GLOBAL STRATEGY FOR THE DIAGNOSIS, MANAGEMENT, AND PREVENTION OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Randy D. Danielsen, PhD, PA, DFAAPA, *PA-C-Emeritus*
Dean & Professor
Arizona School of Health Sciences
A.T. Still University

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Chronic Obstructive Pulmonary Disease (COPD)

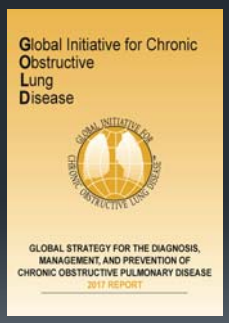
- COPD is currently the fourth leading cause of death in the world.[1]
- COPD is projected to be the 3rd leading cause of death by 2020.[2]
- More than 3 million people died of COPD in 2012 accounting for 6% of all deaths globally.
- Globally, the COPD burden is projected to increase in coming decades because of continued exposure to COPD risk factors and aging of the population.

1. Lozano R, Naghavi M, Foreman K, et al. Global and regional mortality from 235 causes of death for 20 age groups in 1990 and 2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**(9859): 2095-128.
2. Mathers CD, Loncar D. Projections of global mortality and burden of disease from 2002 to 2030. *PLoS Med* 2006; **3**(11): e442.

Chronic Obstructive Pulmonary Disease (COPD)

- Deaths caused by COPD rose by 11;6% during the 25-year study, going from 2.8 million in 1990 to 3.2 million in 2015.
- Cases increased by 44.2%, going from 121 million to 174.5 million.
- In terms of prevalence, the greatest decrease in age-standardized COPD prevalence occurred in countries in the middle and high middle quintiles of the sociodemographic development index (measure calculated on lagged distributed income per capita, average years of education after age 15 years, and total fertility rate).
- Source: 2015 Global Burden of Disease (GBD) published August 16, 2017 in Lancet Respiratory Medicine.

This Lecture will cover.....

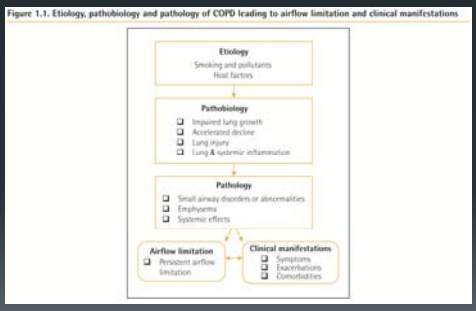


1. Definition and Overview
2. Diagnosis and Initial Assessment
3. Evidence Supporting Prevention & Maintenance Therapy
4. Management of Stable COPD
5. Management of Exacerbations

COPD Definition

- Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.

COPD Etiology, Pathobiology & Pathology



Definition and Overview

OVERALL KEY POINTS (1 of 2):

- Chronic Obstructive Pulmonary Disease (COPD) is a common, preventable and treatable disease that is characterized by persistent respiratory symptoms and airflow limitation that is due to airway and/or alveolar abnormalities usually caused by significant exposure to noxious particles or gases.
- The most common respiratory symptoms include dyspnea, cough and/or sputum production. These symptoms may be under-reported by patients.
- The main risk factor for COPD is tobacco smoking but other environmental exposures such as biomass fuel exposure and air pollution may contribute.

Definition and Overview

OVERALL KEY POINTS (2 of 2):

- Besides exposures, host factors predispose individuals to develop COPD. These include genetic abnormalities, abnormal lung development and accelerated aging.
- COPD may be punctuated by periods of acute worsening of respiratory symptoms, called exacerbations.
- In most patients, COPD is associated with significant concomitant chronic diseases, which increase its morbidity and mortality.

Prevalence

Prevalence of COPD

- Estimated 384 million COPD cases in 2010.
- Estimated global prevalence of 11.7% (95% CI 8.4%–15.0%).
- Three million deaths annually.
- With increasing prevalence of smoking in developing countries, and aging populations in high-income countries, the prevalence of COPD is expected to rise over the next 30 years.
- By 2030 predicted 4.5 million COPD related deaths annually.

Economic and Social Burden

Economic burden of COPD

- COPD is associated with significant economic burden.
- COPD exacerbations account for the greatest proportion of the total COPD burden.

- European Union:
  - Direct costs of respiratory disease ~6% of the total healthcare budget
  - COPD accounting for 56% (38.6 billion Euros) of the cost of respiratory disease.

- USA:
  - Direct costs of COPD are $32 billion
  - Indirect costs $20.4 billion.

Economic and Social Burden

- Global Burden of Disease (GBD) study
- Disability-Adjusted Life Year (DALY) = sum of years lost because of premature mortality and years of life lived with disability, adjusted for the severity of disability.
- COPD is an increasing contributor to disability and mortality around the world.
- In 2013 COPD was 5th leading cause of DALYs lost.
- In the United States, COPD is the second leading cause of reduced DALYs, trailing only ischemic heart disease

Factors that influence disease progression

- Genetic factors
- Age and gender
- Lung growth and development
- Exposure to particles
- Socioeconomic status
- Asthma & airway hyper-reactivity
- Chronic bronchitis
- Infections

Diagnosis and Initial Assessment

OVERALL KEY POINTS (1 of 2):

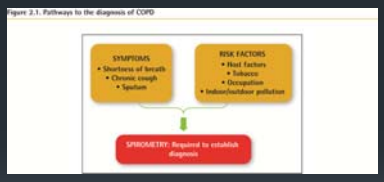
- COPD should be considered in any patient who has dyspnea, chronic cough or sputum production, and/or a history of exposure to risk factors for the disease.
- Spirometry is required to make the diagnosis; the presence of a post-bronchodilator FEV1/FVC < 0.70 confirms the presence of persistent airflow limitation.
- The goals of COPD assessment are to determine the level of airflow limitation, the impact of disease on the patient's health status, and the risk of future events (such as exacerbations, hospital admissions, or death), in order to guide therapy.

