achieved. For example, phenotype-specific treatment should be started with new detection of clinical phenotype or, it can be reduced if manifestation of a clinical phenotype has vanished.

Various types of non-pharmacological treatment are equally important to pharmacological therapies. Above that, all relevant comorbidities should be treated. Patients with advanced COPD and respiratory insufficiency should receive appropriate specialized treatment (e.g., dNIV, LTOT, rehabilitation, psychosocial support) and patients with terminal disease should receive the best supportive/palliative treatment. Complete elaboration is presented in Fig. 11.

12. FUTURE DIRECTIONS AND DEVELOPMENTS

Despite notable progress and changing paradigms during the last twenty years, the integrated effort of researchers and clinicians should be made in several areas in order to improve management and prognosis of COPD (ref.²²⁷).

Early diagnosis in symptomatic, previously undiagnosed populations with high inhalation exposure will probably lead to modifying disease progression. Especially, early smoking cessation is a key factor in effective COPD management. Therefore, screening or early detection programs should be advocated by national and local authorities²²⁸⁻²³⁴. In the Czech Republic, a pivotal early detection programme has been ongoing since 2019 and the results will show if implementation in daily clinical practice will be beneficial – see above Fig. 7 (ref.²³⁵).

The concept of predictive, preventive, personalized and participatory medicine (P4 medicine) for COPD patients has been discussed in recent years²⁶. Personalized approach can better reflect the complexity and heterogeneity of COPD as it provides treatment tailored to the patient's individual needs²⁶. Systems medicine explores disease networks at multiple levels, ranging from the molecular level, through cells, organs, to the population

level²³⁶. A systems medicine approach, integrating genetic, (micro)biological, radiological, clinical, environmental and lifestyle factors in experimental and computational models may advance personalized treatment of COPD (ref.²³⁶).

Another important issue is to identify specific biomarkers or measures not only for early diagnosis and identification of patients responsive to specific treatments, but also for prediction of rapid lung function decline, comorbidities development, exacerbation and mortality risk^{26,237}. Many of these points require a much deeper, integrative and more comprehensive understanding of COPD pathophysiology, natural course of the disease, its genetics and epigenetics and prenatal lung development, along with socioeconomic and environmental factors²⁶. Currently, the most promising target for future therapy development is the pathway of cellular senescence that seems to play an important role in the pathogenesis of COPD and related comorbidities^{35,238}. Other potential targets for new treatment developments include various cytokines or inflammatory molecules involved in the pathogenesis of COPD (ref.²³⁹).

In terms of treatment, a completely new class of inhaled drugs (PDE3/4 inhibitors – ensifentrine, and PDE4 inhibitors) are expected to enter clinical practice soon^{240,241}. Bifunctional bronchodilator molecules with concurrent LABA and LAMA activity are already tested in clinical trials²⁴². Similarly, biopharmaceuticals (particularly anti-IL-5) may be effective in specific subpopulations of patients^{81,243,244}. For currently used treatments, real-life data from daily clinical practice are desired since only a minority of patients are eligible for participation in large RCTs (ref.²⁴⁵). This results in questionable effectiveness of approved treatments for the majority of patient populations. Of non-pharmacological treatment strategies, several new promising bronchoscopic treatment procedures have been developed in recent years, including endobronchial valves or coil placement or liquid nitrogen metered cryospray and targeted lung denervation procedures^{187,246,247}. More emphasis should also be given to pulmonary rehabilitation programs and comorbidity management that are both evolving^{1,248}.

Last but not least, more effort (and at all levels) should be given into preventive programs, measures against smoking and into improvements in occupational and environmental health.

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