Chronic obstructive pulmonary disease (COPD) results in high morbidity and mortality among patients nationally and globally. The Korean clinical practice guideline for COPD was revised in 2018. The guideline was drafted by the members of the Korean Academy of Tuberculosis and Respiratory Diseases as well as the participating members of the Health Insurance Review and Assessment Service, Korean Physicians' Association, and Korea Respiration Trouble Association. The revised guideline encompasses a wide range of topics, including the epidemiology, diagnosis, assessment, monitoring, management, exacerbation, and comorbidities of COPD in Korea. We performed systematic reviews assisted by an expert in meta-analysis to draft a guideline on COPD management. We expect this guideline to facilitate the treatment of patients with respiratory conditions by physicians as well other health care professionals and government personnel in South Korea.

Keywords: Pulmonary Disease, Chronic Obstructive; Guideline; Diagnosis; Treatment
Introduction

According to a survey conducted by the Korean Academy of Tuberculosis and Respiratory Diseases in 2008, people over the age of 40 years have a high chronic obstructive pulmonary disease (COPD) prevalence rate of 13%7. The trends in the prevalence of COPD in Korea using the data from Korea National Health and Nutrition Examination Survey (KNHANES) did not change much, which ranged from 13.1% to 14.6% during the period from 2010 to 20152. According to the National Statistical Office, COPD is one of the 10 major causes of death in South Korea3. The World Health Organization (WHO) expects that the prevalence and mortality rates of COPD will increase worldwide4. The WHO also emphasizes the importance of prevention, early diagnosis, and proper treatment of COPD by selecting it as one of the five noninfectious diseases that must be managed worldwide. In 2012 and 2014, the Korean Academy of Tuberculosis and Respiratory Diseases published the COPD clinical practice guideline (in Korean and summary 2014 revised version in English), which could be used in clinical practice. In 2018, the revised version of the COPD guideline (in Korean) was published on the basis of the findings of new studies published over the previous 4 years. This revision has been made not only by the Korean Academy of Tuberculosis and Respiratory Diseases but also by the Health Insurance Review and Assessment Service, Korean Physicians’ Association, and Korea Respiration Trouble Association. Therefore, the revised clinical practice guideline is more advanced than the original one. We expect this guideline would be helpful not only to medical doctors treating patients with respiratory conditions but also to other health care professionals and government personnel in South Korea.

Definition, Epidemiology, Cause, and Mechanism

COPD can be defined as follows.

“It is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airflow and/or alveolar abnormalities usually caused by smoking, occupational exposure, indoor air contamination, and infection.” As it is a very common disease, it has a severe socioeconomic influence. Acute exacerbation occurs frequently and comorbid diseases are comparatively more common in the general population, influencing the severity and prognosis of COPD.

COPD is a leading cause of morbidity and mortality worldwide5,9. The prevalence of COPD has increased over the decades. This phenomenon is due to consistent exposure to COPD risk factors and global population aging, and it is anticipated to continue into the future. A study by the WHO estimated that in 2007, the global number of patients with COPD was 210 million4, but other large epidemiologic such as Burden of Obstructive Lung Disease estimated that in 2010, number COPD patient was 380 million and prevalence was 11.7% worldwide9. As for the COPD prevalence in Korea, 13.4% of the population over 40 years of age has COPD based on the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria (forced expiratory volume in 1 second/forced vital capacity [FEV1/FVC] <0.7), with 21.6% of the male population and 5.8% of the female population having COPD based on the 2015 KNHANES5. The COPD prevalence is unchanged for 7 years in Korea. However, among patients diagnosed with COPD, only 2.8% were diagnosed with COPD by a doctor, and only 1.6% received treatment. This suggests that most Korean patients with COPD are not diagnosed and treated. COPD is an important cause of mortality in most countries. According to the Global Burden of Disease Study conducted in 1990, COPD ranked sixth among the global causes of death, but it is anticipated to rank third in 2020 and fourth in 20304. According to Statistics Korea, the total number of deaths from COPD, based on disease code, was 3,329 in the year 2000 (2,120 among men and 1,209 among women), and 5,002 in the year 2010 (3,526 among men and 1,476 among women). In 2015, chronic lower airway disease ranked seventh among the overall causes of death, accounting for a total of 7,538 deaths. In an aging population, the risk of death from COPD has been increasing, and it ranks fifth among the overall causes of death in the age group of 80 years or older, with a mortality rate of 3,732 per 100 thousand4.

Additionally, COPD results in a huge socioeconomic burden. In Korea, based on the 2010 data of the Health Insurance Review and Assessment Service, about 284 billion Korean Won is spent on the medical treatment of COPD. According to the 2009 data of the Health Insurance Review and Assessment Service, the medical fee per individual is as high as 3.23 million Won, and it has been increasing rapidly in recent years9. Moreover, in 1990, COPD ranked 12th among the cause of disability-adjusted life years (DALYs) loss in the world, but it is anticipated to rank seventh in 20304. In Korea, DALYs from COPD have rapidly increased from 270 years per 100 thousand in 2002 (ranking 10th) to 550 years per 100 thousand in 2007 (ranking seventh). According to 2012 Korean Burden of Disease Study, DALY from COPD is 1,305 years per 100 thousand and it occupies 6.21% of DALY lost caused by non-communicable disease9.

The most important and well-known risk factor for COPD is smoking. Other risk factors include occupational dust, chemical materials, air pollution, low socioeconomic status, chronic bronchitis, and respiratory infection. Host factors related to COPD include genetics, age, sex, lung growth, and airway hypersensitivity10,11. Smoke and harmful substances induce lung inflammation, and lung parenchyma damage from such inflammation and disruption of the normal repair system can induce emphysema and small airway fibrosis12. Such patho-
logic alteration induces air trapping and airflow limitation.

**Diagnosis and Assessment**

A person over the age of 40 years exposed to cigarette smoke or other risk factors and showing symptoms of dyspnea, cough, and sputum production should be suspected of having COPD. To diagnose COPD, a patient should undergo spirometry that determines the FEV₁, FVC, and the ratio of FEV₁/FVC. FEV₁/FVC <0.7 confirms an airflow limitation, which is an objective diagnostic evidence of COPD. More importantly, spirometry should be performed after short-acting bronchodilator inhalation to confirm the airflow limitation in COPD.

For COPD treatment, spirometry, symptom grade, and exacerbation history should be assessed. First, the severity of COPD on spirometry should be classified into two categories: FEV₁ ≥60% vs. FEV₁ <60%. Second, the symptom grade should also be classified into two categories: the modified Medical Research Council dyspnea scores (mMRC) 0–1 vs. mMRC ≥2, or the score of the COPD assessment test score (CAT) <10 versus CAT ≥10. Third, the exacerbation frequency should be classified as follows: 0–1/yr vs. ≥2/yr. According to this assessment, patients with COPD are classified into three groups: Ga, Na, and Da (Figure 1). Patients with asthma-COPD overlap syndrome exhibit features of both asthma and COPD. Experts suggest that treatment for both asthma and COPD should be administered to such patients.

