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Russian Respiratory Society

Federal guidelines on diagnosis and treatment of chronic obstructive pulmonary disease

Summary

The guidelines have been developed by the Russian Respiratory Society (RRS) based on analysis of papers published during the last 5 years in MEDLINE and ENBASE databases and the Cochrane library. The results of the analysis were subsequently reviewed by independent experts with consideration of the opinion of physicians and general practitioners. A quality and a strength of the evidence were assessed using worldwide criteria.

The guidelines are focused on epidemiology and social burden of chronic obstructive pulmonary disease (COPD), pathogenesis, clinical signs, characterization of phenotypes and severity, current diagnostic and differentiating methods and therapeutic approaches including long-tern oxygen therapy at home, long-term respiratory support at home, surgical treatment, pulmonary rehabilitation, treatment of complications and acute exacerbation of COPD.

The guidelines are fully consistent with requirements of the Healthcare Ministry of Russia for federal guidelines on principal nosologies and treatment techniques.

Key words: chronic obstructive pulmonary disease, guidelines, phenotypes, diagnosis, therapy, long-tern oxygen therapy, long-term respiratory support, medications, surgical treatment, pulmonary rehabilitation.

Methodology

Methods used for gathering / selection of evidence

Electronic databases.

Description of methods used for gathering / selection of evidence

The evidence basis for this document has been publications included in the Cochrane library, ENBASE and MEDLINE databases during the last 5 years.

Methods used for assessment evidence quality:

- expert consensus;
- rating system (Table 1).

Methods used for analysis of the evidence:

- a review of published meta-analyses;
- a systematic review with tables of the evidence.

Description of methods used for analysis of the evidence

While selecting papers as potential sources of evidence, a methodology used in each study has been analyzed to make sure of its validity. Results of this analysis could influence on level of the evidence that in turn could influence on strength of the recommendations (Table 2).

Methodological analysis was based on several key questions which were focused on the study design and greatly influenced on the validity of results and conclusions. The key questions differed according to a type of the study and a system used for the standardized assessment of a paper. The MERGE system was used in the present guidelines; this system was developed by the New South Wales Ministry of Health and was adapted to requirements of the Russian Respiratory Society (RRS) in order to harmonize the balance between strict methodological criteria and practical use. A subjective factor

Table 1
A rating system for assessment evidence quality

Levels of evidence	Description
1++	High quality meta-analyses, systematic reviews of RCTs, or RCTs with a very low risk of bias
1+	Well conducted meta-analyses, systematic reviews of RCTs, or RCTs with a low risk of bias
1–	Meta-analyses, systematic reviews or RCTs, or RCTs with a high risk of bias
2++	High quality systematic reviews of case-control or cohort studies. High quality case-control or cohort studies with a very low risk of confounding, bias, or chance and a high probability that the relationship is causal
2+	Well conducted case-control or cohort studies with a low risk of confounding, bias, or chance and a moderate probability that the relationship is causal
2–	Case-control or cohort studies with a high risk of confounding, bias, or chance and a significant risk that the relationship is not causal
3	Non-analytic studies (e.g. case reports, case series)
4	Expert opinion

RCT – randomized controlled study.

Table 2
A rating system for assessment strength of recommendations

Strength of recommendations	Description
A	At least one meta-analysis, systematic review, or RCT rated as 1 ++ and directly applicable to the target population or a body of evidence consisting principally of studies rated as 1 +, directly applicable to the target population and demonstrating вoverall consistency of results
B	A body of evidence including studies rated as 2 ++, directly applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 1 ++ or 1 +
C	A body of evidence including studies rated as 2 +, applicable to the target population and demonstrating overall consistency of results or extrapolated evidence from studies rated as 2 ++
D	Evidence level 3 or 4 or extrapolated evidence from studies rated as 2 +

In this Table and below the strength of recommendations and the level of evidence are given by Latin letters in round brackets.

could undoubtedly contribute to the assessment, so every study was assessed at least by two independent experts in order to minimize bias. Any inconsistencies in the expert opinions were discussed by the complete Task Force. If the consensus had not been achieved an independent expert was involved.

Evidence tables

Evidence tables were fulfilled by the Task Force members.

Methods used for the recommendation development

Expert consensus.

The Good Practice Points (GPP) indicators

Good Practice was based on clinical experience of the Task Force members.

Economic analysis

A cost analysis was not performed and pharmacoeconomic papers were not analyzed.

The guidelines validation methods

- external assessment;
- internal assessment.

Description of the guidelines validation methods

A preliminary draft of the present guidelines was criticized by independent experts who should evaluate the comprehensibility of the evidence interpretation underlying the guidelines.

General practitioners' and primary care physicians' opinions were considered about importance of the recommendations for everyday practice and ease to understand the evidence.

A preliminary draft was sent to a reviewer, who was not a health professional, to be evaluated from patient perspectives.

The experts' comments were thoroughly systemized and discussed by the Task Force chairman and members. Each point was discussed and all changes in recommendations were registered. In case of refusal to register the changes reasons for refusal were clarified.

Consultation and expert evaluation

The preliminary draft of the guidelines was extensively discussed in RRS website so as persons not participating in the Congress on respiratory disease would have got an opportunity to read, to comment and to improve the guidelines.

The guidelines project was also reviewed by independent experts in order to assess comprehensiveness and accuracy of the evidence interpretation.

The Task Force

The recommendations were revised by the Task Force members for final edition and quality control. The Task Force members concluded that all remarks and commentaries of the experts were considered and risk of bias was minimized.

Principal recommendations

The strength of recommendation (A–D), the level of evidence (1++, 1+, 1–, 2++, 2+, 2–, 3, 4) and GPP indicators are given in the text below.

Definition and epidemiology of chronic obstructive pulmonary disease (COPD)

Definition

COPD is a treatable and preventable disease characterized by persistent airflow limitation that is usually progressive and associated with a significant chronic inflammatory airway response to noxious particles or gases. Acute exacerbations and comorbidities could contribute to severity of COPD in some patients (according to Global Initiative for Chronic Obstructive Pulmonary Disease (GOLD), 2014).

Conventionally, the definition of COPD includes chronic bronchitis and emphysema. Diagnosis of chronic bronchitis is usually clinical and based on cough and sputum production for at least 3 months in two consecutive years. Diagnosis of emphysema is morphological and includes a constant enlargement of the distal airways associated with the alveolar wall destruction but not with fibrosis.

Commonly, patients with COPD have both the conditions that sometimes are hardly distinguishable in early stage of the disease. The definition of COPD excludes bronchial asthma and other diseases associated with partially reversible bronchial obstruction (cystic fibrosis, bronchiectasis, bronchiolitis obliterans, etc.).

Epidemiology

Incidence

Currently, COPD is a global problem. Prevalence of COPD is higher in some countries (in Chile, > 20 %) and is lower in others (i. e. in Mexico). This variability could be explained by differences in the life style, habits and hazardous exposure. A global study (the BOLD project) gave a unique opportunity to evaluate the prevalence of COPD using standardized questionnaires and pulmonary function tests in adult population older than 40 years in developed and emerging countries. According to the BOLD study the prevalence of COPD stage II and higher (GOLD, 2008) was 10.1 ± 4.8 % among subjects over 40 years old including 11.8 ± 7.9 % in males and 8.5 ± 5.8 % in females. An epidemiological survey in Samara region demonstrated that in population aged 30 years and older COPD prevalence was 14.5 % including 18.7 % in males and 11.2 % in females. Another Russian study in Irkutsk region showed the prevalence of COPD in subjects older than 18 years of 3.1 % in urban population and of 6.6 % in rural population.

The prevalence of COPD was increasing with aging and was 10.1 % and 22.6 % in urban males and rural males of 50–69 years old, respectively. In rural regions, COPD was diagnosed almost in every other man older than 70.

Mortality

According to the World Health Organization (WHO) findings, today COPD is the 4th cause of death worldwide. Annually, about 2.75 million people die from COPD that is 4.8 % of the total death number. In Europe, the mortality of COPD significantly varies from 0.20 per 100,000 in Greece, Sweden, Island and Norway to 80 per 100,000 in Ukraine and Romania.

In 1990s – 2000s, the mortality of heart disease at whole and of stroke decreased by 19.9 % and 6.9 %, respectively, whereas the mortality of COPD increased by 25.5 %. The mortality of COPD was particularly high in women.

Mortality predictors in COPD are bronchial obstruction severity, nutritional status [body mass index (BMI)], physical tolerability (according to 6-min walk test results), severity of dyspnea, severity and rate of exacerbations and development of pulmonary hypertension.

Main causes of death in COPD patients are respiratory failure, lung carcinoma and other neoplasms.

Social and economic burdens of COPD

In developed countries, the total cost of care of COPD patients takes the 2nd place among all pulmonary diseases (after lung cancer); the direct cost takes the 1st place with 1.9-fold excess of the direct cost of asthma. Economic burden of one patient with COPD is trice higher than that of a patient with asthma.

A few reports about direct healthcare cost of COPD showed that > 80 % of material resources fell within in-hospital medical care and < 20 % accrued to outpatient medical care. Seventy three per cent of the costs were targeted to treatment of 10 % of patients with severe COPD. Treatment of exacerbations of COPD is the greatest economic burden. In Russia, the economic burden of COPD is 24.1 billion rubles including indirect cost such as absenteeism and presenteeism.

