VA/DoD CLINICAL PRACTICE GUIDELINE FOR MANAGEMENT OF OUTPATIENT CHRONIC OBSTRUCTIVE PULMONARY DISEASE

Department of Veterans Affairs

Department of Defense

QUALIFYING STATEMENTS

The Department of Veterans Affairs (VA) and The Department of Defense (DoD) guidelines are based upon the best information available at the time of publication. They are designed to provide information and assist decision-making. They are not intended to define a standard of care and should not be construed as one. Neither should they be interpreted as prescribing an exclusive course of management.

Variations in practice will inevitably and appropriately occur when providers take into account the needs of individual patients, available resources, and limitations unique to an institution or type of practice. Every healthcare professional making use of these guidelines is responsible for evaluating the appropriateness of applying them in the setting of any particular clinical situation.

Version 2.0 – 2007
390

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With support from:

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Based on evidence reviewed until November 2006

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INTRODUCTION

The Clinical Practice Guideline for the Management of Chronic Obstructive Pulmonary Disease (COPD) was developed under the auspices of the Veterans Health Administration (VHA) and the Department of Defense (DoD) pursuant to directives from the Department of Veterans Affairs (VA). VHA and DoD define clinical practice guidelines as:

"Recommendations for the performance or exclusion of specific procedures or services derived through a rigorous methodological approach that includes:

- Determination of appropriate criteria, such as effectiveness, efficacy, population benefit, or patient satisfaction; and
- Literature review to determine the strength of the evidence in relation to these criteria."

The Intent of the Guideline:

- Reduce current practice variation and provide facilities with a structured framework to improve patient outcomes
- Provide evidence-based recommendations to assist providers and their patients in selecting the optimal choices in the decision-making process for the management and care for COPD
- Establish priorities for future research that are lacking in this field
- Develop outcome measurements to generate practice-based evidence that can ultimately be used to improve clinical guidelines.

Chronic Obstructive Pulmonary Disease (COPD):

- COPD is the fourth leading cause of death in the U.S. and is projected to be the third leading cause of death by the year 2020. COPD was the third leading cause of death in 2004 among adults in the 55 to 64 age group. Analysis of vital statistics data on mortality in the U.S. in the last three decades has shown that the age-standardized death rate (per 100,000 per year) from all causes combined decreased between 1970 and 2002. The largest percentage decreases were in death rates from stroke (63%), heart disease (52%), and accidents (41%). In contrast, death rates doubled from COPD over the entire time interval. Beginning in 2000, women have exceeded men in the number of deaths attributable to COPD.
- Smoking is the primary risk factor for COPD. Approximately 80 to 90 percent of COPD deaths are caused by smoking. Female smokers are nearly 13 times as likely to die from COPD as women who have never smoked. Male smokers are nearly 12 times as likely to die from COPD as men who have never smoked.
- Other risk factors of COPD include air pollution, secondhand smoke, history of childhood respiratory infections, and heredity. Occupational exposure to certain industrial pollutants also increases the odds for COPD.
- In 2004, 11.4 million adults in the U.S. were estimated to have COPD. However, close to 24 million adults in the U.S. have evidence of impaired lung function, indicating an under diagnosis of COPD. In 2004, the cost to the nation for COPD was approximately $37.2 billion, including healthcare expenditures of $20.9 billion in direct healthcare expenditures, $7.4 billion in indirect morbidity costs, and $8.9 billion in indirect mortality costs.

Key Changes in the Guideline Update to Version 2.0

The revised guideline recommendations continue to support the Step-Care Therapy approach suggested first in the 1999 version of the VA/DoD guideline for COPD; however, studies in recent years allowed the Working Group to make firmer recommendations in the following areas:

- The Step-Care Therapy approach is based on symptom scores
- Stronger evidence of the efficacy of each component of therapy
- Substantial evidence supporting the recommendation of long-acting bronchodilators as maintenance therapy
- Firm evidence supporting the recommendation for long-acting beta2-agonists (LABA) and inhaled glucocorticoids
- Accumulating strong evidence for the referral of patients with severe COPD to pulmonary rehabilitation

The format of the guideline has also been changed, combining several modules of the original guideline into one algorithm focusing on primary care and improving the guideline with a shorter version and more practical approach. Great effort was taken in this update to provide clear objectives and direct recommendations in a behavioral format. Establishing a set of desired treatment behaviors will hopefully make implementation much easier. Elaboration of the recommendations and a review of the evidence are included in the Discussion section of each annotation.

Scope of Guideline

The guideline offers best practice advice on the care of adults who have a clinical working diagnosis of COPD including chronic bronchitis, emphysema, and chronic airflow limitation/obstruction. The guideline covers diagnostic criteria and identification of early disease and systemic effects of COPD. The guideline also makes recommendations on the management of stable patients, exacerbations, and preventing progression of the disease.

The guideline addresses pharmacotherapy, oxygen therapy, travel requirements, preoperative requirements, sleep disorders, and management of exacerbations in the outpatient setting.

The guideline does not cover the management of asthma, bronchopulmonary dysplasia, and bronchiectasis, nor does it cover children.

Target population

The target population for this guideline was defined at the outset of the process. The guideline provides care recommendations for adult patients with COPD.

Target audience

The guideline is relevant to healthcare professionals who have direct contact with patients with COPD and make decisions about their care.

Development Process

The development process of this update of the guideline follows a systematic approach described in "Guideline-for-Guideline," an internal working document of VHA's National Clinical Practice Guideline Counsel. Appendix A clearly describes the guideline development process.

This Guideline is the product of many months of diligent effort and consensus building among knowledgeable individuals from the VA, DoD, academia, and guideline facilitators from the private sector. An experienced moderator facilitated the multidisciplinary Working Group.

The draft document was discussed in 2 face-to-face group meetings. The content and validity of each section was thoroughly reviewed through several conference calls. The final document is the product of those discussions and has been approved by all the members of the Working Group.

The list of participants is included in Appendix E to the guideline.

The draft document was reviewed by a diverse group of experts and by independent peer reviewers, whose input was also considered. The final document was submitted for review and approval by the VA/DoD Evidence-Based Practice Working Group.

Implementation

The guideline and algorithms are designed to be adapted to individual facility needs and resources. The algorithm will serve as a guide that providers can use to determine best interventions and timing of care for their patients to optimize healthcare utilization. This should not prevent providers from using their own clinical expertise in the care of an individual patient. Guideline recommendations should facilitate, not replace, clinical judgment.

Although this guideline represents the state of the art practice on the date of its publication, medical practice is evolving and this evolution will require continuous updating of published information. New technology and more research will improve care in the future. The clinical practice guideline can assist in identifying priorities for research efforts and allocation of resources. As a result of implementing a more unified approach to COPD management, followed by data collection and assessment, new practice-based evidence may emerge.

To provide evidence-based action recommendations whenever possible, major clinical randomized controlled trials (RCTs) and other clinical trials published through November 2006 regarding pharmacotherapy interventions in COPD were reviewed. A series of large studies were near completion in late 2006 but had not been published as peer reviewed papers. These studies were conducted by the Towards a Revolution in COPD Health group (TORCH). The TORCH multi-national trial looks specifically at all-cause mortality (primary outcome) and secondarily at other health outcomes such as a decrease in the rate of COPD exacerbations. Another study conducted by the Understanding Potential Long-term Impacts on Function with Tiotropium (UPLIFT) group focuses on reducing the rate of decline of pulmonary function and is nearing completion. Once these studies are published in peer reviewed journals, they will be incorporated.

Goals and Outcomes

By implementing the guideline, providers will recognize the following:

- Respiratory assessment is an integral component of risk prediction in the primary prevention of lung diseases
- Treatment of COPD is an integral component of management of therapy in primary care

- Interventions identified are for modifying the risk for death, acute exacerbations, and progression of the disease and improving the patient's quality of life (QOL) and lung functionality.

Patient Health Outcomes

1. Forced expiratory volume in one second (FEV1)
2. Lung volume
3. Dyspnea
4. Number and frequency of acute exacerbations
5. Exercise endurance
6. Disease modifier; reduction of progression
7. Mortality
8. Adverse effects to therapy (harm)
9. Health-related QOL
10. Healthcare utilization:
    a. Hospital admission
    b. Length of stay

REFERENCES

Hnizdo E, Sullivan, PA, Bang KM, and Wagner G. Association between chronic obstructive pulmonary disease and employment by industry and occupation in the US population: a study of data from the Third National Health and Nutrition Examination Survey. Am J of Epidemiol 2002 Oct 15;156(8):738-46.

Jemal A, Ward E, Hao Y, Thun M. Trends in the leading causes of death in the United States, 1970-2002. JAMA. 2005 Sep 14;294(10):1255-9.

Kochanek KD, Murphy SL, Anderson RN, Scott C. Deaths: final data for 2002. National vital statistics reports. Hyattsville, Maryland: National Center for Health Statistics 2004;53(5).

Mannino DM, Homa DM, Akinbami LJ, Ford ES, Redd SC. Chronic obstructive pulmonary disease surveillance - United States, 1971-2000. MMWR Surveil Summ 2002 Aug 2;51(6):1-16.

American Lung Association . Chronic Obstructive Pulmonary Disease (COPD) Fact Sheet. Available from: http://www.lungusa.org/site/pp.asp?c=dvLUK9O0E&b=35020 (Retrieved September, 2006).

National Center for Health Statistics. Health, United States, 2004. Chartbook on trends in the health of americans. Hyattsville, Maryland: 2004.U.S. Department of Health and Human Services. The health consequences of smoking: A report of the Surgeon General, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office of Smoking and Health, 2004.

U.S. Department of Health and Human Services. The health consequences of smoking: A report of the Surgeon General, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office of Smoking and Health, 2004.

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KEY ELEMENTS ADDRESSED BY THE GUIDELINE

1. Consider the diagnosis of COPD in all smokers and ex-smokers over the age of 45; cigarette smoking accounts for about 85 percent of the risk of developing COPD.
2. Smoking cessation is the single most effective way to reduce the risk of developing COPD and slow the rate of decline in lung function compared to that of non-smokers.
3. The diagnosis of COPD rests on the clinical history and on the requirement that spirometry demonstrates an airflow limitation that is not fully reversible.
4. Spirometry is the most reproducible, standardized, and objective way of measuring airflow limitation and is closely associated with prognosis.
5. Airflow limitation that is not fully reversible is defined as being present when the post-bronchodilator values for the ratio of forced expiratory volume in one second (FEV1) to forced vital capacity (FVC) (FEV1/FVC) is below 0.70.
6. Severity of COPD is based on the level of airflow limitation; tailored therapy for COPD is based on the severity of symptoms and functional limitation.
7. Breathlessness and functional limitation can be rated numerically with the simple Modified Medical Research Council (MMRC) dyspnea scale.
8. Step-Care for bronchodilators:
    - Inhaled bronchodilators provide symptom relief
    - Long-acting bronchodilators provide sustained relief of symptoms in moderate to very severe COPD
    - Combination therapy is useful in moderate and very severe COPD
    - Adding inhaled glucocorticoids to optimize bronchodilator therapy reduces exacerbations in patients with both severe COPD (FEV1 < 50 percent predicted) and frequent exacerbations (> one/year); long-term use of oral glucocorticoids is not recommended.
9. Pulmonary rehabilitation reduces dyspnea, anxiety, and depression; improves exercise capacity and quality of life (QOL); and may reduce hospitalizations
    - Exercise alone or as part of a comprehensive rehabilitation program improves symptoms, self-confidence, endurance, and QOL.
10. Long-term oxygen for more than 15 hours/day prolongs life in hypoxemic patients with PaO_2 of 55 mm Hg or less.
11. Diagnostic sleep tests should be considered if patients with COPD have pulmonary hypertension, hypercapnia, and daytime somnolence or witnessed apneas.
12. End-of-life care in patients with end-stage COPD may be considered.

Structure of the Guideline

Modules A and B include an algorithm that describes the step-by-step clinical process of decisions and interventions that occur in each phase of care. General and specific recommendations for each step in the algorithm are included in annotations following each algorithm. The links to these annotations and recommendations are embedded in the relevant specific steps in the algorithm of each module. Module C includes specific recommendations for use of medication regarding each of the major classes of drugs used in the treatment of COPD.

Each annotation includes a brief discussion of the supporting research and the rationale behind the grading of the quality of the evidence and strength of recommendations. Quality of evidence ratings were assigned for each source of evidence and recommendations were rated using the grading scale presented in the following table.

Evidence Rating System

A	A strong recommendation that the clinicians provide the intervention to eligible patients. *Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.*
B	A recommendation that clinicians provide (the service) to eligible patients. *At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.*
C	No recommendation for or against the routine provision of the intervention is made. *At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
D	Recommendation is made against routinely providing the intervention to asymptomatic patients. *At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.*
I	The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. *Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

Where existing literature was ambiguous or conflicting, or where scientific data were lacking on an issue, recommendations were based on the clinical experience of the Working Group. These recommendations are indicated in the evidence tables as based on "Working Group Consensus" and given the grade [I].

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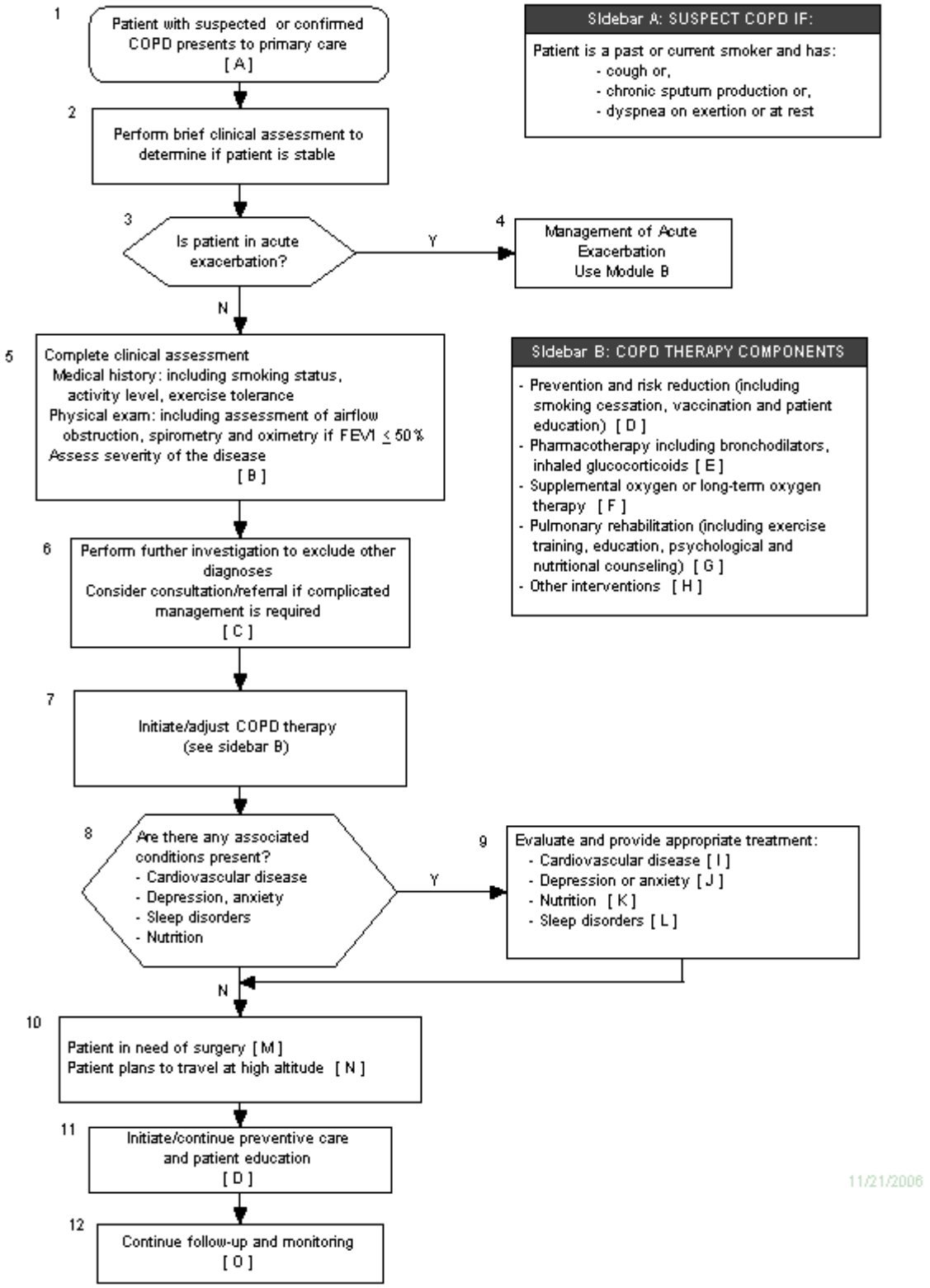
MODULE A: MANAGEMENT OF COPD

MODULE B: MANAGEMENT OF ACUTE EXACERBATION

MODULE C: PHARMACOTHERAPY

VA/DoD Clinical Practice Guideline for Management of COPD
Module A: Management of COPD

A



MODULE A: MANAGEMENT OF COPD

ANNOTATIONS

Annotation A	*Patient with Suspected or Confirmed COPD Presents to Primary Care*

1 Definition and Case Finding of COPD

BACKGROUND

Chronic obstructive pulmonary disease (COPD) is a leading cause of morbidity and mortality worldwide and results in an economic and social burden that is both substantial and increasing. Smoking is the primary risk factor for COPD. Although COPD affects the lungs, it also produces significant systemic consequences.

DEFINITIONS *

Chronic obstructive pulmonary disease (COPD) is a preventable and treatable disease state characterized by expiratory airflow limitation that is not fully reversible. The expiratory airflow limitation is usually progressive and is associated with an abnormal inflammatory response of the lungs to noxious particles or gases, primarily caused by cigarette smoking.

Chronic bronchitis is defined clinically as a chronic productive cough for 3 months in each of 2 successive years in a patient in whom other causes of productive chronic cough have been excluded.

Emphysema is defined pathologically as the presence of permanent enlargement of the airspaces distal to the terminal bronchioles, accompanied by destruction of their walls and without obvious fibrosis.

Asthma is characterized by variable airflow obstruction and differs from COPD in its pathogenic and therapeutic response, and should therefore be considered a different clinical entity. (See the VA/DoD Clinical Practice Guideline for the Management of Asthma.) The high prevalence of asthma and COPD in the general population results in the coexistence of both disease entities in many individuals.

Other conditions: poorly reversible airflow limitation associated with bronchiectasis, cystic fibrosis, and fibrosis due to tuberculosis are not included in the definition of COPD but should be considered in its differential diagnosis.

***** *Source:* American Thoracic Society (ATS)/European Respiratory Society (ERS) in Standards for the Diagnosis and Management of Patients with COPD (ATS/ERS, 2004). *www.thoracic.org/copd;*
Similar definitions may be found in the British Thoracic Society, 1997 and The Global Initiative for Chronic Obstructive Lung Disease (GOLD), 2005 [www.goldcopd.org].

ACTION STATEMENT

The diagnosis of COPD should be suspected in any patient who has a history of tobacco use (smoking) and any of the following [C]:

- Chronic cough, or
- Chronic sputum production, or
- Dyspnea on exertion or rest

The diagnosis of COPD must be confirmed by spirometry. [I]

RECOMMENDATIONS

1. Persons with a history of smoking and the presence of cough or chronic sputum production or dyspnea should be assessed for COPD with spirometry. [C]

RATIONALE

- Persons who smoke or are ex-smokers have an increased incidence of airflow obstruction compared with the general population.

