

Guidelines for the Diagnosis and Treatment of COPD

(Chronic Obstructive Pulmonary Disease)

2nd edition

Pocket Guide



Edition

Committee for the Second Edition of
the COPD Guidelines of The Japanese Respiratory Society

The Japanese Respiratory Society

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Shibata Building 2F, 2-6-4, Uchikanda, Chiyoda-ku, Tokyo,
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Foreword

It is recognized throughout the world that in order to overcome the problem of the under diagnosis of COPD, it is important for clinicians to correctly understand it. To achieve this, it would be valuable to have a pocket guidebook which can provide clinicians with rapidly absorbed and practically applicable information covering all the main points about COPD. This guidebook has been created as a distillation of the essential aspects of the Second Edition of the Guidelines for the Diagnosis and Treatment of Chronic Obstructive Pulmonary Disease. I earnestly hope that it will serve that purpose and will be useful in the early diagnosis and treatment of this disease.

I would like to express my gratitude to all the members of the Committee for the Second Edition of the COPD Guidelines who have worked so hard on producing both the Guidelines and its pocket guide. In particular, I would like to thank Dr. Jun Ueki and Dr. Kuniaki Seyama, who served as the central coordinators of the project, also the staff of Medical Review Co. Concerning the English edition, I would also like to thank Professor J. Patrick Barron, Ms. Keiko Yamamoto and Ms. Kozue Iijima of the International Medical Communications Center of Tokyo Medical University, for their producing the English edition so rapidly in cooperation with Dr. Ueki.

Yoshinosuke Fukuchi
Committee Chairman
Committee for the Second Edition of the COPD Guidelines
of The Japanese Respiratory Society

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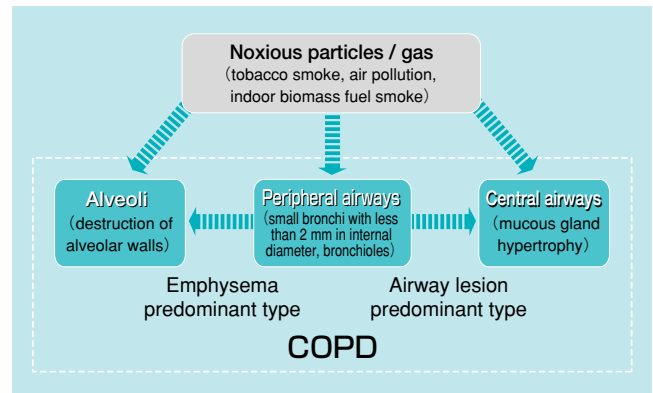
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[1] Definition

- COPD (Chronic Obstructive Pulmonary Disease) is a disease displaying progressive airflow limitation caused by inflammatory reaction in lungs resulting from inhalation of noxious particles or gas. The airflow limitation has various degrees of reversibility, both its onset and progress are gradual, and it can cause dyspnea on exertion.



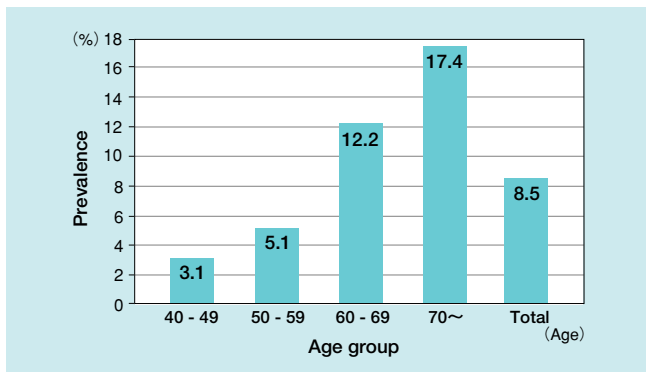
(Figure 1) Diagram of the clinical phenotype of COPD

The clinical phenotype of COPD can be understood by studying the figure above:

- The main cause related to airflow limitation is peripheral airway lesions.
- There are cases in which primarily destruction of the alveolar system leads to conditions favoring emphysema : Emphysema predominant type.
- In some cases, primarily progression of central airway lesions leads to a preponderance of airway lesions : Airway lesion predominant type.
- The concept of COPD encompasses all such alveolar-peripheral airway-central airway lesions.
- Accompanying the progression of these pulmonary lesions, dyspnea on exertion, airway hypersecretions, and various systemic symptoms can appear.
- Effective prevention and management can be achieved by the elimination of risk factors and appropriate treatment.

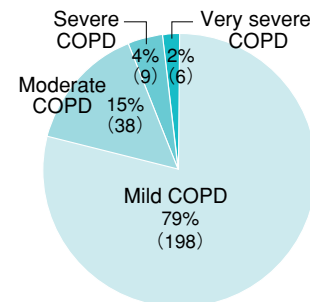
[2] Epidemiology of COPD in Japan

- From the 1960s, the sales and consumption of cigarettes have increased and about 20 years after that trend was seen, there was an increase in mortality in Japan due to “chronic bronchitis and pulmonary emphysema*”.
- According to “Trends in public health”, COPD did not appear among the ten leading causes of death through 1999. In the year 2000, however, it became ranked as the 10th highest cause of death.
- Based on the data concerning the prevalence of COPD obtained by the Nippon COPD Epidemiology (NICE) study, it is estimated that about 5.3 million Japanese suffer from COPD (Figures 2, 3 and 4).

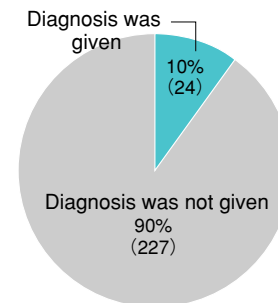


(Figure 2) COPD prevalence according to age (NICE study)
(Reference 1)

*The term “chronic bronchitis and pulmonary emphysema” was used in epidemiological surveys up to the year 2000, but that concept is generally the same as the present COPD.



(Figure 3) Degree of severity of patients given a diagnosis of COPD in the NICE study
(Reference 1)



(Figure 4) Past clinical history of cases given a diagnosis of COPD in the NICE study
(Reference 1)

[3] Risk factors

- Risk factors for COPD include exogenous factors such as smoking and air pollution, as well as endogenous factors of the patients themselves (Table 1). The greatest exogenous factor for COPD is smoking, but since this condition occurs only in some smokers, it is considered that it is easy to develop in patients who are more sensitive to cigarette smoke.
- The most definite endogenous risk factor is the genetically inherited α -antitrypsin deficiency, but this is extremely rare in Japan. In addition, there are several candidate genes related to the cause of COPD, but sufficient evidence is lacking.
- The main exogenous factor is smoking. In addition, there are occupational dusts and chemical materials (vapors, irritant substances, smoke), passive smoking and respiratory infectious diseases.