Diagnosis and Initial Assessment

OVERALL KEY POINTS (2 of 2):

- Concomitant chronic diseases occur frequently in COPD patients, including cardiovascular disease, skeletal muscle dysfunction, metabolic syndrome, osteoporosis, depression, anxiety, and lung cancer. These comorbidities should be actively sought and treated appropriately when present as they can influence mortality and hospitalizations independently.

Diagnosis and Initial Assessment



Diagnosis and Initial Assessment

Table 2.1. Key indicators for considering a diagnosis of COPD	
Consider COPD, and perform spirometry, if any of these indicators are present in an individual over age 40. These indicators are not diagnostic themselves, but the presence of multiple key indicators increases the probability of a diagnosis of COPD. Spirometry is required to establish a diagnosis of COPD.	
Dyspnea that is:	Progressive over time. Characteristically worse with exercise. Persistent.
Chronic cough:	May be intermittent and may be unproductive. Recurrent wheeze.
Chronic sputum production:	Any pattern of chronic sputum production may indicate COPD.
Recurrent lower respiratory tract infections	
History of risk factors:	Host factors (such as genetic factors, congenital/developmental abnormalities etc.). Tobacco smoke (including popular local preparations). Smoke from home cooking and heating fuels. Occupational dusts, vapors, fumes, gases and other chemicals.
Family history of COPD and/or childhood factors:	For example low birthweight, childhood respiratory infections etc.

Diagnosis and Initial Assessment

- Symptoms of COPD
  - Chronic and progressive dyspnea
  - Cough
  - Sputum production
  - Wheezing and chest tightness
  - Others – including fatigue, weight loss, anorexia, syncope, rib fractures, ankle swelling, depression, anxiety.

Diagnosis and Initial Assessment

Table 2.2. Other causes of chronic cough
Intrathoracic
• Asthma
• Lung cancer
• Tuberculosis
• Bronchiectasis
• Left heart failure
• Interstitial lung disease
• Cystic fibrosis
• Idiopathic cough
Extrathoracic
• Chronic allergic rhinitis
• Post nasal drip syndrome (PNDS)
• Upper Airway Cough Syndrome (UACS)
• Gastroesophageal reflux
• Medication (e.g. ACE inhibitors)

Medical History

- Patient's exposure to risk factors
- Past medical history
- Family history of COPD or other chronic respiratory disease.
- Pattern of symptom development
- History of exacerbations or previous hospitalizations for respiratory disorder
- Presence of comorbidities
- Impact of disease on patient's life
- Social and family support available to the patient.
- Possibilities for reducing risk factors, especially smoking cessation.

Diagnosis and Initial Assessment

Table 2.3. Considerations in performing spirometry

Preparation

- Spirometers need calibration on a regular basis.
- Spirometers should produce hard copy or have a digital display of the expiratory curve to permit detection of technical errors or have an automatic prompt to identify an unsatisfactory test and the reason for it.
- The supervisor of the test needs training in optimal technique and quality performance.
- Maximal patient effort in performing the test is required to avoid underestimation of values and hence errors in diagnosis and management.

Bronchodilation

- Possible dosage protocols are 400 mcg short-acting beta$_2$-agonist, 160 mcg short-acting anticholinergic, or the two combined.[a] FEV_1 should be measured 10-15 minutes after a short-acting beta$_2$-agonist is given, or 30-45 minutes after a short-acting anticholinergic or a combination of both classes of drugs.

Performance

- Spirometry should be performed using techniques that meet published standards.[b]
- The expiratory volume/time traces should be smooth and free from irregularities. The pause between inspiration and expiration should be < 1 second.
- The recording should go on long enough for a volume plateau to be reached, which may take more than 15 seconds in severe disease.
- Both FVC and FEV_1 should be the largest value obtained from any of three technically satisfactory curves and the FVC and FEV_1 values in these three curves should vary by no more than 5% or 150 ml, whichever is greater.
- The FEV_1/FVC ratio should be taken from the technically acceptable curve with the largest sum of FVC and FEV_1.

Evaluation

- Spirometry measurements are evaluated by comparison of the results with appropriate reference values based on age, height, sex, and race.
- The presence of a postbronchodilator FEV_1/FVC < 0.70 confirms the presence of airflow limitation.

[a] Pellegrino et al. Eur Respir J 2005; 26(5): 948-68.
[b] Miller et al. Eur Respir J 2005; 26(2): 319-38.

Classification of severity of airflow limitation

Table 2.4. Classification of airflow limitation severity in COPD (Based on post-bronchodilator FEV_1)

In patients with FEV_1/FVC < 0.70:		
GOLD 1:	Mild	$FEV_1 \geq 80\%$ predicted
GOLD 2:	Moderate	$50\% \leq FEV_1 < 80\%$ predicted
GOLD 3:	Severe	$30\% \leq FEV_1 < 50\%$ predicted
GOLD 4:	Very Severe	$FEV_1 < 30\%$ predicted

Assessment of Exacerbation Risk

- COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy.
- Classified as:
  - Mild (treated with SABDs only)
  - Moderate (treated with SABDs plus antibiotics and/or oral corticosteroids) or
  - Severe (patient requires hospitalization or visits the emergency room). Severe exacerbations may also be associated with acute respiratory failure.
- Blood eosinophil count may also predict exacerbation rates (in patients treated with LABA without ICS).