An mMRC dyspnea grade of 2 refers to the situation where a patient walks slower on ground level than a similarly aged person because of shortness of breath, or when a patient stops for breathing when walking at his or her own pace on ground level.

FEV₁ of 50% predicted value, the previous cut-off threshold has been deleted in the GOLD 2017 documents. However, we decide to maintain the previous FEV₁ cut-off threshold of 60% predicted value because spirometry needs to be performed more in most of the primary care clinics in Korea and also because only spirometry value is objective measurements while dyspnea score and exacerbation frequency are subjective.

We have defined the Da group which is an analogy of the combination, both GOLD group C and D. As for the GOLD group C, the proportion of it is very small in a clinical practice setting and the recommended medications are similar to those of the GOLD group D. So we decided the combined group, Da.

In conclusion, we decide not to change the frame of combined assessment in the Korean COPD guideline revised in 2014. So, the contents of diagnosis and assessment are quite same in the Korean COPD guidelines revised both in 2014 and 2018.

**Management of Stable COPD**

The goals of management of stable COPD are to reduce both current symptoms and future risks with minimal side effects from treatment. Ongoing monitoring should ensure that the treatment goals are being met, and it should include continuous evaluation of exposure to risk factors and monitoring of disease progression, the effect of treatment and possible adverse effects, exacerbation history, and comorbidities. Identification and reduction of exposure to risk factors are important in the treatment and prevention of COPD.

1. **Pharmacologic management**

Appropriate pharmacologic therapy can reduce symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance. To date, none of the existing medications for COPD has been shown to modify disease progression or reduce mortality.

1) **Bronchodilators**

Bronchodilators are the cornerstone of pharmacological treatment in COPD (Table 1). Inhalation therapy is preferred over oral, subcutaneous, or intravenous administration, because inhalation therapy can maximize the bronchodilator’s effect on the airway with least systemic side effects. When treatment is administered via inhalation, attention is essential to ensure effective drug delivery and training in inhaler technique. A metered-dose inhaler, dry powder inhaler, soft mist inhaler, or nebulizer can be used for inhalation therapy, according to the patient’s clinical situation.

(1) **β2-agonists**: Short-acting β2-agonists (SABAs) are rec-
ommended as needed for the relief of dyspnea and exercise limitation\textsuperscript{17}. Many trials have proven the clinical benefits of long-acting β2-agonists (LABAs) in COPD, including the improvement of health status, FEV\textsubscript{1}, FVC, and exercise capacity. Therefore, regular treatment with LABAs is more highly recommended than irregular usage of SABAs on an as-needed basis to address the airflow limitation in COPD. Indacaterol is a once daily β2-agonist with duration of action of 24 hours. This bronchodilator’s effect is significantly greater than that of formoterol and salmeterol, and similar to that of tiotropium. Indacaterol has significant effects on breathlessness and health status\textsuperscript{18,19}.

(2) Anticholinergic agents: Long-acting muscarinic agents (LAMAs) provide clinically significant improvements in lung function, reduce acute exacerbation, and improve health status and the effects of pulmonary rehabilitation in patients with COPD\textsuperscript{20,21}. A large, long-term clinical trial on patients with COPD showed no effect of tiotropium added to other standard therapies on the rate of lung function decline and no evidence of cardiovascular risk\textsuperscript{22}. Clinical trials have shown a greater effect on exacerbation rates for LAMA treatment (tiotropium) versus LABA (indacaterol, salmeterol) treatment\textsuperscript{23,24}. The long-acting anticholinergics aclidinium\textsuperscript{25-29} and glycopyrronium\textsuperscript{30-32} seem to have a similar action as tiotropium on lung function and breathlessness; however, far less data are available for other outcomes.

(3) Methylxanthines: Methylxanthines may act as nonselective phosphodiesterase inhibitors, but they have also been reported to have a range of nonbronchodilator actions, whose significance has been disputed. Theophylline is the most commonly used methylxanthine. Theophylline is less effective and less well tolerated than inhaled long-acting bronchodilators, and it is not recommended if the latter drugs are available and affordable. The addition of theophylline to salmeterol produced a greater improvement in FEV\textsubscript{1} and breathlessness than did salmeterol alone\textsuperscript{33}. Low-dose theophylline reduces exacerbations but does not improve postbronchodilator lung function.

(4) Combination bronchodilator therapy: Combining bronchodilators with different mechanisms and durations of action may increase the degree of bronchodilation with equivalent or lesser side effects. There are several combinations of a LABA and LAMA in a single inhaler available. These combinations have shown a significant improvement in dyspnea, health status and lung function as well as a prevention of exacerbation compared with that shown by monotherapy\textsuperscript{34,35}. Combinations of a LABA and LAMA showed not only noninferiority but also consistent superiority to the inhaled steroid and LABA combination for outcomes related to exacerbation, lung function, and health status\textsuperscript{36}.

2) Corticosteroids

(1) Inhaled corticosteroids: Most studies have found that regular treatment with inhaled corticosteroid (ICS) alone does not modify the long-term decline of FEV\textsubscript{1}, nor mortality in patients with COPD\textsuperscript{14,16,37,38}.

(2) Combination of ICSs and long-acting bronchodilators: An ICS combined with a LABA is more effective than the individual components in improving lung function and health status and reducing exacerbations in patients with moderate to very severe COPD\textsuperscript{39,40}. However, a large, prospective clinical trial failed to demonstrate a statistically significant effect of

| Table 1. Available inhaled bronchodilators in Korea (2018) |
| Formulation | Dose (μg/dose) | Dosage | Action duration (hr) |
|-------------|----------------|--------|---------------------|
| SABA        |                |        |                     |
| Salbutamol evohaler | MDI 100–200 | 1–2 puffs/dosage | 4–6 |
| Salbutamol nebulizer | Nebulizer 2.5 mg/2.5 mL | Maximum 8 puffs/day | 4–6 |
| LABA        |                |        |                     |
| Indacaterol | DPI 150, 300   | 1 capsule/day | 24 |
| SAMA        |                |        |                     |
| Ipratropium | Nebulizer 250, 500 μg/mL | 1 capsule/day | 6–8 |
| LAMA        |                |        |                     |
| Tiotropium  | DPI 18        | 1 capsule/day | 24 |
| Aclidinium  | DPI 400       | Twice a day | 12 |
| Umeclidinium | DPI 62.5      | Once a day | 24 |

SABA: short-acting β2-agonist; MDI: metered-dose inhaler; LABA: long-acting β2-agonist; DPI: dry powder inhaler; SAMA: short-acting muscarinic agent; LAMA: long-acting muscarinic agent; SMI: soft mist inhaler.
combination therapy on mortality. Moreover, combination therapy is associated with an increased risk of pneumonia. Post-hoc analysis from several trials and observation studies suggest that eosinophil counts in sputum and blood and asthma COPD overlap may serve as parameter to predict the efficacy of ICS in particular regarding exacerbation prevention. Triple therapy of ICS/LABA/LAMA had clinical benefits compared with tiotropium or ICS/LABA combination with symptomatic COPD and a history of exacerbations in a reduction in the rate of exacerbation and improvement in lung function.