Signs and symptoms of COPD

Usually, COPD develops slowly driven by risk factors such as active or passive smoking, outdoor pollutants, bioorganic fuel, etc., and is gradually progresses. A typical clinical feature of COPD is long-term absence of significant signs and symptoms (D; 3, 4).

First symptoms making the patient to seek medical aid could be cough with or without sputum production and / or breathlessness. These symptoms are more pronounced in the morning. The patients often have got flu in a cold season. These symptoms are the onset of the disease but they could be considered by a physician as smoking-related chronic bronchitis, so, COPD is extremely rarely diagnosed in an early stage.

Chronic cough is a typical early symptom of COPD. It is often underestimated not only by a physician but also by a patient being considered as an expected consequence of smoking and / or of a hazardous ambient exposure. Smokers usually expectorate moderate amount of viscous sputum. Worsening of cough and sputum production is typically noted in winter during infectious exacerbations. The most important symptom of COPD is breathlessness (D; 4). This symptom is a frequent cause for seeking medical aid by the patient and is the main factor limiting physical activity of the patient. Impact of breathlessness on the health status could be assessed by the British Medical Council scale (MRC). In early stage COPD dyspnea occurs during relatively high physical activity such as running on the level or climbing stairs. While the disease is progressing the dyspnea is worsening and could limit everyday physical activity. Further, dyspnea occurs even at rest impeding the patient to leave the house (Table 3). Moreover, dyspnea assessment with the MRC scale is a sensitive tool to predict survival of COPD patients.

When describing clinical features of COPD it is necessary to pay attention on typical signs such as insidious onset, non-specific symptoms, and permanent progression of the disease.

Symptom severity could vary in different phases (stable condition of exacerbation). Stable COPD is generally characterized by symptom severity constant for several weeks or months. As such, the disease progression could be noted only after long-term follow-up of the patient

Table 3
Assessment of dyspnea using MRC scale

Grade	Severity	Description
0	No	I get breathlessness only with strenuous exercise
I	Mild	I get short of breath when hurrying on the level or walking up on a slight hill
II	Moderate	I walk slower than people of the same age on the level because of breathlessness or I have to stop for breath when walking on my own pace on the level
III	Severe	I stop for breath after walking about 100 meters or after a few minutes on the level
IV	Very severe	I am too breathless to leave the house or I am breathless when dressing or undressing

(6 to 12 months). Acute exacerbations (AECOPD) greatly contribute to clinical picture of the COPD. AECOPD is defined as periodical worsening of the patient's condition lasting ≥ 2 to 3 days with increasing severity of symptoms and functional disorders. Increase in the lung hyperinflation and air trapping and reduction in the expiratory airflow are typically seen during exacerbation; this leads to worsening of the dyspnea that could be accompanied by wheezing, chest tightness, and lower physical tolerance. Cough intensity could increase, sputum volume could increase or decrease with change in the sputum color, viscosity and / or expectoration. At this time, parameters of lung function and blood gases could also worsen: the forced expiratory volume in 1 s (FEV_1) and other functional parameters could decrease, hypoxemia and hypercapnia could develop.

Clinical course of COPD encompasses stable condition and exacerbation but their interrelation could differ. A common feature is progressive course of COPD particularly in patients with continuous exposure of inhaled noxious particles or gases.

Also, signs and symptoms are greatly dependent on phenotype which in turn predetermines clinical presentation of the disease. For long time, physicians used to distinguish emphysematous and bronchitic phenotypes of COPD.

The former phenotype is characterized by emphysema as the main pathologic feature with dyspnea predominating over cough. The latter phenotype is characterized by prevalence of bronchitis symptoms (cough, sputum production) with less prominent signs of emphysema. However, "pure" bronchitic or emphysematous phenotype of COPD is very seldom in real clinical practice, so terms "predominantly bronchitic" or "predominantly emphysematous" phenotype are to be more appropriate. In detail, phenotypes of COPD are given in the Table 4.

If a patient has features of both phenotypes, diagnose of the mixed phenotype of COPD should be made. The mixed phenotype is the most frequent in COPD patients.

Recently, other phenotypes have been described. First of all, they include an overlap phenotype (co-existing COPD and asthma). Despite of thorough differentiation between COPD and asthma and important difference in chronic inflammation in these diseases certain patients could have both diseases simultaneously. This phenotype could occur in smoking patients with asthma. Large-scale studies have shown that 20 % to 30 % COPD patients have reversible bronchial obstruction, airway eosinophilic inflammation and good response to inhaled steroids. Some of such patients could be considered as patients with the mixed COPD + asthma phenotype.

Another phenotype that recently has focused attention is a phenotype with frequent exacerbations (> 2 exacerbations per a year or > 1 exacerbation leading to hospitalization). The importance of this phenotype is related to the fact that every exacerbation diminishes functional capacity of the patient. Frequency of exacerbations directly contributes to the patient's survival and requires individual approach to the therapy.

Table 4
Clinical and instrumental characteristics of main phenotypes of COPD

Sign	Predominantly emphysematous phenotype ("pink puffers")	Predominantly bronchitic phenotype ("blue bloaters")
Age at presentation, years	≈ 60	≈ 50
Appearance	Underweight Red face Cold extremities	Overweight Diffuse cyanosis Warm extremities
Prevalent symptom	Dyspnea	Cough
Sputum	Scarce, more often mucous	Abundant, more often mucopurulent
Bronchial infection	Occasionally	Often
Cor pulmonale	Seldom, in terminal stage only	Often
Chest X-ray findings	Hyperinflation, bullous lesions, long narrow heart	Increased lung marking, heart enlargement
Hematocrit, %	35–45	50–55
PaO_2	65–75	45–60
$PaCO_2$	35–40	50–60
Lung diffusing capacity	Decreased	Normal or slightly decreased

PaO_2 – partial oxygen tension in the arterial blood; $PaCO_2$ – partial carbon dioxide tension in the arterial blood.

Thus, distinguishing multiple phenotypes of COPD requires further investigation. Several studies demonstrated clinical differences between men and women suffering from COPD. With similar bronchial obstruction, women with COPD were shown to have more pronounced bronchial hyperresponsibility and more severe breathlessness compared to men. Oxygenation is also better in women than in men with compatible functional values. However, women experience more frequent exacerbations, less benefit of physical rehabilitation, and lower quality of life (QoL) according to standard questionnaires.

Extrapulmonary effects of COPD are well-described. They are caused by the systemic effects of chronic inflammation. First of all, this is pertinent to peripheral skeletal muscle dysfunction that significantly contributes to physical intolerance of the patients. Chronic persistent inflammation involves vascular endothelium and atherosclerosis development in COPD patients that in turn increases morbidity of cardiac disease (ischaemic heart disease (IHD), myocardial infarction, heart failure) and the risk of death. Nutritional disorders are apparent. Poor nutritional status is an independent risk factor of death. The systemic inflammation contributes to osteoporosis. Osteoporosis is more significant in patients with COPD in comparison to subjects of the same age without COPD. Apart from polycythemia, 10 % to 20 % of COPD patients have anemia. The cause of anemia in COPD is not fully understood, however, investigators suppose this is a consequence of chronic systemic inflammation.

Psychological disorders including memory impairment, depression, anxiety and sleep disorders could affect clinical course of COPD.

Comorbid conditions typical for elderly are common in COPD patients (IHD, hypertension, lower limb atherosclerosis). Other comorbidities (diabetes mellitus, gastroesophageal reflux, prostatic adenoma, arthritis) could co-exist with COPD as these diseases are age-related and also influence on clinical course of COPD.

Clinical course of COPD could change as a part of natural history of the disease and complications could develop such as pneumonia, pneumothorax, acute respiratory failure, pulmonary embolism, bronchiectasis, pulmonary hemorrhage, cor pulmonale, chronic heart failure.

Therefore, clinical manifestations of COPD are related to multiple factors. Signs and symptoms of COPD together with risk factors and progression rate modify the patient's image in different periods of his life.

Diagnosis of COPD

The confirmed diagnosis of COPD is primarily based on the key points resulting from the definition of the disease. COPD could be suspected in all patients with coughing, sputum production or breathlessness and with risk factors of COPD. Actually, a smoker with early-stage COPD does not concern about his health because he considers his cough as a normal condition and he is not limited in his physical activity. And later, occurrence of dyspnea is also considered by the patient as a result of ageing or deconditioning.

The key point in medical history of a patient with suspected COPD should be an established pathogenic respiratory exposure, first of all, tobacco smoke. Smoking history is generally expressed as pack-years. Apart from active smoking, one should pay attention on passive smoking. Smoking history should be evaluated in any age including prenatal smoking exposure due to smoking of a pregnant woman or surrounding persons. Other risk factor of COPD could be occupational inhalational hazards including various air pollutants in a workplace (fumes, aerosols) and organic fuel.

Therefore, the diagnosis of COPD should involve the following points:

- identification of risk factors;
- diagnosis of bronchial obstruction;
- monitoring the lung function.

Given this assertion, diagnosis of COPD should include several stages such as:

- creation of the patient's verbal image on the basis of the medical history;
- physical examination;
- laboratory and instrumental investigations, as the diagnosis of COPD should be confirmed by spirometry; postbronchodilator FEV_1 to forced vital capacity (FVC) ratio < 70 % is an obligatory sign of any stage COPD.

Given the absence of specific signs in COPD and the presence of spirometric parameters as diagnostic criteria, the disease could be underestimated. This problem could be aggravated by the fact that most patients with COPD do not fill the illness and do not seek the aid until dyspnea develops. Thus, majority of COPD cases are diagnosed in advanced stages of the disease.

