

Recommendations for the management of patients with chronic obstructive pulmonary disease (COPD) at primary and specialist pulmonary levels in Slovenia

Priporočila za obravnavo bolnika s kronično obstruktivno pljučno boleznijo na primarni in specialistični pulmološki ravni v Sloveniji

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Abstract

The purpose of this paper is to implement the guidelines proposed by GOLD in the Slovenian health-care system, and to describe the cornerstones of the management of this disease. The document is meant to serve as an agreed approach to the management of COPD patients.

Izvleček

Z dokumentom želimo smernice, ki jih predlaga GOLD, umestiti v slovenski prostor in opisati temelje obravnave te bolezni. Dokument naj bi služil čim bolj enotnemu oz. dogovorjenemu pristopu k obravnavi teh bolnikov.

1. Introduction and the purpose of this paper

Chronic obstructive pulmonary disease (COPD) is a common condition dealt with by physicians at all levels of health care. Making differential diagnosis and/or accurate definitive diagnosis within the scope of obstructive pulmonary diseases is often challenging. The purpose of this paper is to implement the GOLD guidelines into the Slovenian health care system, and to describe the basic COPD treatment options (1,2). Moreover, these recommendations should serve as a reference point for a unified and agreed-upon approach to

the management of COPD patients (3). The paper focuses on the cooperation between health providers at different levels of patient treatment.

The organization of patient treatment and the level of cooperation between health providers at different levels of patient care in Slovenia differ from one region to another, mirroring the overall functioning of the regional health care system. Specialists in secondary care should have a role in developing pneumonology in the region and should be involved in the training of general physi-

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cians (GPs). They should be responsible for the accessibility and quality of diagnostic tests. Also, they should be in contact with primary care specialists regarding the referral of emergency patients to appropriate health care centres where they can get the treatment they need, but is unavailable in their region.

Epidemiology

COPD is characterized by an irreversible and progressive obstructive airway disorder, leading to premature death. The condition is common. In recent years approximately 50 persons in Slovenia have died due to the consequences of COPD each year. According to WHO, COPD is the fourth leading cause of death worldwide (4).

COPD most often affects smokers (1). The most characteristic clinical manifestations of COPD include chronic cough, exertional dyspnea and reduced exercise performance. Each smoker who coughs does not necessarily have COPD. Approximately 20 % of smokers develop COPD. The disease is accompanied by exacerbations (aeCOPD). Severe forms of the disease are characterized by frequent, severe and life-threatening aeCOPD.

The GP who first sees a patient with dyspnea and chronic cough should consider COPD in the differential diagnosis, because COPD is one of the most frequent causes of chronic exertional dyspnea. Obstructive airway disorder in patients with COPD is checked by spirometry. Lung function does not normalize after the application of a bronchodilator.

GPs should provide initial diagnostic tests, diagnosis and treatment and are responsible for coordinating the COPD patient's care. Because of a wide variety of conditions that can be considered in the differential diagnosis of obstructive airway disorder, and because these pati-

ents usually present with comorbidities, it is recommended that patients with an obstructive airway disorder be referred to a health care provider at a secondary or tertiary level of health care (1).

3. Diagnosis

Recommendation 1	D
Patients with an undiagnosed COPD are sought among ex- and/or active smokers, as well as among individuals older than 40 years who have been exposed to unfavourable environmental conditions.	
Recommendation 2	A
Spirometry is the basic diagnostic test. We must not diagnose COPD without performing spirometry.	

The following factors should always be checked (1,2,3,5,6) when treating a patient with a suspected COPD:

The patient is a long-time smoker (at least ten packs of cigarettes/year) or an ex-smoker.

- The patient has worked, or is working, in an environment massively exposed to dust or chemicals (vapours, irritants, smoke).
- The patient is older than 40 years.

It is of equal importance to identify patients with mild symptoms who smoke and have been diagnosed with early-stage COPD, because the cessation of smoking stops the progression of the disease.

