VIETNAM NATIONAL GUIDELINE FOR THE DIAGNOSIS AND MANAGEMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE 2018: A SUMMARY

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Chronic obstructive pulmonary disease (COPD) is one of the leading causes of morbidity and mortality worldwide as well as in Vietnam [1 - 3]. It is a growing social and economic burden, however, it is treatable and preventable. The most common risk factors include tobacco smoking and air pollution. The diagnosis of COPD should be considered in patients with chronic cough, dyspnea, and/or sputum production, and can be diagnosed by pulmonary function tests. COPD treatment should focus on individualized management of co-morbidities, prophylactic treatment to avoid acute exacerbations and to delay the disease progression. In addition, other measures such as smoking cessation, pulmonary rehabilitation, and patient education play important roles in the management of patients with COPD [4]. The Vietnam National Guidelines for the diagnosis and management of COPD 2018 were professional guidelines which can be used for the development of effective treatment regimens in health care facilities throughout the country.

Key words: Chronic obstructive pulmonary disease, diagnosis, managment

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I. INTRODUCTION

Chronic obstructive pulmonary disease is a common respiratory disease, one of the leading causes of morbidity and mortality worldwide as well as in Vietnam, resulting in an economic

burden for society and the patient's family. In 2010, the number of cases of COPD was estimated at 385 million, prevalence about 11.7% and 3 million deaths per year [5]. In Vietnam, the incidence rate was about 4.2% for people over 40 years old, with 7,1% in male [3]. In 2016, COPD was the fourth leading cause of death in Viet Nam. With the increase in smoking rates, the incidence of COPD is expected to increase in the future.

In 2015, the Ministry of Health published a document for diagnosis and treatment COPD in Viet Nam. Based on 2015 version, the Vietnam National Guidelines for the diagnosis and management of COPD 2018 was updated with more useful informations. This guidelines which can be used for the development of effective treatment regimens in health care facilities throughout the country.

The diagnosis, treatment stable and exacerbation of COPD, comorbidities, pulmonary rehabilitation and palliative care in COPD are dis cussed in this guideline.

II. METHOD

The authors consensually determined specifc topics to be addressed, on the basis of relevant publications in the literature on COPD with regard to diagnosis, assessment of COPD, non-pharmacologic and pharmacological therapy in treatment, comobidities, pulmonary rehabilitation and palliative care. To review these topics, the experts about COPD was summoned. The subtopics were divided among the author who conducted a nonsystematic review of the literature, but giving priority to major publications in the specifc areas, including original articles, review articles, and systematic reviews. All participants had the opportunity to review and comment on subtopics, producing a document that was approved by consensus at the end of the process

III. SUMMARY OF GUIDELINE

CHAPTER I: DIAGNOSIS AND ASSESSMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

1. Definition

Chronic obstructive pulmonary disease (COPD) is a common respiratory disease which is treatable and preventable. The disease is characterized by persistent respiratory symptoms and airflow obstruction. Risk factors include cigarette smoking, exposure to air pollution, fuel smoke and other noxious particles or gases, as well as other host factors [4].

2. Diagnosis

2.1. Suspected diagnosis without access to spirometry.

Question patients about risk factors and conduct a physical examination to assess for signs and symptoms COPD:

- Men > 40 years old

- History: cigarette smoking, indoor and outdoor air pollution, recurrent respiratory infections, hyperreactive airway.

- Chronic cough not related to other lung diseases such as pulmonary tuberculosis and bronchiectasis.

- Shortness of breath gradually worsens over time, increases on exertion and with respiratory infections.

- Sputum production.

Physical examination: in the early stage, respiratory examination may be normal. In later stages, there is decreased breath sounds or wheezing. In the end stage disease, patients may have signs of chronic respiratory failure such as cyanosis, retractions of respiratory muscles, fatigue, weight loss, loss of appetite, etc.

Upon detecting symptoms of suspected COPD, patients should be referred to medical facilities qualified for diagnostic testing: spirometry, chest x-ray, electrocardiogram, etc.

2.2. The definitive diagnosis with access to spirometry

Patients with suspected COPD should be tested with:

- Pulmonary function tests: Diagnosis is made upon finding an obstructive pattern, which is irreversible with post-BD FEV1/FVC<70%. FEV1 is used to classify the severity of airflow obstruction.

- Chest X-ray: Early stage: may be normal. Advanced stage: bronchial syndrome or emphysema. Chest X-rays may also help to detect other conditions or complications such as lung tumors, bronchiectasis, tuberculosis, pneumothorax, ...

- Electrocardiogram: in the advanced stage, it can show signs of pulmonary hypertension and right heart failure: tall P wave (> 2.5 mm) symmetrical (P waste), right axis deviation (> 110o), right ventricular hypertrophy (R / S at V6 < 1).

- Echocardiography: may show pulmonary hypertension.

- SpO2 and arterial blood gas: assess for respiratory failure.

- Evaluation for RV, total lung capacity: indicated with emphysema; DLCO diffuser; body plethysmography.