Early diagnosis of COPD could be facilitated by a detailed conversation with every smoking patient, as typical signs of the airway chronic inflammation, such as cough, could be found during an active questioning even in the absence of symptoms. A questionnaire for COPD diagnosis could be used (Table 5).

Dyspnea develops as a result of irreversible lesions of the airways and the lung parenchyma. When asking the patients, physician should evaluate severity of dyspnea, its relation to exercise, etc.

In a patient with early-stage COPD the physical examination could found no signs pertinent to COPD; however, this fact does not exclude COPD. When emphysema and irreversible bronchial obstruction worsening, the patient could exhale through pursed lips; this reflects severe expiratory collapse of the small airways and provides slower expiratory airflow and improvement in dyspnea. Other signs of lung hyperinflation could be a barrel chest and decreased cardiac dullness. Physical examination allows diagnosis of bronchial obstruction by detecting wheezing and the chest hyperresonance to percussion which are also hyperinflation signs.

Obligatory laboratory diagnostic methods include complete blood cell count and sputum cytology. Young patients with severe emphysema need blood α_1-antitripsin concentration to be measured. In AECOPD, neutrophil leukocytosis with left shift and increased erythrocyte sedimentation rate are common. Leukocytosis is an addi-

Table 5
*A questionnaire for COPD diagnosis**

Questions	Answers	Score
What is your age (years)?	40–49	0
	50–59	4
	60–69	8
	≥ 70	10
How many cigarettes do you smoke (or used to smoke if you have quitted smoking) daily (pack-years)	0–14	0
How many years do you smoke?		
Pack-days (number of cigarettes smoked daily divided to 10	15–24	2
Pack-years (pack-days × length of smoking), years	25–49	3
	≥ 50	7
What is your weight (kg)?		
What is your height (meters)?		
What is your body mass index (BMI) (kg / m^2)?	< 25,4	5
	25.4–29.7	1
	> 29.7	0
Do you cough in bad weather?	Yes	3
	No	0
	I do not cough	0
Have you got cough and sputum production if you do not have a cold?	Yes	3
	No	0
Do you have cough and sputum production in the morning?	Yes	3
	No	0
How often are you breathless?	Never	0
	Sometimes	4
Have you got allergy or did you have it before?	Yes	0
	No	3

* – according to: Chronic Airways Disease. A Guide for Primary Care Physicians (2005); ≥ 17 indicates that the diagnosis of COPD is probable; ≤ 16 indicates that other diagnosis should be considered including asthma or the patient should be referred to a respiratory specialist.

tional criterion of infection as a cause of exacerbation. Anemia and polycythemia could resulted from the systemic inflammation. Polycythemia (increased erythrocyte number, high hemoglobin > 16 g / dl in females and > 18 g / dl in males; increased hematocrit > 47 % in females and > 52 % in males) indicates long-term existing severe hypoxemia.

Sputum cytology shows a type and severity of inflammation. Atypical cells found in the sputum are suspicious for malignancy and require additional examination.

Sputum bacteriology is required in patients with uncontrolled progressive infection and for rational antibiotic choice. Bacteriology of bronchial lavage could be done for the same reasons.

Chest X-ray should be performed in all subjects with suspected COPD. This method is not very sensitive; however, it allows excluding other disease with clinical signs resembling COPD (malignancy, tuberculosis, chronic heart failure, etc.). In patients with AECOPD, the chest X-ray could diagnose pneumonia, pleural effusion, spontaneous pneumothorax, etc. Moreover, some evidence of bronchial obstruction could be found in X-ray examination such as flattening and impaired contractility of the diaphragm during breathing, an increase in the anteroposterior diameter of the chest, increased retrosternal airspace, vertical small heart.

Bronchoscopic examination is an additional method to diagnose of COPD and to exclude other disease with similar manifestation.

Electrocardiogram (ECG) and echocardiogram could be used to exclude cardiac disese as a cause of respiratory symptoms and for evaluation of the right heart size.

Spirometry should be performed in all patients with suspected COPD.

Functional tests for diagnosis and monitoring of the course of COPD

Spirometry is one of the main diagnostic methods and confirmation of functional abnormalities in COPD. Spirometric parameters underlie spirometric classification of COPD according to severity of obstructive disorders. Spirometry could also contribute to exclusion of other diseases with similar manifestation.

Spirometry is a preferable initial diagnostic test to detect the airway obstruction and to evaluate the severity of obstructive abnormalities (D).

Methodology

Different recommendations on the use of spirometry for diagnosis and severity classification of obstructive lung disease have been published elsewhere.

- Forced spirometry testing is valid if three technically acceptable and reproducible forced respiratory maneuvers have been obtained (the difference between the largest and the next FVC and between the largest and the next FEV_1 should differ by ≥ 150 mL).

If FVC is ≤ 1000 mL, the maximal acceptable difference between the largest and the next FVC and between the largest and the next FEV_1 should be ≤100 mL.

- If reproducible results were not obtained in three maneuvers, the test should be continued to obtain up to eight maneuvers. Further testing could cause the patient's fatigue and sometimes decrease in FVC or FEV_1.
- If spirometric parameters decrease by ≥ 20 % from the baseline during consecutive forced respiratory maneuvers, the test should be stopped for safety reasons and these changes should be reported in a protocol. The protocol should also include graphic and numeric results of at least three best maneuvers.
- Results of technically acceptable but not reproducible maneuvers could be used to make the conclusion with notification that these maneuvers are not reproducible.

Spirometric signs of COPD

COPD is characterized by expiratory airflow limitation due to increased airway resistance (Fig. 1).

Bronchial obstruction is characterized by decreased FEV_1 / FVC ratio < 0.7 (D).

- Depression of the expiratory part of the flow-volume curve is seen on the Fig. 1. The descendent part of the curve is of a concave shape. Delinearity of the end part of the curve is typical for bronchial obstruction even if FEV_1 / FVC > 0.7. A degree of this change is related to bronchoconstriction severity.

Early signs of bronchial obstruction in asymptomatic subjects could be a concave shape of the expiratory part of flow-volume curve and decreased dynamic lung volumes such as mean expiratory flow between 25 % and 75 % of FVC, forced expiratory flow in 50 % of FVC and forced expiratory flow in 75 % of FVC (2+).

- As bronchial obstruction progresses, the expiratory flow continues to decrease, air traps and lung hyperinflation increase and FVC parameters decrease. To exclude mixed obstructive and restrictive abnormalities the total lung volume (TLC) should be measures using body plethysmography.
- To assess emphysema severity TLC and lung diffusing capacity should be measured.

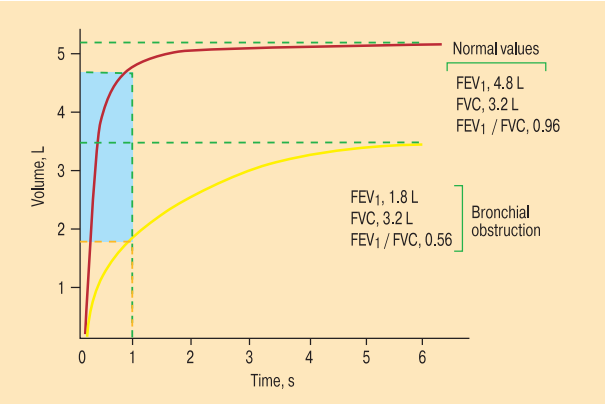

Fig. 1. Examples of spirograms; red line: spirogram of a healthy subject; yellow line: spirogram of a patients with bronchial obstruction

Bronchodilator test

- If a subject demonstrated bronchial obstruction in initial spirometric examination, it is reasonable to perform bronchodilator test to assess bronchoconstriction reversibility.
- Inhaled bronchodilators are used to assess bronchoconstriction reversibility for postbronchodilator FEV_1. Other flow-volume curve parameters are generally calculated from FEV_1 and not recommended for assessment bronchoconstriction reversibility.

Methodology

Short-acting bronchodilators in maximal daily doses are recommended in bronchodilator test:

- β_2-agonists (salbutamol 400 μg);
- anticholinergics (ipratropium bromide 160 μg).

In some cases combinations of short-acting anticholinergics and short-acting β_2-agonists (SABA) in the same doses could be used. Dosing aerosol inhalers should be used with a spacer.

Repeated spirometry should be done in 15 min after inhalation of SABA or in 30–45 min after inhalation of an anticholinergics or combination of an anticholinergics and SABA.

Assessment of bronchodilator response

Bronchodilator test is considered as positive if the bronchodilator response is ≥ 12 % and improvement in absolute units is ≥ 200 mL.

$$\text{Bronchodilator response} = \frac{FEV_{1post}\,(mL) - FEV_{1pre}\,(mL)}{FEV_{1pre}\,(mL)} \times 100\,\%,$$

$$\text{improvement in absolute units (mL)} = FEV_{1post}\,(mL) - FEV_{1pre}\,(mL).$$

FEV_{1pre} is a prebronchodilator FEV_1, FEV_{1post} is a postbronchodilator FEV_1.

Positive bronchodilator response requires achieving both criteria.

A reliable bronchial reversibility should exceed spontaneous variability and a bronchodilator response in healthy subjects. Thus, positive bronchodilator response constitutes improvement in FEV_1 ≥ 12 $\%_{pred.}$ and ≥ 200 mL. When achieving these criteria, bronchial obstruction is defined as reversible (2+).