3) Phosphodiesterase-4 inhibitors
Roflumilast is suggested for patients with COPD with severe airflow limitation (postbronchodilator FEV1/FVC, 0.7; FEV1 <50%), symptoms of chronic bronchitis, and a history of exacerbations, in whom the disease is not adequately controlled by long-acting bronchodilators or fixed dose ICS/LABA. The beneficial effects of roflumilast have been reported to be greater in patients with a prior history of hospitalization for an acute exacerbation. The most frequent adverse effects are nausea, reduced appetite, weight loss, abdominal pain, diarrhea, sleep disturbances, and headache.

4) Other pharmacologic treatments
(1) Vaccination: Influenza vaccination and pneumococcal vaccination are recommended for patients with COPD.
(2) Antibiotics: Although studies have shown some effects of antibiotics on exacerbation rate, the role of this treatment is unclear. Prophylactic antibiotic treatment is not recommended because of an unfavorable balance between the benefits and side effects.

2. Pharmacologic treatment algorithms based on the Korean COPD classification (Figure 2)

1) Group Ga patients
SABA is recommended as a first-line therapy since SABA can improve lung function and decrease dyspnea. If dyspnea (mMRC ≥2) or acute exacerbation develops despite medical treatment, LABA or LAMA can be tried. However, not enough trials have been conducted on group Ga COPD.

2) Group Na patients
LABA or LAMA is recommended as a first-line therapy. Randomized controlled trials comparing LABA and LAMA have shown no significant difference in the outcomes such as pulmonary function, symptomatic improvement, and health status. The choice of long-acting bronchodilators should depend on the patient’s perception of symptom relief, side effects, and clinician’s discretion. For patients with severe breathlessness, the alternative is a combination of long-acting bronchodilators. Combination therapy with LAMA and LABA can be provided for patients who show no improvement of symptoms with single therapy or undergo frequent exacerbation.

3) Group Da patients
Combination therapy with LABA+LAMA can be administered as a first-line therapy. If patients have asthma or high blood eosinophil, ICS/LABA can be considered as a first-line therapy. If dyspnea (mMRC ≥2) or acute exacerbation develops despite first-line treatment, triple therapy with ICS/LABA/LAMA or addition of a phosphodiesterase-4 (PDE4) inhibitor can be tried. Triple therapy of ICS/LABA/LAMA had clinical benefits compared with LABA or LAMA alone.

Add on therapy: exacerbation or mMRC≥2

FEV1≥60% pred. and 0–1 exacerbation/yr
mMRC<2 or CAT<10

FEV1<60% pred. or ≥2 exacerbation/yr or history of AE COPD related admission
mMRC≥2 or CAT≥10

Short-acting beta2-agonist as required

ICS/LABA
LABA+LAMA
LABA or LAMA

LABA+LAMA

ICS+LABA+LAMA
PDE4 inhibitor† or macrolide

ICS/LABA†

Add on therapy: exacerbation or mMRC≥2

Figure 2. Pharmacologic treatment algorithms. *Postbronchodilator FEV1 <50%, symptoms of chronic bronchitis, and a history of exacerbations. †Asthma overlap or high blood eosinophil. COPD: chronic obstructive pulmonary disease; FEV1: forced expiratory volume in 1 second; mMRC: modified Medical Research Council dyspnea score; CAT: COPD assessment test score; AE COPD: acute exacerbation of COPD; SABA: short-acting β2-agonists; LABA: long-acting β2-agonists; LAMA: long-acting muscarinic antagonist; PDE4: phosphodiesterase-4; ICS: inhaled corticosteroid.
benefits compared with tiotropium or ICS/LABA combination with symptomatic COPD and a history of exacerbations in a reduction in the rate of exacerbation and improvement in lung function. PDE4 inhibitors can be administered to this group of patients with COPD and chronic bronchitis phenotype who undergo frequent exacerbations, if the side effects of PDE4 inhibitors, including nausea, diarrhea, and weight loss, are not serious.

3. Nonpharmacologic therapies

1) Smoking cessation
Smoking cessation is one of the most important interventions. It slows the rate of decline in FEV\(_1\) with consequent benefits in terms of progression of symptoms and survival\(^{57}\). Pharmacotherapy and nicotine replacement reliably increase the long-term smoking abstinence rates.

2) Physical activity/Pulmonary rehabilitation
The principal goals of pulmonary rehabilitation are to reduce symptoms, improve quality of life, and increase physical and emotional participation in everyday activities\(^{58}\). All patients who experience shortness of breath when walking on their own pace on level ground should be offered rehabilitation. Several studies have documented an effect of pulmonary rehabilitation in patients with breathlessness, usually mMRC >1, and following acute exacerbations.

3) Oxygen therapy
The long-term administration of oxygen (>15 hr/day) to patients with chronic respiratory failure has been shown to increase survival in patients with severe resting hypoxemia\(^{59}\). Long-term oxygen therapy is indicated for patients who have the following conditions:

- Partial pressure of oxygen (Pa\(_{O_2}\)) at or below 55 mm Hg or arterial oxygen saturation (Sa\(_{O_2}\)) at or below 88%, with or without hypercapnia confirmed twice over a 3-week period; or Pa\(_{O_2}\) between 55 mm Hg and 60 mm Hg, or Sa\(_{O_2}\) of 89%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit >55%).

4) Bronchoscopic lung volume reduction
In a post-hoc analysis, bronchoscopic lung volume reduction (BLVR) in patients with COPD and severe airflow limitation (FEV\(_1\), 15–45% predicted), heterogeneous emphysema on computed tomography (CT), and hyperinflation (total lung capacity >100% and residual volume >150% predicted) induced modest improvements in lung function, exercise tolerance, and symptoms, at the cost of more frequent exacerbations of COPD, pneumonia, and hemoptysis after implantation\(^{60}\). Additional data are required to define the optimal BLVR technique and patient population.

### Acute Exacerbation of COPD

1. Definition

Acute exacerbation of COPD can be defined as episodes of acute worsening of the patient’s respiratory symptoms, particularly dyspnea, cough and sputum production that leads to additional therapy\(^{61}\). Exacerbations also vary in severity, and can be categorized as mild, moderate, or severe according to the intensity of the medical intervention required to control the patient’s symptoms. The indications of admission are listed in Table 2.