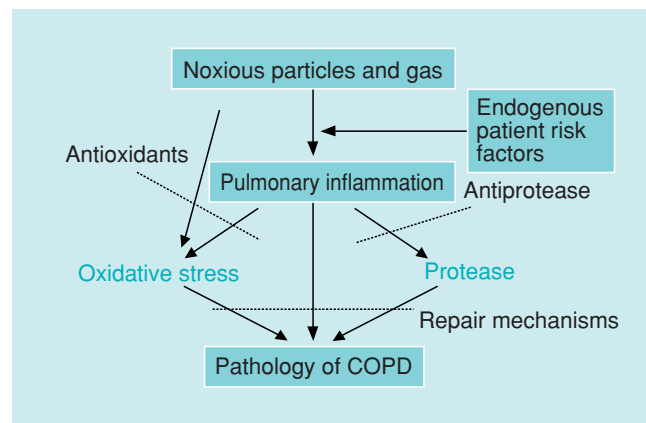
(Table 1) Risk factors of COPD

	Most important factors	Important factors	Possible factors
Exogenous factors	Smoking	Air pollution Passive smoking Exposure to occupational dusts and chemical materials	Infection
Endogenous factors	α 1-AT deficiency		Airway hypersensitivity related to host genetic polymorphism

α 1-AT : α 1-antitrypsin

[4] Etiology

- The main hypothesis explaining the etiology of COPD involves imbalance of protease / antiprotease and imbalance of oxidant / antioxidant (Figure 5).
- New hypotheses are appearing due to the results of recent animal experiments producing pulmonary emphysema. Apoptosis of lung cells may also be involved.



(Figure 5) Etiology of COPD

(Reference 2)

This shows the process of COPD lesion formation due to inflammation of the lung as a result of smoking. Airway inflammation and destruction of alveolar walls occurs as a result of what can be termed pulmonary disorder attack factors such as various proteases or oxidative stress overwhelming the protective factors of antiprotease or antioxidative materials either quantitatively or qualitatively.

[5] Diagnosis

1. Diagnostic criteria

- In the presence of clinical symptoms such as cough, sputum, or dyspnea on exertion, or middle aged or older people who have risk factors such as a history of smoking, COPD must always be suspected (**Table 2**).
- Spirometry is essential for diagnosis of COPD. Airflow limitation is judged to be present when the FEV₁ (Forced Expiratory Volume in one second) / FVC (Forced Vital Capacity) ratio is less than 70% after administration of bronchodilators (**Table 3, 4**).
- For a definitive diagnosis, it is necessary to exclude various other diseases by means of diagnostic imaging and detailed pulmonary function examinations. One of the most problematic differential diagnoses is bronchial asthma (**Table 5**).

(Table 2) Diagnostic reference

COPD must be always thought of as a possibility, and spirometry performed, in the presence of any one of items 1 to 3 below, or even in cases in which there is no clinical symptoms but risk factors for COPD are present, especially a long history of smoking. Spirometry is the most basic examination to establish a diagnosis of COPD.

1. Chronic cough
2. Chronic sputum production
3. Dyspnea on exertion
4. Long-term exposure to tobacco smoke or occupational dusts

(Table 3) Diagnostic criteria

Using the diagnostic references given in Table 2 above,

1. FEV₁ / FVC < 70% on spirometry after bronchodilator administration.
2. Eliminate the possibility of other diseases causing airflow limitation.

(Table 4) Reversibility test for airflow limitation

1. The examination should be performed with the patient in a stable clinical state. The absence of acute respiratory infection should be confirmed.
2. Patients must not take short-acting bronchodilators in the previous 6 hours, or long-acting bronchodilators in the previous 24 hours.
3. The bronchodilator used for the reversibility test is usually a short-acting inhaled β_2 -stimulator. Anticholinergic agents or both can be used.
4. Administration can be with either metered dose inhaler (MDI) inhalation using a spacer or a nebulizer.
5. The examination should be performed 30 to 60 minutes after inhalation of the bronchodilator.
6. The airflow limitation is considered reversible when FEV₁ after administration are at least 12% and 200mL or more greater than the pre-bronchodilator FEV₁.

(Table 5) Differential diagnoses

1. Bronchial asthma
2. Diffuse panbronchiolitis
3. Congenital sinobronchial syndrome
4. Obstructive bronchiolitis
5. Bronchiectasis
6. Pulmonary tuberculosis
7. Pneumoconiosis
8. Pulmonary lymphangiomyomatosis
9. Congestive heart failure

2. Stage classification

- Stage classification of COPD uses FEV₁ value which expresses the degree of airflow limitation. The classification reflects the severity of the disease. The FEV₁ / FVC ratio is not used because it does not appropriately reflect the degree of severity in cases of moderate or more severe COPD. The stage classification uses the post-bronchodilator FEV₁.
- The stages of COPD are stage 0 : the group at risk, stage I : mild COPD (FEV₁ ≥ 80% of predicted value), stage II : moderate COPD (50% ≤ FEV₁ < 80% predicted), stage III : severe COPD (30% ≤ FEV₁ < 50% predicted), stage IV : very severe COPD : (FEV₁ < 30% predicted or FEV₁ < 50% predicted accompanied with chronic respiratory failure or right heart failure) (Table 6).
- The special features of these staging system are the addition of stage 0 : group at risk, stage I : mild COPD, and also addition of the chronic respiratory failure or right heart failure to the classification of stage IV : very severe COPD.

(Table 6) COPD staging classification

Stage	Characteristic features
Stage 0 : group at risk for COPD	Results of spirometry are normal. Presence of chronic symptoms (cough, sputum)
Stage I : mild COPD	FEV ₁ /FVC < 70% FEV ₁ ≥ 80% predicted Regardless of the presence or absence of chronic symptoms (cough, sputum)
Stage II : moderate COPD	FEV ₁ /FVC < 70% 50% ≤ FEV ₁ < 80% predicted Regardless of the presence or absence of chronic symptoms (cough, sputum)
Stage III : severe COPD	FEV ₁ /FVC < 70% 30% ≤ FEV ₁ < 50% predicted Regardless of the presence or absence of chronic symptoms (cough, sputum)
Stage IV : very severe COPD	FEV ₁ /FVC < 70% FEV ₁ < 30% predicted or FEV ₁ < 50% predicted accom- panied with chronic respiratory failure or right heart failure

N.B. The post-bronchodilator FEV₁ should be used for the classification.