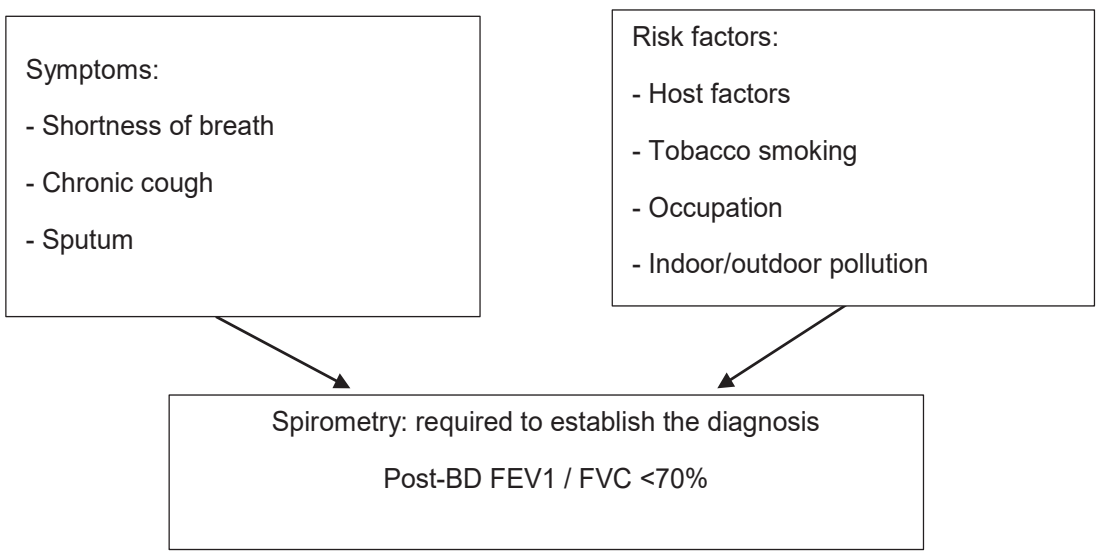


Figure 1. COPD diagnostic flow chart by GOLD 2018 [4]

2.3. Differential diagnosis

The differential diagnosis includes pulmonary tuberculosis, bronchiectasis, congestive heart failure, bronchiolitis, asthma.

3. Assessment of chronic obstructive pulmonary disease.

The purpose of the assessment was to determine the severity of airflow obstruction, the impact of disease on the patient's health status and the risk of future complications such as exacerbations, hospital admissions, and even death [4; 5]. The following aspects should be considered:

- The severity of airflow obstruction: based on FEV1
- The severity of the symptoms and the impact of the disease: based on the mMRC and CAT questionnaires [6; 7]
- Risk of exacerbation: based on history of exacerbation in the past year.

→ COPD assessment by ABCD group:

- Group A: Less symptoms, low risk
- Group B: More symptoms, low risk
- Group C: Less symptoms, high risk
- Group D: More symptoms, high risk

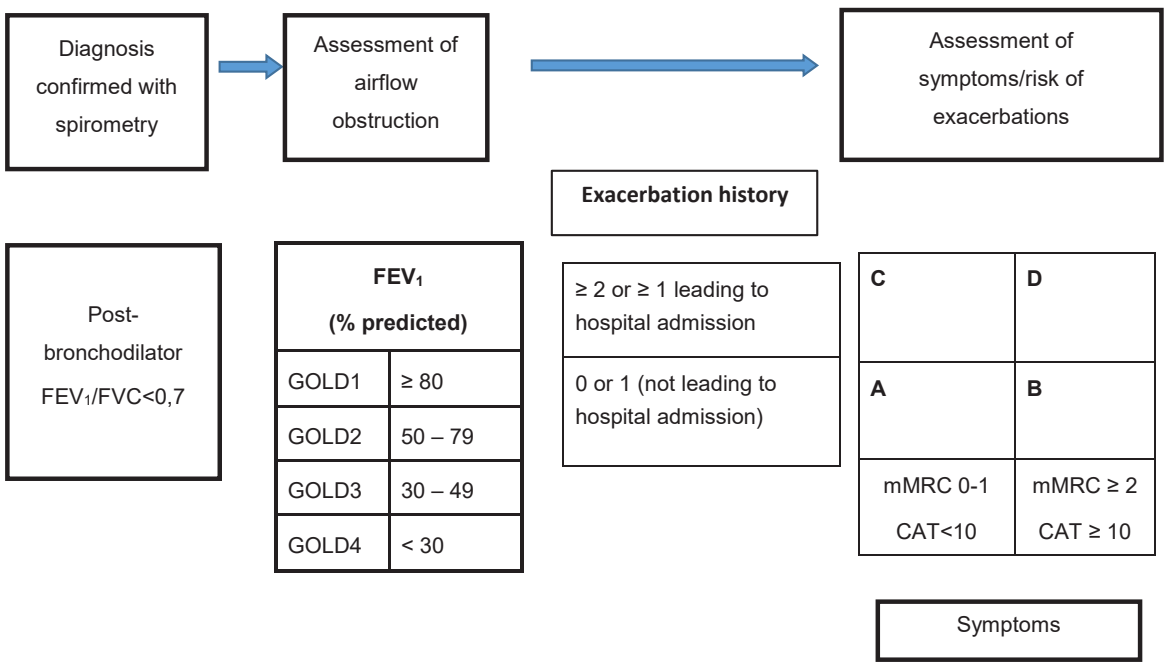


Figure 2. COPD assessment by ABCD grading system (From: GOLD 2018)[4]

4. Phenotypes of COPD [8; 9] :

- Bronchitis predominant
- Emphysema predominant
- Frequent exacerbations (2 or more exacerbations)
- Bronchiectasis
- Asthma-COPD overlap (ACO)

CHAPTER II: MANAGEMENT AND TREATMENT FOR STABLE COPD

1. Non-pharmacologic therapy

- Avoid exposure to risk factors
- Smoking cessation

- Vaccinations: annual influenza vaccine, pneumococcal 23-valent vaccine for patients <65 years old, once every 5 years.

- Pulmonary rehabilitation - Other measures: early diagnosis and treatment of upper/lower respiratory infections and other co-morbidities.

2. Pharmacological therapy

- Bronchodilators are considered the standard for COPD treatment . Long-acting bronchodilators, inhaled or aerosolized, are the first line therapy.

- Doses and route of administration varies with the severity and the stage of COPD.

- Choice of drug delivery device depends on accessibility, cost, prescription and patients' preference. It is necessary to educate the patient on the effective technique for drug administration and re-check this every time the patient is seen.