- When evaluating bronchodilator response, a physician should consider potential adverse effects on the cardiac system such as tachycardia, arrhythmia, hypertension, tremor, agitation.
- Technical variability of spirometric measurements could be minimized by regular calibration of the equipment, thorough instructions of a patient and the personnel training.

Predictive values

Generally, predictive values are related to anthropometric parameters (height, weight, age, and race). Moreover, it is necessary to consider individual normal range variability. In subjects with above-average baseline lung function, parameters would decrease from the baseline after a disease occurs, but they could still maintain within population-based normal range.

Serial measurements

- Serial measurements of FVC and FEV_1 reliably reflect changes in the lung function over time. However, it is necessary to recognize potential technical and biological variability of measurements.
- Changes in FVC and FEV_1 are clinically significant if the difference between serial measurements in the same day exceeds 5 % or the difference between serial measurements in several weeks exceeds 12 %.
- Accelerated lung function decline (> 40 mL per a year) is not an obligatory feature of COPD. This parameter can not be confirmed in an individual as within-test variability of FEV_1 significantly higher and approaches 150 mL.

Measurement of peak expiratory flow rate (PEFR)

- Measurement of PEFR is used to exclude bronchial diurnal hypervariability, which is more typical for asthma, and to evaluate a response to treatment.
- The highest value of three forced expiratory maneuvers performed not later than 2 s after a deep inspiration should be registered. The maneuvers should be performed in the patient's sitting or standing position. More than three maneuvers are recommended if the difference between two highest values exceeds 40 L / min.
- PEFR is used to evaluate the expiratory flow variability in serial measurements during at least 2 weeks. Hypervariability could be seen with serial measurement twice daily. More frequent measurements could improve the assessment accuracy especially in non-compliant patients.
- PEFR variability is better calculated as a difference between the highest and the lowest values (%) relative to the mean or the highest daily PEFR.

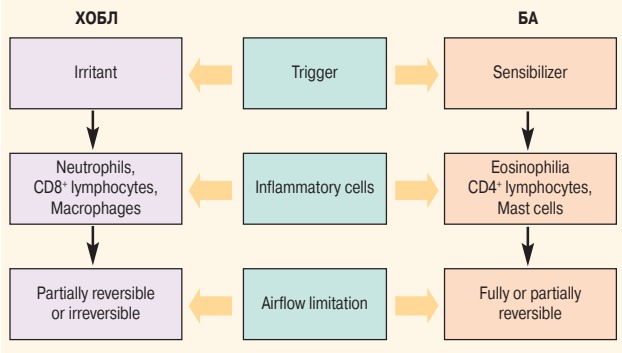

Fig. 2. Inflammation in COPD and asthma

- The upper limit of normal variability of PEFR (% of the best value) is about 20 % if ≥ 4 measurements daily are performed. The upper limit could be lower if measurements are performed twice daily.
- PEFR variability could be higher in diseases resembling asthma. This is a reason for lower specificity of PEFR hypervariability in real clinical practice compared to that in population-based studies.
- Interpretation of PEFR should be done with regard to clinical situation. PEFR monitoring is appropriate only in patients with proven diagnosis of COPD.

Differentiation of COPD

The main task in COPD differentiation is to exclude other diseases with similar manifestations.

Despite of a distinct difference between asthma and COPD in pathogenetic mechanisms, clinical manifestations, treatment and prevention, these diseases have some common features. Moreover, they could co-exist in a patient.

Differentiation of asthma and COPD is based on integral analysis of clinical, functional and laboratory findings. Characterization of inflammation in asthma and COPD is given in the Fig. 2.

Key points in differentiation of asthma and COPD are given in the Table 6.

In certain stages of COPD, particularly in the first presentation, COPD should be distinguished from other

Table 6
Key points in differentiation of asthma and COPD

Asthma	COPD
Inflammation is generally localized in the peripheral airways and does not expand to lung interstitium and parenchyma	Inflammation is generally localized in the peripheral airways and expands to interstitial lung tissue and lung parenchyma resulting in alveolar wall elastic fiber destruction and emphysema development
Risk factors are indoor allergens, pollen, some occupational exposures	Risk factors are tobacco smoking (in ≤ 90 %), fuel combustion products, industrial pollutants and some occupational exposures such as silica, cadmium.
Family history	
Early onset (often)	Age > 35 years
Clinical signs are intermittent and reversible spontaneously or under the treatment and do not progress in uncomplicated asthma	Late onset and slow, but constantly progression of respiratory symptoms. Late diagnosis.
Extrapulmonary allergy	Early diagnosis (in patients with mild course) is possible only during an active detection of cases in high-risk groups
Postbronchodilator FEV_1 improvement ≥ 12 % and ≥ 200 mL	Decline FEV_1 / FVC < 70 %
	Postbronchodilator FEV_1 improvement < 12 % and < 200 mL*

* – positive bronchodilator response does not exclude COPD.

Table 7
Distinguishing features of COPD

Disease	Distinguishing features
Bronchiectasis	Large volume of purulent sputum
	Frequent relapses of bacterial respiratory infection
	Various rhonchi and rales on the auscultation
	Bronchial dilation and thickening of the bronchial wall in chest X-ray or lung CT
Tuberculosis	Onset in any age
	Typical radiological features
	Microbiological confirmation
	Epidemiology (high TB prevalence in the region)
Bronchiolitis obliterans	Onset in young non-smokers
	Previous exposure to hazardous gases or history of rheumatoid arthritis
	Low-density areas in expiratory lung CT
Diffuse panbronchiolitis	Non-smoking males
	History of chronic sinusitis in majority of patients
	Diffuse centrilobular opacities and pulmonary hyperinflation in CT
Chronic heart failure	History of heart disease
	Typical rales in basal zones of the lungs in auscultation
	Enlargement of the heart and pulmonary oedema in chest X-ray
	Restrictive ventilatory abnormalities in most cases

CT – computed tomography.

resembling diseases. Principal distinguishing features of COPD are given in the Table 7.

Different stages of COPD should be distinguished from different conditions. In patients with mild COPD the principal task is to exclude other environmental exposures with asymptomatic or insidious course such as chronic bronchitis. Differential diagnosis is more difficult in patients with severe COPD not only due to severe clinical condition and irreversible abnormalities but also to a number of co-morbidities such as IHD, hypertension, metabolic disorders, etc.

Current classification of COPD. Assessment of severity

Recently, classification of COPD has been based on functional parameters, primarily on postbronchodilator FEV_1. Four stages are determined (Table 8).

The expert panel reviewing GOLD 2011 did not recommend to use the term "COPD stage" given that this staging was based exclusively on FEV_1 and, therefore, inappropriately reflected severity of the disease. Recent studies have demonstrated that stage-to-stage evolution is not always seen in COPD patients and today is not proven. However, FEV_1 is still an actual parameter as it indicates a degree of the airflow limitation from mild (I stage) to very severe (IV stage) and is used for assessment of severity of the patient's condition.

Table 8
Spirometric staging of COPD
(FEV_1 / FVC < 0.7 or 70 %)

COPD stage	Severity degree	FEV_1 $\%_{pred.}$
I	Mild	≥ 80
II	Moderate	50 ≤ FEV_1 < 80
III	Severe	30 ≤ FEV_1 < 50
IV	Very severe	< 30 or < 50 if CRF is present

CRF – chronic respiratory failure.

A new classification of COPD severity, which is based on an integral assessment of the patient, was proposed in

Table 9
COPD Assessment Test (CAT)

For each item below, place a mark (X) in the box that best describes you currently. Be sure to only select one response							
I never cough	0	1	2	3	4	5	I cough all the time
I have no sputum (phlegm) in my chest at all	0	1	2	3	4	5	My chest is completely full of sputum (phlegm)
My chest does not feel tight at all	0	1	2	3	4	5	My chest feels very tight
When I walk up a hill or one flight of stairs I am not breathless	0	1	2	3	4	5	When I walk up a hill or one flight of stairs I am very breathless
I am not limited doing any activities at home	0	1	2	3	4	5	I am very limited doing activities at home
I am confident leaving my home despite my lung condition	0	1	2	3	4	5	I am not at all confident leaving my home because of my lung condition
I sleep soundly	0	1	2	3	4	5	I don't sleep soundly because of my lung condition
I have lots of energy	0	1	2	3	4	5	I have no energy at al

Impact of COPD on the patient's life: 0–10 – low; 11–20 – medium; 21–30 – high; 31–40 – very high.

GOLD 2011. This classification considers not only airflow limitation severity but also clinical information such as exacerbation rate and severity of clinical symptoms according to mMRC scale (the Table 3) and COPD Assessment Test (CAT) (Table 9).

It is well-known that the "gold standard" to assess the disease impact on quality of life (QoL) is the symptom domain of the St. George's Respiratory Questionnaire (SGRQ). CAT is another widespread questionnaire. Today, Clinical COPD Questionnaire (CCQ) is also widely used in clinical practice.

The CCQ questionnaire has been included in GOLD, 2013, and allows more detailed and objective evaluation of daily and weekly symptoms. This questionnaire also allows qualifying and quantifying symptoms (Table 10).

A total score is calculated as a sum of scores of all domains divided by 10. The total score < 1 indicates mild symptoms, the total score ≥ 1 indicates significant symptoms affecting the patient's life. However, CCQ score indicating a significant impact of symptoms on QoL, equally to that of SGRQ, has not yet estimated. Borderline values differing significant symptoms from non-significant symptoms are suggested as 1.0–1.5 (GOLD, 2014).