EVIDENCE STATEMENTS

- The Third National Health & Nutrition Examination Survey, conducted between 1988 and 1994, reported a prevalence of COPD, for individuals aged 25 to 75 years, as 6.9 percent for mild COPD and 6.6 percent for moderate COPD. COPD was estimated to be present in 14.2 percent of current white male smokers, 6.9 percent of ex-smokers, and 3.3 percent of never smokers (NHANES III).
- Forced expiratory volume in one second (FEV1) was reduced in 27 percent of patients who were over 35 years old, were current or ex-smokers, and had a chronic cough (van Shayck, 2002).
- Spirometry should be performed in patients with chronic bronchitis, as a significant proportion have or will develop airflow limitation (Jonsonn, 1998).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**R**
1	Twenty-seven percent of patients over 35 years old were current or ex-smokers who had a chronic cough and a reduced FEV1.	van Shayck, 2002	II-2	Fair	C
2	Significant proportion of patients with chronic bronchitis will develop airflow limitation.	Jonsonn, 1998	II-2	Fair	C

QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)

Annotation B *Clinical Assessment*

2 Assessment, Testing, and Diagnosis

2.1 Clinical Assessment: History and Physical Examination

BACKGROUND

While the diagnosis of COPD is predicated upon spirometry, a meticulous history and physical examination is a central component of the initial diagnosis and ongoing management of patients with COPD.

ACTION STATEMENT

All patients with known or suspected COPD should have a focused history and physical examination to assess for the presence of airflow limitation. [I]

RECOMMENDATIONS

1. The following core elements of the medical history should be evaluated in patients with suspected or proven COPD [I]:
    a. *Shortness of breath* ─ patients should quantify their level of dyspnea (resting vs. exertional). Early in the disease course, patients often complain of exertional dyspnea. As the disease progresses, exercise tolerance worsens and patients may develop resting dyspnea.
    b. *Cough* ─ duration and character of the cough should be quantified. The presence of a productive cough is a second clinical hallmark of COPD. This cough is typically initially worse in the morning, but can be present throughout the day. An isolated nocturnal cough is typically not characteristic of COPD. Chronic bronchitis is defined by the presence of a persistent cough for at least 3 months for 2 or more consecutive years.
    c. *Sputum production* ─ volume (amount) and character (color, thickness) of sputum production should be qualified. Sputum production is required for a diagnosis of chronic bronchitis.
    d. *Risk factor assessment* ─ tobacco use, particularly cigarette smoking, is the primary risk factor for developing COPD. Use should be quantified in pack-years (number of packs per day x number of years = pack-years). A 10-pack year history of smoking is considered to be the threshold for development of COPD. There is no comparable standard for pipes or cigars that may also produce COPD. Environmental pollutant exposure and occupational exposure to vapors, fumes, or irritants are important secondary risk factors.
    e. *Other important elements in the initial evaluation of COPD:*
        - Prior medical history of asthma, allergies, or recurrent respiratory illnesses (particularly in childhood)
        - Family history of COPD
        - Self-reported history of prior COPD exacerbations and/or hospitalizations
        - Presence of comorbid conditions, in particular coronary artery disease, congestive heart failure, depression, and anxiety.
2. The following core elements of the physical examination should be evaluated in patients with suspected or proven COPD [I]:

a. *Vital signs* ─ for patients with COPD, an assessment of pulse oximetry and body mass index (BMI = kg/m^2) should be included with the vital signs.

b. *Inspection* ─ clinical observation should be performed to assess for the following elements:

- Chest wall morphology (e.g., 'barrel-chest'); use of accessory muscles (e.g., 'suprasternal retractions'); pursed-lip breathing (surrogates that suggest airflow limitation); and tracheal tug (sign of hyperinflation)
- Forced Expiratory Time ─ patients should be asked to completely empty their lungs following a maximal inspiratory effort
- Central cyanosis (a surrogate for oxygen saturation); oxygen desaturation may be present in the absence of cyanosis; cyanosis is indicative of severe desaturation
- Miscellaneous signs ─ jugular venous distension suggests elevated right heart pressures; bilateral peripheral edema may suggest cor pulmonale.

c. *Palpation/Percussion* ─ these elements are often unhelpful in patients with COPD, but may be helpful in diagnosing pulmonary hyperinflation.

d. *Auscultation* ─ the following elements should be noted on the cardiopulmonary examination:

- Breath sounds are often diminished or distant in patients with COPD
- A widened split second heart sound is suggestive of cor pulmonale.

EVIDENCE STATEMENTS

- All patients with known or suspected COPD should have a targeted history and physical examination to evaluate for the presence of airflow obstruction (ATS/ERS, 2004; GOLD, 2005; NICE, 2004).

2.2 Spirometry and Reversibility for Diagnosis

BACKGROUND

Chronic expiratory flow limitation is the hallmark of COPD. The diagnostic criteria require documentation of airflow limitation by spirometry. Since the flow limitation is at most partially reversible, the diagnosis is based on post-bronchodilator spirometric FEV1 and forced vital capacity (FVC) or vital capacity (VC). Spirometry is sufficient for documentation of expiratory flow limitation. Lung volumes and diffusing capacity are not required or necessary for documentation of expiratory flow limitation in most patients. Performance of follow-up spirometry is not routinely indicated since many interventions in COPD are based on symptoms. Conditions under which spirometry may be indicated include an unexplained change in respiratory symptoms or for preoperative evaluation.

ACTION STATEMENT

Spirometry should be obtained in all stable patients suspected of or having a diagnosis of COPD. [B]

RECOMMENDATIONS

1. Spirometry should be performed and documented in the medical record. [B]
2. A diagnosis of expiratory airflow limitation can be made if the post-bronchodilator FEV1/FVC or FEV1/VC ratio is 0.70 or less. Where possible, value should be compared to age-related normal values to avoid over diagnosis of COPD in the elderly. [I]

3. Reversibility should not be used to predict response to treatment or to distinguish between COPD and asthma. [B]
4. Spirometry should be repeated if there is a clinically significant unexplained change in respiratory symptoms. [I]
5. All patients presenting with airflow limitation at a relative early age (of the fourth to fifth decade) or with a family history of COPD should be tested for alpha-1-antitrypsin deficiency. [I]
6. Oximetry should be considered in patients with COPD and should be performed in all patients with severe or very severe COPD (FEV1 < 50 percent predicted) to determine the degree of hypoxemia and the potential need for long-term oxygen therapy at rest and/or during exercise. [C]

RATIONALE

- No diagnosis of COPD can be confirmed without a post-bronchodilator spirometry to document expiratory airflow limitation. This is part of the diagnostic criteria for COPD.

- Spirometry can be used to identify patients with an FEV1 below 50 percent predicted (i.e., severe to very severe COPD). Such identification can be used to help guide management of the COPD. These patients have a greater probability of repeated COPD exacerbations which may be reduced by pharmacotherapy such as bronchodilators and inhaled glucocorticoids.

- The best values of FEV1 and FEV1/FVC ratio post-bronchodilator are used to determine whether the patient has airflow obstruction and to determine the severity of airflow obstruction based on spirometry. Both asthma and COPD may be partly reversible, making it difficult to use spirometry results alone to distinguish between asthma and COPD.

- Follow-up spirometry should be used to help resolve clinically significant unexplained changes in respiratory symptoms or to help in preoperative evaluation.

EVIDENCE STATEMENTS

- An evidence-based report has concluded that spirometry is most useful in patients with severe to very severe COPD, since these patients are more likely to have COPD exacerbations for which preventive treatment is available (Wilt et al., 2005).

- Other guidelines recommended that the diagnosis of expiratory airflow limitation be based on spirometry documenting and FEV1/FVC or FEV1/VC ratios, after inhalation of a short-acting bronchodilator (ATS/ERS, 2004; GOLD, 2005; NICE, 2004).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	R
1	Perform spirometry (pre- and post-bronchodilator) in all stable patients suspected or having a diagnosis of COPD.	ATS/ERS, 2004 GOLD, 2005 NICE, 2004	III	Poor	B
2	Spirometry is most useful for the diagnosis of patients with severe to very severe COPD.	Wilt et al., 2005	I	Good	A
3	A diagnosis of expiratory airflow limitation can be made if the post-bronchodilator FEV1/FVC or FEV1/VC ratio is < 0.70.	ATS/ERS, 2004 GOLD, 2005	III	Poor	I
4	Reversibility does not predict response to treatment or distinguish between COPD and asthma.	NICE, 2004	II-3	Fair	B

QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)

2.3 Assessing Severity of the Disease

BACKGROUND

The main characteristic of COPD is airflow limitation. Grading or staging, based on severity of airflow obstruction, facilitates the application of clinical recommendations and attempts to offer a composite picture of disease severity. FEV1 is the most important physiologic tool used in the diagnosis of COPD as well as in the assessment of its severity, progression, and prognosis. However, airway obstruction incompletely represents severity of disease. The 1999 VA/DoD Clinical Practice Guideline for the Management of COPD in Primary Care adopted a classification that is based on both FEV1 and evaluation of symptoms. This classification is also used by ATS/ERS (2004) and GOLD (2005). In severe COPD, other manifestations of disease may be better indicators for disease severity and prediction for risk of death.

The COPD severity rating based on FEV1 classifies patients as *mild* if they have an FEV1 of 80 percent predicted or above. Most studies evaluating treatment included patients with COPD with an FEV1 exclusively below 70 percent predicted. The classification is linked to treatment recommendations. While treatment strategies for patients with FEV1 below 70 percent predicted can be supported by evidence, linking treatment strategies to patients with an FEV1 above 70 percent predicted is speculative, at best. A recent publication has chosen 70 percent predicted as the dividing line between mild and moderate severity of pulmonary function in patients with obstructive pulmonary disease (Pellegrino et al., 2005).

ACTION STATEMENT

COPD severity should be assessed on the basis of percentage of predicted FEV1 or degree of dyspnea related to activities. [I]

RECOMMENDATIONS

1. The forced expiratory volume in one second (FEV1) should be used to stratify disease severity by airflow limitation. [B]

2. The Modified Medical Research Council (MMRC) Dyspnea Scale should be used to grade severity of breathlessness according to the level of exertion required to elicit it and help determine treatment. [C]

   Spirometric classification of disease stages and severity is described in Table 1. The severity of COPD that is based on self-reported symptoms is described in Table 2 using the Dyspnea Scale developed by the Medical Research Council.

Table 1. Severity of COPD Based on Spirometry (*adopted from ATS/ERS, 2004***)**

Stage	Severity	Post-bronchodilator FEV1/FVC	FEV1 % predicted
0	At-Risk [(1)]	> 0.7	≥ 80
1	Mild	≤ 0.7	≥ 80
2	Moderate	≤ 0.7	50 – 79.9
3	Severe	≤ 0.7	30 – 49.9
4	Very Severe	≤ 0.7	< 30

(1) Patients who smoke or are exposed to pollutants; and have cough, sputum or dyspnea; or have family history of respiratory disease. (There is insufficient evidence to support this category.)

FEV1: forced expiratory volume in one second; FVC: forced vital capacity

Table 2. Severity of COPD Based on Dyspnea [(1)]

Severity	Score	Degree of Breathlessness Related to Activities
None	0	Not troubled with breathlessness except with **strenuous exercise**
Mild	1	Troubled by shortness of breath when hurrying or walking up a **slight hill**
Moderate	2	Walks slower than people of the same age due to breathlessness or has to stop for breath when walking at own pace **on the level**
Severe	3	**Stops** for breath after walking approximately 100 meters or after **a few minutes** on the level
Very Severe	4	Too breathless to **leave the house** or breathless when **dressing or undressing**

(1) Modified Medical Research Council (MMRC) Dyspnea Scale (Bestall et al., 1999)

RATIONALE

- COPD is a disease characterized by airflow obstruction which is not fully reversible. The best physiologic tool to assess airflow obstruction is FEV1. The thresholds of airflow limitation are arbitrary and have not been validated. COPD can be present in the absence of symptoms. As disease severity progresses, other manifestations of disease severity reflect systemic involvement.

EVIDENCE STATEMENTS

- Spirometric classification has proved useful in predicting health status (Ferrer et al., 1997), utilization of healthcare resources (Friedman et al., 1999), development of exacerbations (Burge et al., 2003; Dewan et al., 2000) and mortality (Anthonisen et al., 1986) in COPD. It is intended to be applicable to populations (Celli et al., 2003) and not to substitute clinical judgment in the evaluation of the severity of disease in individual patients.

- Dyspnea severity correlates with mortality (Nishimura et al., 2002).

- Body mass index (*B*), the degree of airflow obstruction (*O*), dyspnea (*D*), and exercise capacity (*E*), measured by the 6-minute walk distance test, construct the *BODE* Index, a multi-dimensional 10-point scale in which higher scores indicated higher risk of death. The BODE is better than FEV1 at predicting the risk of death (Celli et al., 2004).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**Net Effect**	**R**
1	FEV1 indicates severity of the disease.	Anthonisen et al., 1986 Burge et al., 2003 Celli et al., 2003 Dewan et al., 2000 Ferrer et al., 1997 Friedman et al., 1999	II-2	Fair	Substantial	B
2	Dyspnea is a better predictor of mortality than FEV1.	Nishimura et al., 2002	II-2	Fair	Substantial	C
3	The BMI, Airflow Obstruction, Dyspnea, Exercise Performance (BODE) Index is a better predictor for the risk of death from COPD.	Celli et al., 2004	II-2	Fair	Moderate	B
QE = Quality of Evidence; Net Effect = Size of Intervention Effect; R = Strength of Recommendation (See Appendix A)						

Annotation C *Further Investigation to Exclude Other Diagnoses*

2.4 Diagnostic Workup

BACKGROUND

The medical history, physical examination, and spirometry (with reversibility testing) may be sufficient to make a diagnosis of COPD. However, at the initial visit or as the disease progresses, additional tests may be necessary or helpful to confirm the diagnosis; determine if there are any co-diagnoses such as asthma; define the type of COPD; or assess the severity, physical, and psychological impact of the disease.

ACTION STATEMENT

Other investigations, in addition to spirometry, may be necessary as clinically indicated. [I]

RECOMMENDATIONS

1. A diagnosis of COPD requires objective evidence of airflow obstruction via pre- and post-bronchodilator spirometry. [B]
2. A chest X-ray should be considered to rule out other diagnoses and for later use as a baseline. A chest X-ray is not sensitive for the diagnosis of COPD. [C]
3. Other investigations may be necessary as clinically indicated [I]:
    a. *CT* ─ can exclude other diseases and define bullae and is essential to identify patients eligible for lung volume reduction surgery
    b. *Oximetry* ─ should be considered in patients with COPD and should be performed in all patients with severe or very severe COPD (FEV1 < 50 percent predicted) to determine the degree of hypoxemia and the potential need for long-term oxygen therapy at rest and/or during exercise. Nocturnal pulse oximetry should be performed in patients considered solely for nocturnal oxygen supplementation.
    c. *Alpha1-antitrypsin (AAT)* ─ AAT deficiency accounts for less than one percent of COPD. It should be suspected if there is early onset of COPD, little or no history of smoking, a family history of COPD, or a predominance of basilar emphysema. If AAT deficiency is suspected, obtain a serum AAT level.
    d. *Arterial blood gases* ─ arterial blood gases should be done in patients with very severe COPD (FEV1 < 30 percent predicted); signs of right heart failure (cor pulmonale); polycythemia (hematocrit > 55 percent); or respiratory failure. Blood gases are an alternative to pulse oximetry in patients being considered for O_2 supplementation. Pulse oximetry can determine arterial oxygen saturation, but pulse oximetry does not yield PCO_2.
    e. *Full pulmonary function tests* ─ lung volumes, carbon monoxide diffusing capacity and flow-volume loops are not required for routine assessment but can provide additional information useful for resolving diagnostic uncertainty and/or assessing surgical risk. A reduced carbon monoxide diffusion capacity may suggest the presence of emphysema.
    f. *Exercise testing* ─ exercise testing may be of value in patients with a disproportionate degree of dyspnea for their FEV1. Exercise testing can quantify impairment and/or disability and help to select patients able to safely undergo lung resection.
    g. *ECG* ─ to assess cardiac status if pulmonary or nonpulmonary heart disease is suspected or present.

h. *Echocardiogram* ─ to assess right and left cardiac status if cardiac dysfunction or disease is suspected or present.

i. *Sputum cultures* ─ consider in patients with persistently purulent sputum or during recurrent infectious exacerbations.

j. *Complete blood count* ─ should be done if anemia or polycythemia is suspected.

DISCUSSION

COPD and asthma are frequently distinguishable on the basis of history (and examination) in untreated patients presenting for the first time. Features from the history and examination (such as those listed in Box 1) should be used to differentiate COPD from asthma whenever possible.

Box 1. Clinical Features Differentiating COPD & Asthma

Clinical Features	COPD	Asthma
Smoker or ex-smoker	Nearly all	Possibly
Symptoms under age 35	Rare	Often
Chronic productive cough	Common	Uncommon
Breathlessness	Persistent and progressive	Variable
Night time waking with breathlessness and or wheeze	Uncommon	Common
Commonly associated with atopic symptoms and seasonal allergies	Uncommon	Common
Significant diurnal or day-to-day variability of symptoms	Uncommon	Common
Favorable response to inhaled glucocorticoids	Inconsistent	Consistent

2.5 Referral to Pulmonary Consultant

ACTION STATEMENT

Patients with severe COPD or comorbidity that requires complicated management should be referred to a pulmonary subspecialist. [I]

RECOMMENDATIONS

1. Patients with COPD should be referred for consultative opinion if they request it, if there is diagnostic uncertainty, if the disease is very severe or complicated, or if the primary care provider chooses so. [I]

RATIONALE

ü Patients with COPD should be referred to a pulmonary subspecialist for any of the following reasons:

- Patient requests a second opinion
- Diagnostic uncertainty (e.g., coexisting COPD and asthma)
- Persistent dyspnea despite optimal therapy
- Symptoms disproportionate to the severity of the airflow obstruction
- Very severe airflow obstruction (FEV1 < 30 percent predicted)
- Rapid decline in FEV1
- Frequent exacerbations (> 2/year)
- Exacerbations requiring hospitalizations
- Chronic or acute respiratory failure (PCO_2 > 50 mm Hg and/or PO_2 < 50 mm Hg)
- Confirmed or suspected alpha 1-antitrypsin deficiency
- Patient requires oxygen therapy
- Patient is a candidate for lung volume reduction surgery
- Patient requires respiratory rehabilitation
- Significant comorbidities, such as cor pulmonale
- Patient requires assisted ventilation
- Patient has very severe disease and requires surgery
- Patient requires lung transplantation
- Sleep disorder is suspected (refer to a sleep specialist)
- Provider discretion.

3 Prevention – Risk Reduction

Annotation D *Prevention and Risk Reduction*

3.1 Patient Education

BACKGROUND

Specific educational packages should be developed for patients with COPD. Educated patients may be better equipped to cope with the disease and adhere to therapy. Patients with moderate and severe COPD should be made aware of the benefits and limitations of pulmonary rehabilitation programs. These programs include a component of patient education and self-management training.

Patients at risk of having an exacerbation of COPD should be given self-management advice that encourages them to respond promptly to the symptoms of an exacerbation. The main aim of self-management is to prevent exacerbations by life style adaptations and to allow patients to acquire the skills to treat their exacerbation at an early stage. Self-management plans need to be structured in a way that takes into account the age and mental status of patients with COPD. There are significant differences in the response of patients with COPD and asthma to education programs. Programs designed for asthma should not be used in COPD.

RECOMMENDATIONS

1. Patient should be educated about the disease, cause, therapy, and complications of COPD. [I]

3.2 Smoking Cessation

BACKGROUND

Tobacco smoking has been shown to cause 80 to 90 percent of COPD cases. Smoking cessation is the single most effective way to reduce the risk of developing COPD and slow the rate of decline in lung function compared to that of non-smokers.