The basic test in diagnosing COPD is **spirometry** (1,2,6). GPs should perform spirometry in long-time smokers or refer them to a secondary level health care center for testing, particularly those with signs of chronic bronchitis and/or

Confirmation: These recommendations were compiled at coordination meetings of a working group of specialists treating pulmonary diseases at the secondary and tertiary levels, and general practitioners. Recommendations were presented at the annual meeting of the Slovenian Respiratory Society on November 27, 2015. After consideration of corrections and suggestions, the recommendations for the management of COPD were confirmed at the Slovenian Respiratory Society Management Board and Member Meeting, held on March 30, 2016 in Ljubljana.

dyspnea on exertion. Perfectly normal spirometry results exclude COPD. On the other hand, it is recommended that all patients with abnormal test results (compatible with obstructive or restrictive disease) be referred to pulmonary outpatient units at the secondary or tertiary levels for lung function testing.

3.1 Evaluation of spirometry results

Recommendation 3	A
A positive bronchodilator test does not exclude COPD. The disease can only be excluded with normal spirometry results after bronchodilator administration (normalized TI, and an increase in FEV ₁ to normal predicted value).	

In a healthy individual, the difference between the measured SVC (slow vital capacity) and FVC (forced vital capacity) should not exceed 10 %. With greater differences, we suspect that dynamic obstruction is caused by forced exhalation. With NHANES III reference values, FEV₆ (forced expiratory volume in 6 seconds) may also be used instead of FVC. Spirometry should be technically sound (7,8).

Obstructions are assessed by the Tiffeneau index (TI). FEV₁ (forced expiratory volume in the first second) is divided by the vital capacity. This index is an indicator of obstruction when reduced by more than 12 % below the reference value. Airway obstruction as defined by the GOLD guidelines is diagnosed at a TI value below 0.70. Using this threshold, the results should be interpreted with caution, particularly in elderly patients (1,9). According to norms, a TI value under 0.70 may be normal and not pathological in this age group, therefore misdiagnosis of COPD is possible in elderly patients with dyspnea (9,10,11).

$$TI = FEV_1 / (VC, FVC \text{ ali } FEV_6)^*$$

* – The greater value is inserted as the denominator.

When spirometry reveals an obstruction, we should always perform a bronchodilator test, using four inhalations (0.4 mg) of salbutamol, preferably through a long extension (12) for adult patients. The medicine from the inhalator should be administered by a nurse. Additionally, the patients should be reminded of the instructions (technique) for proper dosing. Spirometry should be repeated 15 minutes after administering the medicine. The test is positive if the FEV₁ values have increased by at least 12 % from the output value, and at least 200 ml. A borderline or barely positive bronchodilator test is applicable both in asthma and COPD. A positive bronchodilator test does not exclude COPD; it is ruled out only by spirometry normalization after the bronchodilator test (normalization of TI and an increase of FEV₁ to the normal range). In COPD, the FEV₁ and TI values cannot be normalized with a bronchodilator.

In an obstruction that does not respond significantly to the bronchodilator test, it is recommended to conduct further diagnostic testing at the specialist level. A GP, who reasonably suspects COPD can further evaluate the patient using the available examinations. Definitive clarification of the cause of an irreversible obstruction should be in the domain of a secondary- or tertiary- care specialist. An irreversible obstruction may also be a sign of other less common pulmonary diseases, such as bronchiectasis, bronchiolitis, bronchomalacia, some forms of asthma and tracheal stenosis.

4. Disease classification

Recommendation 4

D

The overall assessment of a patient with COPD includes lung function testing, assessment of the impact of dyspnea on exercise performance (the MRC *Medical Research Council* dyspnea scale), assessment of the impact of the disease on the quality of life (the CAT *COPD assessment* scale), and determination of the number of exacerbations per year. Also, we look for associated chronic diseases and define the disease phenotype.