3. Clinical findings

- Many patients are smokers, and the main symptoms are dyspnea on exertion and chronic cough and sputum production (**Table 7**).
- Typical physical findings in COPD usually do not appear until the disease is severe.
- On visual inspection, pursed-lip breathing, barrel chest (i.e. increase in the anteroposterior dimension of the chest), paradoxical movement of the chest (Hoover's sign) are recognized.
- Percussion reveals tympanic resonance due to hyperinflation of the lung, and palpation reveals overall reduction in the movement of the chest during breathing. Auscultation frequently reveals decrease in respiratory sounds and extended expiration, and forced expiration sometimes produces wheezing.
- With progression of the disease, loss of weight and anorexia can become problematic and these are poor prognostic factors. In cases accompanied by hypercapnia, patients complain of headache in the morning. Cases of exacerbation of right heart failure can show exacerbation of dyspnea and sometimes edema of the whole body or nocturnal polyuria can be observed. In cases accompanied by cor pulmonale, exacerbation of right heart failure should be considered when body weight increases rapidly. Furthermore, psychologically, depression and anxiety symptoms are frequently noted.

(Table 7) MRC* breathlessness scale

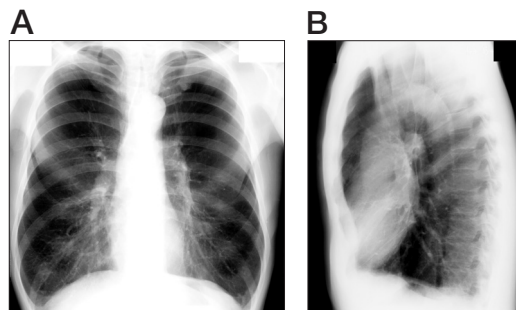
Grade 0	No breathlessness
Grade 1	Breathless with strenuous exercise
Grade 2	Short of breath when hurrying on the level <i>or</i> walking up a slight hill
Grade 3	Walk slower than people of the same age on the level <i>or</i> stop for breath while walking at own pace on the level
Grade 4	Stop for breath after walking about 100 yards <i>or</i> after a few minutes on the level
Grade 5	Too breathless to leave the house <i>or</i> breathless when dressing or undressing

(Reference 3)

* MRC : The British Medical Research Council (MRC) produced this internationally widely used scale. There are three commonly used forms: the five-grade scale from 1 to 5, the five-grade scale with grade 0 added, the five-grade scale from 1 to 5 converted to grades 0 to 4, which is commonly used by the American Thoracic Society.

4. Diagnostic imaging

- A chest X-ray film is used to exclude other diseases or to diagnose relatively advanced pulmonary emphysema or airway lesions (Figure 6).
- It is difficult to detect early stages of COPD on plain chest X-ray film.
- High resolution CT (HRCT) can be effective in the early detection of emphysema predominant type COPD (Figure 7, Table 8).
- On HRCT, pulmonary emphysema lesions appear as low attenuation areas (LAA). Each LAA can be distinguished from the normal lung and they are characterized by not having a capsule.
- Findings suggestive of airway lesions can be detected by HRCT, thus it can be effective in determining the phenotype of COPD.



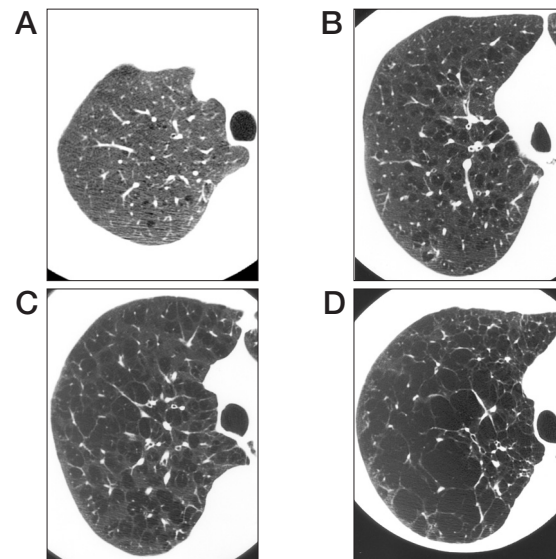
(Figure 6) Plain chest x-ray film of COPD patient

A : P-A view

- (1) Enhanced radiolucency of the lung fields
- (2) Decrease of peripheral blood vessel shadows in the lung fields
- (3) Flattening of the diaphragm
- (4) Decrease in the cardio-thoracic ratio (CTR) due to teardrop heart
- (5) Increase in the intercostal space

B : Lateral view

- (1) Flattening of the diaphragm
- (2) Increase in the intercostal space
- (3) Increase in the retrocardiac space



(Figure 7) HRCT findings of pulmonary emphysema

- A-Goddard classification-1 point : Scattered emphysematous lesions 1 cm or less in diameter.
- B-Goddard classification-2 points : Large size LAA due to the fusion of emphysematous lesions.
- C-Goddard classification-3 points : LAA occupies an even larger area by the more pronounced fusion of the emphysematous lesions.
- D-Goddard classification-4 points : Most of the lung is occupied by emphysematous lesions and only a small amount of normal lung remains.

(Table 8) Visual evaluation of pulmonary emphysema

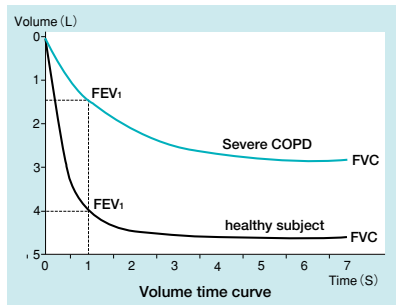
Right and left lungs are divided into six areas consist of the upper, middle and lower lung fields on both sides. The degree of severity of pulmonary emphysema is evaluated using a five-point scale for each lesion.

- 0 point : No emphysematous lesions
- 1 point : Occupying less than 25% of the entire lung field
- 2 points : Occupying from 25 to less than 50% of the entire lung field
- 3 points : Occupying from 50 to less than 75% of the entire lung field
- 4 points : Occupying more than 75% of the entire lung field

Scores from all fields are totaled (maximum total : 24 points)

5. Pulmonary function test

- In COPD, it is essential to establish a diagnosis of the presence of airflow limitation by spirometry.
- A post-bronchodilator FEV₁/FVC less than 70% is considered to indicate the presence of airflow limitation.
- Decrease in the gas exchange function of COPD patients can be grasped by examining the decrease in the diffusing capacity for CO (DLco).