Summary

Table 2.6. Role of spirometry

- Diagnosis
- Assessment of severity of airflow obstruction (for prognosis)
- Follow-up assessment
  - Therapeutic decisions.
    - Pharmacological in selected circumstances (e.g., discrepancy between spirometry and level of symptoms).
    - Consider alternative diagnoses when symptoms are disproportionate to degree of airflow obstruction.
    - Non-pharmacological (e.g., interventional procedures).
  - Identification of rapid decline.

Alpha-1 antitrypsin deficiency (AATD)

AATD screening

- The World Health Organization recommends that all patients with a diagnosis of COPD should be screened once especially in areas with high AATD prevalence.
- AATD patients are typically < 45 years with panlobular basal emphysema
- Delay in diagnosis in older AATD patients presents as more typical distribution of emphysema (centrilobular apical).
- A low concentration (< 20% normal) is highly suggestive of homozygous deficiency.

Differential Diagnosis

Table 2.7. Differential diagnosis of COPD

Diagnosis	Suggestive Features
COPD	Onset in mid-life. Symptoms slowly progressive. History of tobacco smoking or exposure to other types of smoke.
Asthma	Onset early in life (often childhood). Symptoms vary widely from day to day. Symptoms worse at night/early morning. Allergy, rhinitis, and/or eczema also present. Family history of asthma. Obesity coexistence.
Congestive Heart Failure	Chest X-ray shows dilated heart, pulmonary edema. Pulmonary function tests indicate volume restriction, not airflow limitation.
Bronchiectasis	Large volumes of purulent sputum. Commonly associated with bacterial infection. Chest X-ray/CT shows bronchial dilation, bronchial wall thickening.
Tuberculosis	Onset all ages. Chest X-ray shows lung infiltrate. Microbiological confirmation. High local prevalence of tuberculosis.
Obliterative Bronchiolitis	Onset at younger age, nonsmokers. May have history of rheumatoid arthritis or acute fume exposure. Seen after lung or bone marrow transplantation. CT on expiration shows hypodense areas.
Diffuse Panbronchiolitis	Predominantly seen in patients of Asian descent. Most patients are male and nonsmokers. Almost all have chronic sinusitis. Chest X-ray and HRCT show diffuse small centrilobular nodular opacities and hyperinflation.

These features tend to be characteristic of the respective diseases, but are not mandatory. For example, a person who has never smoked may develop COPD (especially in the developing world where other risk factors may be more important than cigarette smoking); asthma may develop in adult and even in elderly patients.

Evidence Supporting Prevention & Maintenance Therapy

OVERALL KEY POINTS (1 of 3):

- Smoking cessation is key. Pharmacotherapy and nicotine replacement reliably increase long-term smoking abstinence rates.
- The effectiveness and safety of e-cigarettes as a smoking cessation aid is uncertain at present.
- Pharmacologic therapy can reduce COPD symptoms, reduce the frequency and severity of exacerbations, and improve health status and exercise tolerance.
- Each pharmacologic treatment regimen should be individualized and guided by the severity of symptoms, risk of exacerbations, side-effects, comorbidities, drug availability and cost, and the patient's response, preference and ability to use various drug delivery devices.
- Inhaler technique needs to be assessed regularly.

Evidence Supporting Prevention & Maintenance Therapy

OVERALL KEY POINTS (2 of 3):

- Influenza vaccination decreases the incidence of lower respiratory tract infections.
- Pneumococcal vaccination decreases lower respiratory tract infections.
- Pulmonary rehabilitation improves symptoms, quality of life, and physical and emotional participation in everyday activities.
- In patients with severe resting chronic hypoxemia, long-term oxygen therapy improves survival.
- In patients with stable COPD and resting or exercise-induced moderate desaturation, long-term oxygen treatment should not be prescribed routinely. However, individual patient factors must be considered when evaluating the patient's need for supplemental oxygen.

Evidence Supporting Prevention & Maintenance Therapy

OVERALL KEY POINTS (3 of 3):

- In patients with severe chronic hypercapnia and a history of hospitalization for acute respiratory failure, long-term non-invasive ventilation may decrease mortality and prevent re-hospitalization.
- In select patients with advanced emphysema refractory to optimized medical care, surgical or bronchoscopic interventional treatments may be beneficial.
- Palliative approaches are effective in controlling symptoms in advanced COPD.

Smoking Cessation

- Smoking cessation has the greatest capacity to influence the natural history of COPD.
- If effective resources and time are dedicated to smoking cessation, long-term quit success rates of up to 25% can be achieved.

Table 3.1. Brief strategies to help the patient willing to quit

ASK:	Systematically identify all tobacco users at every visit. *Implement an office-wide system that ensures that, for EVERY patient at EVERY clinic visit, tobacco-use status is queried and documented.*
ADVISE:	Strongly urge all tobacco users to quit. *In a clear, strong, and personalized manner, urge every tobacco user to quit.*
ASSESS:	Determine willingness and rationale of patient's desire to make a quit attempt. *Ask every tobacco user if he or she is willing to make a quit attempt at this time (e.g., within the next 30 days).*
ASSIST:	Aid the patient in quitting. *Help the patient with a quit plan; provide practical counseling; provide intra-treatment social support; help the patient obtain extra-treatment social support; recommend use of approved pharmacotherapy except in special circumstances; provide supplementary materials.*
ARRANGE:	Schedule follow-up contact. *Schedule follow-up contact, either in person or via telephone.*

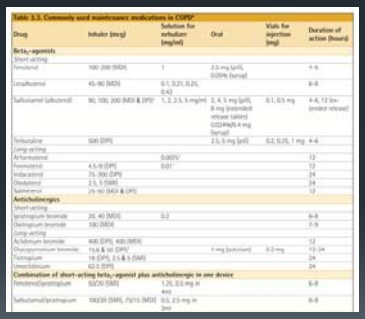
Vaccination

- Influenza vaccination can reduce serious illness (such as lower respiratory tract infections requiring hospitalization)24 and death in COPD patients.
- Pneumococcal vaccinations, PCV13 and PPSV23, are recommended for all patients ≥ 65 years of age