4.1 Assessment of patients with COPD (1,11)

When assessing a patient with COPD we consider:

- the degree of airway obstruction (post-bronchodilator FEV₁),

Table 1: Assessment according to post-bronchodilator FEV₁

GOLD Spirometric stage	All Stages: FEV ₁ /FVC < 70 %
GOLD 1: mild	FEV ₁ > 80 % normal
GOLD 2: moderate	FEV ₁ > 50–80 % normal
GOLD 3: severe	FEV ₁ > 30–50 % normal
GOLD 4: very severe	FEV ₁ < 30 % normal

- the presence of symptoms: CAT questionnaire (COPD assessment test),
- the MRC scale to assess the degree of dyspnea during physical activity (Medical Research Council),
- the number of COPD exacerbations per year,
- the associated diseases (diseases of the cardiovascular system (13), osteoporosis, depression (14), anxiety, mu-

sculoskeletal diseases, metabolic syndrome, lung cancer).

Table 2: Assessment of disease severity (1).

Patient Groups		Exacerbations/Year
C	D	1 hospital,* ≥2 outpatient*
A	B	0–1 outpatient*
MRC: 0–1, CAT <10	MRC >1, CAT >10	

* – Potreba po antibiotiku ali sistemske glukokortikoidu.

The points a, b, c, and d are summarized in Table 2.

The patient requires antibiotic or systemic glucocorticoid treatment.

Group A: Patients with early-stage disease who can be treated by a GP. Cessation of smoking is a key part of treatment, since the decline in lung function in this group is faster than in advanced forms of the disease (C and D).

Group B: Patients presenting with a more rapid decline in lung function and with significant comorbidities, such as cancer and cardiovascular diseases, or patients with significant hyperinflation (emphysema), which makes them more symptomatic than expected in view of the FEV₁ reduction.

Group C: Mildly symptomatic patients, but with FEV₁ below 50 %. These patients represent the smallest group of COPD patients.

Group D: Patients who are both at respiratory and cardiovascular risk and have several disease exacerbations.

Only patients in Group A can be treated by a GP, the others should be managed jointly by a secondary- or tertiary-care specialist and a GP.

Patients with COPD clinically differ from each other in terms of the disease course and their response to treatment. Table 3 describes the basic features of clinical phenotypes of COPD and the principles of treatment of these patients.

5. Principles for treating stable disease

and vaccination, as well as rehabilitation and nutritional intervention.

The cornerstone of initial pharmacological treatment of COPD is the use of long-acting bronchodilators as monotherapy or in combinations. Short-acting bronchodilators are prescribed if necessary.

Recommendation 5

A

Non-pharmacological treatment includes advice on smoking cessation,

The objectives of treatment are reducing symptoms, decelerating the natural course of the disease, improving the quality of life and exercise capacity, reducing

Table 3: Definition of stable COPD by clinical phenotypes of the disease (15,16,17).

Clinical phenotype	Basic characteristics
Prevailing chronic bronchitis	Productive cough for more than 3 months a year, for 2 or more consecutive years.
Prevailing emphysema (hyperinflation)	No productive cough; clinical, radiological, functional signs of emphysema.
Asthma/COPD overlap syndrome (ACOS)	Asthma and COPD characteristics. ACOS is considered in the following cases: • Highly positive bronchodilator test (FEV₁ above 15 % and 400 ml), but without normal lung function; • Increased NO in the exhaled air > 45–50 ppb and/or eosinophilia in an induced sputum (> 3 %); • Previous diagnosis or history of asthma. Important, but less conclusive, are the following criteria: • Positive bronchodilator test (FEV₁ above 12 % and > 200 ml) without normal lung function; • Increased total IgE; • Atopy; • Previous diagnosis of COPD. The disease is usually accompanied by frequent exacerbations and decreased lung function. Specialist pulmonary treatment is required.
COPD/bronchiectasis overlap syndrome	Cough is present on a nearly daily basis, bronchiectasis confirmed by chest X-ray.
COPD with frequent exacerbations	Two or more exacerbations a year, or hospitalization once a year.
COPD with obesity and sleep-related breathing disorder	Confirmed diagnosis of COPD, and sleep related breathing disorder confirmed by a polygraph.
COPD with cachexia	BMI < 21 kg/m ² without any other reason (FFMI < 16/m ² for men or < 15 kg/m ² for women).

Legend: BMI: body mass index, FFMI: fat free mass index measured by bioelectrical impedance.z bioelektrično impedanco.