Table 1. Commonly used maintenance medications in COPD

Drugs	Abbreviations	Examples
Short-acting beta2-adrenergic agonists	SABA	Salbutamol, Terbutaline
Long-acting beta2-adrenergic agonists	LABA	Indacaterol, Bambuterol Salmeterol, Formeterol
Short-acting Anticholinergic	SAMA	Ipratropium
Long-acting Anticholinergic	LAMA	Tiotropium
Combination short-acting beta2-adrenergic plus anticholinergic	SABA+SAMA	Ipratropium/salbutamol Ipratropium/fenoterol
Combination long-acting beta2-adrenergic plus anticholinergic	LABA+LAMA	Indacaterol/Glycopyrronium Olodaterol/Tiotropium Vilanterol/Umeclidinium
Combination of long-acting beta2-adrenergic plus corticosteroids	ICS+LABA	Budesonide/Formoterol Fluticasone/Vilanterol Fluticasone/Salmeterol
Antibiotics, anti-inflammatory	Macrolide Anti-PDE4	Azithromycin Erythromycin Roflumilast
Xanthine derivatives short/long-acting	Xanthine	Theophylline/Theostat

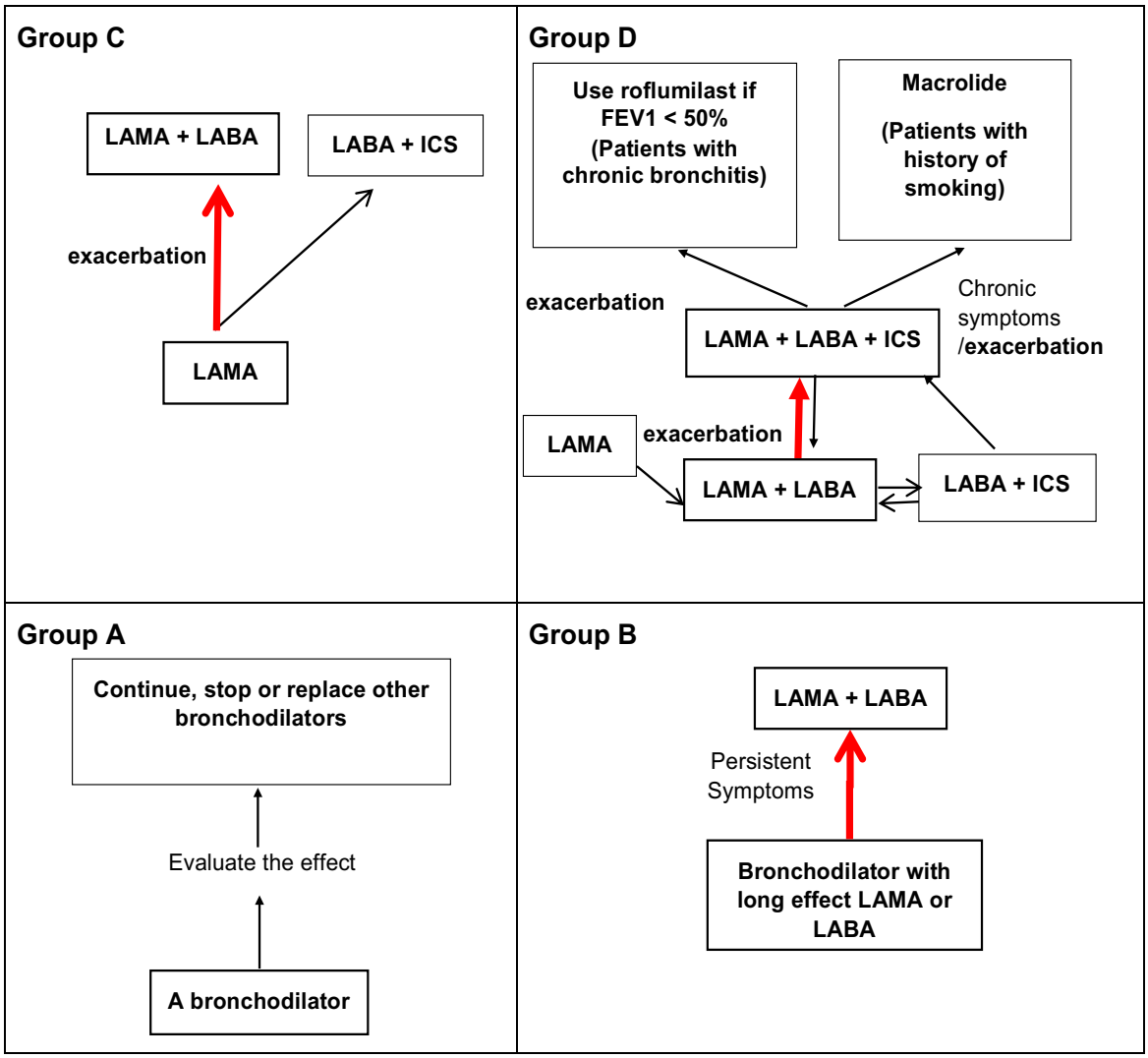
- LABA and LAMA are preferred to short-acting bronchodilators. Patients can be started on any type of LABA. Patients with frequent shortness of breath may take 2 LABA.

- Long-term use of ICS monotherapy and oral corticosteroids is not recommended. ICS should be added to patients with recurrent exacerbations in addition to LABA

- Patients with recurrent exacerbations despite LABA/ICS or LABA/LAMA/ICS therapy, and with severe/very severe obstructive airways, should have PDE4 inhibitors added.

- In patients who are smokers and prone to frequent exacerbations, daily macrolide for one year could be considered.

Table 2. Medications for different groups of severity according to GOLD 2018 [4]



Note: Boxes and arrows in bold are preferred treatment options

Group A Patients

- Bronchodilators are used to help improve shortness of breath. Either short-acting or long-acting bronchodilator can be used.

- Depending on the patient›s response to the treatment and the level of clinical improvement, patients can continue the treatment regimen or change to another bronchodilator group.

Group B Patients

- Long-acting bronchodilator is the optimal therapy, which can be with either LABA or LAMA. Drug selection depends on patients' tolerance and improvement of symptoms.

- Patients with chronic dyspnea despite LABA or LAMA monotherapy, a combination of two LABA/LAMA bronchodilators is recommended.

- Patients with severe shortness of breath, initial therapy with LABA/LAMA combination therapy may be considered.

- If the combination of LABA/LAMA does not improve symptoms, therapy should be decreased ("stepped down") to LABA monotherapy.

Group C Patients

- Start therapy with a long-acting bronchodilator. LAMA is preferred to LABA.