- Mild: controlled with an increased dosage of short acting bronchodilators only
- Moderate: controlled with short acting bronchodilators plus antibiotics and/or oral steroids
- Severe: patient requires hospitalization or visits the emergency room

2. Meaning and importance

Acute exacerbation of COPD can impact the natural course of COPD in the following ways:

- Worsening of quality of life
- Deterioration of symptoms and lung function (requiring a few weeks to recover)
- Acceleration of decline of lung function
- Increase in mortality rate
- Increase in socioeconomic burden

3. Etiology and risk factors

The causes of COPD acute exacerbation are numerous. The most common cause is respiratory infection (viral and/or bacterial)\(^{62,63}\). Air pollution can also cause exacerbation. Discontinuing maintenance medication and poor adherence to COPD medication can also be causes. However, the cause of exacerbation cannot be identified in one-third of the cases. Diseases with similar symptoms (pneumonia, congestive heart failure, pneumothorax, pleural effusion, pulmonary thromboembolism, and arrhythmia) should also be differenti-

| Table 2. Indications of admission |
|-----------------------------------|
| Severe symptoms                   |
| Acute respiratory failure         |
| Newly developed physical signs    |
| (e.g., peripheral edema and/or cyanosis) |
| Presence of severe comorbidity (especially cardiac disease) |
| No response to first-line treatment |
| Insufficient home support         |
ated from COPD exacerbations.

The COPD “Frequent exacer-bator” phenotype is defined by two or more treated exacerbations per year, and the major predictor of frequent exacerbations is a history of prior exacerbations. Other factors that have been associated with an increased risk of exacerbations include an increase in the ratio of the pulmonary artery to aorta cross sectional dimension, a greater percentage of chest CT imaging-determined emphysema or airway wall thickness and the presence of chronic bronchitis.

4. Diagnosis and assessment of severity

Symptoms for COPD acute exacerbations are aggravation of dyspnea, increase in cough and sputum volume, and change in sputum color. Diagnosis of acute exacerbation is based on the presence of these symptoms that are beyond normal day-to-day variations, and a change in the patient's baseline medication regimens.

Severity of exacerbation can be assessed using the following variables.

1) History
- History of previous exacerbation frequency and severity
- Degree of airflow obstruction in the stable state
- Duration and severity of deterioration of symptoms
- Comorbidity (especially, cardiac disease)
- Current medication
- Home O2 therapy

2) Physical examination
- Use of accessory muscle
- Paradoxical respiration, dyssynchrony between rib cage and abdomen
- Cyanosis
- Peripheral edema
- Hemodynamic instability
- Decrease of mentality

3) Laboratory findings
- Pulse oximetry: If oxygen saturation is below 90%, hospitalization should be considered. If respiratory failure is suspected, arterial blood gas analysis (ABGA) should be performed.
- Chest plain radiography: If there is a clear difference in the findings between the initial and follow-up radiographs, hospitalization should be considered.
- Electrocardiography should be performed to check for concomitant heart disease.
- Complete blood count: To check for anemia, polycythemia, and leukocytosis
- Blood chemistry: To check for electrolyte imbalance and hyperglycemia
- Sputum study: The characteristics of the sputum should be checked because antibiotic treatment may be necessary if the sputum is purulent. Culture tests may be helpful in selecting the antibiotics.

5. Medication

The goal for the treatment of COPD exacerbation is to alleviate the patient's symptoms of dyspnea, to stabilize respiratory status, to minimize the negative impact of current exacerbation, and to prevent future exacerbation.

Short-acting bronchodilators, systemic corticosteroids, and antibiotics are major three classes of medications for the pharmacologic treatment.

1) Bronchodilators
SABA with or without SAMA is recommended. Theophylline is not recommended.

2) Steroids
Systemic steroids can reduce the recovery and admission periods. They also improve lung function and oxygen saturation. Systemic steroids can also reduce further exacerbation. Although administration of 30–40 mg of prednisolone for 10–14 days is recommended, 5 days of oral steroids (40 mg of prednisolone or equivalent) would be sufficient for treatment of COPD exacerbations. Intravenous administration is not superior to oral administration.

3) Antibiotics
Antibiotics are reported to reduce treatment failure and mortality. They are recommended when patients have three cardinal symptoms such as increase in dyspnea, sputum volume, and sputum purulence or two symptoms including increased purulence of sputum or for patients on mechanical ventilation.

Initial choice of empirical antibiotic treatment is an aminopenicillin with clavulanic acid, or second or third generation cephalosporin, or advanced-generation macrolides. In high risk patients (i.e., frequent exacerbators, severe lung function impairment, co-morbid cardiac disease, or admission to an intensive care unit), antibiotic choice includes a respiratory fluoroquinolone (levofloxacin, moxifloxacin, azithromycin). In a subgroup of patients who are at risk for infection by Pseudomonas aeruginosa, antipseudomonal antibiotics (ciprofloxacin, antipseudomonal cephalosporin, etc.) are needed.

The duration of the antibiotic treatment has not been well defined, but 5 to 7 days of treatment is as effective as long-duration treatment.
6. Respiratory support

1) Oxygen
Oxygen therapy is a key component of management of COPD exacerbation. The target goal of saturation is 88%–92%. ABGA should be performed 30–60 minutes after oxygen therapy. However, too much oxygen can result in CO2 retention.

2) Ventilatory support
Some patients require admission to the intensive care unit (Table 3). Noninvasive positive pressure ventilation (NIPPV) or invasive mechanical ventilation (IMV) may be needed for such patients.

3) NIPPV
NIPPV is preferred over IMV. Success rate of NIPPV is reported to be 80%–85%. NIPPV improves respiratory acidosis, respiratory rate, and dyspnea. It also reduces complications, such as ventilator-associated pneumonia, and the duration of hospitalization. Moreover, NIPPV also reduces the IMV rate and mortality. The indications of NIPPV are listed in Table 4.

4) IMV
The indications of IMV are listed in Table 5.

7. Hospital discharge and follow-up
Care bundles at hospital discharge are listed in Table 6. Education for smoking cessation, optimization of medication, assessment of the inhaler technique and need for continuing oxygen therapy, early rehabilitation post hospital discharge, and detailed follow-up plans are needed.

8. Prevention of exacerbations
COPD can be prevented by nonpharmaceutical and pharmaceutical treatments

1) Nonpharmaceutical treatment
- Pulmonary rehabilitation
- Smoking cessation
- Vaccination
- Lung volume reduction

2) Pharmaceutical treatment
- Inhaled long-acting bronchodilators: LABA or LAMA or LABA+LAMA
- ICS-containing regimens: ICS+LABA or ICS+LABA+LAMA
- PDE4 inhibitor
- Long term macrolides
- Mucoregulators: N-acetylcysteine, carbocysteine
Comorbidities of COPD

COPD patients are often accompanied by other diseases that may affect prognosis. It is essential to identify and treat comorbidities in the management of COPD patients. The treatment of comorbidities in patients with COPD is not different from that in those without COPD.