ACTION STATEMENT

All patients must be screened for tobacco use and encouraged to stop smoking at every visit, as smoking cessation is the only known intervention to reduce the decline in FEV1. [A]

RECOMMENDATIONS

1. All patients should be counseled not to smoke and to avoid secondhand smoke. [A]
2. All smokers must be told that they need to quit smoking. [A]
3. All smokers should be assessed for willingness to quit. [C]
4. All smokers should be counseled on smoking cessation and be considered for medications that assist in smoking cessation. [A]

Table 3. Suggested Strategies to Promote Smoking Cessation: "5 A's"*

Strategy 1:	*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.
Strategy 2:	*Advise*: Strongly urge all smokers to quit. In a clear, strong, and personalized manner, urge every smoker to quit.
Strategy 3:	*Assess*: Assess smokers willingness to make a quit attempt. Ask every smoker if he or she is willing to make a quit attempt at this time.
Strategy 4:	*Assist*: Aid the patient in quitting. Help patient develop a quit plan, encourage nicotine replacement therapy or bupropion except in special circumstances, give key advice on successful quitting, and provide supplementary materials.
Strategy 5:	*Arrange:* Schedule follow-up contact either in person or via telephone.

Table 4. Motivational Intervention to Promote Smoking Cessation: "5 R's"*

Relevance: Encourage patient to indicate why quitting is personally relevant.

Risks: Ask the patient to identify potential negative consequences of tobacco use.

Rewards: Ask the patient to identify potential benefits of stopping tobacco use.

Roadblocks: Ask the patient to identify barriers or impediments to quitting.

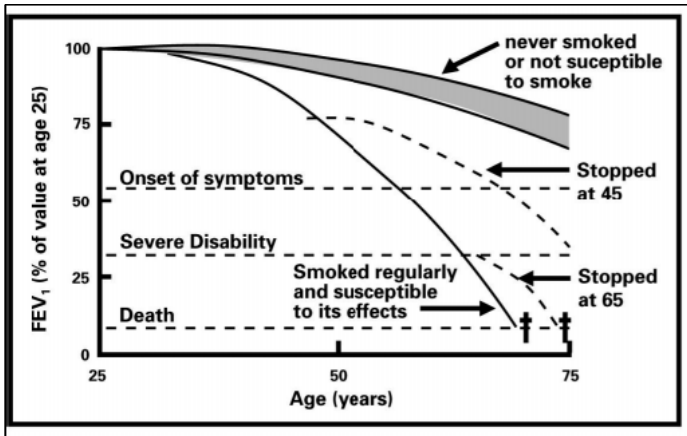
Repetition: The motivational intervention should be repeated every time an unmotivated patient has an interaction with a provider. Tobacco users who have failed in previous attempts should be told that most people make repeated quit attempts before they are successful.

*For detailed recommendations and evidence refer to the VA/DoD Clinical Practice Guideline for Management of Tobacco Use.

RATIONALE

- The risk of developing lung disease, other systemic diseases, and early mortality is significantly higher in smokers. Effective primary prevention of smoking eliminates the need for smoking cessation.

Figure 1. Time Course of COPD (Fletcher & Peto, 1977)



Time Course of COPD

The risks of developing chronic obstructive lung disease: the lines illustrate the natural decline and the effects that smoking and stopping smoking can have on the FEV_1. † = death. This graph shows the rate of loss of FEV_1 for a hypothetical, susceptible smoker, and the potential effect of stopping smoking early or late in the course of COPD. Other susceptible smokers will have different rates of loss, thus reaching 'disability' at different ages. The normal FEV_1 ranges from below 80% to above 120% so this will affect the starting point for the individual's data (not shown).

Adapted from Fletcher, C & Peto, R[7]

EVIDENCE STATEMENTS

- Passive smoke exposure is a risk factor for cough and sputum production and may account for some of the COPD that develops in non-smokers (Leuenberger et al., 1994).

- Quitting smoking can slow the progressive loss of lung function in patients with COPD (Anthonisen et al., 1994).

- Mortality was 6.04 per 1,000 person years in sustained quitters, 7.77 per 1,000 person years in intermittent quitters, and 11.09 per 1,000 person years in continuing smokers (Anthonisen et al., 2005).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	R
1	Passive smoke exposure increases cough and sputum production.	Leuenberger et al., 1994	I	Good	A
2	Smoking cessation decreases the loss of lung function.	Anthonisen et al.,1994	I	Good	A
3	Smoking cessation decreases mortality.	Anthonisen et al., 2005	I	Good	A
QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)					

ADDITIONAL RESOURCES

- Fiore MC, Bailey WC, Cohen SJ, et al. Treating Tobacco Use and Dependence. Quick Reference Guide for Clinicians. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. October 2000.
- http://www.surgeongeneral.gov/tobacco/default.htm
  - ü You Can Quit Smoking: http://www.surgeongeneral.gov/tobacco/5daybook.pdf
  - ü Good Information For Smokers: http://www.surgeongeneral.gov/tobacco/lowlit.pdf
  - ü Treating Tobacco Use and Dependence (Quick Guide for Clinicians): http://www.surgeongeneral.gov/tobacco/tobaqrg.pdf
  - ü Quit Smoking Products For Consumers (order form): http://www.surgeongeneral.gov/tobacco/order.pdf

3.3 Vaccination

BACKGROUND

Elderly persons and persons of any age with certain chronic medical conditions, including chronic pulmonary conditions, are at increased risk for influenza- or pneumococcal-related complications. The Advisory Committee on Immunization Practices (ACIP) recommends influenza and pneumococcal vaccination for persons who have chronic disorders of the pulmonary or cardiovascular systems, including asthma (see also VA/DoD endorsement to the U. S. Preventive Services Task Force (USPSTF) guideline on immunization).

ACTION STATEMENT

Provide an annual influenza vaccine to individuals with COPD. [A]

Provide a pneumococcal polysaccharide vaccine to individuals with COPD. [B]

RECOMMENDATIONS

1. An annual influenza vaccination is recommended for individuals with COPD unless contraindicated due to severe anaphylactic hypersensitivity to egg protein. Only inactivated influenza vaccines should be used. The optimal time to receive influenza vaccine is October - November. [A]
2. Although insufficient data exist for use of pneumococcal vaccination in individuals with COPD, data from elderly populations with or without chronic disease provides supportive evidence for its use. [A]
3. Pneumococcal vaccines are routinely given as a one-time dose (administer if previous vaccination history is unknown). One-time revaccinations are recommended 5 years later for people at the highest risk for fatal pneumococcal infection and for people older than 65 years if the first dose was given prior to the age of 65 and more than 5 years have elapsed since the previous dose. [I]

RATIONALE

- Influenza vaccine has been shown to be effective in preventing illness, complications, and death in high-risk populations.

- Polysaccharide pneumococcal vaccines do not appear to reduce the incidence of pneumonia in elderly adults (55 years and above) with or without chronic illness, but may be able to reduce invasive pneumococcal disease. This evidence is inconclusive. Some evidence suggests that patients with COPD with an FEV1 < 40 percent and under 65 years of age have the greatest benefit for prevention of community acquired pneumonia from pneumococcal vaccination.

EVIDENCE STATEMENTS

3.3.1 Influenza vaccine

Several studies have been conducted in the elderly and high-risk populations as a whole.

- A meta-analysis combining cohort, case-control, and clinical trials (n=15 trials) evaluated the effectiveness of influenza vaccine in persons older than 65 years living in the community. Influenza vaccine was effective in reducing influenza-like illness, hospitalization for pneumonia and influenza, mortality following hospitalization for pneumonia and influenza, and all-cause mortality (Vu et al., 2002).

- Another meta-analysis (n=64 trials) of influenza vaccine in elderly patients living in the community found that vaccine reduced hospitalization for influenza and pneumonia and all-cause mortality but did not reduce the incidence of influenza, influenza-like illness, or pneumonia. In homes for the elderly, vaccination was effective against influenza-like illness, pneumonia, hospitalization, deaths from influenza or pneumonia, and all-cause mortality (Jefferson et al., 2005).

- A Cochrane meta-analysis of randomized controlled trials (RCTs) specific to COPD identified 4 trials (total sample size of n=215) comparing influenza vaccine to placebo. Vaccination resulted in decreased COPD exacerbations (Poole et al., 2006).

- An RCT compared influenza vaccine to placebo in 125 patients with COPD over a 16-month period. The incidence of all influenza-related acute respiratory illness was significantly lower in the group receiving vaccination (6.8 vs. 28.1 per 100 person-years). When broken down by outpatient and inpatient episodes, vaccination resulted in a significantly lower incidence of outpatient influenza-related acute respiratory illness events but not in influenza-related events leading to hospitalization (Wongsurakiat et al., 2004).

- In a retrospective cohort study, outcomes for influenza vaccinated (n=1,366) and unvaccinated patients (n=532) were evaluated in elderly patients with chronic lung disease over a 3-year period. Among the vaccinated group, hospitalization rates for pneumonia and influenza was 45 per 1,000-patient years during the influenza season and 41 per 1,000-patient years during the interim periods. Rates of hospitalization for pneumonia and influenza in the unvaccinated group were 111 per 1,000 patient years during the flu season and 55 per 1,000 patient-years during the interim periods. The overall risk ratio (RR) for hospitalizations for pneumonia and influenza was 0.48 [95%CI: 0.28-0.82] and the odds ratio (OR) for death was 0.30 [95%CI: 0.21-0.43]. There was no significant difference between groups for hospitalization for all respiratory conditions (Nichol et al., 1999a).

3.3.2 Pneumococcal Polysaccharide vaccine (PPV)

The data for pneumococcal vaccination specifically for the COPD population are inconclusive. Most of the published studies are in the general population and address high-risk patients with chronic disease in general. Only a few studies have researched the impact of PPV in COPD patients.

- Two small RCTs (total n=150) evaluating pneumococcal vaccine in patients with COPD were unable to show efficacy (Davis et al., 1987; Leech et al., 1987). One retrospective cohort trial (n=1,898) in elderly patients with chronic lung disease found that pneumococcal vaccination resulted in a reduction in the number of hospitalizations for pneumonia and influenza (adjusted RR=0.57 [95%CI: 0.38, 0.84]). This same study found an additive benefit when patients received both pneumonia and influenza vaccine (Nichol et al., 1999b).

- There are several RCTs evaluating pneumococcal vaccine in the general elderly population, several which included patients with chronic illness such as COPD. Individually, these studies have been criticized, because they were underpowered or may have been methodologically weak. In an effort to increase the power, several meta-analyses or systematic reviews (elderly population) of the RCTs and one in case-control and cohort studies have been conducted. Pneumococcal vaccine does not appear to reduce the risk of all-cause pneumonias; however, it does appear to reduce the risk of bacteremia/invasive pneumococcal disease (Conaty et al., 2004; Cornu et al., 2001).

- Vila-Corcoles et al. (2006), in a prospective cohort study, have shown that PPV was associated with a significant reduction in the risk for hospitalization for pneumonia (hazard ratio 0.74) and in the overall pneumonia rate (0.79). There was a significant reduction in the risk of death (59%) from pneumonia in one region in Spain. However, the study was not aimed at patients with COPD.

- A large cohort study (Jackson et al., 2003) supports the effectiveness of the pneumococcal polysaccharide vaccine for the prevention of bacteremia, but suggests that alternative strategies are needed to prevent nonbacteremic pneumonia, which is a more common manifestation of pneumococcal infection in elderly persons. In one large prospective cohort trial, the RR for total mortality was 0.73 [95%CI: 0.66-0.81] (Hedlund et al., 2003). In a study of the elderly with chronic lung disease, the adjusted RR for death was 0.71 [95%CI: 0.56, 0.91] (Nichol et al., 1999b).

- The recent Cochrane review about injectable vaccines for preventing pneumococcal infection in patients with COPD concluded that, "There is strong evidence that vaccines can protect healthy persons against infection by the pneumococcus bacteria, but little is known about the effectiveness of the vaccine in persons with chronic obstructive pulmonary disease (COPD). The results from the four randomized controlled trials included in this review with 941 participants do not show that

pneumococcal vaccination provides significant protection against disease caused by the bacteria" (Granger et al., 2006).

- In a meta-analysis comparison of ten studies with over 24,000 subjects who were elderly or likely to have impaired immune systems, pneumococcal vaccination was without effect for any outcome (Moor et al., 2000).

- One RCT suggests that COPD patients with an FEV1 < 40 percent and under 65 years of age have the greatest benefit for prevention of community acquired pneumonia from pneumococcal vaccination. There was no significant difference among other subgroups (Alfageme et al., 2006).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**R**
1	In the general elderly population, influenza vaccination reduced hospitalization for pneumonia and influenza and all-cause mortality.	Jefferson et al., 2005 Vu et al., 2002	I	Good	A
2	Influenza vaccination decreased COPD exacerbations.	Poole et al., 2006	I	Good	A
3	Influenza vaccination reduced the incidence of outpatient influenza-related acute respiratory illness events, but not influenza-related events leading to hospitalization.	Wongsurakiat et al., 2004	I	Good	A
4	In elderly patients with chronic lung disease, influenza vaccine reduced hospitalizations for pneumonia and influenza and for death.	Nichol et al., 1999a	II-2	Good	B
5	In the general elderly population, pneumococcal vaccine reduces the risk of bacteremia/invasive pneumococcal disease.	Conaty et al., 2004 Cornu et al., 2001 Jackson et al., 2003	I	Good	A
6	In the general elderly population, pneumococcal vaccine does not appear to reduce the risk of all-cause pneumonias.	Jackson et al., 2003 Moore et al., 2000 Watson et al., 2002	I	Fair	C
7	Pneumococcal vaccine reduces the risk of all-cause pneumonias and risk of death due to pneumonia.	Hedlund et al., 2003 Nichol et al., 1999b Vila-Corcoles et al., 2006	I I II-b	Fair	C
8	PPV decreases the rate of pneumonia and mortality due to pneumina in COPD.	Alfageme et al., 2006	I	Good	A

QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)

4 Therapy Interventions for COPD

Annotation E *Pharmacotherapy Including Bronchodilators and Inhaled Glucocorticoids*

4.1 Pharmacotherapy of COPD

BACKGROUND

Pharmacotherapy for patients with COPD should be tailored in steps to achieve the greatest benefit at the lowest level of therapy with the fewest side effects. Patient preference should also be taken into account when choosing between options which have similar potential benefits and side effects. The patient should be evaluated periodically until symptom control is optimized. Consider one to 6 months for each step. There is no systematic evidence that provides a rationale for what order to use the different pharmacological agents; however, a rationale based upon a consensus of experts advocates a stepped-up approach of treatment of COPD based on the natural history of the disease.
Unless otherwise indicated, when the term *therapy* is used, it refers to pharmacotherapy with bronchodilators and inhaled glucocorticoids. At all steps involving therapy, an as-needed short-acting beta 2-agonist is prescribed for acute relief of symptoms (i.e., rescue). The principles that guide step-care therapy in COPD are as follows: (See Module C: Pharmacotherapy for specific recommendations.)

1. There are no pharmacological therapies at present that have shown to modify the rate of decline in pulmonary function or reduce mortality.
2. Since pharmacological therapies do not modify COPD, the course of therapy is guided by patient symptomatic response, predominantly reduction in dyspnea at rest and exercise, and prevention of future exacerbations. In the absence of symptoms or exacerbations. In the absence of symptoms or exacerbations, no pharmacological therapy may be needed.
3. There are no defined pulmonary function thresholds that provide sufficient guidance to recommend any given bronchodilator therapy over any other for initially treating a patient. This leads to the concept of starting with single bronchodilator therapy and stepping up rather than starting with the maximal bronchodilator therapy and stepping down.
4. All bronchodilator therapies can improve symptoms and reduce exacerbations. Long-acting bronchodilators are more efficacious than short-acting bronchodilators if symptoms persist.
5. Combination bronchodilator therapy provides the potential of added benefit when single bronchodilator therapy has not achieved sufficient symptomatic improvement.
6. A slow release theophylline trial has shown to control nighttime respiratory symptoms, but should be used with caution due to potential adverse effects and insomnia. Theophylline should be discontinued if a symptomatic benefit is not evident within several weeks.
7. Inhaled glucocorticoids have been documented to improve symptoms and reduce exacerbations predominantly in patients with severe COPD (FEV1 < 50 percent predicted). Inhaled glucocorticoids are most effective when combined with a long-acting bronchodilator.
8. Patients should not be prescribed inhaled glucocorticoids before maximal bronchodilator therapy is implemented and has failed to achieve symptomatic control.
9. Short-acting and long-acting anticholinergics should not be combined.
10. Patients with COPD have an element of irreversible pulmonary disease and optimal symptomatic control may still leave a patient stable but symptomatic.

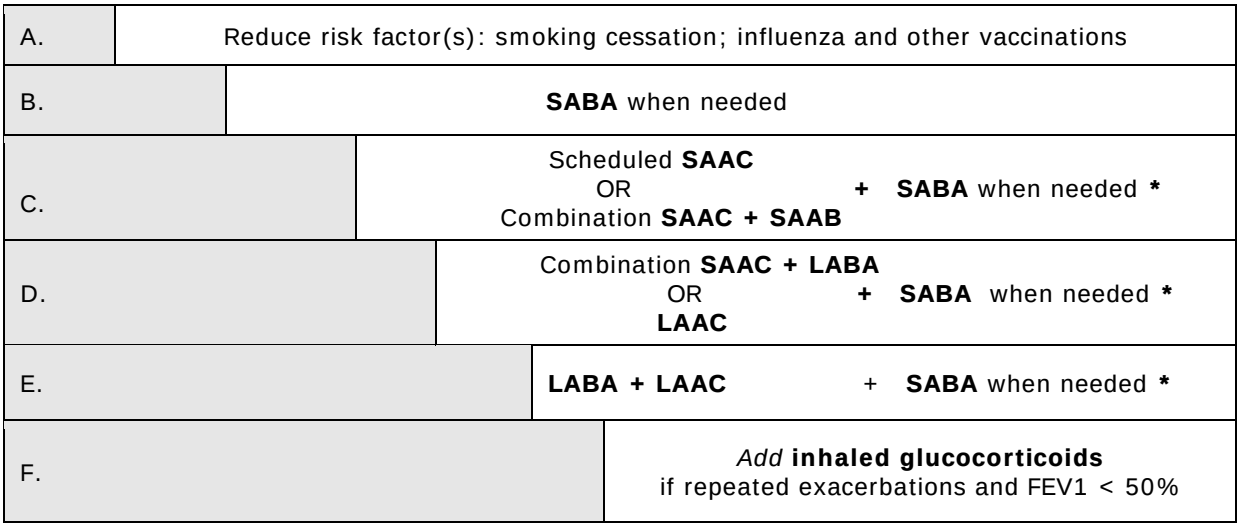
Some patients may initially present to be well-controlled on combination therapy that was not documented. An attempt should be made to carefully step down therapy in such patients to maintain the greatest benefit at the lowest level of therapy with the fewest adverse effects.