- Patients with persistent exacerbations may use LAMA/LABA or ICS/LABA but ICS increases the risk of pneumonia in some patients; therefore LABA/LAMA is the preferred option.

- ICS/LABA may be considered if patients have a history of asthma and/or suspected ACO [10] and/or hypereosinophilia [11].

Group D Patients

- Start therapy with a LABA/LAMA combination inhaler.

-ICS/LABA may be considered if patients have a history of asthma and/or suspected of ACO and/or hypereosinophilia.

- If patients still have exacerbations despite LABA/LAMA regimen, consider one of alternative therapies including:

+ LABA/LAMA/ICS triple therapy

+ Change to LABA/ICS therapy. If LABA/ICS does not improve the symptoms, LAMA may be added.

- If patients treated with LABA/LAMA/ICS still have exacerbations, the following options may be considered:

+ Add roflumilast. This regimen may be applied for patients with FEV1 < 50% along with chronic bronchitis, particularly if theyhad at least one exacerbation resulting in hospital admission in the previous year.

+ Add macrolides (azithromycin or erythromycin): Take antibiotic resistance into consideration before deciding on treatment.

3. Long-term oxygen therapy at home

- Indications: COPD with chronic respiratory failure, hypoxemia:

+ $PaO_2 \leq 55$ mmHg or $SaO_2 \leq 88\%$ on two blood samples within 3 weeks, patients in stable condition, at rest, on optimal treatment and not on oxygen.

+ PaO2 in the range of 56 - 59 mmHg or $SaO_2 \leq 88\%$ with one of these features: signs and symptoms of heart failure, polycythemia (hematocrit > 55%), pulmonary hypertension (echocardiogram...)

- Oxygen flow: 1 - 3 liter/minute, 16 - 18 hours a day. Oxygen supply, including oxygen tank, oxygen concentrator.

4. Non-invasive ventilation

Non-invasive ventilation (BiPAP) for stable COPD with persistent hypercapnia ($PaCO_2 \geq$ 50 mmHg) and history of recent hospitalization. Continuous positive airway pressure (CPAP) can improve survival and reduced hospitalization for COPD patients with sleep apnea (COPD and OSA overlap).

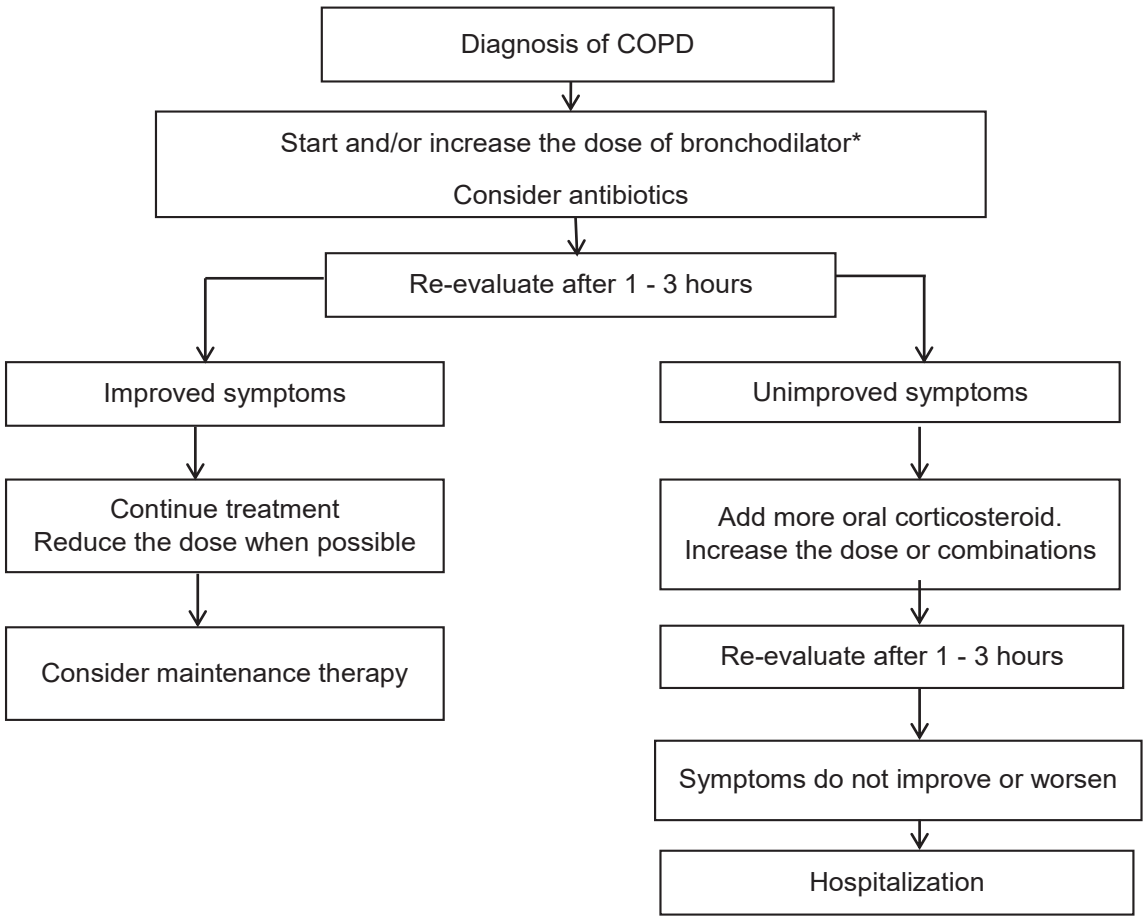


Figure 3. Initial therapy for COPD

*Beta-2 adrenergic agonist: salbutamol 100mcg, 2-4 sprays/dose / time; or salbutamol 5mg aerosol 1 vial/dose, or Terbutaline 5 mg aerosol 1 vial/dose or Ipratropium 2.5 ml aerosol 1 vial/dose; or a combination of Fenoterol / Ipratropium x 2 mL / mL, or salbutamol / ipratropium 2.5 mL, aerosol 1 vial/dose.