Table 3.2. Vaccination for stable COPD

- Influenza vaccination reduces serious illness and death in COPD patients **(Evidence B)**.
- The 23-valent pneumococcal polysaccharide vaccine (PPSV23) has been shown to reduce the incidence of community-acquired pneumonia in COPD patients aged < 65 years with an FEV_1 < 40% predicted and in those with comorbidities **(Evidence B)**.
- In the general population of adults ≥ 65 years the 13-valent conjugated pneumococcal vaccine (PCV13) has demonstrated significant efficacy in reducing bacteremia and serious invasive pneumococcal disease **(Evidence B)**.

Pharmacologic Therapy



Pharmacologic Therapy

Bronchodilators in Stable COPD

Table 3.4. Bronchodilators in stable COPD

- Inhaled bronchodilators in COPD are central to symptom management and commonly given on a regular basis to prevent or reduce symptoms **(Evidence A)**.
- Regular and as-needed use of SABA or SAMA improves FEV_1 and symptoms **(Evidence A)**.
- Combinations of SABA and SAMA are superior compared to either medication alone in improving FEV_1 and symptoms **(Evidence A)**.
- LABAs and LAMAs significantly improve lung function, dyspnea, health status, and reduce exacerbation rates **(Evidence A)**.
- LAMAs have a greater effect on exacerbation reduction compared with LABAs **(Evidence A)** and decrease hospitalizations **(Evidence B)**.
- Combination treatment with a LABA and LAMA increases FEV_1 and reduces symptoms compared to monotherapy **(Evidence A)**.
- Combination treatment with a LABA and LAMA reduces exacerbations compared to monotherapy **(Evidence B)** or ICS/LABA **(Evidence B)**.
- Tiotropium improves the effectiveness of pulmonary rehabilitation in increasing exercise performance **(Evidence B)**.
- Theophylline exerts a small bronchodilator effect in stable COPD **(Evidence A)** and that is associated with modest symptomatic benefits **(Evidence B)**.

Anti-inflammatory Therapy in Stable COPD

Table 3.5. Anti-inflammatory therapy in stable COPD

Inhaled corticosteroids

- 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 exacerbations and moderate to very severe COPD **(Evidence A)**.
- Regular treatment with ICS increases the risk of pneumonia especially in those with severe disease **(Evidence A)**.
- Triple inhaled therapy of ICS/LAMA/LABA improves lung function, symptoms and health status **(Evidence A)** and reduces exacerbations **(Evidence B)** compared to ICS/LABA or LAMA monotherapy.

Oral glucocorticoids

- Long-term use of oral glucocorticoids has numerous side effects **(Evidence A)** with no evidence of benefits **(Evidence C)**.

PDE4 inhibitors

- In patients with chronic bronchitis, severe to very severe COPD and a history of exacerbations:
  - A PDE4 inhibitor improves lung function and reduces moderate and severe exacerbations **(Evidence A)**.
  - A PDE4 inhibitor improves lung function and decreases exacerbations in patients who are on fixed-dose LABA/ICS combinations **(Evidence B)**.

Antibiotics

- Long-term azithromycin and erythromycin therapy reduces exacerbations over one year **(Evidence A)**.
- Treatment with azithromycin is associated with an increased incidence of bacterial resistance **(Evidence A)** and hearing test impairments **(Evidence B)**.

Mucolytics/antioxidants

- Regular use of NAC and carbocysteine reduces the risk of exacerbations in select populations **(Evidence B)**.

Other anti-inflammatory agents

- Simvastatin does not prevent exacerbations in COPD patients at increased risk of exacerbations and without indications for statin therapy **(Evidence A)**. However, observational studies suggest that statins may have positive effects on some outcomes in patients with COPD who receive them for cardiovascular and metabolic indications **(Evidence C)**.
- Leukotriene modifiers have not been tested adequately in COPD patients.

The Inhaled Route

Table 3.6. The inhaled route

- When a treatment is given by the inhaled route, the importance of education and training in inhaler device technique cannot be over-emphasized.
- The choice of inhaler device has to be individually tailored and will depend on access, cost, prescriber, and most importantly, patient's ability and preference.
- It is essential to provide instructions and to demonstrate the proper inhalation technique when prescribing a device, to ensure that inhaler technique is adequate and re-check at each visit that patients continue to use their inhaler correctly.
- Inhaler technique (and adherence to therapy) should be assessed before concluding that the current therapy is insufficient.

Other Pharmacologic Treatments

Table 3.7. Other pharmacological treatments

Alpha-1 antitrypsin augmentation therapy

- Intravenous augmentation therapy may slow down the progression of emphysema **(Evidence B)**.

Antitussives

- There is no conclusive evidence of a beneficial role of antitussives in patients with COPD **(Evidence C)**.

Vasodilators

- Vasodilators do not improve outcomes and may worsen oxygenation **(Evidence B)**.