Table 5. Key Points for Step-up Therapy

Pharmacotherapy for patients with COPD is based on a step-up approach:

1. Therapy to address symptoms should make use of non-pharmacologic intervention to improve outcomes (i.e., smoking cessation, education, rehabilitation, and pulmonary rehabilitation).
2. Pharmacotherapy should balance overall efficacy which includes acceptance and adherence against risks for adverse effects (toxicity).
3. Patient symptomatic responses such as dyspnea, as well as a reduction in exacerbations, should be the primary basis for determining response to therapy.
4. Continue ongoing evaluation of the patient's response to therapy and progression of disease.
5. As COPD progresses, additional pharmacotherapy is usually needed.
6. Patient's preference should be considered to improve acceptance and adherence to therapy.
7. Patients with severe airflow limitation (FEV1 < 50 percent predicted) and minimal symptoms should be considered for a trial of pharmacologic therapy.
8. COPD severity based on symptoms and FEV1 should always be documented initially and reassessed periodically based primarily on symptomatic progression of COPD.
9. The Modified Medical Research Council (MMRC) scale of dyspnea, in addition to clinical assessment, is indicated to grade symptom severity.
10. Treatment is predominantly based on symptoms and a suggested stepped-up approach is recommended (see Table 6).

Figure 2. Step-Care Pharmacotherapy in COPD



**Theophylline may be added at each step with caution regarding adverse effects.*
SAAC – Short-acting anticholinergic; SABA – Short-acting beta-agonist; LABA – Long-acting inhaled beta-agonist; LAAC – Long-acting anticholinergic

Table 6. Step-Care Pharmacotherapy in COPD

Step	Symptoms ①	Maintenance Therapy ②	Rescue therapy	Other Interventions
A	Asymptomatic	No medication indicated	--	Smoking cessation; influenza, and other vaccinations
B	Symptoms less than daily	No scheduled medication indicated	SABA ⑥	Smoking cessation; influenza, and other vaccinations
C	Symptoms not controlled with rescue therapy **or** daily symptoms	Scheduled SAAC **or** Combination SABA + SAAC ③	SABA ⑥	Smoking cessation; influenza, and other vaccinations
D	Symptoms not controlled ②	Combination SAAC + LABA **or** LAAC ④	SABA ⑥	Smoking cessation; influenza, and other vaccinations **Consider Pulmonary Rehabilitation** ⑦
E	Symptoms not controlled ②	Combination LABA + LAAC ④	SABA ⑥	Smoking cessation; influenza, and other vaccinations **Refer to Pulmonary Rehabilitation** ⑦
F	Exacerbations of more than one per year and severe disease (FEV1 < 50%)	Consider adding an inhaled glucocorticoid ⑤	SABA ⑥	Smoking cessation; influenza, and other vaccinations **Refer to Pulmonary Rehabilitation** ⑦

SAAC – Short-acting anticholinergic; *SABA – Short-acting beta-agonist; LABA – Long-acting inhaled beta-agonist; LAAC – Long-acting anticholinergic*

① **Spirometry** is essential to confirm the presence of airflow obstruction (low FEV1 and FEV1/VC ratio). Base therapy on symptoms, but consider alternate diagnoses (heart disease, pulmonary emboli, etc.) if out of proportion to spirometry.

② Use the lowest level of therapy that satisfactorily relieves symptoms and maximizes activity level. Assure compliance and proper use of medications before escalating therapy. It is unusual for patients with COPD with **FEV1 above 70%** to require therapy beyond short-acting bronchodilators; if these patients do not improve they should be considered for alternative diagnoses.

③ Consider use of **inhaler** containing both a short-acting beta 2-agonist and an anticholinergic. Nighttime symptoms are frequently better controlled with a long-acting inhaled beta 2-agonist.

④ Consider adding a **theophylline trial** (slow release theophylline adjusted to the level of 5 to 12 µg/ml) with caution due to adverse effects. Nighttime respiratory symptoms are frequently controlled, but theophylline may lead to insomnia. Discontinue if a benefit is not evident within several weeks.

⑤ Consider high dose **inhaled glucocorticoids** in patients with severe COPD (FEV1 < 50 % predicted) and at least one exacerbation in the prior year. A combination of a high dose inhaled glucocorticoid and a long-acting beta 2-agonist may help provide long-term maintenance for symptomatic COPD and improve quality of life (QOL). The use of oral glucocorticoids for maintenance therapy is discouraged.

⑥ Short-acting inhaled beta 2-agonists (less than12 puffs/day) may continue to be used as needed. Inhaled long-acting beta 2-agonists should not be used as rescue therapy.

⑦ **Pulmonary rehabilitation** should be offered to patients who, despite optimal medical therapy, have reduced exercise tolerance and/or dyspnea limiting exercise.

EVIDENCE

Table 7. Effects of Commonly Used Medications on Clinical Outcomes

OUTCOME / Medication	Improve			Reduce Exacerbation	Other Outcomes	Reduce Mortality	Adverse Effects
	FEV1	Dyspnea	HRQOL				
Short-acting β 2-agonist (**SABA)**	B	B	NA	B		NA	++
Short-acting anticholinergic (**SAAC)** *Ipratropium bromide*	B	B	B	B	No effect on FEV1 rate of decline	NA	+
Long-acting β-agonists (**LABA)** *Formoterol* *Slameterol*	B	A	A (Formoterol) C (Slameterol)	NA (Formoterol) C (Slameterol)	No effect on FEV1 rate of decline	NA	++
Long-acting anticholinergic (**LAAC)** *Tiotropium*	B	A	A	A	Reduce hospitalization (B)	NA	+
Inhaled glucocorticoids (**ICS)** (in severe patients)	C	B	B	A	No effect on FEV1 rate of decline	NA	++
Theophylline	B	A	B	B		NA	+++
Combination SABA + SAAC	B	B	NA	B		NA	++
Combination SAAC +LABA	B	B	NA	B		NA	++
Combination LAAC +LABA	B	NA	NA	NA		NA	++
Combination LABA +Theophylline	B	B	B	NA		NA	+++
Combination ICS + LABA	B	A	A	A		NA	++

The content in each box indicates the strength of recommendation rating for explicit evidence based on RCTs showing positive effect of the drug on clinical outcomes. A,B,C=see Appendix A; NA=evidence not available; No=no effect; Adverse events: + minimal; ++ some; +++ important.

See Module C: Pharmacotherapy for specific recommendations and discussion of the supporting evidence.

Annotation F *Supplemental and Long-Term Oxygen Therapy*

4.2 Oxygen Therapy

BACKGROUND

As COPD progresses, patients often become hypoxic. These patients may exhibit signs of tissue hypoxia, such as pulmonary hypertension, cor pulmonale, erythrocytosis, edema from right heart failure, or impaired mental status. Long-term oxygen therapy (LTOT) reverses and prevents hypoxia, and has been shown to improve life expectancy in hypoxemic patients with chronic lung disease.

As COPD progresses, patients often become hypoxemic during exertion and experience a decline in exercise tolerance and performance, as well as an increase in dyspnea. Patients with advanced COPD, while having normal oxygen saturation during the daytime, may experience desaturation during sleep. Nocturnal desaturation may cause signs of tissue hypoxia.

ACTION STATEMENT

Patients with COPD should be periodically evaluated for the need of supplemental oxygen. Supplemental oxygen for those exhibiting signs of tissue hypoxia may increase survival of patients with severe COPD. Oxygen may also be used for exertional hypoxemia or nocturnal hypoxemia.

RECOMMENDATIONS

1. Oximetry should be considered in patients with COPD and should be performed in all patients with severe or very severe COPD (FEV1 < 50 percent predicted). [I]
2. Evaluation of nocturnal desaturation should be considered in patients with severe or very severe COPD (FEV1 < 50 percent predicted) who exhibit unexplained findings indicating nocturnal hypoxemia (e.g., polycythemia, pulmonary hypertension, and nocturnal restlessness). [I]
3. Oxygen therapy should be initiated in patients who have hypoxemia ($PaO_2 \leq 55$ mm Hg and/or $SaO_2 \leq 88$ percent). [A]
4. Oxygen therapy should be initiated in patients who have hypoxemia (PaO_2 of 56 to 59 mm Hg or $SaO_2 \leq 89$ percent) and signs of tissue hypoxia such as hematocrit above 55, pulmonary hypertension, or cor pulmonale. [A]
5. Oxygen therapy should be provided during exercise in stable patients with COPD with exertional hypoxemia ($SaO_2 \leq 88$ percent). [B]
6. Oxygen therapy should be considered for nocturnal hypoxemia ($SaO_2 < 88$ percent). [I]
7. Patients who started to receive oxygen therapy while unstable or on suboptimal medical therapy should be reevaluated within one to 3 months for need of long-term oxygen therapy (LTOT). If repeated evaluation indicates a patient no longer qualifies for oxygen, cessation of oxygen should be considered. [B]
8. Patients who continue to receive long-term oxygen therapy (LTOT) should be reevaluated at least annually for continued need of LTOT. [I]
9. Patients prescribed oxygen should be cautioned about the potentially extreme fire hazard of smoking or lighting cigarettes in the presence of oxygen. [I]

EVIDENCE STATEMENTS

4.2.1 Long-term oxygen therapy (LTOT)

Mortality is reduced and survival benefits have been shown in patients with chronic hypoxia when long-term oxygen therapy is administered.

- Patients who have a PaO_2 ≤55 mm Hg or lower and/or SaO_2 ≤ 88 percent will have mortality benefit with LTOT (Cranston et al., 2005; GOLD, 2005; MRC, 1981).
- Long-term home oxygen therapy improved survival in a selected group of patients with COPD with severe hypoxemia (arterial PaO_2 less than 55 mm Hg [8.0 kPa]). Oxygen therapy did not appear to improve survival in patients with mild to moderate hypoxemia or in those with only arterial desaturation at night (Cranston et al., 2005; Gorecka et al., 1997).
- Patients who have PaO_2 above 60 mm Hg did not demonstrate a mortality benefit with LTOT (Cranston et al., 2005).
- Patients with an FEV1 below 35 percent predicted would be considered at higher risk of developing hypoxia (NICE, 2004).
- LTOT for 15 to 18 hours per day can reverse the progression of pulmonary hypertension in patients with severe COPD (Weitzenblum et al., 1985). The British Medical Research Council (MRC) compared hypoxemic patients receiving oxygen for 15 hours per day with patients receiving no oxygen. Oxygen was associated with significant reduction in mortality (MRC, 1981). Continuous oxygen therapy for 24 hours/day demonstrated further reduction in mortality (NOTT, 1980).

4.2.2 Oxygen supplementation during exercise

Exercise tolerance is increased and dyspnea improved in patients with stable COPD with exertional desaturation when they are provided oxygen therapy during exercise.

- Two studies demonstrated an improvement in hypoxia as measured by a 6-minute walk with only one showing statistical significance (Eaton et al., 2002; Fujimoto et al., 2002).
- Oxygen therapy during exercise demonstrated improvement in dyspnea as measured by the Borg scale (Eaton et al., 2002; McDonald et al., 1995).
- Oxygen therapy during exercise demonstrated improvement in exercise tolerance measured by distance walked in meters (Eaton et al., 2002; Fujimoto et al., 2002; Garrod et al., 2000; McDonald et al., 1995; Rooyackers et al., 1997; Stein et al., 1982).
- A systematic review of randomized trials to determine the efficacy of ambulatory oxygen in patients with COPD during exercise identified thirty one studies (contributing 33 data sets), randomizing 534 participants to oxygen and placebo. Oxygen improved all pooled outcomes relating to endurance exercise capacity (distance, time, number of steps) and maximal exercise capacity. Oxygen improved breathlessness, SaO_2/PaO_2 and ventilation at isotime with endurance exercise testing. The results of the review may be affected by publication bias and the small sample sizes in the studies. Although positive, the findings of the review require replication in larger trials with more distinct subgroups of participants (Bradley & O'Neill, 2005).

4.2.3 Evaluation of nocturnal saturation

There are no clear data that patients who have nocturnal desaturation (SaO_2 < 90 percent) without evidence of severe daytime hypoxemia (PaO_2 ≤ 55 mm Hg) should have nocturnal oxygen therapy. Patients with

nocturnal desaturation should be monitored more closely as they are at risk for progression to daytime hypoxia.

Reversal of daytime hypoxia is known to result in an increased survival by 6 or more years. Furthermore, there are individuals with mild hypoxia that do not meet criteria for LTOT that may have worsening hypoxia at night. Although treatment of nocturnal hypoxia does not appear to improve survival, there is fairly high progression of nocturnal hypoxia to resting daytime hypoxia which would have survival implications.

- Nocturnal desaturation increases mortality (Kimura et al., 1998). However, nocturnal oxygen therapy does not appear to improve survival (Chaouat et al., 1999; Fletcher et al., 1992; NOTT, 1980).
- There was no difference in mortality between patients on nocturnal oxygen therapy and those in the control group (Chaouat et al., 1999).
- Nocturnal oxygen therapy does improve pulmonary hypertension (Fletcher et al., 1992).
- In a 5-year follow-up, approximately 29 percent of patients (12/41) with nocturnal desaturation went on to require LTOT (Chaouat et al., 1999).
- In the Nocturnal Oxygen Therapy Trial there was no change in survival at 12 months between patients on nocturnal oxygen therapy vs. LTOT; increased survival was observed with LTOT patients at 24 months (NOTT, 1980).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**R**
1	Patients who have $PaO_2 \leq 55$mm Hg and/or $SaO_2 \leq 88$ percent will have mortality benefit with LTOT.	Cranston et al., 2005 NOTT, 1980	I	Good	A
2	Oxygen administration slows progression of pulmonary hypertension in hypoxic patients with COPD.	MRC, 1981 NOTT, 1980 Weitzenblum et al., 1985	I	Good	A
3	Patients with mild to moderate hypoxemia without signs of tissue hypoxia did not demonstrate a survival benefit after 3 years of LTOT.	Gorecka et al., 1997 Cranston et al., 2005 Crockett et al., 2000	I	Good	D
4	Oxygen supplementation during exercise improves dyspnea, exercise tolerance, and performance.	Bradley & O'Neill, 2005 Eaton et al., 2002 Fujimoto et al., 2002 Garrod et al., 2000 McDonald et al., 1995 Rooyackers et al., 1997 Stein et al., 1982	I	Good	A
5	Nocturnal oxygen therapy improves pulmonary hypertension.	Fletcher et al., 1992	I	Good	A
6	Nocturnal oxygen therapy does *not* improve survival.	Chaouat et al., 1999	I	Good	A

QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)

Annotation G *Pulmonary Rehabilitation*

4.3 Pulmonary Rehabilitation

BACKGROUND

Despite optimal pharmacological management, patients with COPD frequently have persistent symptoms, reduced exercise tolerance, inability to perform their activities of daily living, and reductions in health and functional status. Pulmonary rehabilitation complements standard medical therapy and provides additional benefits in these areas.

Pulmonary rehabilitation is a multidisciplinary program of care that comprises a variety of interventions grouped into categories: exercise training, education, and psychological and nutritional counseling. This therapy may result in significant clinical improvement in multiple outcome areas, including reduction in dyspnea as well as improvements in exercise endurance, muscle strength, health status, and healthcare utilization. While the individual components have benefits, the greatest efficacy is derived from a comprehensive, integrated program. Pulmonary rehabilitation should be one part of disease management of symptomatic patients with COPD. Clear goals should be developed for each patient and communicated to the healthcare team. Comprehensive programs are delivered by multidisciplinary teams of healthcare professionals.

- The dyspnea and fatigue associated with physical activity leads patients with COPD to avoid such activities. As demanding physical activities are avoided, the cardiovascular system and peripheral muscles become deconditioned. These deconditioned muscles can be reconditioned with a structured exercise program. Such a structured exercise program can improve dyspnea, exercise endurance, maximal exercise, muscle strength, and QOL.

- The goals of an exercise program are to improve daily function, exercise tolerance, and the dyspnea accompanying daily activities and exercise.

- The effect of pulmonary rehabilitation on healthcare utilization is less clear; however, pulmonary rehabilitation that includes patient education may reduce inpatient length of stay.

- The major components and benefits that may be obtained with pulmonary rehabilitation are summarized in Tables 8 and 9 and are subsequently dealt with in detail in the sections of exercise training, dyspnea, education, nutritional, and psychological intervention.

Table 8. Major Elements of Pulmonary Rehabilitation

Elements of Pulmonary Rehabilitation	Anticipated Benefit	R
Exercise training	Improves exercise endurance and maximal exercise capacity	A
Strength training of upper and lower extremities	Improves strength of upper and lower extremities	A
Psychosocial and educational training	May be beneficial long term to improve QOL and coping with chronic disease, which may reduce utilization of care	B

R = Strength of Recommendation (See Appendix A)

Table 9. Outcomes from Implementing the Elements of Pulmonary Rehabilitation

Outcome	Anticipated Benefit	Quality of Evidence
Dyspnea	Dyspnea reduced	Meta-analysis of RCTs showing substantial benefit
Quality of Life (QOL)	Health-related QOL improved	Meta-analysis of RCTs showing substantial benefit
Healthcare Utilization	Reduced number of hospitalization days	Randomized trials and cohort studies indicating moderate effect
Survival	No effect	Insufficient evidence

ACTION STATEMENT

Pulmonary rehabilitation should be offered to all patients with COPD, who, despite optimal medical therapy, have reduced exercise tolerance and/or dyspnea limiting exercise. [A]

All patients with COPD with exertional symptoms should be offered a structured program with exercise training to reduce dyspnea and improve exercise tolerance and health-related QOL. [A]

Pulmonary rehabilitation programs with educational components and self-management training reduce healthcare use. [B]

RECOMMENDATIONS

Selection of Patients

1. Pulmonary rehabilitation should be considered for patients with COPD who have dyspnea, reduced exercise tolerance, a restriction in activities, or impaired health status. [A]

2. Pulmonary rehabilitation should be offered to all patients who consider themselves disabled by COPD (Level 3 and above on the dyspnea scale). [B]
3. Pulmonary rehabilitation is recommended for patients with reduced exercise tolerance and restricted activities because of dyspnea. [A]

Exercise Training

4. The exercise program should be supervised and should provide cardiovascular reconditioning with endurance and muscle strength training. [A]
5. The initial exercise program should be of sufficient length, duration, and frequency (see Appendix B: Structured Exercise Training Program). [B]
6. Endurance training should be performed to improve physical endurance. [A]
7. Lower limb strength training should be performed to improve exercise tolerance (walking, cycling); upper extremity training improves arm strength. [B]
8. In order to maintain benefits, subsequent exercise training is needed. [B]
9. As studies show conflicting results, respiratory muscle training is not recommended to be part of a rehabilitation exercise program. [B]

Education and Self-Management

10. Patients with COPD with a prior hospitalization should be referred for pulmonary rehabilitation. [A]
11. Educational components and self-management programs should be included in rehabilitation programs, as it can reduce COPD exacerbations, hospital admission, and length of stay. [B]
12. Self-management programs should include the following [B]:
    a. Skills training to optimally control the disease
    b. Education about medications and devices and how to use them properly
    c. Instruction on how to deal with exacerbations
    d. Other aspects of coping with the disease.
13. The benefit of education, psychosocial support, and nutritional therapy as a single intervention, without exercise, are less well-documented. [I]

RATIONALE

- Patients with COPD who have dyspnea and reduced QOL despite optimal pharmacotherapy can benefit from rehabilitation programs that improve exercise tolerance. As the care of patients with COPD is largely symptomatic, reductions in dyspnea and improvements in exercise tolerance and consequent QOL are the primary outcomes in respiratory rehabilitation.

- Pulmonary rehabilitation for patients with COPD improves dyspnea. The dyspnea accompanying exercise increases when the muscles and cardiovascular system are deconditioned. As cardiovascular deconditioning improves and muscle strength increases with the exercise component of pulmonary rehabilitation, dyspnea improves as a consequence.

- Due to dyspnea and muscle fatigue, patients with COPD frequently limit their physical exertion. Consequently a vicious cycle develops - muscle deconditioning occurs, exercise tolerance becomes even more limited, and the dyspnea accompanying exercise increases. Cardiovascular and muscle deconditioning can be reversed with exercise training. Endurance training improves endurance and strength training improves strength with some overlap between these entities. With improvements in

muscle function, endurance and strength increase and the sensation of dyspnea accompanying the exercise decreases. As exercise tolerance improves, the accompanying dyspnea is reduced and the overall health-related QOL improves.