(Figure 8) Spirograms of a healthy individual and a severe COPD patient FEV₁ and FVC

An FEV₁% volume less than 70% after bronchodilator administration indicates the presence of airflow limitation. The ratio of the FEV₁ to the predicted FEV₁ (%FEV₁) is used to determine the stage (degree of severity) of the disease.

$$\text{FEV}_1\% = \text{FEV}_1 / \text{FVC} \times 100\%$$

$$\%FEV_1 = \text{Actually measured FEV}_1 / \text{Predicted FEV}_1 \times 100\%$$

The airflow limitation of COPD is not completely reversible. To evaluate that, it is necessary to compare the results of spirometry before and after administration of bronchodilator agent. To ensure uniform bronchodilator quantity administration, a calibrated inhaler should be used. The FEV₁ is used as the index of reversibility.

The following improvement ratio (% change ratio) is evaluated:

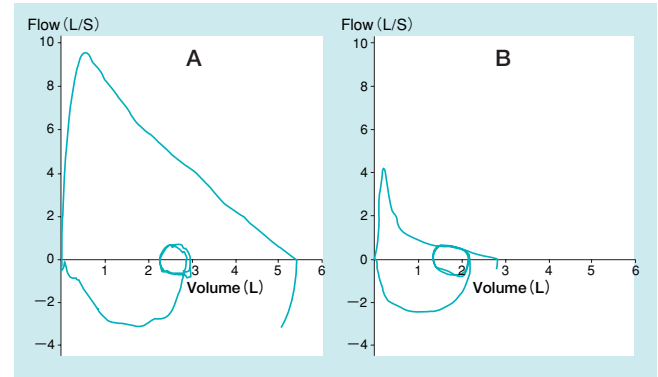
$$\% \text{ change ratio} = \frac{\text{the value after administration of bronchodilator agent} - \text{the value before administration of the bronchodilator agent}}{\text{the value before administration of the bronchodilator agent}} \times 100$$

If the FEV₁ increase by 12% and 200mL or more than the value before administration, the change is judged to be reversible.

The extent of variation of the FEV₁, measured in healthy subjects is reported to be less than 5%. The standard predicted value of FEV₁ in Japanese non-smoking healthy subjects is obtained by the following formula.

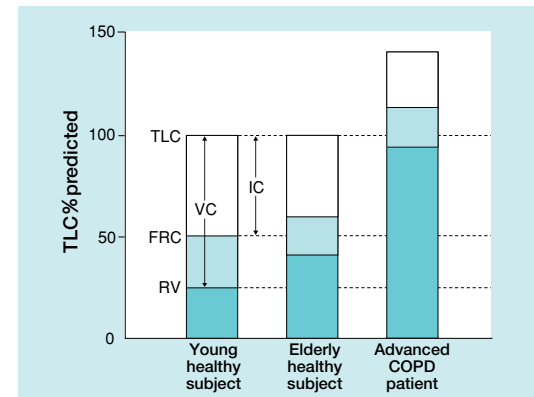
$$\text{Men FEV}_1 (\text{L}) = 0.036 \times \text{height (cm)} - 0.028 \times \text{age} - 1.178$$

$$\text{Women FEV}_1 (\text{L}) = 0.022 \times \text{height (cm)} - 0.022 \times \text{age} - 0.005$$



(Figure 9) Flow volume curve

A: Healthy subject B: Severe COPD patient



(Figure 10) Changes in lung volume in an elderly healthy subject and a COPD patient

TLC: Total lung capacity, FRC: Functional residual capacity, RV: Residual volume, VC: Vital capacity, IC: inspiratory capacity

(Reference 5)

6. Exercise tests, respiratory muscle function tests, sleep studies

- The exercise test is useful for evaluating the degree of severity, clarifying the exercise limiting factors of the respiratory and circulatory systems, deciding on the therapeutic strategy and its effectiveness, and also for prognostic evaluating.
- In COPD, the ventilation system is the major limiting factor of exercise. In severe cases, hypoxemia during exercise, pulmonary circulation disturbance and decreased oxygen transport capability may also limit the exercise capacity.
- Both inspiratory and expiratory muscle strength is reduced in COPD, but the degree of decrease is greater in inspiratory muscle strength.
- There is a tendency toward marked decrease in the arterial blood oxygen saturation during sleep in patients who show a decrease in the partial oxygen pressure (PaO₂) when awake. In these patients, a tendency towards hypoxemia is particularly marked during REM sleep.

7. Arterial blood gas measurement

- PaO₂ value of a 60 Torr or less at rest breathing room air is diagnosed as respiratory failure. If the PaCO₂ is 45 Torr or more, it is judged to indicate the accumulation of carbon dioxide.
- Measurement of SpO₂ using a pulse oxymeter allows continuous non-invasive measurement, but it is necessary to understand all points requiring caution for the measurement.

8. Evaluation of pulmonary hypertension and cor pulmonale

- In respiratory diseases primarily affecting ventilation such as COPD, the pulmonary hypertension is considered to be indicated by an mean pulmonary arterial pressure of 20 Torr.
- Cases of COPD usually do not have severe pulmonary hypertension and the pattern of progression is gradual, but it can increase transiently on episodes of exacerbation, under exercise loading, or during sleep in sleep-related respiratory disorders.

9. QOL assessment

- The purpose of treatment for COPD is to improve QOL by alleviating respiratory symptoms, reducing the chronological decrease in pulmonary function, and avoiding exacerbation.
- In COPD, QOL should be quantitatively assessed using standardized questionnaires which evaluate the effects of disease on the activities of daily living, and the degree of well-being.

Disease-specific HRQL instrument for COPD

	Items	Japanese version
St. George's Respiratory Questionnaire (SGRQ)	76	Available
Chronic Respiratory Disease Questionnaire (CRQ)	20	Available

When considering QOL to examine the relationship between health and disease in the field of medicine, two types of assessments are made : general QOL and health-related QOL (HRQL) . The QOL assessment skills can be largely divided into scales (instruments) for assessment of general health (generic HRQL) and disease-specific HRQL, aimed specifically at COPD. The generic HRQL assessment scales can also be effective in comparing the degree of disorder in COPD and other respiratory diseases or diseases affecting other organs. Disease-specific HRQL assessment scales developed for COPD are more reliable and sensitive than generic HRQL scales, and are suited for evaluation of changes in HRQL after medical intervention, including prospective clinical trials.