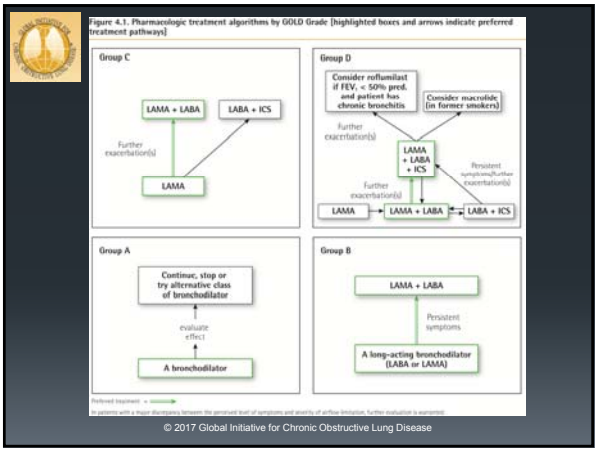
Rehabilitation, Education & Self-Management

Table 3.8. Pulmonary rehabilitation, self-management and integrative care in COPD
Pulmonary rehabilitation
• Pulmonary rehabilitation improves dyspnea, health status and exercise tolerance in stable patients **(Evidence A)**.
• Pulmonary rehabilitation reduces hospitalizations among patients who have had a recent exacerbation (≤ 4 weeks from prior hospitalization) **(Evidence B)**.
Education and self-management
• Education alone has not been shown to be effective **(Evidence C)**.
• Self-management intervention with communication with a health care professional improves health status and decreases hospitalizations and emergency department visits **(Evidence B)**.
Integrated care programs
• Integrated care and telehealth have no demonstrated benefit at this time **(Evidence B)**.

Oxygen Therapy & Ventilatory Support in Stable COPD

- ***During exacerbations of COPD.*** Noninvasive ventilation (NIV) in the form of noninvasive positive pressure ventilation (NPPV) is the standard of care for decreasing morbidity and mortality in patients hospitalized with an exacerbation of COPD and acute respiratory failure

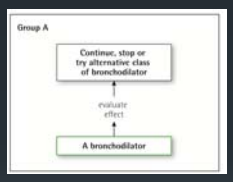
Table 3.10. Oxygen therapy and ventilatory support in stable COPD
Oxygen therapy
• The long-term administration of oxygen increases survival in patients with severe chronic resting arterial hypoxemia **(Evidence A)**.
• In patients with stable COPD and moderate resting or exercise-induced arterial desaturation, prescription of long-term oxygen does not lengthen time to death or first hospitalization or provide sustained benefit in health status, lung function and 6-minute walk distance **(Evidence A)**.
• Resting oxygenation at sea level does not exclude the development of severe hypoxemia when traveling by air **(Evidence C)**.
Ventilatory support
• NPPV may improve hospitalization-free survival in selected patients after recent hospitalization, particularly in those with pronounced daytime persistent hypercapnia ($PaCO_2 \geq 52$ mmHg) **(Evidence B)**.



Pharmacologic treatment algorithms

Group A

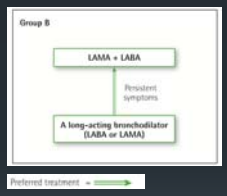
- All Group A patients should be offered bronchodilator treatment based on its effect on breathlessness. This can be either a short- or a long-acting bronchodilator.
- This should be continued if symptomatic benefit is documented.



Pharmacologic treatment algorithms

Group B

- Initial therapy should consist of a long acting bronchodilator. Long-acting inhaled bronchodilators are superior to short-acting bronchodilators taken as needed i.e., *pro re nata* (prn) and are therefore recommended.
- There is no evidence to recommend one class of long-acting bronchodilators over another for initial relief of symptoms in this group of patients. In the individual patient, the choice should depend on the patient's perception of symptom relief.
- For patients with persistent breathlessness on monotherapy the use of two bronchodilators is recommended.



Pharmacologic treatment algorithms

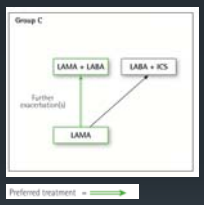
Group B (continued)

- For patients with severe breathlessness initial therapy with two bronchodilators may be considered.
- If the addition of a second bronchodilator does not improve symptoms, we suggest the treatment could be stepped down again to a single bronchodilator.
- Group B patients are likely to have comorbidities that may add to their symptomatology and impact their prognosis, and these possibilities should be investigated.

Pharmacologic treatment algorithms

Group C

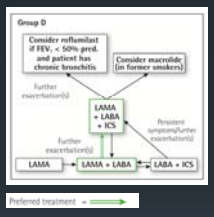
- Initial therapy should consist of a single long acting bronchodilator. In two head-to head comparisons the tested LAMA was superior to the LABA regarding exacerbation prevention, therefore we recommend starting therapy with a LAMA in this group.
- Patients with persistent exacerbations may benefit from adding a second long acting bronchodilator (LABA/LAMA) or using a combination of a long acting beta$_2$-agonist and an inhaled corticosteroid (LABA/ICS). As ICS increases the risk for developing pneumonia in some patients, our primary choice is LABA/LAMA.



Pharmacologic treatment algorithms

Group D

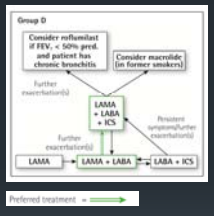
- We recommend starting therapy with a LABA/LAMA combination because:
  - In studies with patient reported outcomes as the primary endpoint LABA/LAMA combinations showed superior results compared to the single substances. If a single bronchodilator is chosen as initial treatment, a LAMA is preferred for exacerbation prevention based on comparison to LABAs (for details see GOLD 2017 Chapter 3).
  - A LABA/LAMA combination was superior to a LABA/ICS combination in preventing exacerbations and other patient reported outcomes in Group D patients (for details see GOLD 2017 Chapter 3).
  - Group D patients are at higher risk of developing pneumonia when receiving treatment with ICS.