- Rehabilitation programs may include education about the disease; medications available and how to use them; and presentation and management of COPD exacerbations. Educated patients may seek healthcare interventions earlier. The self-management programs that include these educational components as well as easy access to required COPD exacerbation treatment (antibiotics and/or systemic glucocorticoids) may reduce admission, emergency room visits, and/or primary care unscheduled visits.

EVIDENCE STATEMENTS

4.3.1 Effect on symptoms of dyspnea

- A meta-analysis of RCTs looked at the rehabilitation in patients with COPD in which QOL and/or functional or maximal exercise capacity were measured. Rehabilitation was defined as exercise training for at least four weeks with or without education and/or psychological support. Control groups received conventional community care without rehabilitation. Twenty-three RCTs met inclusion criteria which included an FEV1 below 70 percent predicted and was frequently at a mean of one liter or less. There were statistically significant improvements for all the outcomes. The authors concluded that rehabilitation forms an important component of the management of COPD (Lacasse et al., 2002).

- A meta-analysis of RCTs measuring the effect of rehabilitation on exercise capacity or shortness of breath included patients with symptoms and FEV1 below 70 percent predicted or FEV1/FVC below .70. The rehabilitation group received at least 4 weeks of rehabilitation and the control group received no rehabilitation. The rehabilitation groups of 20 trials (979 patients) did significantly better than the control groups on the walking test. The rehabilitation groups of 12 trials (723 patients) had significantly less shortness of breath than did the control groups. Trials that used respiratory muscle training only showed no significant difference between rehabilitation and control groups, whereas trials that used at least lower-extremity training showed that rehabilitation groups did significantly better than control groups on the walking test and shortness of breath. Patients with mild/moderate COPD benefit from short- and long-term rehabilitation, whereas patients with COPD who have FEV1 < 50 percent predicted may benefit from rehabilitation programs of at least 6 months (Salman et al., 2003).

- A total of 1,218 patients with severe emphysema underwent pulmonary rehabilitation before and after randomization to lung volume reduction surgery (LVRS) or continued medical management. Lung function, exercise tolerance, dyspnea, and QOL were evaluated at regular intervals. Significant ($p < 0.001$) improvements were observed consistently in exercise (cycle ergometry, 6-minute walk), dyspnea, and QOL. Patients who had not undergone prior rehabilitation improved more than those who had. In multivariate models, only prior rehabilitation status predicted changes after rehabilitation. Overall, changes after rehabilitation did not predict differential mortality or improvement in exercise (primary outcomes) by the treatment group (Ries et al., 2005).

- The purpose of this analysis was to evaluate the minimum clinically important difference for the UCSD Shortness of Breath Questionnaire (SOBQ). Subjects completed 2 disease-specific [SOBQ, Chronic Respiratory Questionnaire (CRQ)], and 2 generic Health-Related Quality of Life (HRQOL) measures [RAND-36 and Quality of Well-Being Scale (QWB)]. HRQOL measures correlated moderately with measures of maximum exercise tolerance but not with lung function (FEV1, FVC). HRQOL and exercise capacity improved significantly after pulmonary rehabilitation. A change of 5 units for the SOBQ appears to be a reasonable minimum clinically important difference for this instrument. HRQOL measures provide information that is complementary and distinct from physiological measures (Kupferberg et al., 2005).

- In a prospective, randomized, single-blind, one-year trial, patients with stable COPD (N = 103; age 66 +/- 8, females 57; FEV1 44.8 percent +/- 14 percent predicted) were randomly assigned to either: (1) Dyspnea self-management program (DM); (2) DM plus 4 supervised exercise sessions (DM-exposure); or (3) DM plus 24 supervised exercise sessions (DM-training). The dyspnea self-management program included individualized education and demonstration of dyspnea self-management strategies, an individualized home walking prescription, and biweekly nurse telephone calls. Outcomes were measured at baseline and every 2 months for one year. The DM-training group had significantly greater improvements in dyspnea during incremental treadmill tests and in exercise performance on the incremental and endurance treadmill tests at 6 and 12 months compared with the other 2 groups. The greater number of supervised exercise training sessions improved laboratory dyspnea and performance more than the other 2 doses of exercise. In the long term, the improvement in dyspnea with activities of daily living and physical functioning was similar for all 3 groups (Carrieri-Kohlman et al., 2005).

- The effects of a home-based pulmonary rehabilitation program on lung function, dyspnea, exercise tolerance, and QOL was examined in 23 Koreans with moderate to severe chronic lung disease. The outcome measures were FEV1, percent predicted, Borg score, 6-minute walking distance (6MWD), and chronic respiratory disease questionnaire (CRDQ). The experimental group (n=15) performed the 8-week home-based pulmonary rehabilitation program, composed of inspiratory muscle training, upper and lower extremity exercise, relaxation, and telephone visit. Patients in the control group (n=8) were only given educational advice. The experimental group showed a lower level of exertional dyspnea, more exercise tolerance, and greater improvement in health-related QOL than the control group ($p < 0.05$). Lung function was not statistically different. This study yielded evidence for the beneficial effects of a home-based pulmonary rehabilitation program (Oh, 2003).

4.3.2 Exercise training

- All patients with COPD with exertional symptoms, regardless of their Medical Research Council (MRC) dyspnea score, can benefit from a rehabilitation program (Wedzicha et al., 1998). Improvements in walking distance are not related to age, gender or FEV1 (ZuWallack et al., 1991). However, patients with the greatest ventilatory reserve at baseline have the greatest improvements with exercise training. In addition, patients with the largest prerehabilitation maximal exercise test showed the largest improvement (Moser et al., 1980). In a large multivariate model, it was shown that patients most likely to respond were those who had less ventilatory limitation, smaller reductions in exercise capacity, and reduced peripheral muscle strength; patients least likely to respond were those with extreme ventilatory impairment and little muscle weakness (Troosters et al., 2001).

- Pulmonary rehabilitation improves exercise capacity in COPD (Lacasse et al., 2003; Ries et al., 1995; Troosters et al., 2001). Specifically, rehabilitation has been shown to improve maximal exercise tolerance, peak oxygen uptake, endurance time during submaximal testing, and functional walking distance. These improvements are both statistically and clinically significant. In a large meta-analysis (Ries et al., 1995) reviewing rehabilitation exercise programs with different designs (disease severity, type of exercise, duration, intensity, etc.) it was concluded that the mean 6-minute walking distance (6MWD) improved 49 m (95% CI: 26-72 m) and that maximal exercise capacity increased 5.4 watts (95%CI: 0.5-10.2 watts). Statistically significant improvements in cycle ergometry and 6MWD were also seen with rehabilitation in the NETT trial (Ries et al., 2005) which enrolled 1,218 patients randomized to LVRS or medical management.

- The components of rehabilitation programs can be found in various position papers (Lacasse et al., 1997; The Chartered Society of Physiotherapy, 2003). The Cochrane meta-analysis (Lacasse et al., 2003) suggested a trend for greater improvement in the 6MWD if programs were supervised and longer. The minimum length of an effective program is estimated to be 2 months (Troosters et al., 2005). In one randomized study of patients with severe COPD undergoing an 8-week rehabilitation program improvements in exercise capacity were maintained for up to 6 months, but these were not sustained for one year (Bestall et al., 2003). No effective programs have yet been developed that maintain the effects over time (Ries et al., 2003).

- As cardiovascular conditioning and muscle strength improvement are postulated to be similar in patients with COPD and normal subjects, similar principles of optimal training as determined in normal subjects are thought to apply (American College of Sports Medicine, 1998; Pollock et al., 1977). Hence, training sessions need to be of adequate intensity, should last for 30 to 45 minutes each day and occur 3 to 5 days per week (Cooper, 2001; Troosters et al., 2005).

- As the response to training is dependent of the training stimulus, endurance training will improve endurance. Optimal cardiovascular endurance training should occur at 60 to 80 percent of the maximal exercise capacity. Greater physiological and cardiovascular benefits accrue in patients with COPD, if they exercise at higher intensities compared to those who exercise for a longer duration but lower intensity (Casaburi et al., 1991). Thus, in patients with moderate COPD, high intensity training results in improved benefits. High intensities may not be achievable in patients with severe disease (Maltais et al., 1997). In patients with severe disease and symptoms, limited exercise tolerance training at lower intensity can still result in physiological benefits (Clarke et al., 1996; O'Donnell et al., 1998; Ries et al., 1995).

- Patients with COPD often have weak peripheral muscles and there is an inverse relationship between muscle strength and dyspnea (Hamilton et al., 1995). Weight training can improve peripheral muscle strength and mass (Bernard et al., 1999). Strength and endurance training of the upper limbs improve arm function and strength but does not improve QOL or exercise tolerance (Bernard et al., 1999). There is controversial evidence that weight training of the lower limbs per se increases endurance (Casaburi et al., 2004, Troosters et al., 2005). However, other studies suggest that the addition of weight training increases endurance and the 6MWD and maximal exercise capacity (Bernard et al., 1999; Casaburi et al., 2004; Ortega et al., 2002; Simpson et al., 1992; Spruit et al., 2002; Troosters et al., 2005). Because of these complementary effects, weight training should be combined with endurance exercise in pulmonary rehabilitation programs.

- Respiratory muscle training has been examined in 2 meta-analyses and results were conflicting. The first meta-analysis (Smith et al., 1992) included 17 RCTs and found little evidence in support of respiratory muscle training, except for an increase in respiratory muscle strength as measured by maximum voluntary ventilation. The second meta-analysis (Lotters et al., 2002) concluded that inspiratory muscle training significantly improved inspiratory muscle strength and respiratory muscle endurance as measured and reduced dyspnea during loaded breathing. Thus, it can be concluded that respiratory muscle strength can be improved with respiratory muscle training. However, as it is not clear (Lotters et al., 2002; Troosters et al., 2005) that the inspiratory muscle training leads increased exercise tolerance or improved QOL, it can not be recommended.

4.3.3 Self-management and education

- Pulmonary rehabilitation that included exercise and education (about psychological issues related to chronic disability) did not reduce the number of patients hospitalized at least once, but reduced the total number of hospitalizations and length of stay in patients with COPD who were admitted to hospital (Griffiths et al., 2000).

- In the same study, analysis of the data excluding the patients who died in the hospital showed a nonsignificant difference (Griffiths et al., 2000).

- Pulmonary rehabilitation significantly reduced the number of COPD exacerbations. The number of hospital admissions was fewer in the rehabilitation group but did not reach statistical significance (Guell et al., 2000). Pulmonary rehabilitation nonsignificantly reduced the length of stay (Ries et al., 1995).

- Self-management programs that include education about the medications and how to use them, that guide behavior change, and provide emotional support reduced the number of admissions because of COPD exacerbations, hospital admission, and length of stay. This study also provided access to a nurse and a prescription for antibiotics and systemic glucocorticoids (Bourbeau et al., 2003; Gadoury

et al., 2005; Gallefoss & Bakke, 2000). A systematic review of existing literature up to October 2001 did not show reduction in healthcare use with educational programs. However, the studies reviewed in the systematic review did not include access to COPD exacerbation treatments (antibiotics and/or systemic glucocorticoids) (Monninkhof et al., 2003). Thus, it appears that healthcare utilization diminished with educational programs that had plans for treatment of COPD exacerbations.

4.3.4 Psychological-based intervention

- A systematic review summarized results of 6 RCTs in which an intervention including a psychological component had been performed and assessed. Included study interventions were: psychologically-based interventions to treat anxiety and/or panic in patients with COPD (e.g., exercise with education and stress management, pulmonary rehabilitation, relaxation, analytic psychotherapy, supportive psychotherapy, and counseling). The variation across studies involving relaxation and exercise suggests there is no convincing evidence that they are effective elements of a rehabilitation program in the treatment of anxiety in patients with COPD (Rose et al., 2002).

4.3.5 Nutrition

- A meta-analysis summarized data from 11 RCTs evaluating 352 participants: 2 studies included an inpatient component, 9 were entirely outpatient based, 7 studies included only undernourished patients, and 4 included undernourished and nourished participants. All except one used oral supplementation. The authors concluded that there is no evidence from this analysis that simple nutritional supplementation confers benefit to patients with COPD in terms of clinical outcomes such as lung function or health-related QOL, when nutritional supplementation is given as part of a multidisciplinary rehabilitation program including exercise therapy (Ferreira et al., 2000).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	Net Effect	R
1	Significant improvement in dyspnea and COPD QOL (measured by the CRDQ).	ACCP/AACVPR, 1997 Lacasse et al., 2002	I	Good	Substantial	A
2	Significant improvement in dyspnea and exercise capacity for patients with an FEV1 above 35 percent for long-and short-term programs. Patients with FEV1 below 35 percent required at least 6 months of program.	Salman et al., 2003	I	Good	Substantial	A
3	Rehabilitation improved dyspnea, QOL and exercise capacity.	Kupferberg et al., 2005 Ries et al., 2005	II-2	Fair	Substantial	B
4	Addition of supervised exercise to a dyspnea self-management program that included unsupervised home exercise (walking) led to greater improvement in	Carrieri-Kohlman et al., 2005	I	Good	Substantial	A

	Evidence	Source	QE	Overall Quality	Net Effect	R
	dyspnea, QOL and exercise capacity.					
5	Home-based rehabilitation improved exertional dyspnea (Borg), QOL (CRDQ) and exercise capacity.	Oh, 2003	I	Fair	Moderate	B
Exercise						
6	Rehabilitation improves exercise endurance and maximal exercise capacity.	ACCP/AACVPR, 1997 Lacasse et al., 2002	I	Good	Substantial	A
7	Rehabilitation improves peripheral muscle strength.	Troosters et al., 2005	I	Good	Moderate	B
8	Improvements in exercise tolerance are maintained for 6 months to a year.	Bestall et al., 2003	I	Fair	Small	C
9	Respiratory muscle training can improve strength of these muscles, but this does not lead to increased exercise tolerance or better QOL.	Lotters et al., 2002 Smith et al., 1992	I	Good	Zero	D
Education and Self-Management						
10	Pulmonary rehabilitation program with educational components and structured treatment recommendations for COPD exacerbation reduce healthcare use.	Bourbeau et al., 2003 Gadoury et al., 2005 Gallefoss & Bakke, 2000 Griffiths et al., 2000 Guell et al., 2000 Troosters et al., 2005	I	Fair	Moderate	B
11	Self-management programs (that include education about the medications and how to use them, guide behavior change, and provide emotional support) reduce COPD exacerbations, and hospital admissions, and length of stay.	Bourbeau et al., 2003 Gallefoss & Bakke, 2000 Guell et al., 2000 Monninkhof et al., 2003 Troosters et al., 2005	I	Fair	Moderate	B

QE = Quality of Evidence; Net Effect = Size of Intervention Effect; R = Strength of Recommendation (See Appendix A)

Annotation H *Other Interventions*

4.4 Mucolytics, Antioxidants, and Antitussives

BACKGROUND

Patients with COPD often have difficulty with expectoration. Suppression of an irritating cough may enhance patient comfort, but on the other hand could decrease clearance of secretions.

ACTION STATEMENT

The use of mucolytics, antioxidants, or antitussive medications has little evidence of any effect on lung function. [D]

RECOMMENDATIONS

1. N-acetylcysteine (NAC) is not recommended for patients with COPD for the purpose of cough suppression. [D]
2. N-acetylcysteine (NAC) 600 mg by mouth every day may be considered to decrease the number of exacerbations in selected patients with COPD with primarily chronic bronchitis who are not on inhaled glucocorticoids. [B]
3. Antioxidants, such as alpha-tocopherol (contained in vitamin E preparations) or beta-carotene, should not be administered to patients with COPD, as they have no significant effect on phlegm, cough, or dyspnea. [D]
4. Antitussives are not indicated in stable COPD. [I]

RATIONALE

- ü It is thought that enhanced expectoration of viscous sputum may reduce symptoms and exacerbations. The research on this hypothesis is controversial with positive effects generally small and confined to patients with chronic bronchitis.
- ü It is thought that antioxidants may decrease phlegm, exacerbations, and the decline in lung function and dyspnea, but studies so far have been negative.
- ü Cough suppression has been studied with various medications and results are inconclusive. There is also inconclusive evidence for benefits of protussive devices.

EVIDENCE STATEMENTS

- o N-acetylcysteine (NAC) has both mucolytic and antioxidant properties. Over a 3-year period, patients with COPD randomly assigned to NAC (600 mg/day) or placebo had no difference in the rate of decline in lung function or exacerbations. A subgroup analysis suggested that a decrease in exacerbations occurs in patients with chronic bronchitis who are not on inhaled glucocorticoids with NAC from 1.29 to 0.96 per year compared to placebo. Hyperinflation may also be reduced with NAC (Decramer et al., 2005).

- Other review articles on NAC, iodinated glycerol, and other mucolytics concluded that exacerbations were reduced in chronic bronchitis (Grandjean et al., 2000; Poole & Black, 2003, 2006; Stey et al., 2000).

- Large studies have determined that there is no significant effect on dyspnea, phlegm, or cough with the administration of the antioxidants alpha-tocopherol or beta-carotene (Rautalahti et al., 1997; The ATBC Cancer Prevention Study Group, 1994).

- Randomized clinical trials on cough suppression have numerous methodological problems (underpowering, small sample size, biases, etc.) making interpretation difficult (NICE, 2004).

- There are no adequate trials with protussive devices in COPD.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	R
1	There is *no* effect of NAC on rate of decline in FEV1 or exacerbations in COPD.	Decramer et al., 2005	I	Good	D
2	Exacerbations may be decreased with NAC 600 mg by mouth every day or other mucolytics in patients with chronic bronchitis not on inhaled glucocorticoids.	Decramer et al., 2005 Grandjean et al., 2000 Poole & Black, 2003; 2006 Stey et al., 2000	I	Good	B
3	The antioxidants alpha-tocoferol and beta-carotene are *not* effective in COPD.	ATBC Cancer Prevention Study Group, 1999 Rautalahti et al., 1997	I	Good	D
4	Antitussives *not* effective in COPD.	NICE, 2004	III	Poor	I

QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)

4.5 Alpha l-Antitrypsin Augmentation Therapy

BACKGROUND

Alpha 1-antitrypsin (AAT) deficiency is a genetic disorder that predisposes the patient to early-onset emphysema and chronic liver disease. Whereas AAT is produced in the liver, it functions in the lung to protect it against proteolytic damage from neutrophil elastase. AAT deficiency accounts for less than one percent of COPD. It should be suspected if there is early-onset emphysema with no or only a brief history of smoking, a family history of COPD, or a predominance of basilar emphysema. Smoking in the presence of AAT deficiency can accelerate the decline in lung function. If an AAT deficiency is suspected, a serum AAT level should be obtained. A level below 80 mg/dl by radial immunodiffusion is diagnostic of homozygous alpha1-antitrypsin deficiency.