[6] Treatment and management

1. Smoking cessation

- Smoking is the main risk factor of COPD, causing air flow limitation and accelerating the reduction in pulmonary functions. There are reports that the progression of decrease in pulmonary function can be delayed through smoking cessation.
- Smoking cessation is the single most important and effective, and cost-effective, method of intervention to reduce the risk of the occurrence of COPD and to hold back its progress.
- Smoking is considered to be a type of drug addiction, i.e. addiction to nicotine. To decide on the addiction, the Fagerström nicotine dependence test is often used.
- It is reported that even with a short three-minute period of smoking cessation advice from the clinician causes an increase in the rate of quitting smoking.
- Smoking cessation treatment is promoted by combining an active scientific approach for behavioral therapy, and a pharmacological approach.

Nicotine replacement therapy : This is performed simultaneously with smoking cessation. The patient is instructed not to smoke while using nicotine products. When using nicotine gum, the patient should be instructed to chew the gum slowly, to place it for sometime between the cheek and the teeth, and to allow the nicotine to be absorbed through the oral cavity membrane. When the oral cavity becomes acidic, the absorption of nicotine is prevented, so the patient is instructed not to drink coffee, juice or carbonated beverages for 15 minutes before or during chewing. Even if the patient is able to stop feeling the need for the nicotine gum in two or three months, the patient should be instructed to always carry one piece of gum in order to feel secure. Nicotine patches can have high, medium, and low nicotine contents. The patient should start with a high content patch. Generally the high content patch is used for 4 weeks, then the medium content patch for 2 weeks, and the low nicotine patch for 2 weeks, gradually reducing the dose. Even if the patient begins smoking again, the clinician should encourage the patient to try to stop once again, and it is very important for the clinician also, not to give up.

(Table 9) Strategy to help a patient quit smoking

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 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 if appropriate ; provide supplementary materials.

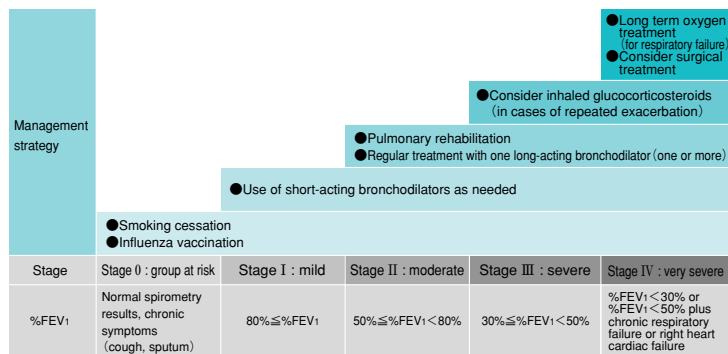
Arrange

Schedule follow-up contact.
Schedule follow-up contact, either in person or via telephone.

(Reference 6)

2. Management of stable COPD

- Stage I (mild) COPD : in addition to smoking cessation, the use of short-acting bronchodilators is recommended when needed in order to alleviate symptoms.
- Stage II (moderate) COPD : in addition to decreasing symptoms, the main purpose should be to improve QOL and improve exercise capacity. Regular treatment with long-acting bronchodilators and pulmonary rehabilitation is recommended.
- Stage II–IV (moderate to very severe) COPD : the main strategy of pharmacotherapy is the regular use of long-acting bronchodilators. Depending on the effectiveness, more than one long-acting bronchodilator can be administered. Further evaluation is necessary concerning the evaluation of the effectiveness of mucolytic agents.
- Stage III–IV (severe to very severe) COPD : prevention of exacerbation is a very important topic. In cases with repeated exacerbations (e.g., three episodes of exacerbations in the past three years) decrease in the frequency of exacerbation and suppression of the deterioration of QOL can be achieved by the use of inhaled glucocorticosteroids.



(Figure 11) Management according to stage of chronic stable COPD

A. Pharmacologic treatment

- There are no effective drugs against the pulmonary and airway inflammation or the accompanying progression of airflow limitation. However, pharmacologic treatment can reduce symptoms, prevent exacerbation, and increase QOL and exercise capacity. Therefore pharmacologic treatment should be pursued positively.
- Bronchodilator medications which are central to pharmacologic treatment should be given on a step-by-step basis in response to the degree of severity of the disease. The action of each individual patient should be studied and the most appropriate drug should be selected and given continuously.
- Various bronchodilators such as anticholinergics, β_2 -agonists and methylxanthines, all have different bronchodilator mechanisms. Considering the balance between effect and adverse reactions rather than increasing the dose of a single agent, it is preferable to use multiple agents.
- Continuous administration of inhaled glucocorticosteroids does not suppress the deterioration of respiratory function, but in cases in which the %FEV₁ is less than 50% with frequent episodes of exacerbation, it has been reported that such treatment can reduce the number of episodes of exacerbation and reduce the speed of deterioration of QOL.
- It has been reported that rather than single drug administration of inhaled glucocorticosteroids and long-acting β_2 -agonists, the combined use of these agents improves the FEV₁ and reduces the exacerbation and improves QOL significantly.
- The use of influenza vaccines has been reported to reduce by 50% the mortality of COPD cases due to exacerbation of the condition, thus all COPD cases should be given vaccines.

(Figure 12) Drugs used for the management of COPD in the stable stage

Drug	Metered dose inhaler (µg)	Dry powder inhaler (µg)	Nebulizer (mg/mL)	Oral (mg)	Injection (mg)	Patch (mg)	Duration of action (hours)
I. Bronchodilators							
1. Anticholinergics							
1) Short-acting type							
Ipratropium bromide	20						6-8
Oxotripium bromide	100						7-9
2) Long-acting type							
Tiotropium		18					≥24
2. β₂-agonists							
1) Short-acting type							
Salbutamol	100		5	2	0.2		4-6
Terbutaline				2			4-6
Hexoprenaline				0.5			4-6
Procaterol	5-10		0.1	25-50 µg			8-10
Tulobuterol				1			8
Fenoterol	100			2.5			8
Clenbuterol				10 µg			10-12
Mabuterol				25-50 µg			8-10
2) Long-acting type							
Salmeterol		25-50					≥12
Formoterol		4.5-12					≥12
Tulobuterol (Patch)						0.5-2	24*
3. Methylxanthines							
Aminophylline					250		Variable, maximum 24 hours
Theophylline (Slow release)				50-400			Variable, maximum 24 hours
II. Inhaled glucocorticosteroids							
1) Topical administration (inhalation)							
Beclomethasone	50-100						
Fluticasone	50-100	50-200					
Budesonide		100-200					
2) Systemic administration (oral, injection)							
Prednisolone				5			
Methylprednisolone				2-4	40-125		
III. Combined drugs (long-acting β₂-agonists plus glucocorticoid in one inhaler)							
Salmeterol/Fluticasone		50/100,250,500					
Formoterol/Budesonide		4.5/100,200					
VI. Mucousregulatory drugs							
Bromhexine			2	4	4		
Carbocisteine				250-500			
Fudosteine				200			
Ambroxol				15			
Acetylcysteine			200				

*Tulobuterol (Patch) needs to be examined further in terms of the sequence of the bronchodilator since the data is based on blood concentrations.