Cardiovascular diseases are the most common and important comorbidities of COPD patients. Ischemic heart disease, heart failure, arrhythmia, peripheral vascular disease, and hypertension are the most common. Beta-1 blockers are recommended as treatments to increase the survival rate of patients with heart failure. Patients with COPD should be prescribed a selective beta-1 blocker, which has proven safe for COPD patients.

Noninvasive positive ventilation improves the prognosis of patients with hypercapnic respiratory failure due to heart failure as well as COPD exacerbation.

Even though osteoporosis is a major comorbidity in COPD, it is often overlooked or its diagnosis is delayed, worsening the general condition and prognosis. Since systemic corticosteroids significantly increase the risk of osteoporosis, frequent use of systemic corticosteroids should be avoided whenever possible.

Anxiety and depression are major comorbidities of COPD and are associated with poor prognosis of COPD. The prevalence of depression in Korean COPD patients is 17%–55%, which is higher than that of the general population (15.3%) (83-85). Korean Patient Health Questionnaire-9 is recommended as a screening tool to diagnose depression in patients with COPD.

The close link between COPD and lung cancer has been proven through several studies. The best way to prevent lung cancer in COPD patients is smoking cessation. In the United States, lung cancer screening tests using low-dose chest CT in patients aged 55 to 74 years with a history of cigarette smoking of at least 30 pack-years, and, if former smokers, with a smoking cessation period of less than 15 years have improved survival rates (86,92). However, there have been concerns about overdiagnosis of benign nodules, mortality and morbidity resulting from biopsy of benign nodules, patient anxiety, and improper follow-up.

Metabolic syndrome and type 2 diabetes mellitus are very common in COPD patients. Diabetes mellitus has a negative effect on the prognosis of COPD patients, leading to an increase in the length of hospital stay and mortality in exacerbation of COPD patients with diabetes. Weight reduction aimed at achieving a body mass index of less than 21 kg/m² is not recommended for patients with severe COPD.

Gastroesophageal reflux disease is often associated with COPD patients, reducing the quality of life and increasing the risk of exacerbations. The prevalence of gastroesophageal reflux disease in Korean COPD patients is estimated to be 28%.

Chest CT is widely used in patients with COPD, and the diagnosis of bronchiectasis is increasing. Inhaled corticosteroids may have to be avoided in patients with bacterial colonization or recurrent lower respiratory tract infections.

Sleep deprivation is a common problem in COPD patients. Patients with COPD and obstructive sleep apnea syndrome (OSA) are referred to as COPD-OSA overlap syndrome. These patients have poorer quality of life and lower nighttime peripheral oxygen saturation than patients with isolated disease, resulting in cardiac arrhythmia and pulmonary hypertension. It has been reported that continuous positive airway pressure treatment for patients with COPD-OSA overlap syndrome reduces exacerbation and mortality of COPD.

As the elderly population grows, many people have two or more diseases at the same time, and COPD is a major disease of multiple diseases. It is important to simplify the medicines for those with multiple diseases.

Authors’ Contributions

Conceptualization: Oh YM, Yoo KH, Rhee CK. Methodology: Park YB, Yoon HK, Lim SY, Lee JH, Ahn JH. Formal analysis: Park YB, Rhee CK. Data curation: Rhee CK, Lee JH. Software: Rhee CK. Validation: Yoon HK, Ahn JH. Investigation: Park YB, Rhee CK, Yoon HK, Oh YM, Lim SY, Lee JH, Yoo KH, Ahn JH. Writing - original draft preparation: Rhee CK, Yoon HK, Oh YM. Writing - review and editing: Yoo KH, Oh YM. Approval of final manuscript: all authors.

Conflicts of Interest

No potential conflict of interest relevant to this article was reported.

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References

1. Yoo KH, Kim YS, Sheen SS, Park JH, Hwang YI, Kim SH, et al. Prevalence of chronic obstructive pulmonary disease in Korea: the fourth Korean National Health and Nutrition Examination Survey. 2008. Respirology 2011;16:659-65.
2. Hwang YI, Park YB, Yoo KH. Recent trends in the prevalence of chronic obstructive pulmonary disease in Korea. Tuberc Respir Dis 2017;80:226-9.

3. Statistics Korea. The result of causes of death statistics in 2010. Daejeon: Statistics Korea; 2011.

4. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med 2006;3:e442.

5. Lopez AD, Shibuya K, Rao C, Mathers CD, Hansell AL, Held LS, et al. Chronic obstructive pulmonary disease: current burden and future projections. Eur Respir J 2006;27:397-412.

6. Soriano JB, Rodriguez-Roisin R. Chronic obstructive pulmonary disease overview: epidemiology, risk factors, and clinical presentation. Proc Am Thorac Soc 2011;8:363-7.

7. Adeloye D, Chua S, Lee C, Basquill C, Papana A, Theodoratou E, et al. Global and regional estimates of COPD prevalence: systematic review and meta-analysis. J Glob Health 2015;5:020415.

8. Kim C, Yoo KH, Rhee CK, Yoon HK, Kim YS, Lee SW, et al. Health care use and economic burden of patients with diagnosed chronic obstructive pulmonary disease in Korea. Int J Tuberc Lung Dis 2014;18:737-43.

9. Yoon J, Seo H, Oh IH, Yoon SJ. The non-communicable disease burden in Korea: findings from the 2012 Korean burden of disease study. J Korean Med Sci 2016;31 Suppl 2:S158-67.

10. Lamprecht B, McBurnie MA, Vollmer WM, Gudmundsson G, Welte T, Nizankowska-Mogilnicka E, et al. COPD in never smokers: results from the population-based burden of obstructive lung disease study. Chest 2011;139:752-63.

11. Eiser MD, Anthonisen N, Coul tas D, Kuenzli N, Perez-Padilla R, Postma D, et al. An official American Thoracic Society public policy statement: novel risk factors and the global burden of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2010;182:693-718.

12. Barnes PJ, Shapiro SD, Pauwels RA. Chronic obstructive pulmonary disease: molecular and cellular mechanisms. Eur Respir J 2003;22:672-88.

13. Vestbo J, Hurd SS, Agusti AG, Jones PW, Vogelmeier C, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. Am J Respir Crit Care Med 2013;187:347-65.

14. Burge PS, Calverley PM, Jones PW, Spencer S, Anderson JA, Maslen TK. Randomised, double blind, placebo controlled study of fluticasone propionate in patients with moderate to severe chronic obstructive pulmonary disease: the ISOLDE trial. BMJ 2000;320:1297;303.