CHAPTER III: DIAGNOSIS AND TREATMENT OF EXACERBATION OF COPD

An exacerbation of COPD is an acute worsening of respiratory symptoms such as increased shortness of breath, increased cough and wheezing, increased sputum purulence and volume, which results in the need for additional therapy [12].

1. Triggers

- Infections: account for approximately 70 - 80% of exacerbations. Respiratory viruses (rhinovirus, influenza virus, parainfluenza virus, RSV virus, etc.) are much more common than bacteria (Haemophilus influenzae, Streptococcus pneumoniae)

- Others: Air pollution, change in ambient temperature, etc.

2. Diagnosis of exacerbation of COPD

Patients diagnosed with COPD who meet the criteria according to Anthonisen's (1987):

• Increased shortness of breath

• Increased productive cough and wheezing

• Increased sputum purulence and volume

If hospitalized, patients should have further investigation: SpO_2, arterial blood gas, Chest X-ray, electrocardiogram, echocardiogram, biochemical blood test, etc.

3. Assessment of the severity and risk factors of the disease

- Assessment of the severity based on symptoms: speech, consciousness, use of accessory muscles, respiratory rate, level of dyspnea, sputum characteristics, pulse, ABG, assessment of the severity.

- Classification of severity according to Anthonisen's criteria: Severe: increased dyspnea, increased sputum volume, purulent sputum. Moderate: 2 of the 3 above 3 symptoms; Mild: 1 of the 3 above symptoms.

- Assessment of respiratory failure: no respiratory failure, non-life-threatening acute respiratory failure and life-threatening acute respiratory failure.

- Consider factors that may increase the severity of exacerbations, such as cognitive dysfunction, initial treatment failure, ≥ 3 exacerbations in the previous year, severe illness, history of intubation, long-term oxygen usage, long-term mechanical ventilation at home and co-morbidities.

- Risk factors for Pseudomonas aeruginosa infection: Evidence of severe COPD, initial FEV1 < 50%, Pseudomonas aeruginosa isolation in sputum from previous visits/ treatment, bronchiectasis, recurrent antibiotic use, recurrent hospitalizations and regular systemic corticosteroid use.

4. Management of exacerbation of COPD

- Hospitalization criteria: Severe symptoms such as sudden worsening of dyspnea, high respiratory rate, decreased oxygen saturation, confusion, drowsiness, acute respiratory failure, onset of new symptoms (peripheral edema, cyanosis), acute COPD exacerbation not responsive to initial treatment, severe co-morbidities (heart failure, arrhythmia…) or lack of support resources at home [4].

Treatment of mild exacerbation

- Add short-acting inhaled β2-agonists with or without short-acting anticholinergics.

- For patients with oxygen at home: titrate oxygen to maintain SpO_2 at 88-92%;

- For patients with non-invasive ventilation at home: appropriate pressure adjustment.

- Consider use of long-acting bronchodilators.

Treatment for moderate exacerbation (at district or provincial hospitals or in appropriately resourced settings)

- Similar to treatment of mild exacerbation.

- Use antibiotic when patient is diagnosed with severe or moderate exacerbation (with purulent sputum) for 5 - 7 days.

- Oral or IV corticosteroid, at a dose of 1mg/kg/day, for not more than 5 - 7 days

Treatment for severe exacerbation (at provincial or national hospitals or in appropriately resourced settings)

• Continue with the treatments mentioned above. Monitor pulse, blood pressure, respiratory rate and SpO2.

• Supplemental oxygen 1 – 3 liters/minute to maintain SpO2 of 88 - 92%. Arterial blood gas should be done to adjust the oxygen flow.

• Short-acting nebulized β2-agonists or the combination of β2-agonists and anticholinergics.

• If patients do not respond to nebulized medicine, use salbutamol or terbutalin continuous intravenous at the dose of 0.5 to 2 mg/hour, adjusting the dose according to patient's response. Infusion by electronic infusion pump or infusion machine.

• Methylprednisolone 1 - 2 mg/kg IV. The duration of use is usually not more than 5 - 7

days.

• Antibiotics: IV cefotaxime 1 - 2g x 3 times daily or ceftriaxone 2g x 1 - 2 times daily or ceftazidime 1 - 2g x 3 times daily. Coordinated with aminoglycoside 15mg / kg / day or quinolone (levofloxacin 750mg / day, moxifloxacin 400mg / day ...)

• Recommendation for duration of antibiotic treatment during COPD exacerbation:

- Mild exacerbation: outpatient treatment, duration of antibiotic treatment is 5 - 7 days.

- Moderate to severe exacerbation: duration of antibiotic treatment is 7 - 10 days.

- The duration of antibiotic treatment depends on the severity of the acute exacerbation and the response of the patient.