Anticholinergics

Reversible airway constriction in COPD patients depends mainly on acetylcholine deriving from the vagus nerve. Consequently, the most effective single agent to dilate the airways would appear to be an anticholinergic agent. There is no evidence of decrease in effectiveness (resistance) with long-term administration. Long-acting anticholinergic agents (scheduled to be available commercially in Japan from winter 2004) have effects for 24 hours after inhalation with significant improvement in FEV₁ and FVC remaining until the morning after administration. There have been reports that anticholinergic agents can cause urinary retention in patients with prostate hypertrophy and can exacerbate glaucoma.

β₂-agonists

The most rapid initiation of bronchodilating effects is through the use of short-acting β₂-agonists inhalation. A single administration of inhalation-type long-acting β₂-agonists yields effects for 12 hours and no decrease in effectiveness (resistance) is seen with long-term administration. Good compliance can be anticipated with the use of patch-type β₂-agonists.

Methylxanthines

While these drugs are not as effective in improving the FEV₁ value compared to inhaled bronchodilators, from a theoretical point of view, when these are given orally, they should have a better effect on dilation of peripheral airways and reduce the overexpansion of the lung and ameliorate dyspnea on exertion. It has been suggested that low-dose theophylline reduces the amount of inflammatory cells in the airway.

Inhaled glucocorticosteroids

Inhalation of glucocorticosteroids can help reduce the number of episodes of exacerbation of COPD in patients with %FEV₁ of less than 50% of the predicted value and can reduce the rate of deterioration of QOL. There are few reports on dose-response relationship of inhaled steroids in COPD patients. In large-scale trials, high-dose inhaled steroids have been used.

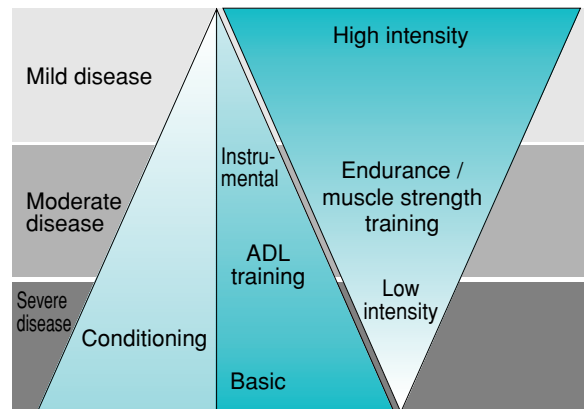
B. Comprehensive pulmonary rehabilitation

- Pulmonary rehabilitation can contribute to the improvement of the effectiveness of patients, even those who have already on pharmacologic therapy.
- Pulmonary rehabilitation is, in principle, a team medical effort. An even greater positive effect can be anticipated by having multiprofessional team working on an comprehensive program (Figure 13).
- Exercise therapy is a central structural component of pulmonary rehabilitation. When starting exercise training, it is desirable to condition patient by adjusting their breathing patterns and providing them with flexibility training to ensure efficient exercise training (Figure 14).
- Exercise training should be performed continuously and regularly, as in the correct practice of regular inhalation pharmacologic therapy. Following the induction phase of the program, the maintenance phase consists of central components including endurance and muscle strength training. By this time it is desirable for the patients to have formed an exercise habit and incorporated it into their lifestyle (Figure 15).



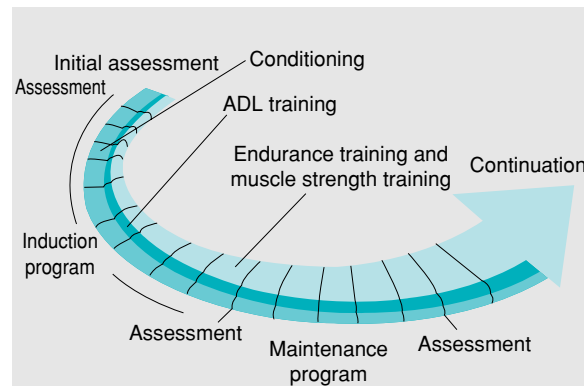
(Figure 13) Comprehensive pulmonary rehabilitation
Basic structure and three main strings

(Reference 7)



(Figure 14) Structure of the program at the beginning
of the exercise training

(Reference 8)



(Figure 15) Programed development of exercise training

(Reference 8)

The induction program is performed under supervision in the outpatient department at least two times a week (three times or more in many cases), normally six to eight weeks.

C. Patient education

- Patient education occupies an extremely important position in all processes of prevention, diagnosis and management of COPD.
- Specialists from multiple fields should participate in patient education (Table 10). The most effective educational method is to conduct patient education systematically in a programed comprehensive pulmonary rehabilitation.
- In the management of COPD and other chronic diseases, adherence must be enhanced.