15. Anthonisen NR, Conn et JE, Kiley JP, Altose MD, Bailey WC, Buist AS, et al. Effects of smoking intervention and the use of an inhaled anticholinergic bronchodilator on the rate of decline of FEV1. The Lung Health Study. JAMA 1994;272:1497-505.

16. Vestbo J, Sorensen T, Lange P, Brix A, Torre P, Viskum K. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 1999;353:1819-23.

17. Se stini P, Cappi ello V, Aliani M, Martucci P, Sena A, Vaghi A, et al. Prescription bias and factors associated with improper use of inhalers. J Aerosol Med 2006;19:127-36.

18. Donohue JE, Fogarty C, Lotvall J, Mahler DA, Worth H, Yorgancioglu A, et al. Once-daily bronchodilators for chronic obstructive pulmonary disease: indacaterol versus tiotropium. Am J Respir Crit Care Med 2010;182:155-62.

19. Kornmann O, Dahl R, Centanni S, Dogra A, Owen R, Lassen C, et al. Once-daily indacaterol versus twice-daily salmeterol for COPD: a placebo-controlled comparison. Eur Respir J 2011;37:273-9.

20. Barr RG, Bourbeau J, Camargo CA, Ram FS. Inhaled tiotropium for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005;2(2):CD002876.

21. Kesten S, Casaburi R, Kuka fka D, Cooper CB. Improvement in self-reported exercise participation with the combination of tiotropium and rehabilitative exercise training in COPD patients. Int J Chron Obstruct Pulm Dis 2008;3:127-36.

22. Tashkin DP, Celli B, Senn S, Burk hart D, Kesten S, Menjoge S, et al. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. N Engl J Med 2008;359:1543-54.

23. Decramer ML, Chapman KR, Dahl R, Frith P, Devouassoux G, Fritscher C, et al. Once-daily indacaterol versus tiotropium for patients with severe chronic obstructive pulmonary disease (INVIGORATE): a randomised, blinded, parallel-group study. Lancet Respir Med 2013;1:524-33.

24. Vogelmeier C, Hederer B, Glaab T, Schmidt H, Rutten-van Molken MP, Beeh KM, et al. Tiotropium versus salmeterol for the prevention of exacerbations of COPD. N Engl J Med 2011;364:1093-103.

25. Jones PW, Singh D, Bateman ED, Agusti A, Lamarca R, de Miguel G, et al. Efficacy and safety of twice-daily aclidinium bromide in COPD patients: the ATTAIN study. Eur Respir J 2012;40:830-6.

26. Kerwin E, Hebert J, Gallagher N, Martin C, Overend T, Alagappan VK, et al. Efficacy and safety of NVA237 versus placebo and tiotropium in patients with COPD: the GLOW2 study. Eur Respir J 2012;40:1106-14.

27. Beier J, Kirsten AM, Mroz R, Segarra R, Chuecos F, Caracta C, et al. Efficacy and safety of aclidinium bromide compared with placebo and tiotropium in patients with moderate-to-severe chronic obstructive pulmonary disease: results from a 6-week, randomized, controlled Phase IIIb study. COPD 2013;10:511-22.

28. D’Urzo A, Kerwin E, Rennard S, He T, Gil EG, Caracta C. One-year extension study of ACCORD COPD I: safety and efficacy of two doses of twice-daily aclidinium bromide in patients with COPD. COPD 2013;10:500-10.
29. Gelb AF, Tashkin DP, Make BJ, Zhong X, Garcia Gil E, Caracta C, et al. Long-term safety and efficacy of twice-daily aclidinium bromide in patients with COPD. Respir Med 2013;107:1957-65.

30. Beeh KM, Singh D, Di Scala L, Drollmann A. Once-daily NVA237 improves exercise tolerance from the first dose in patients with COPD: the GLOW3 trial. Int J Chron Obstruct Pulmon Dis 2012;7:503-13.

31. Chapman KR, Beeh KM, Beier J, Bateman ED, D’Urzo A, Nutbrown R, et al. A blinded evaluation of the efficacy and safety of glycopyrronium, a once-daily long-acting muscarinic antagonist, versus tiotropium, in patients with COPD: the GLOW5 study. BMC Pulm Med 2014;14:1.

32. D’Urzo A, Kerwin E, Overend T, D’Andrea P, Chen H, Goyal P. Once daily glycopyrronium for the treatment of COPD: pooled analysis of the GLOW1 and GLOW2 studies. Curr Med Res Opin 2014;30:493-508.

33. ZuWallack RL, Mahler DA, Reilly D, Church N, Emmett A, Rickard K, et al. Salmeterol plus theophylline combination therapy in the treatment of COPD. Chest 2001;119:1661-70.

34. Buhl R, Maltais F, Abrahams R, Maltais F, Bjermer L, Derom E, Ferguson G, et al. Tiotropium and olodaterol fixed-dose combination versus mono-components in COPD (GOLD 2-4). Eur Respir J 2015;45:969-79.

35. Wedzicha JA, De Crancer M, Ficker JH, Niewoehner DE, Sandstrom T, Taylor AF, et al. Analysis of chronic obstructive pulmonary disease exacerbations with the dual bronchodilator QVA149 compared with glycopyrronium and tiotropium (SPARK): a randomised, double-blind, parallel-group study. Lancet Respir Med 2013;1:199-209.

36. Wedzicha JA, Banerji D, Chapman KR, Vestbo J, Roche N, Ayers RT, et al. Indacaterol-glycopyrronium versus salmeterol-fluticasone for COPD. N Engl J Med 2016;374:2222-34.

37. Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins CJ, Jones PW, et al. Salmeterol and fluticasone propionate and long-term survival in chronic obstructive pulmonary disease. N Engl J Med 2007;356:775-89.

38. Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, et al. Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. European Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med 1999;340:1948-53.

39. Szafanski W, Cuikier A, Ramírez A, Menga G, Sansores R, Nahabedian S, et al. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J 2003;21:74-81.

40. Calverley P, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, et al. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2003;361:449-56.

41. Vestbo J, Papi A, Corradi M, Blazhko V, Montagna I, Francisco C, et al. Single inhaler extrafine triple therapy versus long-acting muscarinic antagonist therapy for chronic obstructive pulmonary disease (TRINITY): a double-blind, parallel group, randomised controlled trial. Lancet 2017;389:1919-29.

42. Singh D, Papi A, Corradi M, Pavlisova I, Montagna I, Francisco C, et al. Single inhaler triple therapy versus inhaled corticosteroid plus long-acting beta2-agonist therapy for chronic obstructive pulmonary disease (TRILOGY): a double-blind, parallel group, randomised controlled trial. Lancet 2016;388:963-73.

43. Lipson DA, Barnacle H, Birk R, Brealey N, Locantore N, Lomas DA, et al. FULFIL trial: once-daily triple therapy for patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2017;196:438-46.