Pharmacologic treatment algorithms

Group D (continued)

- In some patients initial therapy with LABA/ICS may be the first choice. These patients may have a history and/or findings suggestive of asthma-COPD overlap. High blood eosinophil counts may also be considered as a parameter to support the use of ICS, although this is still under debate (for details see Chapter 2 and Appendix).
- In patients who develop further exacerbations on LABA/LAMA therapy we suggest two alternative pathways:
  - Escalation to LABA/LAMA/ICS. Studies are underway comparing the effects of LABA/LAMA vs. LABA/LAMA/ICS for exacerbation prevention.
  - Switch to LABA/ICS. However, there is no evidence that switching from LABA/LAMA to LABA/ICS results in better exacerbation prevention. If LABA/ICS therapy does not positively impact exacerbations/symptoms, a LAMA can be added.

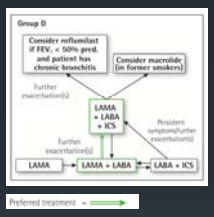


Pharmacologic treatment algorithms

Group D (continued)

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

- Add roflumilast. This may be considered in patients with an FEV1 < 50% predicted and chronic bronchitis,13 particularly if they have experienced at least one hospitalization for an exacerbation in the previous year.
- Add a macrolide. The best available evidence exists for the use of azithromycin. Consideration to the development of resistant organisms should be factored into decision making.
- Stopping ICS. A reported lack of efficacy, an elevated risk of adverse effects (including pneumonia) and evidence showing no significant harm from withdrawal supports this recommendation (see Chapter 3 for further details).



Non-Pharmacologic Treatment

- Education and self-management
- Physical activity
- Pulmonary rehabilitation programs
- Exercise training
- Self-management education
- End of life and palliative care
- Nutritional support
- Vaccination
- Oxygen therapy

Non-Pharmacologic Treatment

Education and self-management

- Self-management education and coaching by healthcare professionals should be a major component of the "Chronic Care Model" within the context of the healthcare delivery system.
- The aim of self-management education is to motivate, engage and coach the patients to positively adapt their health behavior(s) and develop skills to better manage their disease.

Table 4.8. Non-pharmacologic management of COPD

Patient group	Essential	Recommended	Depending on local guidelines
A	Smoking cessation (can include pharmacologic treatment)	Physical activity	Flu vaccination Pneumococcal vaccination
B–D	Smoking cessation (can include pharmacologic treatment) Pulmonary rehabilitation	Physical activity	Flu vaccination Pneumococcal vaccination

Non-Pharmacologic Treatment

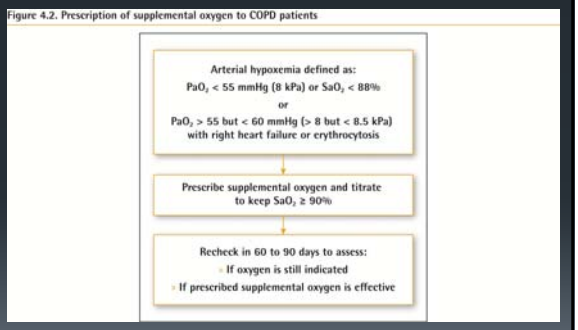
Oxygen therapy

Long-term oxygen therapy is indicated for stable patients who have:

- PaO_2 at or below 7.3 kPa (55 mmHg) or SaO_2 at or below 88%, with or without hypercapnia confirmed twice over a three week period; or
- PaO_2 between 7.3 kPa (55 mmHg) and 8.0 kPa (60 mmHg), or SaO_2 of 88%, if there is evidence of pulmonary hypertension, peripheral edema suggesting congestive cardiac failure, or polycythemia (hematocrit > 55%).

Non-Pharmacologic Treatment

Figure 4.2. Prescription of supplemental oxygen to COPD patients



Non-Pharmacologic Treatment - Summary

Table 4.9. Key points for the use of non-pharmacological treatments

Education, self-management and pulmonary rehabilitation
• Education is needed to change patient's knowledge but there is no evidence that used alone it will change patient behavior.
• Education self-management with the support of a case manager with or without the use of a written action plan is recommended for the prevention of exacerbation complications such as hospital admissions **(Evidence B)**.
• Rehabilitation is indicated in all patients with relevant symptoms and/or a high risk for exacerbation **(Evidence A)**.
• Physical activity is a strong predictor of mortality **(Evidence A)**. Patients should be encouraged to increase the level of physical activity although we still don't know how to best insure the likelihood of success.
Vaccination
• Influenza vaccination is recommended for all patients with COPD **(Evidence A)**.
• Pneumococcal vaccination: the PCV13 and PPSV23 are recommended for all patients > 65 years of age, and in younger patients with significant comorbid conditions including chronic heart or lung disease **(Evidence B)**.
Nutrition
• Nutritional supplementation should be considered in malnourished patients with COPD **(Evidence B)**.
End of life and palliative care
• All clinicians managing patients with COPD should be aware of the effectiveness of palliative approaches to symptom control and use these in their practice **(Evidence D)**.
• End of life care should include discussions with patients and their families about their views on resuscitation, advance directives and place of death preferences **(Evidence D)**.

Non-Pharmacologic Treatment – Summary (continued)

Treatment of hypoxemia

- In patients with severe resting hypoxemia long-term oxygen therapy is indicated **(Evidence A)**.
- In patients with stable COPD and resting or exercise-induced moderate desaturation, long term oxygen treatment should not be routinely prescribed. However, individual patient factors may be considered when evaluating the patient's needs for supplemental oxygen **(Evidence A)**.
- Resting oxygenation at sea level does not exclude the development of severe hypoxemia when travelling by air **(Evidence C)**.

Treatment of hypercapnia

- In patients with severe chronic hypercapnia and a history of hospitalization for acute respiratory failure, long term non-invasive ventilation may be considered **(Evidence B)**.