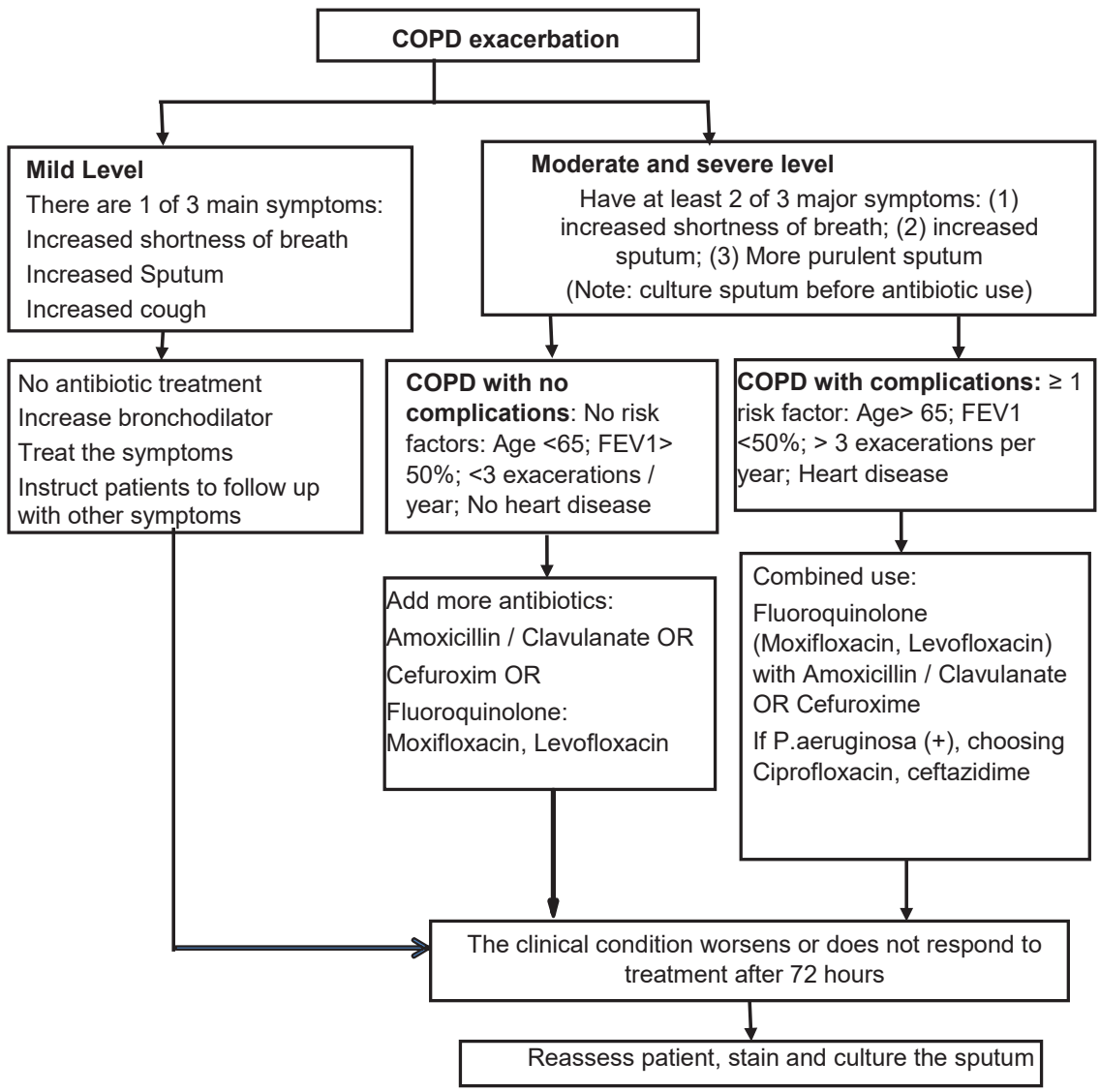


Figure 4. Antibiotic therapy for moderate COPD exacerbation

Non-invasive mechanical ventilation (NIV): use Bilevel positive airway pressure (BiPAP) when there are at least two criteria:

- Moderate to severe dyspnea with use of accessory respiratory muscles and irregular respiration
- Respiratory acidosis: pH ≤ 7.35 and / or $PaCO_2$ ≥ 45mmHg.
- Respiratory rate > 25 times per minute.

After 60 minutes of non-invasive mechanical ventilation, if PaCO2 keeps increasing and PaO_2 keeps decreasing or clinical symptoms worsen, then invasive ventilation should be initiated.

I nvasive mechanical ventilation: Severe respiratory failure, failure to tolerate or respond to NIV, respiratory or cardiac arrest or life-threatening hypoxemia