44. Rabe KF, Bateman ED, O’Donnell D, Witte S, Bredenbroeker D, Bethke TD. Roflumilast: an oral anti-inflammatory treatment for chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2005;366:563-71.

45. Calverley PM, Rabe KF, Goehring UM, Kristiansen S, Fabbri LM, Martinez FJ, et al. Roflumilast in symptomatic chronic obstructive pulmonary disease: two randomised clinical trials. Lancet 2009;374:685-94.

46. Calverley PM, Sanchez-Toril F, McIvor A, Teichmann P, Bredenbroeker D, Fabbri LM. Effect of 1-year treatment with roflumilast in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007;176:154-61.

47. Fabbri LM, Calverley PM, Izuquierdo-Alonso JL, Bundschuh DS, Brose M, Martinez FJ, et al. Roflumilast in moderate-to-severe chronic obstructive pulmonary disease treated with longacting bronchodilators: two randomised clinical trials. Lancet 2009;374:695-703.

48. Chong J, Leung B, Poole P. Phosphodiesterase 4 inhibitors for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2017;9:CD002309.

49. Bateman ED, Rabe KF, Calverley PM, Goehring UM, Brose M, Bredenbroeker D, et al. Roflumilast with long-acting beta2-agonists for COPD: influence of exacerbation history. Eur Respir J 2011;38:553-60.

50. Lee SD, Hui DS, Mahayiddin AA, Roa CC Jr, Kwa KH, Goehring UM, et al. Roflumilast in Asian patients with COPD: a randomized placebo-controlled trial. Respirology 2011;16:1249-57.

51. Martinez FJ, Calverley PM, Goehring UM, Brose M, Fabbri LM, Rabe KF. Effect of roflumilast on exacerbations in patients with severe chronic obstructive pulmonary disease uncontrolled by combination therapy (REACT): a multicentre randomised controlled trial. Lancet 2015;385:857-66.

52. Martinez FJ, Rabe KF, Sethi S, Pizzichini E, McIvor A, Anzueto A, et al. Effect of roflumilast and inhaled corticosteroid/long-acting beta2-agonist on chronic obstructive pulmonary disease exacerbations (RE(2)SPOND): a randomized clinical trial. Am J Respir Crit Care Med 2016;194:539-67.

53. Seemungal TA, Wilkinson TM, Hurst JR, Perera WR, Saps-
ford RJ, Wedzicha JA. Long-term erythromycin therapy is associated with decreased chronic obstructive pulmonary disease exacerbations. Am J Respir Crit Care Med 2008;178:1139-47.

54. Sethi S, Jones PW, Theron MS, Miravitlles M, Rubinstein E, Wedzicha JA, et al. Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Respir Res 2010;11:10.

55. Albert RK, Connnett J, Bailey WC, Casaburi R, Cooper JA Jr, Criner GJ, et al. Azithromycin for prevention of exacerbations of COPD. N Engl J Med 2011;365:689-98.

56. Uzun S, Djamin RS, Khytman JA, Mulder PG, van’t Veer NE, Ermens AA, et al. Azithromycin maintenance treatment in patients with frequent exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2014;2:361-8.

57. Strassmann R, Bausch B, Spaar A, Kleijnen J, Braendli O, Strassmann R, Bausch B, Spaar A, Kleijnen J, Braendli O, et al. Randomised controlled trial of long-term inhaled tiotropium in chronic obstructive pulmonary disease. Lancet 2006;368:432-9.

58. Sethi S, Jones PW, Theron MS, Miravitlles M, Rubinstein E, Wedzicha JA, et al. Pulsed moxifloxacin for the prevention of exacerbations of chronic obstructive pulmonary disease (COLUMBUS): a randomised, double-blind, placebo-controlled trial. Lancet Respir Med 2014;2:361-8.

59. Stoller JK, Panos RJ, Krachman S, Doherty DE, Make BJ, Long-term Oxygen Treatment Trial Research Group. Oxygen therapy for patients with COPD: current evidence and the long-term oxygen treatment trial. Chest 2010;138:179-87.

60. Siciura FC, Ernst A, Herth FG, Strange C, Criner GJ, Marquette CH, et al. A randomized study of endobronchial valves for advanced emphysema. N Engl J Med 2010;363:1233-44.

61. Global Initiative for Chronic Obstructive Lung Disease. Global Strategy for the diagnosis, management, and prevention of Chronic Obstructive Lung Disease 2017 [Internet]. Global Initiative for Chronic Obstructive Lung Disease; 2017 [cited 2018 Jan 5]. Available from: http://www.goldcopd.org.

62. Wedzicha JA, Seemungal TA. COPD exacerbations: defining their cause and prevention. Lancet 2007;370:786-96.

63. Sethi S, Murphy TF. Infection in the pathogenesis and course of chronic obstructive pulmonary disease. N Engl J Med 2008;359:2355-65.

64. Hurst JR, Vestbo J, Anzueto A, Locantore N, Mullerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med 2010;363:1128-38.

65. Wells JM, Washko GR, Han MK, Abbas N, Nath H, Mamary AJ, et al. Pulmonary arterial enlargement and acute exacerbations of COPD. N Engl J Med 2012;367:913-21.

66. Han MK, Kazarooen EA, Lynch DA, Liu LX, Murray S, Curtis Jl, et al. Chronic obstructive pulmonary disease exacerbations in the COPDGene study: associated radiologic phenotypes. Radiology 2011;261:274-82.

67. Burgel PR, Nesme-Meyer P, Chanez P, Caillaud D, Carré R, Perez T, et al. Cough and sputum production are associated with frequent exacerbations and hospitalizations in COPD subjects. Chest 2009;135:975-82.

68. Kim V, Han MK, Vance GB, Make BJ, Newell JD, Hokanson JE, et al. The chronic bronchitic phenotype of COPD: an analysis of the COPDGene Study. Chest 2011;140:626-33.

69. Leuppi JD, Schuetz P, Bingisser R, Bodmer M, Bresser T, et al. Short-term vs conventional glucocorticoid therapy in acute exacerbations of chronic obstructive pulmonary disease: the REDUCE randomized clinical trial. Jama 2013;309:2223-31.

70. Walters JA, Tan DJ, White CJ, Wood-Baker R. Different durations of corticosteroid therapy for exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2014;(12):CD006897.

71. Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary disease. Ann Intern Med 1987;106:196-204.

72. Masterton RG, Burley CJ. Randomized, double-blind study comparing 5- and 7-day regimens of oral levofloxacin in patients with acute exacerbation of chronic bronchitis. Int J Antimicrob Agents 2001;18:503-12.

73. Barnes PJ, Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J 2009;33:1163-85.

74. Soriano JB, Visick GT, Muellerova H, Payvandi N, Hansell AL. Patterns of comorbidities in newly diagnosed COPD and asthma in primary care. Chest 2005;128:2099-107.