Table 4: Pharmacological treatment of stable COPD (3,20-23)

Group	Initial treatment	Options of treatment intensification, if necessary
A	Bronchodilators short-acting	In the case of favourable effects, continue the treatment; long-acting bronchodilators may be added in symptomatic individuals
B	LABA or LAMA	LABA + LAMA
C	LAMA	LABA+LAMA, LABA+IGC*
D	LABA+LAMA, LABA+IGC**	LABA/LABA/IGC AZITHROMYCIN*** ROFLUMILAST***

*–For group C: IGC (inhaled glucocorticoid) and LABA (long-acting beta-agonist) in frequent exacerbations and ACOS (asthma-COPD overlap syndrome), otherwise the first choice is LABA and LAMA (long-acting muscarinic antagonist/anticholinergic).

**–For group D: initial combination LABA+LAMA; if there is a possibility of ACOS, the LABA+IGC combination is preferred

***FOR AZITHROMYCIN: phenotype of frequent disease exacerbations despite maximal inhalation therapy

***FOR ROFLUMILAST: persistence of chronic bronchitis despite maximal inhalation therapy and FEV1 under 50 %.

Key: LA: long-acting; IGC: inhaled glucocorticoid

Table 5: Treatment recommended according to the disease phenotype

Clinical phenotype	Method of treatment
Predominant chronic bronchitis	Pulmonary physiotherapy, roflumilast, antibiogram-based antibiotic therapy, otherwise a therapy following guidelines.
Predominant emphysema (hyperinflation)	Bronchoscopic and/or surgical lung volume reduction methods (reduction of disturbances in breathing mechanics), theophylline, otherwise a therapy following guidelines.
Asthma-COPD overlap (ACOS)	LA anticholinergic + LA beta-agonist + IGC (regardless of FEV1);
COPD and bronchiectasis overlap	Learning expectoration techniques, an antibiogram-based antibiotic therapy; consider the introduction of azithromycin 250 mg 3 times per week for several months in a row **
COPD with frequent exacerbations	LA anticholinergic + LA beta-2-agonist + IGC, option of adding roflumilast, antibiogram-based antibiotic therapy; consider the introduction of azithromycin 250 mg 3 times per week for several months in a row **
COPD with obesity and sleep breathing disorder	CPAP or BiPAP +/- oxygen and pharmacological treatment of COPD, body weight reduction, treatment of metabolic syndrome, if present
COPD with cachexia	Nutritional supplements, pulmonary rehabilitation patient (hospital), other therapy guidelines .

**–Only in centres with expertise. The treatment is repeated in the event of a reduction in the frequency of exacerbations and the absence of side effects.

the frequency of disease exacerbations and decreasing COPD mortality (1).

1. Step:

We recommend the **cessation of smoking to all patients** regardless of the

stage of the disease. It is by far the most effective treatment for COPD as it slows down the decline in lung function (1,18). Continued smoking accelerates the progression of the disease regardless of its stage (19).

The measures undertaken by a GP and a pulmonologist include: rapid intervention (determining the smoking status, advice on how to quit, offering assistance) and individual counselling in accordance with the principles of motivational interviewing and behavioural therapy.

2. Step:

- a. **Non-pharmacological advice:** physical activity, rehabilitation and education about the disease, and learning the prescribed inhalation therapy.
- b. **Treatment of associated diseases.**
- c. **Pharmacological measures** (mainly inhaled medication and vaccination against influenza and pneumococcal infections, home oxygen therapy for chronic respiratory failure, dietary intervention).

The selection of medicines in each group depends on their accessibility and on the patient's response to them (Table 4).

6. Diagnostic methods and treatment in family medicine practice

Recommendation 6

D

In family medicine clinics, symptoms of COPD are actively sought among smokers and ex-smokers older than 40 years. Patients known to have COPD are treated yearly by a family medicine clinic team.

The patient's GP can raise a reasonable suspicion of COPD, but definitive differential diagnostic clarification and confirmation of the diagnosis should be in the domain of a pulmonologist.

The so-called "reference clinics" represent a new form of organization of family medicine services at the primary level (24). By the end of 2017, the organizational changes will be gradually adopted in all family medicine clinics. The essential novelty is that the team will be extended to include a nurse working at least half-time. The purposes of this reorganization are effective management of chronic patients and early detection of common chronic diseases. In accordance with recommendations, family medicine reference clinics also conduct the screening of patients/smokers for COPD.