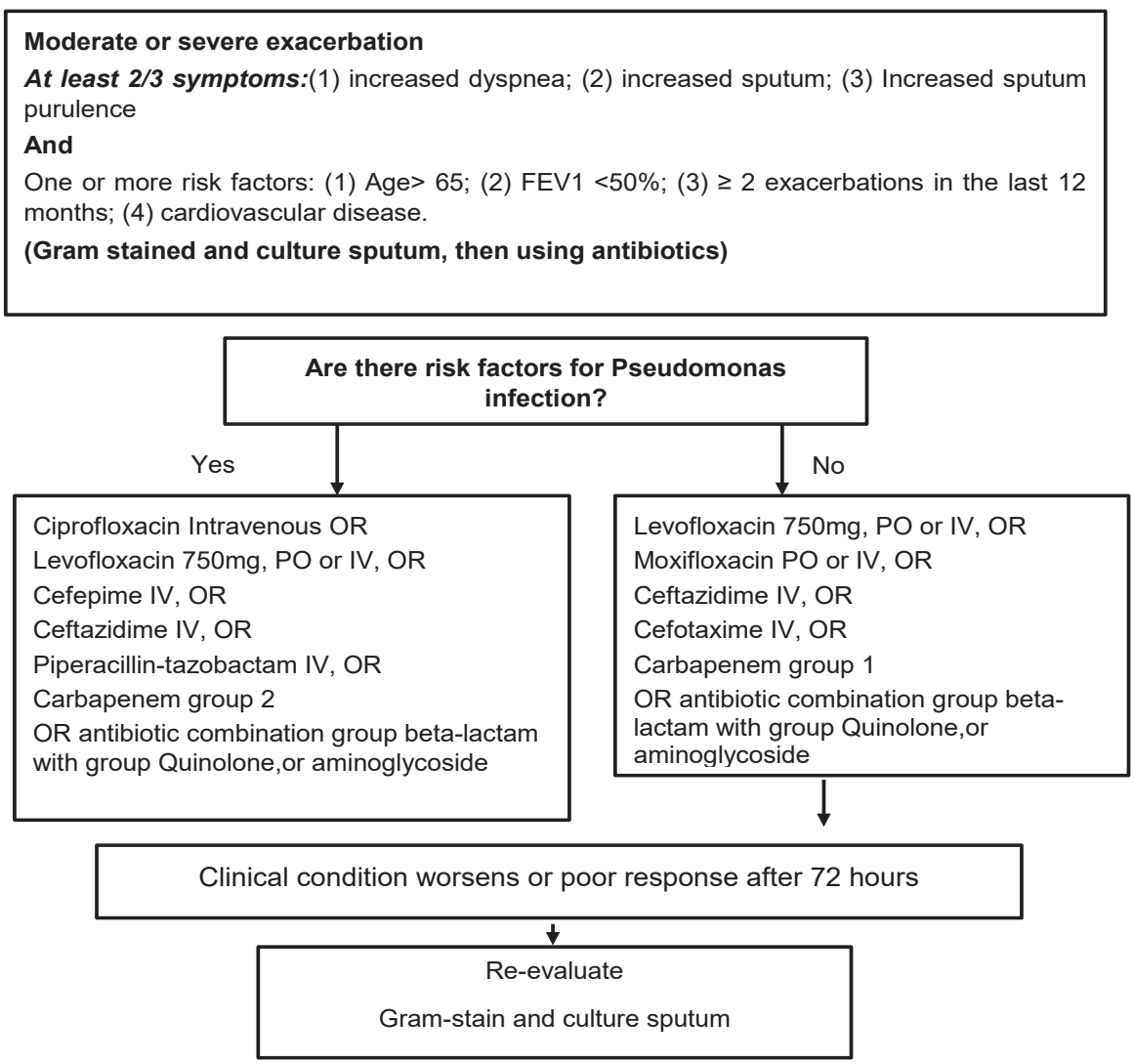


Figure 5: Antibiotic therapy for hospitalized COPD patients

CHAPTER IV: COMORBIDITIES OF COPD

Comorbidities significantly affect the clinical presentation and prognosis of COPD [13 - 15]. Comorbidities of COPD include:

1. Cardiovascular disease

- Hypertension: Occurs in 40-60% of COPD patients, treated according to current guidelines for optimal control.

- Heart failure: Symptoms may overlap with COPD, no difference in treatment of heart failure in COPD.

- Ischemic heart disease: should be assessed in all patients with COPD, treatment is according to the current guidelines

- Arrhythmia: Atrial fibrillation is the most common. SABA and theophylline may promote atrial fibrillation and make it difficult to control ventricular response rate.

- Peripheral vascular disease: due to atherosclerosis, which can affect the quality of life of the patient.

2. Respiratory disease:

- Obstructive sleep apnea: consequences such as decreased oxygen saturation during sleep, increased blood CO2, arrhythmia, pulmonary arterial hypertension. If OSA is suspected, polysomnography should be performed if available. It can be treated with CPAP or BiPAP, oral devices, and/or oxygen if needed.

- Lung cancer: Diagnosed with low-dose chest CT scan

- Bronchiectasis: Often underdiagnosed, identified with HRCT. Treatment: ICS may not be indicated, particularly in patients with colonized bacteria in the airways and recurrent respiratory infections. Macrolides or Roflumilast can be used instead [16].

- Tuberculosis: COPD patients have high risk of TB. It can adversely affect COPD with more frequent exacerbations and even premature death. Both COPD and TB should be treated if they are co-existing [17].

3. Gastroesophageal reflux

An independent risk factor of exacerbations, treated with proton pump inhibitors.

4. Metabolic syndrome and diabetes

COPD patients usually have many risk factors leading to Metabolic syndrome and diabetes. Treatment should follow current guidelines for these conditions.

5. Osteoporosis

Common, associated with low BMI, decreased muscle mass, frequent/long-term corticosteroid use and Vitamin D deficiency. Treatment should follow current guidelines.

6. Anxiety and depression

Important comorbidities, associated with poorer prognosis, treated with antidepressant and/or cognitive behavior therapy [18].

VII. CHAPTER V: PULMONARY REHABILITATION AND PALLIATIVE CARE IN COPD

1. Pulmonary rehabilitation

- Goals: Decrease symptoms, improve quality of life, increase physical and social activity in daily life [19].

- Indications: All COPD patients including those with early stage disease, especially in patients with dyspnea and chronic respiratory symptoms, hypoxemia, poor quality of life, decreased general health status, difficulty in carrying out daily activities, anxiety, depression, malnutrition, increased use of medical services and metabolic disorders.

- Contraindications: patient with an orthopedic or neurological problem that might limit their ability to walk or co-ordinate physical

movements, mMRC score > 4, comorbidities such as mental illness or unstable cardiovascular disease.

2. Components of Pulmonary rehabilitation program:

- Patient evaluation

+ Physical activity: is a major component, including endurance exercise, muscle strength training and respiratory muscle exercises [20]. Intensity of training: this should be compatible with the severity of the disease, comorbidities, the patient's level of physical activity tolerance. Supportive measures: bronchodilator before training, oxygen supplementation and mobility aids [21; 22].

+ Health and Self-Management Education: Educate the patients about patho-physiology, dealing with the disease, nutrition, techniques on airway clearance (cough and/or forced exhalation, postural drainage, chest percussion), speech therapy (pursed lip breathing technique), prevention and early diagnosis of exacerbations of COPD, control of anxiety and panic disorders, smoking cessation...

- Pulmonary rehabilitation program:

+ Stable stage of disease: Effective, safe, convenient, including > 20 training sessions, or 6 to 8 weeks with > 3 training sessions per week, or 2 training sessions at a medical facility and 1 at home under supervision, with a duration of 20-30 minutes for each session [23].

+ Post-exacerbations: Initiation of pulmonary rehabilitation within 3 weeks after an exacerbation could help improve exercise tolerance, relieve symptoms, increase quality of life, decrease mortality and prevent repeat hospitalizations [4].

3. Palliative care

- Nutrition support: Assess weight-based nutritional status, BMI, Fat-free Mass Index (FFMI). Nutritional adjustment: Calculate basic energy demand (male 24 kcal/kg/24h, female 22kcal/kg/24h), high-fat diet should be used in patients with hypercapnia [24 - [26].

- Mental support: Assess mental status by screening questionnaires and identify various mental states of patient such as anxiety, panic disorders, etc. Treatment: patients with mild mental illness should have a good social support system and be trained on how to deal with stress/anxiety/depression. Patients with moderate and severe mental illness should be referred to specialists [18; 27].

- Palliative treatment for dyspnea: Oxygen therapy, non-invasive ventilation, morphine, chest percussion, pursed-lip breath technique [28; 29].