75. Mannino DM, Thorn D, Swensen A, Holguin F. Prevalence and outcomes of diabetes, hypertension and cardiovascular disease in COPD. Eur Respir J 2008;32:562-9.

76. Sin DD, Anthonisen NR, Soriano JB, Agusti AG. Mortality in COPD: role of comorbidities. Eur Respir J 2006;28:1245-57.

77. Fahbri LM, Luppi F, Beghe B, Rabke KF. Complex chronic comorbidities of COPD. Eur Respir J 2008;31:204-12.

78. Lipworth B, Wedzicha J, Deveuex G, Vestbo J, Dransfield MT. Beta-blockers in COPD: time for reappraisal. Eur Respir J 2016;48:880-8.

79. Masa JF, Gomez de Terreros J, Abruto M, Esteban C, Prats E, et al. Noninvasive ventilation for severely acidoic patients in respiratory intermediate care units: precision medicine in intermediate care units. BMC Pulm Med 2016;16:97.

80. Madsen H, Brixen K, Hallas J. Screening, prevention and treatment of osteoporosis in patients with chronic obstructive pulmonary disease. J Intern Med 2016;279:299-316.

81. Hanania NA, Mullerova H, Locantore NW, Vestbo J, Watkins ML, Wouters EJ, et al. Determinants of depression in the ECLIPSE chronic obstructive pulmonary disease cohort.
82. Ng TP, Niti M, Tan WC, Cao Z, Ong KC, Eng P. Depressive symptoms and chronic obstructive pulmonary disease: effect on mortality, hospital readmission, symptom burden, functional status, and quality of life. Arch Intern Med 2007;167:60-7.
83. Chiu HJ, Lee KH, Park CS, Son CW, Lee HY, Yu SK, et al. Prevalence and risk factors of depression in patients with chronic obstructive pulmonary disease. Tuberc Respir Dis 2008;65:191-7.
84. Ryu YJ, Chun EM, Sim YS, Lee JH. Depression and anxiety in outpatients with chronic obstructive pulmonary disease. Tuberc Respir Dis 2007;62:11-8.
85. Cho HJ, Chae JH, Jun TY. The overview of clinical assessment tools for depression. J Korean Neuropsychiatr Assoc 2007;46:110-21.
86. Hwang YI, Kim HJ, Won WY, Joh JS, Oh YM, Jung KS, et al. Screening for depression in patients with chronic obstructive pulmonary disease: a systematic review. Korean J Med 2012;83:468-75.
87. Choi HS, Choi JH, Park KH, Joo KJ, Ga H, Ko HJ, et al. Standardization of the Korean version of Patient Health Questionnaire-9 as a screening instrument for major depressive disorder. J Korean Acad Fam Med 2007;28:114-9.
88. Lim KH, Park YN, Kim DH, Shin IH, Lee WS, Kim JB. A preliminary study of the standardization of the Korean version of the Patient Health Questionnaire-9 as a screening instrument for major depressive disorder. J Korean Acad Fam Med 2007;28:114-9.
89. McGarvey LP, Magder S, Burkhart D, Kesten S, Liu D, Manuel RC, et al. Cause-specific mortality adjudication in the UPLIFT(R) COPD trial: findings and recommendations. Respir Med 2012;106:515-21.
90. Oelsner EC, Carr JJ, Enright PL, Hoffman EA, Folsom AR, Kawut SM, et al. Per cent emphysema is associated with respiratory and lung cancer mortality in the general population: a cohort study. Thorax 2016;71:624-32.
91. National Lung Screening Trial Research Team, Aberle DR, Adams AM, Berg CD, Black WC, Clapp JD, et al. Reduced lung cancer mortality with low-dose computed tomographic screening. N Engl J Med 2011;365:395-409.
92. Infante M, Cavuto S, Lutman FR, Passera E, Chiarenza M, Chiesa G, et al. Long-term follow-up results of the DANTE trial, a randomized study of lung cancer screening with spiral computed tomography. Am J Respir Crit Care Med 2015;191:1166-75.
93. Parappil A, Depczynski B, Collett P, Marks GB. Effect of comorbid diabetes on length of stay and risk of death in patients admitted with acute exacerbations of COPD. Respir Care 2010;55:18-22.
94. Garcia Rodriguez LA, Ruigomez A, Martin-Merino E, Johansson S, Wallander MA. Relationship between gastroesophageal reflux disease and COPD in UK primary care. Chest 2008;134:1223-30.
95. Takada K, Matsumoto S, Kojima E, Iwata S, Okachi S, Ninomiya K, et al. Prospective evaluation of the relationship between acute exacerbations of COPD and gastroesophageal reflux disease diagnosed by questionnaire. Respir Med 2011;105:1531-6.
96. Kim J, Lee JH, Kim Y, Kim K, Oh YM, Yoo KH, et al. Association between chronic obstructive pulmonary disease and gastroesophageal reflux disease: a national cross-sectional cohort study. BMC Pulm Med 2013;13:51.
97. O’Brien C, Guest PJ, Hill SL, Stockley RA. Physiological and radiological characterisation of patients diagnosed with chronic obstructive pulmonary disease in primary care. Thorax 2000;55:635-42.
98. Mermigkis C, Kopanakis A, Foldvary-Schaefer N, Golish J, Polychronopoulos V, Schiza S, et al. Health-related quality of life in patients with obstructive sleep apnoea and chronic obstructive pulmonary disease (overlap syndrome). Int J Clin Pract 2007;61:207-11.
99. Shepard JW Jr, Garrison MW, Grither DA, Evans R, Schweitzer PK. Relationship of ventricular ectopy to nocturnal oxygen desaturation in patients with chronic obstructive pulmonary disease. Am J Med 1985;78:28-34.
100. Bradley TD, Rutherford R, Grossman RF, Lue F, Zamel N, Moldofsky H, et al. Role of daytime hypoxemia in the pathogenesis of right heart failure in the obstructive sleep apnea syndrome. Am Rev Respir Dis 1985;131:835-9.
101. Weitzenblum E, Krieger J, Apprill M, Vallee E, Ehrhart M, Ratomaharo J, et al. Daytime pulmonary hypertension in patients with obstructive sleep apnea syndrome. Am Rev Respir Dis 1988;138:345-9.
102. Stanchina ML, Welicky LM, Donat W, Lee D, Corrao W, Malhotra A. Impact of CPAP use and age on mortality in patients with combined COPD and obstructive sleep apnea: the overlap syndrome. J Clin Sleep Med 2013;9:767-72.
103. Machado MC, Vollmer WM, Togeiro SM, Bilderdijk AL, Oliveira MV, Leitao FS, et al. CPAP and survival in moderate-to-severe obstructive sleep apnoea syndrome and hypoxemic COPD. Eur Respir J 2010;35:132-7.