Thus, COPD classification according to the recent GOLD recommendations is the follow (Table 11):

While assessing a risk it is recommended to choose the greatest degree according to the airflow limitation (spirometric classification) or to exacerbation rate.

According to the GOLD, 2013, the patient should be considered as having the high risk if he experienced even one exacerbation leading to hospitalization (i. e. severe exacerbation) in the previous year.

Thus, the diagnosis of COPD could include the following items:

- phenotype (if available);
- degree of severity of the airflow limitation (I – mild, II – moderate, III – severe, IV – very severe);
- degree of severity of symptoms: severe (CAT ≥ 10, mMRC ≥ 2, CCQ ≥ 1), non severe (CAT < 10, mMRC < 2, CCQ < 1);
- exacerbation rate: rare (0–1) or frequent (≥ 2);
- co-morbidity.

Table 10
Clinical COPD Questionnaire (CCQ)

Please circle the number of the response that best describes how you have been feeling during the past 7 days (choose only one response for each question)							
On average, during the past 7 days, how often did you feel:	Never	Hardly ever	A few times	Sometimes	Often	Very often	Almost all the time
• Short of breath at rest?	0	1	2	3	4	5	6
• Short of breath doing physical activities?	0	1	2	3	4	5	6
• Concern about getting a cold or that your breathing getting worse?	0	1	2	3	4	5	6
• Being depressed because of your breathing problems?	0	1	2	3	4	5	6
In general, during the past 7 days how much time:							
• Did you cough?	0	1	2	3	4	5	6
• Did you produce sputum?	0	1	2	3	4	5	6
On average, during the past 7 days how limited were you in the following activities because of your breathing problems:	Not limited at all	Very slightly slightly limited	Slightly limited	Moderately limited	Very limited	Extremely limited	Totally limited or not enable to do
• Strenuous physical activity (such as climbing stairs, hurrying, doing sports)?	0	1	2	3	4	5	6
• Moderate physical activity (such as walking, housework, carrying things)?	0	1	2	3	4	5	6
• Daily activity at home (dressing, washing yourself)?	0	1	2	3	4	5	6
• Social activity (such as talking, being with children, visiting friends or relatives)?	0	1	2	3	4	5	6

Table 11
Current COPD classification according to GOLD, 2011

Patients' groups	Description	Spirometric classification	Exacerbation rate (for a year)	Dyspnea assessment according to mMRC	COPD assessment according to CAT
A	Low risk Less symptoms	I–II	≤ 1	0–1	< 10
B	Low risk More symptoms	I–II	≤ 1	≥ 2	≥ 10
C	High risk Less symptoms	III–IV	≥ 2	0–1	< 10
D	High risk More symptoms	III–IV	≥ 2	≥ 2	≥ 10

A role of co-morbidity is very important for evaluating the severity of COPD. However, it has not been demonstrated appropriately even in the newest revision of GOLD, 2013.

Therapy of stable COPD

The main goal of therapy of stable COPD is preventing exacerbations (Table 12).

Main therapeutic options for stable COPD

- Non-pharmacological treatment:
  - reduction of risk factor exposure
  - educational programmes
- Pharmacological treatment.

Non-pharmacological treatment options are given in Table 13.

In patients with severe COPD (GOLD II–IV stages), pulmonary rehabilitation should be considered as an obligatory therapeutic method.

Pharmacological treatment

A choice of pharmacological treatment is related to severity of symptoms, postbronchodilator FEV_1 and exacerbation rate (Tables 14, 15).

Pharmacological management of COPD with regard to the comprehensive severity assessment (exacerbation rate, clinical symptoms, spirometric staging) are given in Table 16.

Other treatment methods are long-term oxygen therapy, long-term non-invasive home ventilation and surgical treatment.

Long-term oxygen therapy (LTOT)

One of the most serious complications of COPD is chronic respiratory failure (CRF) which occurs in the advance disease. The main sign of CHR is hypoxemia which is a low oxygen tension in the arterial blood. Oxygen treatment of hypoxemia is the most reasonable therapeutic method for CRF. Compared to other urgent conditions, such as pneumonia, pulmonary oedema,

Table 12
Principal goals of therapy of stable COPD

Short-term goals (to reduce symptoms)	Long-term goals (to reduce risk)
Relief symptoms	Prevent disease progression
Improve exercise tolerance	Prevent and treat exacerbations
Improve QoL	Reduce mortality

Table 13
Non-pharmacological treatment options

Patients' groups	Principal (active) treatment options	Recommended measures	According to national programmes
Any severity COPD	Quitting smoking (using pharmacological methods if needed)	Physical activity	Vaccination against influenza and pneumococcal infection

Table 14
Pharmacological treatment options for patients with stable COPD (according to the level of evidence)

Class of drugs	Administration and effects
Bronchodilators	Bronchodilators are the main drugs for therapy of COPD (A, 1+)
	Inhalation therapy is preferable
	Bronchodilators are administered as needed or regularly (A, 1++)
	LABA are preferable (A, 1+)
	Tiotropium bromide with 24-h action reduces frequency of exacerbations and hospitalization, improves symptoms and QoL (A, 1++) and increases efficiency of pulmonary rehabilitation (B, 2++)
	Formoterol and salmeterol improve FEV_1 and other lung volumes, QoL, reduce symptom severity and exacerbation rate and do not affect mortality and lung function decline (A, 1+)
	Ultra-LABA indacaterol significantly increases FEV_1, reduces dyspnea and frequency of exacerbations and improves QoL (A, 1+)
Combinations of LABA	Combinations of LABA increase treatment efficacy, reduce risk of adverse events and better improve FEV_1 compared to single LABA (B, 2++)
ICS	ICS improve symptoms, lung function, QoL, reduce frequency of exacerbations; do not effect FEV_1 decline and all-cause mortality (A, 1+)
LABA + ICS combinations	Combinations of LABA + ICS could decrease mortality of COPD (B, 2++)
	Combinations of LABA + ICS could increase a risk of pneumonia, but other adverse events were not noted (A, 1+)
	Adding tiotropium bromide to a combination of LABA + ICS could improve lung function and QoL and prevent recurrent exacerbations (B, 2++)
PDE-4 inhibitors	Roflumilast could reduce frequency of moderate to severe exacerbations in patients with severe and very severe COPD c bronchitic phenotype with frequent exacerbations (A, 1++)
Methylxanthines	Theophylline acts as a moderate bronchodilator in comparison to placebo in COPD (A, 1+). Low-dose theophylline could reduce frequency of exacerbations without any effect on postbronchodilator lung function (B, 2++)
Antioxidants	Antioxidants, such as NAC, could play a role in treatment of COPD patients with recurrent exacerbations (B, 2++). In steroid-naive COPD patients, treatment with NAC or carbocisteine could reduce frequency of exacerbations (B, 2++)

LABA – long-acting β_2-agonists; ICS – inhaled steroids;PDE-4 – phosphodiesterase-4; NAC – N-acetylcysteine; QoL – quality of life.

Table 15
Basic medications for therapy of COPD registered in Russia

Medication		Single dose			Duration of action
		by inhalation (device, μg)	by nebulisation, mg / mL	orally, mg	
Short-acting β_2-agonists (SABA)					
Fenoterol		100–200 (MDI)	–	–	4–6
Salbutamol		200 (MDI)	2.5–5.0	4	4–6
Long-acting β_2-agonists (LABA)					
Formoterol		4.5–12.0 (MDI, PI)	–	–	12
Indacaterol		150–300 (DPI)	–	–	24
Olodaterol		2.5 (Respimat)	–	–	24
Anticholinergics					
Short-acting anticholinergics	Ipratropium bromide	4–80 (MDI)	0.25–0.50	–	6–8
Long-acting anticholinergics	Tiotropium bromide	18 (DPI), 5 (Respimat)	–	–	24
	Glycopyrronium bromide	50 (DPI)			24
Combination of SABA + anticholinergics					
Fenoterol + ipratropium bromide		100 / 40 – 200 / 80 (MDI)	1.0 / 0.5	–	6–8
Salbutamol + ipratropium bromide		–	2.5 / 1.5	–	6–8
Methylxanthines					
Theophylline SR		–	–	100–600	≤ 24
ICS					
Beclomethasone dipropionate		50–500 (MDI)	0.2– 0.4	–	–
Budesonide		100; 200; 400 (DPI)	0.25; 0.5; 1.0	–	–
Fluticasone propionate		50–500 (MDI)	–	–	–
Combination of LABA + ICS in a single inhaler					
Formoterol + budesonide		4.5 / 160 (DPI) 9.0 / 320 (DPI)	–	–	–
Salmeterol + fluticasone		50 / 250; 50 / 500 (DPI) 25 / 250 (MDI)	–	–	–
Beclomethasone dipropionate + formoterol		100 / 6 (MDI)	–	–	–
PDE-4 inhibitors					
Roflumilast, μg		–	–	500	24

MDI – metered dosing inhaler; DPI – dry powder inhaler.