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REFERENCES

1. Bộ Y tế (2014). Hướng dẫn chẩn đoán và điều trị bệnh hô hấp,

2. Ngô Quý Châu et al (2002). Tình hình chẩn đoán và điều trị bệnh phổi tắc nghẽn mạn tính tại khoa Hô hấp bệnh viện Bạch Mai trong 5 năm 1996 - 2000. *Thông tin Y học Lâm sàng,* 50 - 58.

3. Nguyễn Thị Xuyên, Đinh Ngọc Sỹ, Nguyễn Viết Nhung et al (2010). Nghiên cứu tình hình dịch tễ bệnh phổi phế quản tắc nghẽn mạn tính ở Việt Nam. *Tạp chí Y học thực hành,* **(2),** 8 - 11

4. Global strategy for the Diagnosis,

Management, and Prevention of Chronic Obstructive Pulmonary Disease: Update 2018. http://ww.goldcopd.org.

5. GOLD 2017, Global strategy for the diagnosis, management and prevention of chronic obstructive pulmonary disease, 2017 report.,

6. Bestall J.C, Paul EA, Garrod R, et al (1999). Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. *Thorax,* **54 (7)**, 581 - 586.

7. Jones, P, Harding G, Berry P et all (2009). Development and first validation of the COPD Assessment Test. *Eur Respir J*, **34(3),** 648 - 654.

8. Yingmeng Ni and Guochao Shi (2017). Phenotypes contribute to treatments. *European Respiratory Journal*, **49 (5)**, 1700054.

9. Mirza S. và Benzo R. (2017). Chronic Obstructive Pulmonary Disease Phenotypes: Implications for Care. *Mayo Clinic proceedings,* **92 (7)**, 1104 - 1112.

10. Miravitlles M, Soler - Cataluña JJ, Calle M, Soriano JB et all (2013). Treatment of COPD by clinical phenotypes: putting old evidence into clinical practice. *Eur Respir J*, **41 (6),** 1252 - 1256.

11. Klaus F. Rabe, Bianca Beghé and Leonardo M. Fabbri (2017). Peripheral eosinophil count as a biomarker for the management of COPD: not there yet. **50 (5),** 1702165.

12. Burge S; Wendzicha J.A. (2003). COPD exacerbations: definitions and classifications. *Eur Respir J Suppl*, **41**, 46s - 53s.

13. Klaus F. Rabe, Jadwiga A. Wedzicha and Emiel F.M. Wouters (2013). ERS monograph: COPD and comobidy.

14. Weiss S.T, Stoller J.K, Hollingsworth H (2017). Chronic obstructive pulmonary disease: Prognostic factors and comorbid conditions. In UpToDate. Available from: https://www.uptodate.com/contents/chronic - obstructive - pulmonary - disease - prognostic - factors - and - comorbid - conditions

15. Divo M, Cote C, de Torres JP, et al (2012). Comorbidities and risk of mortality in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*, **186 (2)**, 155 - 161.

16. Martinez - Garcia MA, Miravitlles M. (2017). Bronchiectasis in COPD patients: more than a comorbidity? *International journal of chronic obstructive pulmonary disease*, **12,** 1401 - 1411.

17. Halil Ibrahim Yakan, Hakan Gunen, Erkan Pehlivan, Selma Aydogan, (2017). The role of tuberculosis in COPD. I*nternational journal of chronic obstructive pulmonary disease,* **12**, 323 - 329.

18. Dowson CA, Cuijer RG, Mulder RT (2004). Anxiety and self - management behaviour in chronic obstructive pulmonary disease: what has been learned? *Chron Respir Dis,* **1 (4),** 213 - 220.

19. Ries A. L., Bauldoff G. S., Carlin B. W. et al (2007). Pulmonary Rehabilitation: Joint ACCP/AACVPR Evidence - Based Clinical Practice Guidelines. *Chest,* **131 (5 Suppl)**, 4s - 42s.

20. Magadle R, McConnell AK, Beckerman M, Weiner P (2007). Inspiratory muscle training in pulmonary rehabilitation program in COPD patients. *Respir Med,* **101 (7),** 1500 - 1505.

21. Ngô Quý Châu (2017). Chiến lược toàn cầu về chẩn đoán, quản lý và dự phòng Bệnh phổi tắc nghẽn mạn tính, Bản dịch tiếng Việt, *Nhà xuất bản Y học*,

22. O'Brien K, Geddes EL, Reid WD, Brooks D, Crowe J et al (2008). Inspiratory muscle training compared with

other rehabilitation interventions in chronic obstructive pulmonary disease: a systematic review update. *J Cardiopulm Rehabil Prev,* **28 (2),** 128 - 141.

23. Spruit M. A., Singh S. J., Garvey C. et all (2013). An official American Thoracic Society/European Respiratory Society statement: key concepts and advances in pulmonary rehabilitation. *Am J Respir Crit Care Med,* **188 (8),** e13 - 64.

24. Ferreira I. M., Brooks D., Lacasse Y. et al (2000). Nutritional support for individuals with COPD: a meta - analysis. **Chest, 117 (3)**, 672 - 678.

25. Creutzberg E. C., Wouters E. F., Mostert R. et al (2003). Efficacy of nutritional supplementation therapy in depleted patients with chronic obstructive pulmonary disease. *Nutrition,* **19 (2),** 120 - 127.

26. Schols AMWJ, Fredrix EW, Soeters PB,Westerterp KR, Wouters EFM (1991). Resting energy expenditure in patients with chronic obstructive pulmonary disease. *Am J Clin Nutr,* **54 (6),** 983 - 987.

27. McCathie HC, Spence SH, Tate RL (2002). Adjustment to chronic obstructive pulmonary disease: the importance of psychological factors. *Eur Respir J*, **19 (1),** 47 - 53.

28. Bianchi R, Gigliotti F, Romagnoli I et al (2004). Chest wall kinematics and breathlessness during pursed - lip breathing in patients with COPD. *Chest,* **125 (2),** 459 - 465.

29. Markciniuk DD, Goodridge D, Hernandez P et al (2011). Managing dyspnea in patients with advanced chronic obstructive pulmonary disease: a Canadian Thoracic Society clinical practice guideline. *Can Respir J,* **18 (2)**, 69 - 78.