Intervention bronchoscopy and surgery

- Lung volume reduction surgery should be considered in selected patients with upper-lobe emphysema **(Evidence A)**.
- Bronchoscopic lung volume reduction interventions may be considered in selected patients with advanced emphysema **(Evidence B)**.
- In selected patients with a large bulla surgical bullectomy may be considered **(Evidence C)**.
- In patients with very severe COPD (progressive disease, BODE score of 7 to 10, and not candidate for lung volume reduction) lung transplantation may be considered for referral with at least one of the following: (1) history of hospitalization for exacerbation associated with acute hypercapnia (PCO_2 > 50 mm Hg); (2) pulmonary hypertension and/or cor pulmonale, despite oxygen therapy; or (3) FEV_1 < 20% and either DLCO < 20% or homogenous distribution of emphysema **(Evidence C)**.

Monitoring and Follow-up

Monitoring disease progression and development of complications and/or comorbidities

- ***Measurements.*** Decline in FEV_1 can be tracked by spirometry performed at least once a year.
- ***Symptoms.*** At each visit, information on symptoms since the last visit should be collected, including cough and sputum, breathlessness, fatigue, activity limitation, and sleep disturbances.
- ***Exacerbations.*** The frequency, severity, type and likely causes of all exacerbations should be monitored.
- ***Imaging.*** If there is a clear worsening of symptoms, imaging may be indicated.
- ***Smoking status.*** At each visit, the current smoking status and smoke exposure should be determined followed by appropriate action.

Monitoring and Follow-up

Pharmacotherapy and other medical treatment

In order to adjust therapy appropriately as the disease progresses, each follow-up visit should include a discussion of the current therapeutic regimen.

Monitoring should focus on:

- Dosages of prescribed medications.
- Adherence to the regimen.
- Inhaler technique.
- Effectiveness of the current regime.
- Side effects.

Treatment modifications should be recommended.

Management of Exacerbations

OVERALL KEY POINTS (1 of 3):

- An exacerbation of COPD is defined as an acute worsening of respiratory symptoms that results in additional therapy.
- Exacerbations of COPD can be precipitated by several factors. The most common causes are respiratory tract infections.
- The goal for treatment of COPD exacerbations is to minimize the negative impact of the current exacerbation and to prevent subsequent events.
- Short-acting inhaled beta$_2$-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation.

Management of Exacerbations

OVERALL KEY POINTS (2 of 3):

- Maintenance therapy with long-acting bronchodilators should be initiated as soon as possible before hospital discharge.
- Systemic corticosteroids can improve lung function (FEV_1), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not be more than 5-7 days.
- Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should be 5-7 days.
- Methylxanthines are not recommended due to increased side effect profiles.

Management of Exacerbations

OVERALL KEY POINTS (3 of 3):

- Non-invasive mechanical ventilation should be the first mode of ventilation used in COPD patients with acute respiratory failure who have no absolute contraindication because it improves gas exchange, reduces work of breathing and the need for intubation, decreases hospitalization duration and improves survival.
- Following an exacerbation, appropriate measures for exacerbation prevention should be initiated (see GOLD 2017 Chapter 3 and Chapter 4).

Management of Exacerbations

COPD exacerbations are defined as an acute worsening of respiratory symptoms that result in additional therapy.

- They are classified as:
  - Mild (treated with short acting bronchodilators only, SABDs)
  - Moderate (treated with SABDs plus antibiotics and/or oral corticosteroids) or
  - Severe (patient requires hospitalization or visits the emergency room). Severe exacerbations may also be associated with acute respiratory failure.

Management of Exacerbations

Classification of hospitalized patients

No respiratory failure:
Respiratory rate: 20-30 breaths per minute; no use of accessory respiratory muscles; no changes in mental status; hypoxemia improved with supplemental oxygen given via Venturi mask 28-35% inspired oxygen (FiO_2); no increase in $PaCO_2$.

Management of Exacerbations

Classification of hospitalized patients

Acute respiratory failure — non-life-threatening:
Respiratory rate: > 30 breaths per minute; using accessory respiratory muscles; no change in mental status; hypoxemia improved with supplemental oxygen via Venturi mask 25-30% FiO_2; hypercarbia i.e., $PaCO_2$ increased compared with baseline or elevated 50-60 mmHg.

Management of Exacerbations

Classification of hospitalized patients

Acute respiratory failure — life-threatening:
Respiratory rate: > 30 breaths per minute; using accessory respiratory muscles; acute changes in mental status; hypoxemia not improved with supplemental oxygen via Venturi mask or requiring FiO_2 > 40%; hypercarbia i.e., $PaCO_2$ increased compared with baseline or elevated > 60 mmHg or the presence of acidosis (pH ≤ 7.25).

Management of Exacerbations

Table 5.1. Potential indications for hospitalization assessment*

- Severe symptoms such as sudden worsening of resting dyspnea, high respiratory rate, decreased oxygen saturation, confusion, drowsiness.
- Acute respiratory failure.
- Onset of new physical signs (e.g., cyanosis, peripheral edema).
- Failure of an exacerbation to respond to initial medical management.
- Presence of serious comorbidities (e.g., heart failure, newly occurring arrhythmias, etc.).
- Insufficient home support.

*Local resources need to be considered.

Management of Exacerbations

Table 5.2. Management of severe but not life-threatening exacerbations*

- Assess severity of symptoms, blood gases, chest radiograph.
- Administer supplemental oxygen therapy, obtain serial arterial blood gas, venous blood gas and pulse oximetry measurements.
- Bronchodilators:
  - Increase doses and/or frequency of short-acting bronchodilators.
  - Combine short-acting beta 2-agonists and anticholinergics.
  - Consider use of long-active bronchodilators when patient becomes stable.
  - Use spacers or air-driven nebulizers when appropriate.
- Consider oral corticosteroids.
- Consider antibiotics (oral) when signs of bacterial infection are present.
- Consider noninvasive mechanical ventilation (NIV).
- At all times:
  - Monitor fluid balance.
  - Consider subcutaneous heparin or low molecular weight heparin for thromboembolism prophylaxis.
  - Identify and treat associated conditions (e.g., heart failure, arrhythmias, pulmonary embolism etc.).