ACTION STATEMENT

Patients with COPD due to confirmed or suspected alpha 1-antitrypsin (AAT) deficiency should be referred to a pulmonary subspecialist. [C]

Alpha 1-antitrypsin augmentation therapy should be considered in patients with severe hereditary alpha 1-

antitrypsin (AAT) deficiency and established emphysema. [C]

RECOMMENDATIONS

1. Patients with COPD due to alpha1-antitrypsin (AAT) deficiency should be provided the usual COPD therapy – smoking cessation, preventive vaccinations, bronchodilators, supplemental oxygen if indicated, and pulmonary rehabilitation. [I]
2. Patients with severe alpha1-antitrypsin (AAT) deficiency who have stopped smoking and with moderate to severe COPD (FEV1 30 to 60 percent predicted) should be considered for AAT augmentation therapy. Furthermore, benefits are not clear for those with FEV1 either below 30 percent or above 60 percent predicted. [C]
3. Augmentation therapy is not indicated for patients without emphysema. [D]

RATIONALE

- The goal of infusion of AAT (purified from pooled human plasma) is to raise and maintain the serum AAT concentration above the protective threshold for progression of emphysema. Such infusions could slow the decline in lung function, reduce infection rates, and enhance survival. Although some of these effects were found in some studies, there are conflicting findings and hence, the interpretation is open to question. Therefore, uncertainty about the cost-effectiveness of this expensive treatment (~ $29,000 to $65,000 per patient annually) remains.

EVIDENCE STATEMENTS

- Three purified AAT preparations obtained from pooled human plasma (Aralast, Prolastin, and Zemaira) have been approved by the FDA. It has been shown that weekly infusions of AAT can raise and maintain AAT levels above the protective threshold for progression of emphysema. There is also biochemical evidence that the functional capacity of the infused AAT is preserved (ATS/ERS, 2003; Stoller & Abboussouan, 2005).

- Clinical evidence of efficacy (rate of decline in FEV1, exacerbations, and mortality) has primarily been obtained from observational cohort studies (Alpha-1-Antitrypsin Deficiency Registry Study Group, 1998; ATS/ERS, 2003; Stoller & Abboussouan, 2005) and one small double-blind, placebo-controlled, randomized study (Dirksen et al., 1999). The largest (n=1129) observational study (Alpha-1-Antitrypsin Deficiency Registry Study Group, 1998) suggested augmentation therapy was associated with a reduced mortality rate (RR=0.64, 95 CI: 0.43-0.94; p=0.02) and (in a subgroup analysis) a reduced rate of decline in FEV1 of 27 ml/year in patients with FEV1 35 to 49 percent predicted. In the small (n=56) randomized study (Dirksen et al., 1999) no difference in rate of decline in FEV1 was found with augmentation therapy, but the CT densitometry suggested a trend toward a slower decline in lung tissue (p=0.07) with augmentation therapy.

- Despite the uncertainties in the interpretation of the data, international societies (American, Canadian, and European) have recommended use of augmentation therapy in selected cases (Stoller & Abboussouan, 2005).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	R
1	AAT augmentation therapy may slow the decline in lung function, reduce infection rates, and enhance survival in patients with emphysema and severe AAT deficiency.	Alpha-1-Antitrypsin Deficiency Registry Study Group, 1998 ATS/ERS, 2003 Dirksen et al., 1999 Stoller & Abboussouan, 2005	II-2	Fair	C
2	AAT therapy may be most effective in patients with FEV1 30 to 60 percent predicted and is probably ineffective in patients outside that range.	Alpha-1-Antitrypsin Deficiency Registry Study Group, 1998	II-2	Good	C

QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)

4.6 Lung Volume Reduction Surgery

BACKGROUND

The goal of lung volume reduction surgery (LVRS) is to relieve disabling dyspnea in patients in whom emphysema has limited activities of daily living despite optimal medical management. Following surgery, improvement has been noted in lung elastic recoil, respiratory function, ventilation/perfusion matching, improved diaphragmatic function, and cardiovascular function. A variety of surgical approaches and reduction techniques have been used. In view of the potential for serious morbidity and mortality, all surgical treatments for COPD require careful assessment by an experienced thoracic medical and surgical team.

LVRS is a high-risk surgery with complex postoperative care. Its success depends on proper screening of the referred subjects, pulmonary rehabilitation before and after the surgery, and comprehensive postoperative care. LVRS includes several steps. Familiarity with screening, preoperative pulmonary rehabilitation, education, perioperative care, surgical experience, and postoperative pulmonary rehabilitation and medical care are all important components of successful programs. Thus, referral to a center with relevant experience is important.

ACTION STATEMENT

Consider lung volume reduction surgery (LVRS) in carefully selected patients with very severe COPD who comply with selection criteria used in studies demonstrating benefit from this intervention. [A]

RECOMMENDATIONS

1. Referral for lung volume reduction surgery (LVRS) may be considered for patients with very severe COPD if they meet the following criteria [A]:
    a. High-resolution computed tomography (CT) confirming bilateral emphysema
    b. Total lung capacity before rehabilitation and after treatment with bronchodilators is greater than 100 percent predicted and residual volume is greater than 150 percent predicted
    c. Post-bronchodilator FEV1 is less than 45 percent predicted

d. $PaCO_2$ less than 60 mm Hg, and PaO_2 greater than 45 mm Hg

e. Patient has completed a pulmonary rehabilitation program.

2. Lung volume reduction surgery (LVRS) should not be considered in patients whose FEV1 is less than 20 percent predicted and who either have homogenous emphysema or carbon monoxide diffusing capacity that is less than 20 percent or have non-upper lobe emphysema and high baseline exercise capacity. [D]

3. Lung volume reduction surgery (LVRS) should only be performed in medical centers with appropriately trained surgeons and availability of necessary equipment. [I]

RATIONALE

- As COPD progresses, the accompanying emphysema typically becomes worse, lung compliance increases, and consequently, lung volumes increase and airflow (FEV1) decreases. Resection of these redundant, dilated airspaces via pneumectomy or lung volume reduction surgery improves compliance and may reexpand normal lung tissue that had become atelectatic due to local surrounding bullous emphysematous changes. Improved lung compliance and reduced hyperinflation can lead to improvements in spirometry, arterial blood gases, dyspnea, and exercise tolerance.

EVIDENCE STATEMENT

- A systematic review (Stirling et al., 2001) concluded that when LVRS was compared with medical management, at 2 years LVRS was associated with a higher FEV1 and at least equivalent survival. The use of staple excision of selected areas of the lung appeared to be more efficacious than laser ablation. In highly selected patients with emphysema, LVRS is deemed an acceptable treatment. To fully evaluate the safety and efficacy of LVRS, outcomes beyond 2 years must be included.

- A meta-analysis (Berger et al., 2005) summarized the results of 6 studies (306 patients) with 3- to 12-month follow-up. Key baseline features of these RCTs populations included heterogeneous emphysema, comparable inclusion/exclusion criteria and, in retrospect, low-walking capacity as measured by the 6-minute walk distance (6MWD). This profile closely resembles NETT's predominantly upper lobe-low exercise tolerance emphysema cohort. The LVRS arm of the meta-analysis population showed better results than the medical cohort in terms of pulmonary function (FEV1 $p < 0.0001$; FVC $p < 0.0001$; residual volume $p < 0.0001$; total lung capacity $p = 0.004$), gas exchange (arterial partial pressure of oxygen $p < 0.0001$) and exercise capacity (6MWD $p = 0.0002$). The authors concluded that a selected subset of patients with advanced, heterogeneous emphysema and low exercise tolerance experienced better outcomes from LVRS than from medical therapy.

- Results from the NETT showed that a subgroup of patients with predominantly upper-lobe emphysema and low baseline exercise capacity might have improved survival as well (NETT Research Group, 2001).

- The National Emphysema Treatment Trial (NETT) (Fishman et al., 2003), comparing LVRS vs. medical therapy of 1,218 patients, including pulmonary rehabilitation, has shown:

  - There was benefit from LVRS over 24 months.

  - LVRS increased the chance of improved exercise capacity, lung function, dyspnea, and QOL but did not confer survival advantage vs. medical therapy alone. Most patients' improvements returned to baseline after 2 years.

- LVRS increased mortality compared to optimum medical therapy in patients with COPD with FEV1 below 20 percent predicted and homogenous emphysema in a chest CT scan or diffusing capacity below 20 percent.

- LVRS demonstrated increased mortality and no functional improvement for patients with non-upper lobe.

- Another RCT involving 55 patients with heterogeneous emphysema found that LVRS improved health-related QOL, lung function, and exercise capacity that were sustained at 12 months compared to no surgery (Goldstein et al., 2003).

- Two additional years of follow-up provide valuable information regarding durability after LVRS compared to medical therapy in the NETT group. Updated analyses (4.3 versus 2.4 years median follow-up), including 40 percent more patients with functional measures 2 years after randomization, demonstrates an overall survival advantage for LVRS, with a 5-year risk ratio for death of 0.86 ($p = 0.02$). Improvement was more likely in the LVRS than in the medical group for maximal exercise through 3 years and for health-related QOL (St. George's Respiratory Questionnaire [SGRQ]) through 4 years. The upper-lobe patients with low exercise capacity demonstrated improved survival (5-year RR, 0.67; $p = 0.003$), exercise throughout 3 years ($p < 0.001$), and symptoms (SGRQ) through 5 years ($p < 0.001$ years 1 to 3, $p = 0.01$ year 5). Upper-lobe-predominant and high-exercise-capacity LVRS patients obtained no survival advantage but were likely to improve exercise capacity ($p < 0.01$ years 1 to 3) and SGRQ ($p < 0.01$ years 1 to 4) (Naunheim et al., 2006).

- Eight high-quality studies (1,663 participants) met the entry criteria of a systematic review (including the NETT trial accounting for 73% of the participants recruited). Ninety day mortality was significantly greater in all those who underwent LVRS (odds ratio 6.57 (95% CI 3.34 to 12.95; 4 studies, N = 1,415). A subgroup analysis by risk status suggested that there was a subgroup of participants who were consistently at a significant risk of death, although this was only measured in one large study. Improvements in lung function, QOL, and exercise capacity were more likely with LVRS than with usual follow-up. The findings from the NETT trial indicated that in patients who survive up to three months post-surgery, there were significant improvements in health status and lung function outcomes in favor of surgery compared with usual medical care. Patients identified post hoc as being of high-risk of death from surgery were those with particularly impaired lung function and poor diffusing capacity and/or homogenous emphysema (Tiong et al., 2006).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	R
1	LVRS yielded a survival advantage only for patients with upper lobe emphysema and low baseline exercise capacity.	Fishman et al., 2003	I	Good	B
2	LVRS demonstrated increased mortality and no functional improvement for patients with non-upper lobe emphysema.	Berger et al., 2005 Fishman et al., 2003	I	Good	D
3	LVRS improved exercise capacity and QOL after 2 years among patients with upper lobe emphysema.	Fishman et al., 2003 Naunheim et al., 2006 Tiong et al., 2006	I	Good	A
4	LVRS increases mortality compared to optimum medical therapy in patients with COPD with FEV1 < 20 percent and homogenous emphysema in chest CT scan or diffusing capacity < 20 percent.	Fishman et al., 2003	I	Good	D

QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)

4.7 Lung Transplantation Surgery

BACKGROUND

During the past few decades multiple surgical interventions have been suggested to improve symptoms in patients with COPD. These include bullectomy, lung volume reduction surgery, and lung transplantation in appropriately selected patients with very advanced COPD. Lung transplantation is limited by the shortage of donor organs, which has led some centers to adopt the single lung technique.

ACTION STATEMENT

For patients with severe symptoms, despite maximal medical therapy, lung volume reduction surgery and transplantation may be an option. [C]

RECOMMENDATIONS

1. Lung transplantation may be considered in selected patients with advanced COPD. The choice of single lung transplantation (SLT) or bilateral lung transplantation (BLT) for COPD remains controversial. [C]

Patient Selection

In selecting candidates, several issues must be considered, including the patient's pulmonary disability, projected survival without transplantation, comorbid conditions and patient preferences. There are general selection guidelines for candidate for lung transplantation in COPD (Orens, 2006); however, these are subject to change and the practitioner should consult with an appropriate specialist, usually pulmonary, before referring a patient.

Relative contraindications:

- Age older than 65 years. Older patients have less optimal survival, likely due to comorbidities, and therefore, recipient age should be a factor in candidate selection. Although there cannot be

endorsement of an upper age limit as an absolute contraindication (recognizing that advancing age alone in an otherwise acceptable candidate with few comorbidities does not necessarily compromise successful transplant outcomes), the presence of several relative contraindications can combine to increase the risks of transplantation above a safe threshold.

- Critical or unstable clinical condition (e.g., shock, mechanical ventilation or extra-corporeal membrane oxygenation).
- Severely limited functional status with poor rehabilitation potential.
- Colonization with highly resistant or highly virulent bacteria, fungi, or mycobacteria.
- Severe obesity defined as a body mass index (BMI) exceeding 30 kg/m^2.
- Severe or symptomatic osteoporosis.
- Mechanical ventilation. Carefully selected candidates on mechanical ventilation without other acute or chronic organ dysfunction, who are able to actively participate in a meaningful rehabilitation program, may be successfully transplanted.
- Other medical conditions that have not resulted in end-stage organ damage, such as diabetes mellitus, systemic hypertension, peptic ulcer disease, or gastroesophageal reflux should be optimally treated before transplantation. Patients with coronary artery disease may undergo percutaneous intervention before transplantation or coronary artery bypass grafting concurrent with the procedure.

Absolute contraindications:

- Malignancy in the last 2 years, with the exception of cutaneous squamous and basal cell tumors. In general, a 5-year disease-free interval is prudent. The role of lung transplantation for localized bronchioalveolar cell carcinoma remains controversial.
- Untreatable advanced dysfunction of another major organ system (e.g., heart, liver, or kidney). Coronary artery disease not amenable to percutaneous intervention or bypass grafting, or associated with significant impairment of left ventricular function, is an absolute contraindication to lung transplantation, but heart-lung transplantation could be considered in highly selected cases.
- Non-curable chronic extrapulmonary infection including chronic active viral hepatitis B, hepatitis C, and human immunodeficiency virus.
- Significant chest wall/spinal deformity.
- Documented nonadherence or inability to follow through with medical therapy or office follow-up, or both.
- Untreatable psychiatric or psychologic condition associated with the inability to cooperate or comply with medical therapy.
- Absence of a consistent or reliable social support system.
- Substance addiction (e.g., alcohol, tobacco, or narcotics) that is either active or within the last 6 months.

COPD disease-specific guidelines for candidate selection for lung transplantation:

Guidelines for Referral

- BODE index exceeding 5 (Celli et al., 2004) (Stands for BMI, Obstructive pulmnary function, dyspnea by MMRC and Exercise by 6-minute walk distance)

Guidelines for Transplantation

- Patients with a BODE index of 7 to 10 or at least 1 of the following:
    - History of hospitalization for exacerbation associated with acute hypercapnia (PCO_2 exceeding 50 mm Hg).
    - Pulmonary hypertension or cor pulmonale, or both, despite oxygen therapy.
    - FEV1 of less than 20 percent and either DLCO of less than 20 percent or homogenous distribution of emphysema.

EVIDENCE STATEMENTS

- The common complications seen in COPD patients after lung transplantation, apart from operative mortality, are acute rejection and bronchiolitis obliterans, CMV, other opportunistic fungal (Candida, Aspergillus, Cryptococcus, Carini) or bacterial (Pseudomonas, Staphylococcus species) infections, lymphoproliferative disease, and lymphomas (Theodore & Lewiston, 1990).

Pulmonary function

- Following single lung transplantation for COPD, FEV1 is expected to rise to approximately 50 percent of the predicted normal value and FVC to approximately 70 percent of the predicted normal value (Bando et al., 1995; Mal et al., 1994 , Patterson et al., 1991).

- Following bilateral lung transplantation, FEV1 increases to 78 to 85 percent and FVC to 66 to 92 percent of the predicted normal values (Bando et al., 1995; Williams et al., 1990).

Survival

- Average actuarial survival following lung transplantation for recipients with COPD is 81.7, 61.9 and 43.4 percent at 1, 3 and 5 yrs (UNOS online data base).

- Compared to patients with other cardiopulmonary diseases, patients with emphysema exhibit the best overall survival after transplantation (Hosenpud et al., 2001).

- Data on whether transplantation actually confers a survival advantage compared to the natural history of the disease are conflicting (Charman et al., 2002; Mal et al., 1994).

- By 5 years following lung transplantation, the prevalence of chronic allograft rejection (obliterative bronchiolitis), the leading cause of long-term morbidity and mortality, is as high as 50 to 70 percent among survivors (Heng et al., 1998).

For further information, see: American Thoracic Society COPD management recommendations at: http://www.thoracic.org/COPD/10/surgery_for_copd.asp .

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**R**
1	Lung transplantation results in highly selected patients improved: pulmonary function, exercise capacity.	Arcasoy & Kotloff, 1999 Bando et al., 1995 Mal et al., 1994	III	Fair	C
2	Lung transplantation results in highly selected patients improved quality of life	Orens et al., 2006	III	Good	C
3	Lung transplantation results in highly selected patients improved survival.	Hosenpud et al., 1998	III	Poor	I

QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)

5 Management of Associated Conditions

Annotation I *Evaluate and Provide Appropriate Treatment for Cardiovascular Disease*

5.1 Pulmonary Hypertension and Cor Pulmonale in COPD

BACKGROUND

Patients with advanced COPD may develop pulmonary hypertension (defined as a mean PA pressure > 25 mm Hg). The pulmonary hypertension is to various degrees the result of hypoxic-induced pulmonary vasoconstriction, vascular remodeling, and destruction of the pulmonary capillary bed. The pulmonary artery pressure may be estimated non-invasively with Doppler echocardiography, but is more accurately and reliably measured via right heart catheterization – the gold standard.

Patients with COPD with pulmonary hypertension may also develop right heart failure – cor pulmonale. Cor pulmonale is defined as right ventricular hypertrophy (and right heart failure) secondary to lung disease. COPD is the most common cause of cor pulmonale. As a clinical syndrome it is characterized by fluid retention, peripheral edema, and raised venous pressure in patients who have no other cause of ventricular dysfunction. The increased pulmonary artery pressure, hypoxemia, and renal mechanisms lead to fluid retention and pedal edema – signs of right heart failure, but that are often mistaken for and treated as left heart failure.

The diagnosis of cor pulmonale is made from symptoms (fatigue, lethargy, dyspnea on exertion, and exertional syncope), signs (loud P2, RVH, raised CVP, and pedal edema), and cardiopulmonary assessment (CXR, ECG, Doppler echocardiogram, MRI, and ultimately right heart catheterization).

ACTION STATEMENT

Patients with pulmonary hypertension and/or cor pulmonale should be referred to a specialist for the management of COPD and be provided long-term oxygen, if needed, and optimized. [A]

RECOMMENDATIONS

1. Patients with diagnosed or suspected cor pulmonale should be referred to a pulmonary subspecialist. [C]
2. Patients with pulmonary hypertension and/or cor pulmonale should be assessed for hypoxemia and provided long-term oxygen, if needed. [A]
3. Bronchodilators should be optimized and edema treated cautiously with diuretics. [C]
4. The management of cardiovascular diseases in patients with COPD should follow existing guidelines, including routine treatment with beta-blockers. [B]

RATIONALE

- As hypoxic-induced pulmonary vasoconstriction plays a role in the pathogenesis of pulmonary hypertension, this reversible increase in pulmonary artery pressure can be corrected with oxygen therapy. Long-term oxygen administration slows the progression of pulmonary hypertension in hypoxemic patients with COPD. Reduction of fluid overload with cautious use of diuretics can decrease right ventricular distension and improve right and left ventricular function. Increasing right

ventricular contractility with digoxin is not effective. Directly decreasing pulmonary artery pressure with vasodilators seems rational, but can lead to worsening gas exchange and benefits have yet to be shown.

- Use diuretics judiciously in cor pulmonale. Although cautious use of diuretics can reduce volume overload of the right ventricle and thereby improve overall ventricular function, over enthusiastic usage of diuretics also can induce a metabolic alkalosis with concomitant development of hypercapnia, consequent hypoxemia, increased pulmonary artery pressure, and further fluid retention – resulting in a vicious cycle.