Table 16
Pharmacological management of COPD (GOLD, 2014)

Patients' groups	First choice treatment	Alternative treatment	Other drugs
Mild to moderate COPD (postbronchodilator $FEV_1 \geq 50\ \%_{pred.}$) with rare exacerbations and few symptoms (Group A)	The 1st regimen: long-acting anticholinergics as needed The 2nd regimen: SABA as needed	The 1st regimen: long-acting anticholinergics The 2nd regimen: LABA The 3rd regimen: combination of long-acting anticholinergics + LABA	Theophyllines
Mild to moderate COPD (postbronchodilator $FEV_1 \geq 50\ \%_{pred.}$) with frequent exacerbations and few symptoms (Group C)	The 1st regimen: long-acting anticholinergics The 2nd regimen: LABA	The 1st regimen: combination of long-acting anticholinergics + LABA	Short-acting anticholinergics and / or SABA Theophyllines
Severe to very severe COPD (postbronchodilator $FEV_1 < 50\ \%_{pred.}$) with frequent exacerbations and few symptoms (Group C)	The 1st regimen: LABA + ICS The 2nd regimen: long-acting anticholinergics	The 1st regimen: combination of long-acting anticholinergics + LABA The 2nd regimen: combination of long-acting anticholinergics + PDE-4 inhibitor The 3rd regimen: combination of LABA + PDE-4 inhibitor	Short-acting anticholinergics and / or SABA Theophyllines
Severe to very severe COPD (postbronchodilator $FEV_1 < 50\ \%_{pred.}$) with frequent exacerbations and significant symptoms (Group D)	The 1st regimen: LABA + ICS The 2nd regimen: long-acting anticholinergics in addition to the 1st regimen The 3rd regimen: long-acting anticholinergics	The 1st regimen: combination of LABA + ICS + long-acting anticholinergics The 2nd regimen: combination of LABA + ICS + long-acting anticholinergics The 3rd regimen: combination of long-acting anticholinergics + LABA The 4rd regimen: combination of LABA + PDE-4 inhibitor	Carbocisteine, NAC* Short-acting anticholinergics and / or SABA Theophyllines

* – NAC – N-acetylcysteine is widely used in Russia.

Table 17
Indications for LTOT

Indications	PaO_2, mm Hg	SaO_2, %	Special conditions
Strong indications	≤ 55	≤ 88	No
Special indications	55–59	89	Cor pulmonale, peripheral oedema, polycythemia (hematocrit > 55 %)
No indication (excluding special conditions)	≥ 60	≥ 90	Exercise-induced oxygen desaturation
			Sleep-related oxygen desaturation
			Severe dyspnea caused by respiratory disease and improved with supplemental oxygen

trauma, oxygen therapy in patients with chronic hypoxemia should be continued for long time and at home as well.

Hypoxemia has been shown to decrease survival, worsen QoL, increase risk of sleep-related cardiac arrhythmias and result in polycythemia and pulmonary arterial hypertension. LTOT allows diminishing or resolving all negative hypoxemic effects.

Currently, LTOT is one of a few therapeutic methods that enable reduction mortality of COPD patients (A).

Before administering LTOT, it is necessary to ensure that the optimal pharmacotherapy cannot increase PaO_2 above the borderline values.

LTOT is indicated to the following situations (Table 17). In patients with cor pulmonale LTOT should be administered earlier.

Blood gas levels underlying administration LTOT should be assessed in the patient's stable condition only, i. e. 3 to 4 weeks after AECOPD (C) as this time is needed to recover the blood gas exchange and oxygen transport after an episode of acute respiratory failure (ARF).

LTOT is intended to improve hypoxemia and to achieve the target levels of PaO_2 > 60 mm Hg and SaO_2 > 90 %.

LTOT is not recommended to COPD patients if they:

- continue smoking;
- receive suboptimal pharmacological therapy for COPD (bronchodilators, ICS, etc.);
- are not motivated enough for such treatment.

Oxygen flow of 1–2 L / min is recommended for most COPD patients, but in severe patients it could be increased up to 4–5 L / min. The MRC and NOTT studies demonstrated that the efficient duration of LTOT is ≥ 15 h / day (A). The longest oxygen treatment gap should not exceed two hours.

LTOT algorithm in COPD patients is given in Fig. 3.

LTOT > 15 h /day increases survival of COPD patients with CRF and severe resting hypoxemia (B, 2++).

Oxygen concentrators, which are independent oxygen sources, are used for LTOT at home. They separate the atmospheric air into oxygen and nitrogen using a "molecular sieve" which constitutes zeolyte or aluminosilicate filters.

Long-term non-invasive home ventilation

Hypercapnia (increase $PaCO_2$ tension in the arterial blood) ≥ 45 mm Hg) is a marker of reduced ventilation reserve in the terminal stage of chronic lung disease; it is a poor prognostic factor for COPD patients. Nighttime hypercapnia changes the respiratory centers' sensitivity to CO_2 (resetting) resulting in increased daytime $PaCO_2$ level and dysfunction of the heart, the brain and respiratory muscles. Respiratory muscle dysfunction together with high resistive, elastic and threshold load on the respiratory system leads to further worsening in hypercapnia in patients with COPD; thus, a "vicious circle" develops. This relationship could be broken only by respiratory support (ventilation). Given irreversible structural abnormalities underlying functional disorders in COPD, the respiratory support should be performed for long time as in the case of LTOT including home ventilator support. Long-term non-invasive home ventilation is a method of long-term respiratory support in patients with stable CRF who do not need intensive therapy.

In COPD patients long-term non-invasive home ventilation is accompanied by certain pathophysiological effects such as improvement in the gas exchange (increase in PaO_2), exercise tolerability (A), decrease in $PaCO_2$ (A), improvement in respiratory muscle function (B) and quality of sleep (B), reduction in the lung hyperinflation (B).

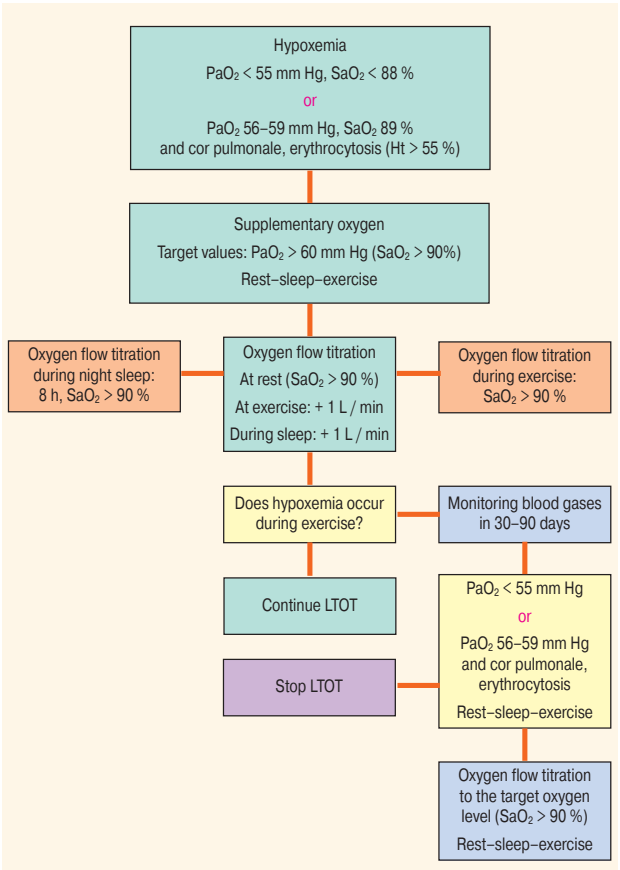

Fig. 3. Algorithm of LTOT

Long-term non-invasive home ventilation should be administered to COPD patients if they have:

- respiratory failure symptoms (fatigue, breathlessness, morning headache);
- any of the following signs:
- $PaCO_2 > 55$ mm Hg;
- $PaCO_2$ 50–54 mm Hg plus nighttime desaturation ($SpO_2 < 88$ % during > 5 min under supplemental oxygen 2 L / min);
- $PaCO_2$ 50–54 mm Hg plus frequent hospitalizations due to recurrent exacerbations (≥ 2 hospitalizations for the previous 12 months).

Patients who receive long-term non-invasive home ventilation should use a respirator at night and could use it for several hours at daytime (B). Parameters of ventilation are generally chosen in a hospital; then, patients should be followed regularly at home and the respirator should be maintained by specialists. Commonly, the long-term non-invasive home ventilation is accompanied by oxygen supplementation using an oxygen concentrator or a reservoir with liquid oxygen. Supplemental oxygen should be dosed as in LTOT (to achieve $PaO_2 > 60$ mm Hg and $SaO_2 > 90$ %).

The combination of the long-term non-invasive home ventilation and LTOT could be effective in certain patients especially in those having significant daytime hypercapnia.

The long-term non-invasive home ventilation is not recommended to COPD patients if they have:

- severe dysphagia and uncontrolled expectoration (if a mask is used);
- low adherence and compliance;
- agitation;
- severe cognitive disorders;
- need in continuous (24-h) respiratory support;
- insufficient financial or insurance resources;
- inability to provide the patient's follow-up.

Technical support for the long-term non-invasive home ventilation

Portable respirators are usually used at home. They have small size and low cost, are easy to control and can control even significant leak. However, such respirators do not have functions of monitoring and alarm similar to respirators for critical care. Most portable respirators used a single circuit (inspiratory) and expiratory volume is withdrawn through an expiratory valve or special orifices in a mask or a circuit.

Surgical treatment

Lung volume reduction surgery is a resection of a part of the lung in order to reduce lung hyperinflation and improve respiratory muscle work. This surgical method is applied in COPD patients with emphysema of the upper lung areas and low exercise tolerance.

Lung transplantation could improve QoL and lung function in thoroughly selected patients with very severe COPD. Selection criteria are $FEV_1 < 25$ % $_{pred.}$, $PaO_2 < 55$ mm Hg, $PaCO_2 < 50$ mm Hg while breathing the room air, and pulmonary hypertension (Ppa > 40 mm Hg).