If COPD is suspected, the patient undergoes spirometry, and in the case of obstructive airway disorders, a bronchodilator test is performed. It is recommended that a bronchodilator test be carried out only when spirometry is technically sound (8), otherwise the test has no diagnostic value.

When there is a reasonable suspicion of COPD, the GP should refer the patient to a secondary- or tertiary-care specialist for definitive clarification and confirmation of the diagnosis.. The patient's GP prescribes a short-term bronchodilator (SABA), or a combination of SAMA and SABA (in symptomatic patients until the diagnosis is confirmed at the secondary or tertiary levels. In smokers, it is mandatory to include measures for the cessation of smoking.

In a family medicine clinic a patient with COPD is treated by a team following the treatment protocol (Appendix 1). There a COPD patient registry is established. The patients who are newly diagnosed with COPD in the screening

program, or are discovered incidentally, are entered in the COPD registry. The registry includes patients with COPD diagnosed or confirmed by a secondary- or tertiary-care specialist. Newly diagnosed patients and those already included in the COPD registry, are invited to attend for assessment of the disease state by a RN at least once a year. The results are reported to the doctor (GP), with whom the family medicine clinic cooperates. At least once a year, the patient is treated by his GP.

In the case of suspected COPD, we recommend:

- Spirometry;
- Chest X-ray;
- ECG;
- Blood oxygen saturation measurement;
- Assessment of the associated diseases;
- Treatment of the patient by a secondary- or tertiary- care specialist, who either confirms or refutes the working diagnosis;
- Urgent treatment of “fragile” patients (known hypercapnia, frequent exacerbations with hospitalization, long-term home oxygen therapy (LTOT), non-invasive mechanic ventilation or a history of intubation and mechanical ventilation, pulmonary heart disease) at the secondary or tertiary levels.

Management of stable COPD

- Verification of smoking status;
- Examination of inhaled medicine use;
- CAT score once per year, in symptomatic patients at every examination;
- Spirometry;
- Cooperation with a secondary- or tertiary-care specialist.

6.1 Recommended frequency of treatment based on disease severity

Group A: Treatment by a GP once per year.

Group B: The diagnosis should be provided by a secondary- or tertiary-care specialist, recommended annual treatment by a secondary- or tertiary-care specialist (more or less often depending on the clinical status), and annual treatment by a GP (more often if required by the clinical status).

Group C: The diagnosis should be provided by a secondary- or tertiary-care specialist, recommended annual treatment by a specialist in secondary or tertiary care (more or less often depending on the clinical status), annual treatment by a GP (more often if required by the clinical status).

Group D: The diagnosis should be provided by a secondary- or tertiary-care specialist, recommended bi-annual treatment by a secondary- or tertiary-care specialist (more or less often depending on the clinical status), and annual treatment by a GP (more often if required by the clinical status).

Because of a multitude of possible medicines for COPD, the selection of appropriate combinations may be challenging. The treatment of COPD includes non-pharmacological therapy (rehabilitation) (25,26). It is therefore appropriate that COPD patients in groups B, C, and D are managed and have their treatment optimized by a secondary- or tertiary-care specialist.

“Fragile” patients are identified by in secondary or tertiary specialist services, or by a GP. For these patients, the type of treatment should be determined in advance, in cooperation with their GP. The patients should bring their previous

medical records every appointment with any doctor.

7. Treatment in clinics with specialist pulmonology programs

Recommendation 7

D

The COPD diagnosis is made by ruling out other possible reasons for irreversible obstruction; therefore a pulmonologist should either confirm or refute the diagnosis of COPD .