- Consider treatment with vasodilators to reduce pulmonary artery pressure. Studies with calcium channel blockers have been disappointing and use of these drugs is not recommended. Assessment of efficacy of newer vasodilator drugs [e.g., endothelin-receptor antagonists (bosentan) or PDE-5 inhibitors (sildenafil)] awaits further studies. There is inadequate information at this time to recommend these drugs.

EVIDENCE STATEMENTS

- Oxygen administration relieves hypoxic-induced pulmonary vasoconstriction (Wiedeman & Matthay, 1990). Long-term oxygen administration to hypoxemic patients will reduce the progressive rise in pulmonary artery pressure (MRC Working Party, 1981) and might even reduce that pressure slightly (Nocturnal Oxygen Therapy Trial Group, 1980), although not to normal. This beneficial decrease in pressure with long-term oxygen therapy was also seen in a long follow-up study in a small group of patients (Weitzenblum et al., 1985). Oxygen also reduces the abnormal rise in pulmonary artery pressure that occurs during exercise in these patients (Timms et al., 1985) and thereby prevents the fall in right ventricular ejection fraction (MacNee et al., 1985).

- Pulmonary hypertension and cor pulmonale usually occur in patients with very severe COPD (FEV1 < 30 percent predicted) with hypoxemia and hypercapnia (MacNee, 1994). It carries a poor prognosis (Biernacki et al., 1988; Oswald-Mammosser et al., 1995). The severity of the pulmonary hypertension correlates with the degree of airflow obstruction and impairment in gas exchange (Scharf et al., 2002; Weitzenblum et al., 1984). Optimal use of bronchodilators will improve spirometry and gas exchange and thereby may minimize the development of pulmonary hypertension.

- There are no trials to support the use of diuretics in cor pulmonale. If the right ventricle is fluid overloaded, this distension may be reduced with diuretics and hence any septal deviation would be reduced and left ventricular function improved. On the other hand, over-diuresis can reduce cardiac output. Over-diuresis may also cause a metabolic alkalosis with consequent development of hypercapnia and hypoxemia with resultant increases in pulmonary artery pressure, so that a vicious cycle can occur. Thus, diuretics have to be employed with caution (Brijker et al., 2002).

- Digoxin is of no benefit in cor pulmonale per se (Brown et al., 1984; Green & Smith, 1977).

- Various vasodilators have been used to reduce pulmonary artery pressure. Small studies have been performed with ACE inhibitors, nitrates, hydralazine, PGE1 and calcium channel blockers (Wiedemann & Matthay, 1990). With calcium channel blockers, small decreases in pulmonary artery pressure (~ 10 to 20 percent) have been documented, but exercise capacity was not affected and long-term efficacy was disappointing (Agostoni et al., 1989; Bratel et al., 1986; Dal Nogare & Rubin, 1986; Singh et al., 1985). Furthermore, gas exchange was deleteriously affected with decreases in PO_2. Therefore, these drugs cannot be recommended. Nitric oxide when given in the inhaled form acts as a selective pulmonary artery vasodilator. It reduces pulmonary artery pressure but also deleteriously affects gas exchange (Barbera et al., 2003). As it is difficult to administer and as there are no long-term results, its use cannot be recommended. Currently, there is no systematic information on endothelin-receptor antagonists (e.g., bosentan) in COPD. A randomized, placebo-

controlled trial of the efficacy of the PDE-5 inhibitor (sildenafil) in COPD has started, but further recommendations have to await the results of this trial.

- Beta-blocker therapy has a proven mortality benefit in patients with hypertension, heart failure and coronary artery disease. These drugs have traditionally been considered contraindicated in patients with COPD. The effect of cardioselective beta-blockers on the respiratory function of patients with COPD was reviewed in a Cochrane review to identify randomized blinded controlled trials from 1966 to May 2005 that studied the effects of cardioselective beta-blockers on the forced expiratory volume in 1 second (FEV1) or symptoms in patients with COPD. In eleven studies of single-dose treatment and 9 of treatment for longer durations, ranging from 2 days to 12 weeks, cardioselective beta-blockers, given as a single dose or for longer duration, produced no change in FEV1 or respiratory symptoms compared to placebo, and did not affect the FEV1 treatment response to beta 2-agonists. A subgroup analysis revealed no change in results for those participants with severe chronic airways obstruction or for those with a reversible obstructive component (Salpeter et al., 2005).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	R
1	Oxygen administration slows progression of pulmonary hypertension in hypoxic patients with COPD.	MRC Working Group, 1981 NOTT, 1980 Weitzenblum et al., 1985	I	Good	A
2	Use diuretics with caution.	Brijker et al., 2002	II-2	Fair	C
3	Digoxin is not useful in cor pulmonale.	Brown et al., 1984 Green & Smith, 1977	II-2	Fair	D
4	Vasodilators can decrease pulmonary artery pressure but may worsen gas exchange. Long-term efficacy of calcium channel blockers is marginal and unknown for newer drugs such as sildenafil.	Agostoni et al., 1989 Barbera et al., 2003 Bratel et al., 1986 Dal Nogare & Rubin, 1986 Singh et al., 1985	II-2	Fair	D
5	Cardioselective beta-blockers do not produce adverse respiratory effects.	Salpeter et al., 2005	I	Good	A

QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)

Annotation J *Evaluate and Provide Appropriate Treatment for Depression or Anxiety*

5.2 Mental Health (Depression and Anxiety)

BACKGROUND

COPD leads to disabling and distressing symptoms. Patients often become socially isolated and give up enjoyable activities. These factors may lead to the development of anxiety and or depression. The signs and symptoms of depression and anxiety may be similar to those of COPD itself and therefore may be overlooked. The presence of depression or anxiety has negative impact on the patient's QOL. The depressed mood reduces the patient's ability to cope with physical symptoms that are becoming less tolerable, and as a result can lead to increased depression. Treatment options for patients with COPD include pharmacotherapy and psychotherapy as a part of a pulmonary rehabilitation program.

ACTION STATEMENT

Healthcare providers should be alert to the possibility of presence of depression in patients with COPD and treat them according to depression guidelines.

RECOMMENDATIONS

1. Patients with COPD should be screened for depression and anxiety using validated screening and assessment tools. [B]
2. Patients diagnosed with depression or anxiety should be treated with pharmacotherapy and psychotherapy suitable for patients with COPD and the patient's age. [B]
3. Sedative anxiolytic for the treatment of anxiety should be avoided in patients with severe COPD. [D]

See the VA/DoD Clinical Practice Guideline for Major Depressive Disorder.

EVIDENCE STATEMENTS

- Depression and anxiety are more common in patients with severe COPD and particularly in those who are hypoxemic or severely dyspneic (Kunik et al., 2005).
- A variety of assessment tools to evaluate depression and anxiety have been used, but some have not been validated for use in patients with chronic disease (NICE, 2004).
- Trials of nortriptyline, buspirone, and sertraline have been found to reduce symptoms of anxiety. Similarly, cognitive-behavioral programs that focus on relaxation and changes in thinking also produced declines in anxious symptoms. Finally, multicomponent pulmonary rehabilitation programs can also result in reductions in anxious symptoms. Patients who participate in pulmonary rehabilitation programs that include psychotherapy have a reduction in anxiety and depression (Brenes, 2003).
- Patients found to be depressed or anxious should be treated with conventional pharmacotherapy (NICE, 2004).
- Nortriptyline treatment was found to be superior to placebo for treatment of depression (Borson et al., 1992; NICE, 2004).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	R
1	Nortriptyline, buspirone, and sertraline have been found to reduce symptoms of anxiety. Cognitive-behavioral programs that focus on relaxation and changes in thinking also produced declines in anxious symptoms.	Brenes, 2003	II	Good	B
2	Multicomponent pulmonary rehabilitation programs can result in reductions in anxious symptoms.	NICE, 2004 Brenes, 2003	I	Fair	B

QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)

Annotation K *Evaluate and Provide Appropriate Treatment for Nutrition*

5.3 Malnutrition

BACKGROUND

Malnutrition is present in patients with stable COPD independent of their degree of airflow limitation. Malnutrition is more prevalent among patients with emphysema. The prevalence of malnutrition among inpatients is even higher, approaching 50 percent. Malnutrition in COPD has been associated with increased mortality.

ACTION STATEMENT

Malnutrition and weight loss in patients with COPD carry a poor prognosis and should be assessed and intervention considered.

RECOMMENDATIONS

1. Body Mass Index (BMI) should be monitored in patients with COPD. [B]
2. Patients who are losing weight over time (BMI $\leq$ 21 kg/m^2) should be referred for dietary evaluation and advice. [B]
3. Alternate causes of weight loss associated with COPD, such as lung cancer and lung infection, should be considered. [I]
4. Dietary supplementation in combination with exercise and nutritional consultation should be considered in the management of patients with COPD with weight loss or malnutrition. [B]

RATIONALE

- Malnutrition is prevalent in patients with COPD and carries a poor prognosis. Malnutrition can be present at all stages of disease irrespective of FEV1, although it is more prevalent among patients with emphysema and low diffusing capacity for carbon monoxide. The causes of weight loss are not well understood but could reflect systemic inflammation and circulating cytokines. Nutritional supplementation combined with exercise should be considered to reverse weight loss.

EVIDENCE STATEMENTS

- Malnutrition can be present in stable COPD (Sahebjami et al., 1993; Schols et al., 1993; Wouters & Schols, 1993).
- Low BMI is associated with increased mortality (Prescott et al., 2002; Schols et al., 1993).
- Combination nutritional supplementation, anabolic glucocorticoids, and exercise may reverse weight loss (Celli et al., 2004; Ferreira et al., 2000; Schols et al., 1998).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	R
1	Malnutrition is present at all stages of COPD.	Sahebjami et al., 1993 Schols et al., 1993 Wouters & Schols, 1993	II	Good	B
2	Low BMI is associated with increased mortality in COPD.	Gray et al., 1996 Prescott et al., 2002 Schols et al., 1993	II	Fair	B
3	Weight loss in patients with COPD can be reversible.	Celli et al., 2004 Ferreira et al., 2000 Schols et al., 1998	I	Fair	B

QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)

Annotation L *Evaluate and Provide Appropriate Treatment for Sleep Disorders*

5.4 Sleep Disorders in Patients with COPD

BACKGROUND

Sleep disorders such as insomnia, sleep apnea with a greater severity of arterial oxygen desaturations, and restless leg syndrome are more common in patients with COPD. More than 50 percent of patients with COPD complain about insomnia and more than 25 percent report daytime sleepiness. Sleep in patients with COPD is characterized by longer sleep onset latency, frequent arousals and awakenings, frequent sleep stage shifts, and lower sleep efficiency. Disturbed sleep in patients with COPD is associated with the severity of airflow obstruction and decreased QOL. Presence and extent of sleep problems can be established when a provider obtains the medical history.

ACTION STATEMENT

All patients with COPD should be questioned about symptoms of sleep disturbance and possible associated sleep apnea syndromes, such as snoring, witnessed apnea during sleep, and excessive daytime sleepiness.

RECOMMENDATIONS

1. Patients with COPD should be evaluated for sleep disorders by using medical interview, which should include standardized screening questionnaires for sleep disorders (e.g., insomnia, sleep apnea). [I]
2. Patients complaining of insomnia should be managed in outpatient primary care and may be treated with hypnotics cautiously. [I]
3. Patients with other sleep-related disorders (such as sleep apnea) should be referred to a sleep specialist. [I]

RATIONALE

- Disturbed sleep is frequently seen in patients with COPD. The management of sleep disorders often requires specific diagnostic tools and management that are better managed by a sleep disorder specialist. Since insomnia can be evaluated and managed based on medical interviewing, it should be managed by the primary care provider.

EVIDENCE STATEMENTS

- Prevalence of insomnia, nightmares, and daytime sleepiness is higher in patients with COPD than the general population (Klink & Quan, 1987; Kutty, 2004).
- Sleep in COPD is characterized by longer latency to sleep onset, more frequent arousals and awakenings, more frequent stage changes, and poorer sleep efficiency than normal individuals (George & Bayliff, 2003, Klink & Quan, 1987; Kutty, 2004).
- Prevalence of sleep apnea in patients with COPD does not differ from the normal population. However, arterial oxygen desaturations during sleep are more profound in patients with COPD who have sleep apnea (ATS/ERS, 2004).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	R
1	Identify patients who may benefit from sleep evaluation.	ATS/ERS, 2004 George & Bayliff, 2003 Klink & Quan, 1987 Kutty, 2004	III	Poor	I
2	Evaluate patients for insomnia, sleep related breathing disorders, and restless legs syndrome.	ATS/ERS, 2004 George & Bayliff, 2003 Klink & Quan, 1987 Kutty, 2004	III	Poor	I

QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)

Annotation M *Special Considerations for a Patient in Need of Surgery*

6 Special Considerations for a Patient in Need of Surgery

BACKGROUND

Patients with COPD undergo surgical procedures at a rate commensurate with the general population. Administration of local anesthesia presents a very low risk, even in the presence of severe COPD. General anesthesia increases the risk for pulmonary emboli. The likelihood of specific postoperative pulmonary complications is associated with the type and location of the procedure:

- Head and neck: increased risk of pneumonia
- Orthopedic: increased risk of venous thromboembolic disease

- Lower abdominal surgery: no increased risk
- Upper abdominal surgery: increased risk of pulmonary complications

  [COPD is an independent risk factor in patients receiving upper abdominal surgery. Smoking, obesity, advanced age, and heart disease increase risk in this group. Laparoscopic surgical approaches reduce the risk of postoperative pulmonary complications in patients with COPD.]
- Cardiac surgery: COPD is a risk factor for prolonged intubation following cardiac surgery
- Patients with severe COPD (FEV1 < 35 percent predicted) are at risk of prolonged ICU stays.

ACTION STATEMENT

The preoperative evaluation of a patient with COPD depends upon the type and acuity of surgery and the severity of COPD.

RECOMMENDATIONS

Emergency Surgery

1. Emergency surgeries should not be delayed pending preoperative consultation. [I]

Low-Risk

2. Clinically stable patients with COPD who are undergoing minor procedures under local anesthesia do not need additional preoperative testing. [I]
3. Clinically stable patients with mild to moderate COPD (FEV > 50 percent predicted) who are undergoing any operation under general anesthesia do not need additional preoperative testing. [I]

High-Risk

4. Patients with severe COPD (FEV1 < 50 percent predicted) undergoing any operation that is done under general anesthesia should be considered for preoperative evaluation including pulmonary function test, gas exchange, and chest X-ray. [I]
5. Patients with severe COPD (FEV < 50 percent predicted) planned for high-risk surgery should be referred to a pulmonary specialist. [I]

Optimization of Pre- and Postoperative Care

6. Bronchodilator therapy should be optimized prior to planned surgery. [I]
7. Patients should be encouraged to quit smoking and instructed to stop smoking at least 6 to 8 weeks before surgery. [I]
8. Deep breathing, incentive spirometry, early mobilization, and adequate pain control should be encouraged to reduce postoperative pulmonary complications in patients with COPD. [I]
9. Patients who are on oral glucocorticoids should receive stress doses of intravenous glucocorticoids in the perioperative period to reduce the risk of adrenal insufficiency. [I]
10. Pulmonary consultation should be obtained prior to surgery in patients with an FEV1 below 35 percent predicted and in patients who are to undergo lung volume reduction surgery. [I]

RATIONALE

- Patients with COPD have a 2.7 to 4.7 fold increase in the risk of postoperative pulmonary complications depending upon the type, location, and urgency of the surgical procedure (Trayner & Celli, 2001). The appropriate evaluation and management of patients with COPD in the perioperative period is important to reduce untoward complications.

EVIDENCE STATEMENTS

- Smoking cessation 6 to 8 weeks prior to surgery reduces the risk of postoperative pulmonary complications (Warner et al., 1989).
- Patients on chronic oral glucocorticoids receiving systemic glucocorticoids in the perioperative period have a lower incidence of adrenal insufficiency (Pien et al., 1988).
- Early mobilization, deep breathing, incentive spirometry, and adequate pain control reduce the incidence of postoperative complications in patients with COPD undergoing upper abdominal surgery (Tarhan et al., 1973).

Annotation N *Special Considerations for a Patient Planning to Travel at High Altitude*

7 Planning Air Travel for a Patient with Stable COPD

BACKGROUND

Commercial airliners typically are pressurized at 6,000 to 8,000 feet. This is equivalent to an inspired O_2 concentration at sea-level of about 15 percent. A 5 percent drop in O_2 concentration in patients with severe COPD may induce a 25 to 30 mm Hg drop in PO_2 and this may cause significant arterial oxygen desaturation. To prevent arterial oxygen desaturation, supplemental O_2 may need to be prescribed for in-flight use. The O_2 flow prescribed depends on the sea level PO_2, the patient's FEV1, and any comorbid conditions.

ACTION STATEMENT

Patients with severe COPD who are on long-term oxygen therapy or have sea level PO_2 below 80 mm Hg should be evaluated pre-flight for supplementary oxygen during air travel. [C]

RECOMMENDATIONS

1. Perform pre-flight estimation of the expected degree of hypoxemia. [C]
2. Prescribe sufficient oxygen in flight to raise PO_2 (Alt) to around ~ 60 mm Hg. [C]
3. Warn patients with known bullous disease of the increased risk for pneumothorax during air travel. [C]
4. Arrange in-flight O_2 supplementation with the airline.

The expected in-flight PO_2 values may be calculated using the following steps outlined in Table 10 or may be looked up in the Table 11.

Table 10. How to Calculate Expected In-flight PO_2

Step 1: Calculate expected in-flight PO_2 (Alt) based on sea level PO_2 (SL) and FEV1 according to the formula:

$$PaO_2 \text{ (Alt)} = 0.453 [PaO_2SL] + 0.386 [\text{FEV1 \% predicted}] + 2.44$$

Pre-calculated values of predicted in-flight PaO_2 can be looked up in Table 11.

Step 2: A flow rate of 1L/minute increases inspired PO_2 by about 20 mgHg (2 liter/minute increases inspired PO_2 by about 40 mm Hg)

Step 3: Adjust the O_2 flow for any comorbid conditions such as hypercapnia (aim for in-flight SaO_2~90%), cardiac or cerebrovascular disease (aim for in-flight SaO_2 > 95%)

The values of PaO_2(Alt), calculated from the above formula, for given values of PaO_2 (SL) in the range of 60 to 80 mm Hg and FEV1 from 30 to 100 percent predicted can be found in Table 11 (Dillard et al., 1989). If the PaO_2 (SL) is above 80 mm Hg, the patient probably does not need oxygen for travel.

Table 11. Predicted In-flight PaO_2 Based on PaO_2 at Sea Level and FEV1

FEV1 % Predicted		**100**	**90**	**80**	**70**	**60**	**50**	**40**	**30**
PaO_2 at sea level	80	56.2	54.9	52.7	50.9	49.2	47.4	45.7	44.9
	70	51.6	49.9	48.1	46.4	44.6	42.9	41.1	39.4
	60	47.1	45.4	43.6	41.9	40.1	38.4	36.6	34.9

Dillard et al., 1989

RATIONALE

- When exposed to low concentrations of O_2, as occurs during flight, normal subjects compensate with hyperventilation to maintain normal or near PO_2. Patients with reduced PO_2 (< 80 mm Hg), severely reduced FEV1, or hypercapnia may be unable to compensate to maintain near normal PO_2 in-flight. Therefore, these patients may experience hypoxemia during flight. Exercise (walking) may exacerbate in-flight hypoxemia. Furthermore, long-term hypoxemia can be hazardous. To prevent these untoward consequences, O_2 supplementation is required for these patients.