Exacerbation of COPD

Definition and a role of exacerbation of COPD

An exacerbation is a typical event in the course of COPD. According to the definition of COPD (2013), an exacerbation is an acute event characterized by a worsening of respiratory symptoms beyond their day-to-day variability which requires change in the therapy.

Exacerbations of COPD are one of the most frequent causes of seeking an emergent medical aid by the patient. Frequent exacerbations of COPD lead to long-term (up to several weeks) decrease in lung function and in the blood gas exchange, more rapid progression of the disease, significant decrease in QoL and in high healthcare costs. Moreover, an exacerbation of COPD could be accompanied by a worsening of co-morbid chronic diseases. Severe exacerbations of COPD are the most frequent cause of death of these patients. A risk of acute myocardial infarction increases more than twice in first 5 days of exacerbation of COPD.

Classification of exacerbations of COPD

One of the most renowned classifications of exacerbations of COPD is given in the Table 18. This classification was proposed by the Task Force on definition of exacerbation of COPD.

A new scale has been developed to evaluate prognosis of hospitalized patients with AECOPD. Five strongest mortality predictors were selected, such as dyspnea severity according to eMRCD scale, peripheral blood eosinopenia (< 0.05 cells $\times 10^9$ / L), consolidation of the lung parenchyma according to the chest X-ray examination, blood acidosis (pH < 7.3) and atrial fibrillation. These signs were grouped in the DECAF scale (Table 19).

Causes of exacerbation of COPD

The most common causes of exacerbation of COPD are bacterial and viral respiratory infections and air pollutants. In 20–30 % of cases the cause of exacerbation is not found.

The most important bacteria causing exacerbation of COPD are untypable strains of Haemophilus influenzae, Streptococcus pneumoniae and Moraxella catarrhalis. Studies showed that the most frequent pathogens in patients with severe exacerbation of COPD are gram negative microorganisms and Pseudomonas aeruginosa (Table 20).

Table 18
Severity of exacerbation of COPD

Severity	Treatment
Mild	Enhancement the therapy self-managed by the patient
Moderate	Enhancement the therapy by a physician in an outpatient setting
Severe	Hospitalization is required due to an obvious and / or rapid worsening the patient's condition

Table 19
DECAF scale for evaluating prognosis in patients with exacerbation of COPD

Parameter	Score
Dyspnea	
eMRCD 5a*	1
eMRCD 5b**	2
Peripheral blood eosinopenia (< 0.05 cells × 10^9 / L)	1
Consolidation	1
Acidosis (pH < 7.3)	1
Atrial fibrillation	1
Total score	

* – eMRCD 5a – dyspnea in low physical exercise, but the patient enables washing himself and dressing independently; ** – eMRCD 5b – dyspnea in low physical exercise; the patient does not enable self-care.

Rhinoviruses are a frequent cause of acute respiratory viral infection and could be an important cause of exacerbation of COPD. Exacerbations of COPD are noted to occur more often in autumn and winter. An increase in exacerbation rate in this season could be related to increased prevalence of viral respiratory infections and increased sensitivity of the upper airway epithelium to respiratory viruses in a cold season. Conditions resembling or worsening exacerbation are pneumonia, pulmonary embolism, chronic heart failure, arrhythmias, pneumothorax, and pleural effusion. These diseases should be distinguished from exacerbation of COPD and require an appropriate treatment.

Treatment of exacerbation of COPD

Management of patients with exacerbation of COPD according to its severity is given in the Table 18.

Inhales bronchodilators

Inhaled bronchodilators are one of the most important components of therapy of exacerbation of COPD (A, 1++).

Routinely, SABA (salbutamol, fenoterol) or short-acting anticholinergics (ipratropium) are administered in patients with exacerbation of COPD. The efficacy of SABA and ipratropium in exacerbation of COPD is equal (B, 2++). An advantage of SABA is more rapid onset of action; an advantage of anticholinergics is a good safety and tolerability. Combination of SABA plus ipratropium is currently supposed as the optimal management strategy in exacerbation of COPD (B, 2++) especially in severe exacerbation.

Steroids

Clinical trials with hospitalized patients with exacerbation of COPD showed that therapy with systemic steroids shortens duration of exacerbation, improves lung function (FEV_1) and arterial hypoxemia (PaO_2) and could reduce a risk of early relapse and treatment failure and shorten a hospitalization length (A, 1+). Routinely, 30–40 mg of prednisolone is administered daily for 5–14 days (B, 2++). According to recent study results, patients with exacerbation of COPD and blood eosinophilia > 2 % better respond to systemic steroids (C, 2+). Inhaled and particularly nebulized steroids are a safe alternative for systemic steroids in exacerbation of COPD (B, 2++).

Antibacterial therapy

Bacterial infection is a cause of about 50 % of all exacerbations of COPD. Hence, it is important to define indications for antibiotic administration in exacerbation of COPD. According to current guidelines antibiotics should be used in patients with severe exacerbation, i. e. with Anthonisen type 1 (worsening dyspnoea with increased sputum volume and purulence) or type 2 (change in any two of these symptoms) exacerbations (B, 2++). Antibacterial therapy is most effective in such patients as exacerbations of these types are caused by bacterial infection. Antibiotics should also be used in patients with severe exacerbation of COPD needed mechanical or non-invasive ventilation (NIV) (D, 3). Diagnosis and treatment approach to exacerbation of COPD could be improved when biomarkers are used such as C-reactive protein (CRP) (C, 2+). Increased CRP ≥ 10–15 mg / L in a patient with exacerbation of COPD is a sensitive marker of bacterial infection.

A choice of the optimal antibacterial drug to treat exacerbation of COPD depends on many factors such as severity of COPD, risk factors of poor outcome (elderly, low FEV_1, history of frequent exacerbations, co-morbidity, previous antibacterial treatment) (D, 3). In patients with mild to moderate exacerbation of COPD without risk factors, amoxicillin, newer macrolides (azithromycin, clarithromycin), and cephalosporins (cefepim, etc.) are recommended (the Table 20), The first-line therapy in

Table 20
Possible causative pathogens in exacerbation of COPD with regard to severity of the disease

Severity of COPD	FEV_1, $\%_{pred.}$	The most common pathogens	First-choice antimicrobial
Mild to moderate without risk factors	> 50	H. influenzae, Moraxella catarrhalis, S. pneumoniae, Chlamydia pneumoniae, Mycoplasma pneumoniae	Amoxicillin, macrolides (azithromycin, clarithromycin), 3rd generation cephalosporins (cefepim, etc.)
Mild to moderate with risk factors*	> 50	H. influenzae, M. catarrhalis, PRSP	Amoxicillin / clavulanate, respiratory quinolones, (levofloxacin, gemifloxacin, moxifloxacin)
Severe	30–50	H. influenzae, M. catarrhalis, PRSP, gram negative microorganisms	
Very severe	< 30	H. influenzae, PRSP, gram negative microorganisms, P. aeruginosa**	Ciprofloxacin and other antipseudomonas antibiotics

PRSP – penicillin-resistant S. pneumoniae, * – risk factors: age ≥ 65 years old; heart co-morbidity; frequent exacerbations (≥ 2 per a year); ** – P. aeruginosa infection predictors: frequent antibiotic treatment (> 4 for the previous year); FEV_1 < 30 $\%_{pred.}$; yielding P. aeruginosa during previous exacerbations; P. aeruginosa colonization; frequent courses of systemic steroids (prednisolone > 10 mg / day during previous 2 weeks); bronchiectasis.

patients with severe exacerbation and risk factors is amoxicillin / clavulanate or respiratory quinolones, (levofloxacin, gemifloxacin, moxifloxacin) (B, 2++). In patients with high probability of P. aeruginosa infection ciprofloxacin and other antipseudomonas antibiotics are recommended (B, 2++).

Supplemental oxygen

Hypoxemia is a life-threatening condition; hence, supplemental oxygen is the crucial component of therapy of ARF in exacerbation of COPD (B, 2++). This therapy is intended to maintain PaO_2 level as high as 55-65 mm Hg and SaO_2 88–92 %. In COPD patients with ARF nasal cannulae or a Venturi mask could be used to deliver oxygen. When cannulae are used, the oxygen flow rate of 1–2 L / min is sufficient for most patients (D, 3). The Venturi mask is preferable way to deliver oxygen as the oxygen fraction in the inspired gas mixture (FiO_2) can be maintained more constantly with this mask independently on minute ventilation and the patient's inspiratory flow. In average, PaO_2 increases by 10 mm Hg under the therapy with supplemental oxygen at FiO_2 24 % and by 20 mm Hg at FiO_2 28 %. It is recommended to perform blood gas analysis in 30–60 min after the oxygen therapy had been started or changed (D, 3).

Non-invasive ventilation

A novel approach to respiratory support, non-invasive ventilation (NIV), that is pulmonary ventilation without use of artificial airways, allows safe and effective unloading respiratory muscles, improve gas exchange and dyspnea in patients with ARF. The patient is connected to a respirator with a nasal or face mask (or helmet and mouthpiece that is uncommon). During NIV the patient is conscious and usually does not need sedation or muscle relaxation. Another advantage of NIV is the ability to stop and renew it as quickly as needed.