1. Treatment of COPD at the secondary level (note: all the examinations listed are not necessarily carried out in each patient)
 - a. Medical history (dyspnea, chronic cough, risk factors: smoking, working and living environment, family medical history);
 - b. Clinical examination (BMI, RR, pulse oximetry, heart rate, respiratory rate);
 - c. Spirometry – bronchodilator test → $FEV_1/FVC < 70$;
 - d. Diffusion capacity*, plethysmography*;
 - e. Image diagnostics: chest X-ray*, high-definition CT* (consultation with a radiologist);
 - f. Laboratory diagnostics (basic biochemistry, hemogram)*;
 - g. ECG;
 - h. Six- minute walk test*;
 - i. CAT test, mMRC;
 - j. Determining a f alpha-1-antitrypsin deficiency (measurement of alpha-1-antitrypsin blood concentration)*.

* These tests are not contained in the minimum set of specialist services provided in pneumonology clinics;

the patient should be referred to institutions where they are available.

2. Differential diagnosis
 - a. Asthma
 - b. Heart failure
 - c. Bronchiectasis
 - d. Tuberculosis – post-effects
 - e. Bronchiolitis
 - f. Tracheal stenosis, tracheobronchomalacia
 - g. Vocal cord dysfunction
3. Treatment of patients with COPD
 - A. Stable COPD:
 - a. Group A:
 - Cessation of smoking (and other non-pharmacological measures).
 - b. Groups B, C, D: introduction of therapy (personalized treatment, therapy modification):
 - CAT, smoking cessation, a six-minute walk test or assessment of exercise capacity;
 - Selection of pharmacotherapy according to guidelines and with respect to the GOLD groups;
 - Comorbidity assessment: cardiovascular disease, depression, anxiety, osteoporosis, skeletal muscle dysfunction, metabolic syndrome, lung cancer, cachexia, sleep breathing disorder;
 - Testing and learning the correct use of inhalators;
 - Assessment of the need for LTOT;
 - Assessment of pulmonary hypertension, especially in patients who are potential candidates for LTOT, and those with a disproportionately severe dyspnea according to the results of pulmonary function;

- COPD school;
 - Health education and rehabilitation;
 - Vaccination against influenza and pneumococcal pneumonia.
- B. In the case of exacerbation–exacerbation assessment:
- Medical history and clinical examination;
 - Arterial blood gas analysis, chest X-ray in two projections;
 - Standard hematological and biochemical blood tests;
 - Introduction of an empirical antibiotic therapy and/or systemic glucocorticoid, when indicated;
 - Spirometry not indicated at deterioration;
- Repeated outpatient treatment within 3 days from the start of exacerbation;
 - Outpatient treatment between 3 and 6 weeks after hospitalization.

8. Treatment of patients with COPB exacerbation

Recommendation 8	D
Patients with respiratory failure, a history of invasive and/or non-invasive mechanical ventilation, occurrence of right-sided heart failure, negative initial response to treatment, and significant comorbidities should be referred to a hospital.	

Table 6: Indications for an urgent hospital referral due to a COPD exacerbation (3,27-29).

– Respiratory failure or exacerbation of chronic respiratory failure in LTOT at home;
– Severe worsening of symptoms, such as sudden dyspnea at rest;
– Exacerbation of the disease in patients with severe COPD (history of ICU treatments);
– Worsening of chronic hypercapnic respiratory failure;
– Occurrence of new symptoms (e.g. cyanosis, peripheral oedema);
– Poor response to the current outpatient treatment;
– Significant comorbidities;
– Newly occurred cardiac arrhythmia;
– Uncertain diagnosis;
– Inconvenient situation at home.

9. Identification and evaluation of evidence

The recommendations are set forth in accordance with the GINA (Global Initiative for Asthma) guidelines. Individual recommendations are scalable depending on the available studies or expert group opinion (Table 7).

Table 7: Recommendation evaluation (30–33).