(Table 10) Structure of patient education program in COPD

1. Instruction concerning the disease
 - The structure and function of the lung
 - Explanation and interpretation of the respiratory disease of the individual patient
2. Smoking cessation guidance and improvement of environmental factors
 - Explanation of the damage to health caused by smoking (including passive smoking)
 - Avoidance of occupational dust exposure and prophylaxis
3. Guidance on pharmacologic treatment
 - Explanation of the effects and adverse reactions of the drugs prescribed to the individual patient
 - Give information about methods, frequency and times of taking medicine or inhalation
4. Guidance concerning avoiding infection
 - Inform about the meaning of the prevention of respiratory infections
 - Vaccinations
5. Efforts to adapt limitations to daily life (energy conservation, simplification of daily activities)
 - Walking, washing, toilet, bathing and other aspects of daily life
6. Dietary guidance
 - The necessity and points of caution concerning nutrition
 - Adjustments to diet intake and timing
7. Guidance concerning home oxygen therapy and home ventilator therapy (as necessary)
8. Patient self-management
9. Psychological support
 - Handling anxiety and panic
 - Stress management
 - Traveling and entertainment
10. Access to social welfare services

(Reference 9)

D. Nutrition management

- Approximately 25% of COPD patients with moderate or more severe disease and approximately 40-50% of very severe COPD, the percent IBW (percent ideal body weight) has decreased to less than 90% or there has been a decrease in lean-body mass (LBM).
- The development of respiratory failure and cumulative mortality are high in patients in which loss of body weight is seen. Loss of body weight (decrease in %IBW, BMI) is a prognostic factor independent of airflow limitation.
- In cases of %IBW < 90%, there is usually a disturbance in nutrition. Dietary treatment* is indicated in the cases of COPD in which %IBW < 90%. Particularly, cases in which %IBW < 80% accompany decrease in LBM. This is a strong indication for a very positive ini-

(Table 11) Recommended evaluation items

Essential evaluation item	Body weight (%IBW,BMI), eating habits, the presence / absence of clinical symptoms when eating
Desirable evaluation items	Dietary investigation (analysis of the amount of nutrition), energy consumption at rest (resting energy expenditure; REE), % upper arm circumference (%AC), %triceps muscle of arm subcutaneous fat thickness (%TSF), %arm muscle circumference (%AMC; AMC=AC- π ×TSF), serum albumin
Evaluation items to be measured if possible	Body component analysis (LBM, FM, etc.), RTP measurement, plasma amino acid analysis (BCAA / AAA), grip strength, respiratory muscle strength, immunocompetence

IBW:80≤%IBW<90: mild decrease, 70≤%IBW<80:moderate decrease, %IBW<70: marked decrease
BMI: low body weight<18.5, standard body weight 18.5-24.9, excess body weight 25.0-29.9, FM:Fat Mass

*Dietary treatment : Generally, when an increase in body weight is aimed at, an REE of 1.5 times or more is necessary with non-protein energy. As a countermeasure against the nutritious disturbance in COPD, the basic approach is a high energy, high protein diet. The protein source should contain large quantities of branched amino acids. P, K, Ca, Mg are important for the contraction of respiratory muscles, therefore a sufficient intake of these materials is necessary. Especially, in COPD, it has been suggested that there is an increased incidences of osteoporosis, therefore, Ca intake is important. When it is difficult to increase the amount of diet, or in cases of moderate or more decrease in %IBW, then nutritional supplementation method can be considered.

tiation of nutritional supplementation therapy. However, there is no consensus concerning the most appropriate treatment method, including prevention, thus this topic must be studied further.

- For behavioral therapy in nutritional guidance, nutritionists, physicians and nurses should form a team.

E. Oxygen therapy

- In cases of COPD exhibiting hypoxemia, long-term oxygen therapy (LTOT), 15 hours or more per day, can improve the survival rate.
- Oxygen therapy is indicated in cases of severe chronic respiratory failure in patients with a PaO₂ of 55 Torr or less, or in cases with PaO₂ of 60 Torr or less in whom there is remarkable hypoxia during sleep or during exercise, and in whom the physician believes home oxygen therapy is necessary. The decision on the indication for the procedure can be made based on the measurement of PaO₂ by pulse oxymeter oxygen saturation measurement.
- During induction, it is important to educate not only the patient, but also the family, concerning the oxygen therapy.
- In cases of hypoxemia at rest or with a lower limit of normal PaO₂ (70 Torr or less), travel by airplane can result in an exacerbation of hypoxemia.

F. Ventilatory support

- It is important to have the support of an comprehensive approach based on a multiprofessional medical team for the introduction and continuation of mechanical ventilation therapy.
- At present, there is no persuasive evidence as to the effectiveness of noninvasive intermittent positive pressure ventilation (NIPPV) treatment for chronic stable

COPD patients. In the future, randomized clinical trials are necessary to determine this point.

- For home tracheostomy intermittent positive pressure ventilation (TIPPV), there is a great necessity for a diagnostic and therapeutic system as well as a nursing or home help support system. Therefore, it is necessary to prepare a system for the education of the helpers and a system of initiation of home help and home care.

G. Lung volume reduction surgery (LVRS)

- Indications for LVRS are as follows: (1) a definitive diagnosis of emphysema has been obtained based on clinical findings or spirometry, (2) despite fully sufficient medicinal treatment, dyspnea has continued, (3) Fletcher-Hugh-Jones stage III or more (MRC rate: 3 or more), (4) Chest CT and ventilatory blood flow on scintigraphy show inhomogeneous lesion distribution (emphysematous change).
- The National Emphysema Treatment Trial (NETT) study shows that surgical treatment contributed to survival in cases in which the emphysematous changes were more predominant in the upper lobes of the lung and in which there was a low exercise capability.
- There are data indicating that three years postoperatively, the physiological functions are better than before operation.

H. Lung transplantation

- COPD is the most frequent indication of lung transplantation worldwide.
- In Japan, primary pulmonary hypertension has been the greatest indication followed by idiopathic interstitial pneumonia, while for COPD, there has only been one case of lung transplantation.

1. Home management

- Home management treatment is based on respect of the wishes and hopes of the patient, and is intended to release the patient from the restrictive environment of hospitalization, while enhancing the environment of the home, to increase the level of QOL of the patient and the family, enabling support for a more independent lifestyle.
- The indications of home management care for COPD patients are (1) severe COPD, (2) patients requiring a high level of respiratory management, (3) patients requiring continued pulmonary rehabilitation.
- Certification as the 4th class or more disability can be obtained by LTOT patients and that of the 3rd class or more by patients on home mechanical ventilation in Japan. In order to reduce the burden on the patient and the family, the disability certification should be used (Table 12).
- In nursing certification, the COPD patients are not correctly evaluated, and there is not sufficient understanding by the Japanese government. As a result, it is necessary to write in as much detail as possible in the section No. 5 “other notable items” in the document prepared by the attending physician.