*Local resources need to be considered.

Management of Exacerbations - Summary

Table 5.3. Key points for the management of exacerbations

- Short-acting inhaled beta$_2$-agonists, with or without short-acting anticholinergics, are recommended as the initial bronchodilators to treat an acute exacerbation **(Evidence C)**.
- Systemic corticosteroids can improve lung function (FEV_1), oxygenation and shorten recovery time and hospitalization duration. Duration of therapy should not be more than 5–7 days **(Evidence A)**.
- Antibiotics, when indicated, can shorten recovery time, reduce the risk of early relapse, treatment failure, and hospitalization duration. Duration of therapy should be 5–7 days **(Evidence B)**.
- Methylxanthines are not recommended due to increased side effect profiles **(Evidence B)**.
- Non-invasive mechanical ventilation should be the first mode of ventilation used in COPD patients with acute respiratory failure **(Evidence A)**.
- NIV should be the first mode of ventilation used in COPD patients with acute respiratory failure who have no absolute contraindication because it improves gas exchange, reduces work of breathing and the need for intubation, decreases hospitalization duration and improves survival **(Evidence A)**.

Management of Exacerbations

Pharmacologic treatment

The three classes of medications most commonly used for COPD exacerbations are:

- Bronchodilators
  - Although there is no high-quality evidence from RCTs, it is recommended that short-acting inhaled beta$_2$-agonists, with or without short-acting anticholinergics, are the initial bronchodilators for acute treatment of a COPD exacerbation.
- Corticosteroids
  - Data from studies indicate that systemic glucocorticoids in COPD exacerbations shorten recovery time and improve lung function (FEV1). They also improve oxygenation, the risk of early relapse, treatment failure, and the length of hospitalization.
- Antibiotics

Management of Exacerbations

Respiratory support

Table 5.4. Indications for respiratory or medical intensive care unit admission*

- Severe dyspnea that responds inadequately to initial emergency therapy.
- Changes in mental status (confusion, lethargy, coma).
- Persistent or worsening hypoxemia (PaO_2 < 5.3 kPa or 40 mmHg) and/or severe/worsening respiratory acidosis (pH < 7.25) despite supplemental oxygen and noninvasive ventilation.
- Need for invasive mechanical ventilation.
- Hemodynamic instability—need for vasopressors.

*Local resources need to be considered.

Table 5.5. Indications for noninvasive mechanical ventilation (NIV)

At least one of the following:

- Respiratory acidosis ($PaCO_2$ ≥ 6.0 kPa or 45 mmHg and arterial pH ≤ 7.35).
- Severe dyspnea with clinical signs suggestive of respiratory muscle fatigue, increased work of breathing, or both, such as use of respiratory accessory muscles, paradoxical motion of the abdomen, or retraction of the intercostal spaces.
- Persistent hypoxemia despite supplemental oxygen therapy.

Management of Exacerbations

Respiratory support

Table 5.6. Indications for invasive mechanical ventilation

- Unable to tolerate NIV or NIV failure.
- Status post - respiratory or cardiac arrest.
- Diminished consciousness, psychomotor agitation inadequately controlled by sedation.
- Massive aspiration or persistent vomiting.
- Persistent inability to remove respiratory secretions.
- Severe hemodynamic instability without response to fluids and vasoactive drugs.
- Severe ventricular or supraventricular arrhythmias.
- Life-threatening hypoxemia in patients unable to tolerate NIV.

Management of Exacerbations

Table 5.7. Discharge criteria and recommendations for follow-up

- Full review of all clinical and laboratory data.
- Check maintenance therapy and understanding.
- Reassess inhaler technique.
- Ensure understanding of withdrawal of acute medications (steroids and/or antibiotics).
- Assess need for continuing any oxygen therapy.
- Provide management plan for comorbidities and follow-up.
- Ensure follow-up arrangements: early follow-up < 4 weeks, and late follow-up < 12 weeks as indicated.
- All clinical or investigational abnormalities have been identified.

1–4 Weeks Follow-Up

- Evaluate ability to cope in his/her usual environment.
- Review and understanding treatment regimen.
- Reassessment of inhaler techniques.
- Reassess need for long-term oxygen.
- Document the capacity to do physical activity and activities of daily living.
- Document symptoms: CAT or mMRC.
- Determine status of comorbidities.

12–16 Weeks Follow-Up

- Evaluate ability to cope in his/her usual environment.
- Review understanding treatment regimen.
- Reassessment of inhaler techniques.
- Reassess need for long-term oxygen.
- Document the capacity to do physical activity and activities of daily living.
- Measure spirometry: FEV_1
- Document symptoms: CAT or mMRC.
- Determine status of comorbidities.

Management of Exacerbations

Table 5.8. Interventions that reduce the frequency of COPD exacerbations

Intervention class	Intervention
Bronchodilators	LABAs LAMAs LABA + LAMA
Corticosteroid-containing regimens	LABA + ICS LABA + LAMA + ICS
Anti-inflammatory (non-steroid)	Roflumilast
Anti-infectives	Vaccines Long term macrolides
Mucoregulators	N-acetylcysteine Carbocysteine
Various others	Smoking cessation Rehabilitation Lung volume reduction

GOLD Website
www.goldcopd.org