The level of strength or credibility of a recommendation	
A	The recommendation is supported by at least one meta-analysis or a set of experimental study evidence (controlled randomized studies), or systematic reviews of experimental studies with a minimal bias, showing consistent results, and directly relevant to the target population
B	The recommendation is supported by high-quality systematic case reviews with case-control or cohort research, or with actual case studies with case-control or cohort research with a very low risk of bias.
C	The recommendation is supported by high-quality research of cases with case-control and cohort studies with a low risk of bias.
D	The recommendation is supported by evidence from cases or groups of cases or by opinions of experts

References

- Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary diseases 2017 report[cited 4.12.2016]. Available from: <http://www.goldcopd.com/>.
- Šušković S, Košnik M. Nove smernice za trajno zdravljenje KOPB. *Zdrav Vestn.* 2013;82(7):530–532.
- Šarc I, Jeric T, Zihlerl K, Šušković S, Košnik M, Anker SD, et al. Adherence to treatment guidelines and long-term survival in hospitalized patients with chronic obstructive pulmonary disease. *J Eval Clin Pract.* 2011 Aug;17(4):737–43.
- World Health Report 2000 [cited 17.5.2016]. Available from: <http://www.who.int/whr/2000/en>.
- Carpenter G, Bernabei R, Hirdes J. Building evidence on chronic disease in old age. *BMJ.* 2003;32(7234):528–9.
- Freeman D, Nordyke RJ, Isonaka S, Nonikov DV, Maroni JM, Pride D, et al. Question for COPD diagnostic screening in a primary care setting. *Respir Med.* 2005;99(10):1311–8.
- Miller MR, Hankinson J, Brusasco V, Burgos F, Casaburi R, Coates A, et al. Standardisation of spirometry. *Eur Resp J.* 2005 26(2):319–338.
- Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault JC. Lung volumes and forced ventilatory flows. Report Working Party Standardization of Lung Function Tests, European Community for Steel and Coal. Official Statement of the European Respiratory Society. *Eur Respir.* 1993;16 Suppl 6:5–40.
- van Dijk W, Tan W, Li P, Guo B, Li S, Benedetti A, et al. Clinical relevance of fixed ratio vs lower limit of normal of FEV₁/FVC in COPD: patient reported outcomes from the canCOLD cohort. *Annals of family medicine.* 2015;13(1):41–8.
- Güder G, Brenner S, Angermann CE, Ertl G, Held M, Sachs AP, et al. GOLD or lower limit of normal definition. A comparison with expert based diagnosis of chronic obstructive pulmonary disease in prospective cohort study. *Resp Res.* 2012;13(1):13.
- Lange P, Marrot JL, Vestbo J, Olsen KR, Ingebrigtsen TS, Dahl M, et al. Prediction of the clinical course of chronic obstructive pulmonary disease, using the new GOLD classification: a study of the general population. *Am J Respir Crit Care Med.* 2012;186(10):975–81.
- Fleržar M, Šušković S, Škrgat K, Košnik M. How to choose and interpret lung function tests in asthma and COPD. *Zdrav Vestn.* 2011;80(5):337–345.
- Marčun R, Suštic A, Brguljan PM, Kadivec S, Far-kaš J, Košnik M, et al. Cardiac biomarkers predict outcome after hospitalisation for an acute exacerbation of chronic obstructive pulmonary disease. *Int J Cardiol.* 2012 29;161(3):156–9.
- Regvat J, Žmitek A, Vegnuti M, Košnik M, Šuško-vič S. Anxiety and depression during hospital treatment of exacerbation of chronic obstructive pulmonary disease. *J Int Med Res.* 2011;39(3):1028–38.
- Bateman ED, Reddel HK, van Zyl-Smit RN, Agusti A. The asthma-COPD overlap syndrome: towards a revised taxonomy of chronic airways diseases? *Lancet* 2015;3719–728.
- Miravittles M, Soler-Cataluña JJ, Calle M, Molina J, Almagro P, Quintano JA, et al. Spanish Guideline for COPD (GesEPOC). Update 2014. *Arch Bronconeumol* 2014;50(Suppl 1):1–16.
- Koblizek V, Chlumsky J, Zindr V, Neumannova K, Zatloukal J, Zak J, et al. Chronic obstructive pulmonary disease: official diagnosis and treatment guidelines of the Czech Pneumological and Phthi-siological Society; a novel phenotypic approach to COPD with patient oriented care. *Biomed Pap Med Fac Univ Palacky Olomouc Czech Repub* 2013;157(2):189–201.
- Anthonesen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE, et al. The effects of a smoking cessation intervention on 14.5-year mortality: a randomised clinical trial. *Ann Intern Med* 2005;142(4):233–9.
- Lee PN, Fry JS. Systematic review of the evidence relating FEV₁ decline to giving up smoking. *BMC Med* 2010;8:84.
- Wedzicha JA, banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, et al. Indacaterol-Glycopyr-ronium versus Salmeterol-Fluticasone for COPD. *NEJM* 2016;374(23):2222–34.