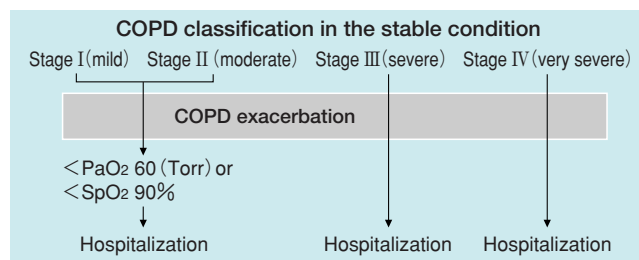
(Table 12) Respiratory function disorder level in Japan

	Activity ability	FEV ₁ / predicted VC	PaO ₂
Class 1	So difficult to breathe that the patient cannot take care of things	Impossible to measure / 20 or less	50 Torr or less
Class 3	Even walking slowly bit by bit, the patient becomes breathless	20~30	50~60Torr
Class 4	Cannot climb stairs even slowly, unless stopping from time to time to take breath / cannot walk at the same speed as other people, but can walk slowly	30~50	60~70Torr

3. Management during exacerbations

A. Evaluation of exacerbations and indications for hospitalization

- The appearance of exacerbation increases the frequency of hospitalization of the COPD patient, increases the mortality ratio and has a very seriously negative effect on prognosis. It is one of the most important factors in the clinical phenomena of COPD.
- There is no concrete classification of the exacerbation of COPD or the severity of exacerbation, including in the GOLD classification. In the West, various definitions of the exacerbation or severity of exacerbation have been published.
- The most common causes of exacerbation are respiratory tract infection and air pollution. However, the causes are unknown in about one-third of the cases.



(Figure 16) Indications for hospitalization for exacerbations of COPD according to stage classification

Indications of hospitalization for exacerbations of COPD

- 1) Hospitalization in principle on exacerbations at stage III or IV (severe or very severe COPD)
- 2) Indications of hospitalization for exacerbations of stage I or II COPD (mild or moderate COPD)
 - Appearance of dyspnea, exacerbation
PaO₂<60 Torr or SpO₂<90% breathing room air
 - Appearance of symptoms suggestive of severe disease
Use of accessory respiratory muscles, paradoxical chest movement, exacerbation of central cyanosis or its *de novo* appearance, appearance of peripheral edema, symptoms of right heart failure, hemodynamic instability
 - Uncertainty concerning treatment for exacerbation
- 3) In elderly cases of exacerbation, hospitalization is indicated.

B. Pharmacologic therapy of exacerbations

- To control exacerbation of COPD, it is essential to either increase the dose or the frequency of administration of bronchodilators. Short-acting β_2 -agonists are frequently employed.
- Systemic administration of glucocorticosteroids (orally or intravenously) can shorten the time to recovery and can also hasten recovery of lung function.
- Cases with increase of sputum or increase of purulence are probably related to bacterial airway infections, therefore administration of antibacterial agents is recommended.
- In the outpatient clinic, administration of oral penicillin and new quinolone drugs are recommended, and in hospitalized cases, injection of β -lactam drugs/ β -lactamase inhibitors, third generation or fourth genera-

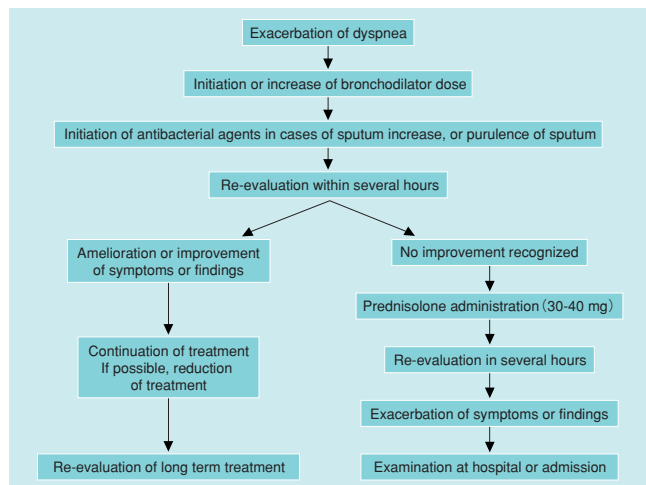
tion cephem drugs, carbapenem drugs, and new quinolone drugs are recommended.

C. Elimination of airway secretions

- Administration of anti-bacterial agents, steroids, or bronchodilators is effective in reducing airway secretions and to improve airway clearance in the period of exacerbation.
- There is no consensus on the effectiveness of respiratory physical therapy for elimination of sputum, but this is performed widely in cases of acute exacerbation as well as chronic stable condition.

D. Ventilatory support

- NIPPV should be used initially because of the ease of initiation, simplicity, and lack of invasiveness, but in cases of dysphagia and in cases with viscous or copious secretions, it is necessary to first maintain the airway, therefore IPPV should be performed.
- NIPPV has been shown to be effective in 80-85% of cases, based on clinical evidence such as improvement of blood gas findings, reduction of dyspnea, and shortening of hospitalization time. There are reports on improved mortality rate and reduction of intubations due to NIPPV.
- The indications of mechanical ventilation treatment during episodes of exacerbation should be decided based on the global assessment, taking into consideration the wishes of the patient, family, the clinical course, and the evaluation of the reversibility of cases of exacerbation. It is also necessary to discuss with the patient and family, preferably during the stable period, whether NIPPV should be the maximum therapeutic effort.



(Figure 17) Algorithm for home and outpatient management of COPD

[7] Ethical issues

(Table 13) Indications of NIPPV

1. Severe dyspnea
2. No response to pharmacologic therapy (including oxygen therapy)
3. Remarkable use of accessory respiratory muscles and paradoxical respiration
4. Respiratory acidosis or high CO₂ levels of blood (pH < 7.35 or PaCO₂ > 45)

(Table 14) Criteria for elimination of NIPPV

1. Respiratory arrest, or patients with extremely unstable respiratory circulatory condition
2. Patient cooperation cannot be obtained
3. Cases in which some kind of airway maintenance is necessary
4. Cases of injury or burns in the head or neck region

- Informed consent must be obtained before treatment. Information must be provided to the patient and family from their point of view giving them full information concerning all the problem options, and also giving them the choice of changing options during treatment.
- Advance directives include a wide range of instructions of living will and “do not resuscitate” directives. Health care providers should inform the patient about objectives and also take into consideration the opinion of the patient for terminal care. They also should inform the patient about aspects of intensive care during future periods of exacerbation.
- In all aspects of medical treatment, the privacy of the patient must be given primary consideration. The patients must also be fully informed that their privacy is completely protected.

E. Prognosis

- Cases with stage III and IV COPD (severe, very severe cases), not only show a decrease in QOL due to exertional dyspnea but also have very poor prognosis.
- Studies in Japan on long-term oxygen therapy (LTOT) have shown that the outcome for women is better than that of men, and there was no difference in outcome in relation to the level of carbon dioxide.

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