NIV is recommended in COPD patients with ARF and the following features:

- symptoms and signs of ARF:
- significant resting breathlessness;
- the respiratory rate >24 per a minute, involvement of accessory respiratory muscles, paradoxical retraction of the lower costal margin during inspiration.
- gas exchange abnormalities:
  - $PaCO_2 > 45$ mm Hg, pH < 7.35;
  - $PaO_2 / FiO_2 < 200$.

NIV is not recommended in COPD patients with ARF if they have:

- respiratory arrest;
- unstable hemodynamics (hypotonia, uncontrolled arrhythmias, myocardial ischaemia);
- a risk of injury of the airways (coughing or swallowing disorders)
- excessive bronchial hypersecretion;
- consciousness disorders (agitation or consciousness impairment), poor compliance.

Ineligible candidates for this method of respiratory support are patients with AFR required an urgent tracheal intubation and mechanical ventilation (C, 2+). NIV is the only proven therapeutic method which could reduce mortality in COPD patients with AFR (A, 1++).

Mechanical ventilation

Mechanical ventilation should be performed in COPD patients with ARF who failed to improve with medications or other non-invasive treatment (NIV) (B, 2++). Despite a lack of conservative treatment efficacy and severity of functional abnormalities, a rate of decline and potential reversibility of the disease underlying ARF should be considered before starting the mechanical ventilation.

Strong indications for mechanical ventilation in patients with acute exacerbation of COPD and ARF:

- respiratory arrest;
- significant consciousness disorders (spoor, coma);
- unstable hemodynamics (systolic arterial pressure < 70 mm Hg, the heart beat rate < 50 / min or > 160 / min);
- respiratory muscle dysfunction.

Special indications for mechanical ventilation in patients with acute exacerbation of COPD and ARF:

- respiratory rate > 35 / min;
- arterial blood pH < 7.25;
- $PaO_2 < 45$ mm Hg despite of supplemental oxygen.

Commonly, a comprehensive clinical and functional evaluation of the patient is performed before starting the respiratory support. COPD patients should be weaned from mechanical ventilation as soon as possible (B, 2++), as every additional day with invasive respiratory support dramatically increases a risk of complications such as ventilator-associated pneumonia (A, 1+).

Mobilisation and elimination of bronchial mucus

Mucus hyperproduction and impaired transport from the airways could constitute a great problem in many patients with severe exacerbation of COPD.

In recent studies, mucoactive drugs, such as NAC or erdosteine, stimulate resolution of COPD exacerbation and contribute to reduction in systemic inflammation (C, 2+). Special methods to improve the airway drainage, such as high-frequency percussive ventilation, could significantly improve the patient's condition. The high-frequency percussive ventilation is a respiratory therapeutic method when small air volume are delivered to the patient's airways with a high controlled frequency of 60 / min to 400 cycles / min and with a controlled pressure using a special open breathing circuit phasitron. Percussive ventilation could be delivered via a mask, mouthpiece, tracheal or tracheostomic tubes. Another method is high-frequency chest wall oscillations which are transferred to the airways and the airflow through the chest wall. High-frequency oscillations are produced with an inflatable vest which clings to the chest and is connected with an air compressor.

COPD and co-morbidity

COPD together with hypertension, IHD and diabetes mellitus forms a group of chronic diseases accounting >

Table 21
The most prevalent co-morbidity in COPD

Co-morbidity	The prevalence rate, %
Cardiac disease	42.0
Osteoporosis	28–34
Depression	35–42
Lower respiratory tract infection	67–72
Sleep apnea syndrome	17–26
Cataract	31–32
Pulmonary embolism	10–20
Impotency	37–43

30 % of the total morbidity. Co-morbidity in COPD often worsens prognosis. The most prevalent co-morbidity in COPD is given in the Table 21.

In patients with COPD, the risk of death increases as number of co-morbidity increases; the risk of death is not related to FEV1 (Fig. 4).

Common causes of death in COPD patients are given in the Table 22.

In large population-based studies, a risk of cardiac death in COPD patients was 2–3-fold higher that in patients of the same age not suffering from COPD and was about 50 % of all-cause death rate.

The commonest co-morbidity in COPD is cardiac disease. This is the most frequent and the most serious co-morbidity in COPD. This group of diseases includes IHD, CHF, atrial fibrillation and hypertension; the latter is the most frequent co-morbidity in COPD.

Sometimes, treatment of co-morbidity in COPD patients is controversial as drugs administered for the cardiac pathology, such as angiotensin-converting enzyme inhibitors or β-adrenoblockers, could worsen the course of COPD (a risk of increasing cough, dyspnea, developing or worsening bronchoconstriction) whereas medication for therapy of COPD (bronchodilators, ICS) could affect the course of cardiac disease (a risk of arrhythmias and hypertension). The cardiac disease in COPD patients should be treated in line with guidelines; evidence are lacking that the cardiac disease in COPD patients should be treated in a different way. If a patient with COPD and cardiac co-morbidity needs treatment with a β-adrenoblocker, a selective β-adrenoblocker should be preferred. Osteoporosis and depression are important co-morbidities that are frequently underdiagnosed. However, these diseases are associated with decreased health status and poor prognosis. It is recommended to avoid repeated courses of systemic steroids for exacerbation of COPD as they significantly increase a risk of osteoporosis and bone fractures. Recently, metabolic syndrome and diabetes mellitus are frequent co-morbidities in COPD patients. Diabetes significantly impacts COPD course and worsens prognosis. Patients with COPD and type 2 diabetes demonstrated more severe respiratory failure, more frequent exacerbations, more severe IHD, CHF and hypertension, progressive pulmonary hypertension despite of milder pulmonary hyperinflation.

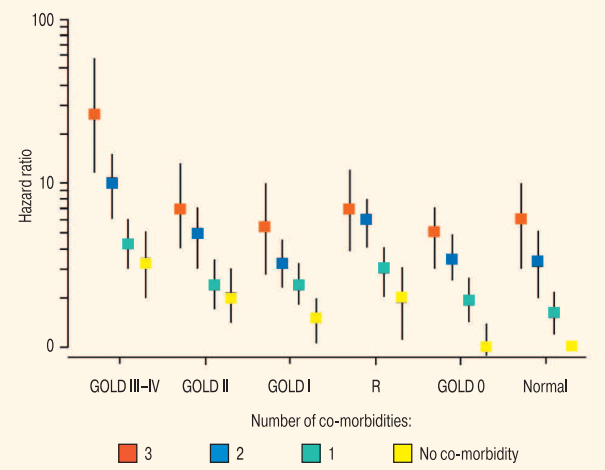

Fig. 4. Relation between comorbidity and risk of death in COPD

Table 22
The main causes of death in COPD patients, %

Lung disease	35
Cardiac disease	27
Malignancy	21
Other	10
Unknown	7

The most common cause of death in patients with mild COPD is lung carcinoma. In patients with severe COPD surgical treatment of lung carcinoma is significantly limited because of declined lung function.

Pulmonary rehabilitation and education of COPD patients

One of recommended adjuvant therapeutic methods in COPD stage II and higher is pulmonary rehabilitation. This method was demonstrated to improve physical tolerability (A, 1++) and daily activity, to reduce in dyspnea perception (A, 1++) and severity of anxiety and depression (A, 1+), to decrease rate and length of hospitalizations (A, 1++) and recovery time after discharge, to improve QoL (A, 1++) and survival.

Pulmonary rehabilitation is a multidisciplinary program based on a patient-oriented treatment. Besides physical training, it includes educational and psychosocial programs intended to improve physical and emotional status and the patient's adherence to the treatment. According to ERS / ATS recommendations, 2013, the rehabilitation course should be continued for 6–12 weeks (≥ 12 sessions with duration of ≥ 30 min each twice a week) and should include the following parts:

- physical training;
- nutritional support;
- the patient's education;
- psychosocial support.

This program could be hold both in outpatient and inpatient setting under the supervision of medical staff or independently after education and training. Group education of COPD patients is less effective compared to an individual training (D) as the group education does not lead to reduction in number of exacerbations though it could reduce exacerbation severity (B).

The principal component of pulmonary rehabilitation is physical training which increases the efficacy of treatment with LABA (B, 2++). A comprehensive approach to physical training includes strength and endurance exercises, walking, training of upper and lower extremities muscles using expanders and dumbbells, stepping and cycling. These types of training also involve different joints and improve fine motor skills of the wrist. Physical training could be performed in different ways: prolonged training, interval training, or resistive training. Low-flow oxygen and / or NIV could be given to the patient during a training session if needed. A physical training program should be individualized and take into account COPD course (it is possible to start training early after the exacerbation of COPD), severity of the disease and co-morbidity, functional parameters. First sessions should be hold with the control of blood saturation, breathing rate, heart beat rate, blood pressure; ECG monitoring is also recommended.

Skeletal muscle training should be accompanied by breathing techniques intended to train the optimal breathing pattern that could be of additional benefit (C, 2++). The breathing techniques should include respiratory muscle training (D) with special trainers (Thresholds PEP and IMT) which selectively train inspiratory and expiratory muscles.

Nutritional support is targeted to muscle strength maintenance using high protein and vitamin diet. The nutritional support is necessary not only for cachectic and hypotrophic patients but also for obese patients (BMI $\geq$ 30 kg / m^2).

Apart from physical rehabilitation, significant attention should be paid to the patient's self-management of the disease.

In regions with limited healthcare resources, the pulmonary rehabilitation could be minimize to physical training only (B).

The present guidelines are fully consistent with requirements of the Healthcare Ministry of Russia for federal guidelines on principal nosologies and treatment techniques.