21. Ferguson GT, Fležar M, Korn S, Korducki L, Grönke L, Abrahams R, et al. Efficacy of Tiotropium + Olodaterol in Patients with Chronic Obstructive Pulmonary Disease by Initial Disease Severity and Treatment Intensity: A Post Hoc Analysis. *Adv Ther.* 2015;32(6):523–36.
22. Buhl R, Maltais F, Abrahams R, Bjermer L, Derom E, Ferguson G, Fležar M, Hébert J, McGarvey L, Pizzichini E, Reid J, Veale A, Grönke L, Hamilton A, Korducki L, Tetzlaff K, Waitere-Wijker S, Watz H, Bateman E. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2–4). *Eur Respir J.* 2015;45(4):969–79.
23. Fležar M, Jahnz-Rózyk K, Enache G, Martynenko T, Kristufek P, Škrinjaric-Cincar S, et al. SOSPEs: SPIRIVA® observational study measuring SGRQ score in routine medical practice in Central and Eastern Europe. *Int J Chron Obstruct Pulmon Dis.* 2013;8:483–92.
24. Poplas Susič T, Švab I, Kersnik J. Projekt referenčnih ambulant v Sloveniji. *Zdrav Vestn* 2013;82(10):635–47.
25. Benedik B, Farkas J, Kosnik M, Kadivec S, Lainscak M. Mini nutritional assessment, body composition, and hospitalisations in patients with chronic obstructive pulmonary disease. *Respir Med.* 2011;105 Suppl 1:S38–43.
26. Lainscak M, von Haehling S, Doehner W, Sarc I, Jeric T, Zihlerl K, Kosnik M, Anker SD, Suskovic S. Body mass index and prognosis in patients hospitalized with acute exacerbation of chronic obstructive pulmonary disease. *J Cachexia Sarcopenia Muscle.* 2011;2(2):81–86.
27. Gryparis A, Forsberg B, Katsouyanni K, Analtis A, Touloumi G, Schwartz J, Samoli E, Medina S, Anderson HR, Niciu EM, Wichmann HE, Kriz B, Kosnik M, Skorkovsky J, Vonk JM, Dörtbudak Z. Acute effects of ozone on mortality from the “air pollution and health: a European approach” project. *Am J Respir Crit Care Med.* 2004;170(10):1080–7.
28. Škrat S, Šifrer F, Kopčavar Guček N, Osolnik K, Eržen R, et al. Stališče do obravnave akutnega poslabšanja KOPB. *Zdrav Vestn.* 2009;78(1):19–32.
29. Lainscak M, Kadivec S, Košnik M, Benedik B, Bratkovic M, Jakhel T, et al. Discharge coordinator intervention prevents hospitalizations in patients with COPD: a randomized controlled trial. *J Am Med Dir Assoc.* 2013;14(6):450.e1–6.
30. Geršak K, Fras Z, Rems M. Ali vemo, kakšne morajo biti dobre klinične smernice? *Zdrav Vestn.* 2016;85(1):6–14.
31. Fras Z, Robida A, Brubnjak-Jevtič V, Rems M, Jug B, Kersnik J, et al. Priročnik za smernice. Ljubljana: Ministrstvo za zdravje; 2003. p. 1–32.
32. Harbour R, Miller J, Scottish Intercollegiate Guidelines Network Grading Review Group. A new system for grading recommendations in evidence based guidelines. *BMJ.* 2001;323(7308):334–6.
33. Scottish Intercollegiate Guidelines Network. SIGN grading system 1999–2012. Edinburgh: Scottish Intercollegiate Guidelines Network, Healthcare Improvement Scotland; National Academy Press; 2014 [cited 2016 May 1]. Available from: <http://www.sign.ac.uk/guidelines/fulltext/50/annexoldb.html>