EVIDENCE STATEMENTS

- In patients with COPD, walking down an aisle during a flight can provoke symptomatic severe hypoxemia (Christensen et al., 2000) or right heart failure resulting in urgent requests for oxygen (Dillard et al., 1991).

- Regression equations to predict in-flight PO_2 are applicable to the majority of patients with COPD (Dillard et al., 1989; 1993; 1995). However, applicability is limited for patients with borderline values of predicted PaO_2 at altitude or patients with hypercapnia. The altitude PaO_2 (Alt) can be estimated from the sea level PaO_2 (SL) and the FEV1 using the following equation:

  $$PaO_2 \text{ (Alt) mm Hg} = 0.453\ [PaO_2\text{(SL) mm Hg}] + 0.386\ [\text{FEV1 \% predicted}] + 2.44$$

- Since FEV1 influences PaO_2 (Alt), it is important to optimize FEV1 by pharmacotherapy before and during air travel.

- If a patient's PaO_2 during commercial air travel is predicted by regression equations to be borderline (51 to 54), that patient should be individually evaluated, especially if the patient has cardiac or cerebrovascular disease.

- Patients with hypercapnia have not been included in the patient populations from which the above prediction equation was developed. To prevent hyperoxic induced depression in ventilation in these patients, the in-flight PO_2 should be approximately 55 to 60 mm Hg (SaO_2 ~ 85 to 90 percent).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**R**
1	Patients with COPD during flight may develop severe hypoxemia or symptoms and right heart failure resulting in urgent requests for oxygen and can affect morbidity and mortality.	Christensen et al., 2000 Dillard et al., 1991 Speizer et al., 1989	II-b	Fair	C
2	Predicting PaO_2 at altitude from PaO_2 at ground level.	Dillard et al., 1989; 1993; 1995	II-b	Fair	C
3	LTOT patients should increase flow by one to 2 liter/minute during flight.	Gong, 1992	II-b	Fair	C

QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)

Annotation O *Continue Follow-up and Monitoring*

8 Follow-Up/Monitoring

8.1 Schedule Follow-Up

BACKGROUND

Patients with COPD live with the disease and its progression for years and often die prematurely from it or its complications. Since lung function can be expected to worsen over time, symptoms and objective measures of airflow limitation should be monitored and actively managed to determine when to modify therapy.

ACTION STATEMENT

Patients with moderate to severe COPD should be reevaluated at least once a year. [I]

RECOMMENDATIONS

1. Patients with COPD should be assessed on a periodic basis, based on the severity and progression of their disease. [I]
2. Periodic evaluations of patients with COPD should include a review of their symptoms, their current treatment regimen, reported exacerbations, and spirometry testing. [I]

Table 12. Evaluation of a Patient with COPD

	√	
		Prevention
Clinical Assessment		Smoking status & readiness to quit
		Vaccination
		Symptom control:
		– breathlessness
		– exercise tolerance
		– exacerbation frequency
		– sleep disruption
		– cough & sputum
		Use of drug treatment
		– adherence
		– adverse effect
		– inhaler technique
		Manage complications (in severe COPD)
		– presence of cor pulmonale
		– presence of depression
		– presence of sleep disorder
		– need for LTOT
		– change in nutritional status
		Need for pulmonary rehabilitation
Measurements		**Spirometry FEV1 & FVC**
		Calculate BMI
		MRC dyspnea score

RATIONALE

Deterioration of lung function usually requires the progressive introduction of more treatments, both pharmacologic and non-pharmacologic, to attempt to limit the impact of these changes. There are no data to guide decisions on how frequently patients with COPD should be reviewed. The frequency of evaluation should vary according to individual circumstances and the severity of the patient's disease. Patients with mild or moderate COPD should be reviewed at least once per year or more frequently if indicated. Spirometry is an important part of evaluating patients with COPD and remains the gold standard for monitoring the progression of COPD. Useful information about lung function decline is unlikely from spirometry measurements performed more than once a year. However, spirometry should be performed if there is a substantial increase in symptoms or an exacerbation (see Annotation 2.2).

8.2 Palliative Care

BACKGROUND

Patients with COPD experience acute exacerbations of their disease, which may result in respiratory failure and death. Decisions about ventilatory support and other interventions require open communication with the patient/family to promote a care plan consistent with the patient's goals of care that limit patient suffering. Most patients with COPD and their families wish to actively participate in decisions about life support and palliative care. However, many patients with COPD and their families may benefit from substantial support and shared decision from the care team, including the primary healthcare provider, to identify appropriate goals of care given their disease and prognosis.

ACTION STATEMENT

Healthcare providers should assist patients with COPD and their families during stable periods of health to promote discussion about advanced care planning, including end-of-life care. [I]

The clinical care team will provide regular, ongoing assessments of distressing symptoms (especially dyspnea) and actively seek to relieve suffering through a comprehensive approach to the physical, psychological, social, and spiritual aspects. [I]

RECOMMENDATIONS

1. Healthcare providers should assess the needs of patients with COPD and their families for advanced care planning and initiate advanced care in patients with poor prognosis (e.g., hospitalized with exacerbations). [I]
2. Patients with COPD and their families should be encouraged to participate in the planning and management of their treatment to improve their ability to cope with COPD in the future. [I]
3. The referral of the patient and their family to appropriate expertise in palliative care to assist in the relief of suffering may be considered when the patient/family's needs require such or are otherwise indicated. [I]

RATIONALE

- Patients with COPD and their families can benefit from advanced care planning, through increased understanding of the patient's disease, the prognosis, the care needs, and the patient-specific goals of care. Through honest communication with the care team, patients and families can collaboratively seek to meet the patient-specific goals through appropriate interventions (Lynn & Goldstein, 2003; Teno et al., 2004; Weissman, 2004).

- Many patients with COPD and their families gain solace in learning about palliative interventions, which they believe will protect them from experiencing discomfort at the end-of-life.

EVIDENCE STATEMENTS

- Only 19 percent of patients with advanced lung disease enrolled in pulmonary rehabilitation programs have discussed, with their physicians, the appropriateness of life supportive care relative to their lung condition. In addition, only 15 percent of patients have discussed, with their physicians, the nature of intubation and mechanical ventilation and less than 15 percent of patients with advanced lung disease have confidence that their physicians understand their end-of-life wishes (Heffner et al., 1996).

- In the circumstances of being hospitalized with a serious illness, 72 percent of patients stated that they would want to decide for themselves about life support (Heffner et al., 1996).

- Two barriers were significantly associated with lack of communication, as follows: "I don't know what kind of care I want," and "I'm not sure which doctor will be taking care of me." The greater the number of barriers endorsed by patients, the less likely they were to have discussed end-of-life care with physicians ($p < 0.01$) (Knauft et al., 2005).

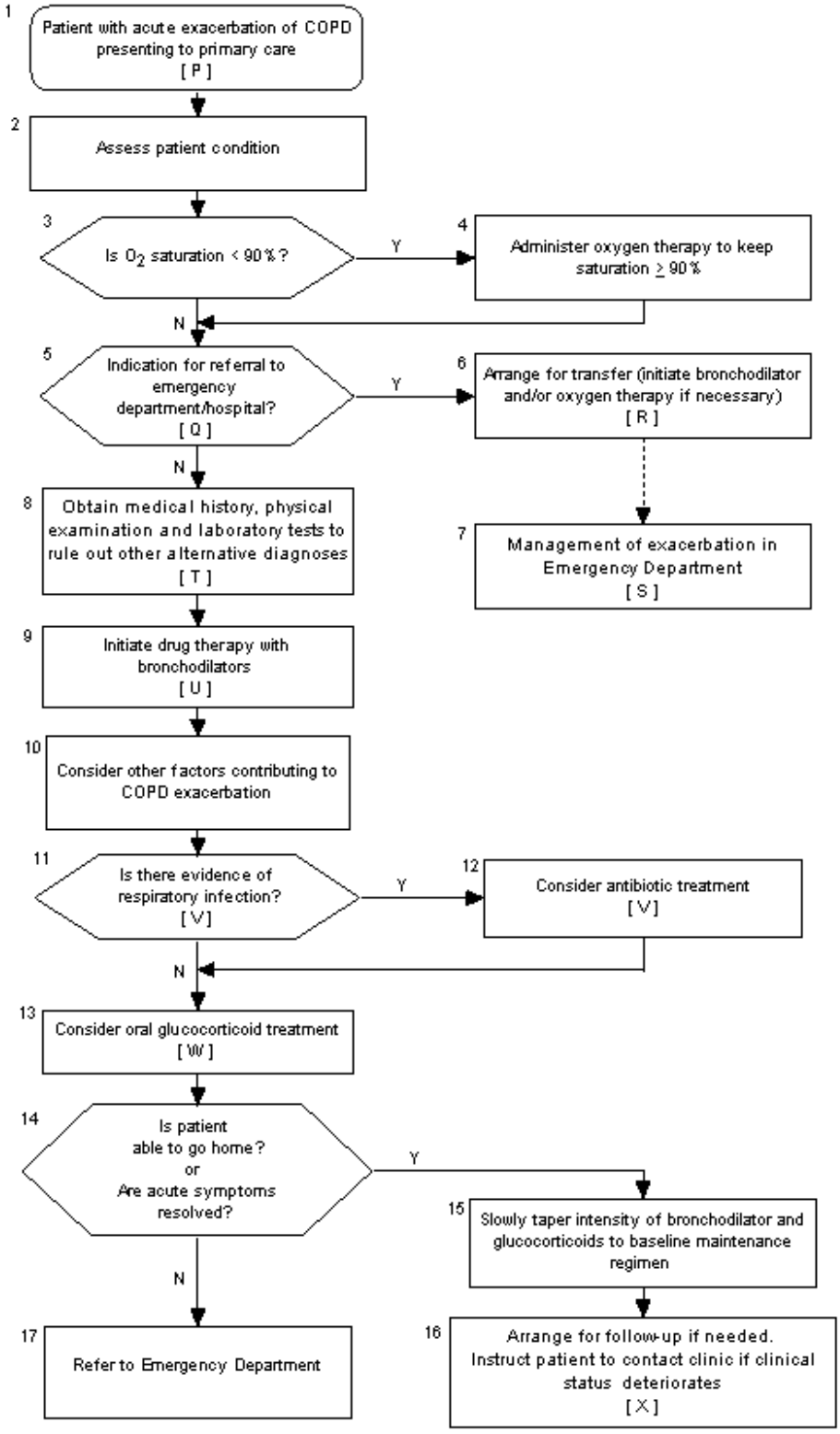
- Physicians can promote a dialogue for advanced care planning by involving families and encouraging discussions within families regarding the end-of-life decisions that patients with COPD may eventually face (Jennings et al., 1988).

- Four percent of 988 terminally ill patients were residents of an institution, such as a nursing home, residential hospice, or hospital (Emanuel et al., 1999).

- At the end-of-life, patients with COPD need reassurance that their caregivers will stay involved and will not abandon them (Youngner et al., 1985).

VA/DoD Clinical Practice Guideline for Management of COPD
Module B: Acute Exacerbation

B



12/29/2006

MODULE B: MANAGEMENT OF COPD ACUTE EXACERBATION

ANNOTATIONS

Annotation P *Patient with Acute Exacerbation of COPD Presenting to Primary Care*

9 Definition of Acute Exacerbation

DEFINITON

An exacerbation is a sustained worsening of the patient's respiratory symptoms and function from his or her usual stable state that is beyond normal day-to-day variations, and is acute in onset. Commonly reported symptoms are worse breathlessness, cough, increased sputum production, and change in sputum color. The change in the patient's condition often necessitates a change in medication.

10 Referral to the Emergency Department

Annotation Q *Are there Indications for Referral to the Emergency Department/Hospital?*

10.1 Criteria for Referring to the Emergency Department/Hospital

BACKGROUND

Most patients with an exacerbation of COPD can be evaluated in an outpatient clinic setting and managed at home. However, certain conditions may require referral of the patient to a higher care facility (emergency department/hospital).

ACTION STATEMENT

More severe exacerbation or inadequate resources in the outpatient setting may require evaluation and management of the patient in the emergency department or a hospital setting. [I]

RECOMMENDATIONS

1. Patients evaluated for acute exacerbation of COPD should be considered for referral to the emergency department or admission to the hospital if they present with any of the following indications [I]:
    a. Unstable vital signs
    b. Impaired level of consciousness or altered mental status
    c. Severe breathlessness
    d. New or worsening hypoxemia (SaO_2 < 90 percent)
    e. Inadequate disease management resources at home
    f. Lack of appropriate resources to evaluate or manage the patient in a clinic setting.

Annotation R *Arrange for Transfer to the Hospital*

10.2 Initiation of Short-Acting Bronchodilator and/or Oxygen Therapy if Necessary

BACKGROUND

Increased breathlessness is a common feature of an exacerbation of COPD. This is usually managed with increased doses of short-acting bronchodilators. Hypoxemia can develop or worsen with an exacerbation and can be life-threatening. This hypoxemia can be readily alleviated with low flow oxygen. Patients referred for further evaluation and management to an emergency department or hospital should receive these therapies promptly, if available.

ACTION STATEMENT

Early initiation of bronchodilator therapy and oxygen (in hypoxemic patients) is appropriate prior to full assessment and treatment in the emergency department or hospital.

RECOMMENDATIONS

1. Initial treatment for patients experiencing an initial acute exacerbation of COPD who have been referred to the emergency department or admitted directly to the hospital should include [I]:
    a. Short-acting bronchodilator, by nebulizer or metered dose inhaler, if readily available
    b. Low flow oxygen therapy to maintain SAO_2 at 90 percent.

Annotation S *Management of Exacerbation in the Emergency Department*

10.3 Assessment of Acute Exacerbation in the Emergency Department

In the emergency department, patients experiencing an acute exacerbation of COPD should be evaluated for the potential factors that contribute to the exacerbation. Assessment and treatment should proceed simultaneously in these patients. The emergency department should have the ability to perform these evaluations and treatments in a timely fashion. Increased respiratory symptoms in COPD can be due to a number of cardiac or pulmonary causes. Appropriate management mandates knowledge of the cause while simultaneously treating the severely ill patient.

All patients with possible COPD acute exacerbations who either present directly to the emergency department or who are referred from outpatient settings should have the following differential diagnoses considered, assessed, and treated as necessary:

- Congestive heart failure
- Pneumonia
- Pneumothorax
- Pulmonary embolism
- Cardiac ischemia

- Cardiac arrhythmia
- Upper airway infection; e.g., acute sinusitis
- Upper airway obstruction
- Pleural effusion
- Recurrent aspiration
- Noncompliance with medications
- Inappropriate oxygen therapy which may produce hypercapnia
- Adverse effects of medications; e.g., sedatives.

Clinical evaluation and diagnostic workup for patients admitted to the emergency department for acute exacerbation of COPD will cover the following:

a. Clinical evaluation:

- Vital signs including oximetry
- Mental status
- Clinical evidence of impending respiratory failure (tachypnea, accessory muscle use, abdominal paradox, and cyanosis)
- Clinical signs and symptoms (e.g., cardiovascular disease, pulmonary embolism).

b. Diagnostic testing may include:

- Chest X-ray
- Arterial blood gases
- Complete blood count and differential
- Bun, creatinine, and electrolytes
- ECG
- Theophylline level, if patient is on theophylline
- Sputum cultures if pseudomonas is suspected (when there is underlying structural lung disease, chronic oral glucocorticoid use, recurrent antibiotic therapy, and malnutrition).

c. Patients in acute respiratory distress should receive nebulized bronchodilator therapy, systemic glucocorticoids, and antibiotics and oxygen, if indicated, while simultaneously being assessed for the need for non-invasive or invasive ventilation.

11 Management of Acute Exacerbation in the Outpatient Setting

Annotation T *Obtain Medical History, Physical Examination, and Laboratory Tests to Assess Severity, Rule Out Alternatives, and Confirm Diagnoses*

11.1 Assessment, Testing, and Diagnosis

BACKGROUND

The diagnosis of an exacerbation is usually based on clinical evaluation and subjective parameters. A careful and comprehensive clinical evaluation is therefore critical to the appropriate diagnosis and management of exacerbations of COPD. Patients with COPD frequently suffer from other comorbid conditions that may impact upon the treatment of an acute exacerbation. Other cardiorespiratory conditions prevalent in patients with COPD can present with symptoms similar to an acute exacerbation and need to be clinically excluded.

ACTION STATEMENT

Patients with COPD with acute exacerbation should be assessed to confirm the diagnosis, rule out other causes for worsening symptoms and determine the severity of the exacerbation, and the priorities for treatment.

RECOMMENDATIONS

Clinical assessment should include:

1. The diagnosis of acute exacerbation of COPD should be confirmed and other causes excluded based upon clinical evaluation with additional diagnostic tests in selected cases. [I]
2. The severity of an exacerbation of COPD should be determined based upon medical history, symptoms, physical examination, and pulmonary function tests. [I]
3. Medical history with a patient with acute exacerbation should include:
    a. Onset, duration, and type of symptoms (cough, sputum production, dyspnea, fever, decreased exercise tolerance, confusion, or acute mental status changes)
    b. Current medication use
    c. History of prior COPD exacerbations or hospitalizations (frequency, ICU admissions, and prior intubation)
    d. The severity of the underlying COPD
    e. Presence of comorbid conditions; e.g., heart disease.
4. Physical examination with a patient with acute exacerbation should include:
    a. Vital signs
    b. Level of consciousness
    c. A careful pulmonary examination
    d. Cardiovascular examination
    e. Oxygenation.

5. Laboratory testing that may be considered with a patient with acute exacerbation:
    a. Oximetry (in all patients with moderate or worse COPD)
    b. Arterial blood gas in patients with deteriorating clinical status
    c. Spirometry, if available, in patients who are able to perform the test and for whom there is baseline data available for comparison
    d. Chest X-ray to exclude other causes if clinically suspected
    e. ECG if clinically indicated.
6. Alternative causes of increased symptoms that need to be clinically excluded include:
    a. Congestive heart failure
    b. Pneumonia
    c. Pneumothorax
    d. Pulmonary embolism
    e. Cardiac ischemia
    f. Cardiac arrhythmia
    g. Upper airway infection; e.g., acute sinusitis
    h. Upper airway obstruction
    i. Pleural effusion
    j. Recurrent aspiration
    k. Noncompliance with medications
    l. Inappropriate oxygen therapy
    m. Adverse effects of medications; e.g., sedatives.

RATIONALE

- Patients with COPD often have other medical comorbid problems. Worsening respiratory symptoms in patients with COPD may result from cardiovascular or respiratory conditions other than acute COPD exacerbation. Proper diagnosis of these events will help to better manage this syndrome.

12 Pharmacotherapy for Acute Exacerbation in Outpatient Settings

Annotation U *Initiate Drug Therapy with Bronchodilators*

12.1 Bronchodilators

BACKGROUND

Pharmacotherapy should be initiated in the acute exacerbation to hasten resolution of the signs/symptoms of the exacerbation and prevent complications. This treatment may include antibiotics, systemic glucocorticoids, and bronchodilators. Patients who present with acute exacerbations of COPD need immediate relief of dyspnea. The approach is to provide inhaled short-acting bronchodilators delivered either by a metered dose inhaler or aerosol nebulization. These are provided until the patient's dyspnea is sufficiently reduced, which may take as few as one treatment or many treatments over a number of hours or days.

ACTION STATEMENT

Provide relief of symptoms and improve FEV1 with short-acting inhaled bronchodilator therapy. [B]

RECOMMENDATIONS

1. A short-acting bronchodilator (short-acting anticholinergic or short-acting beta 2-agonist) or a combination of both, using a metered dose inhaler with a spacer or aerosol mobilization, should be administered as soon as possible and as frequently as necessary. The choice of agent should be made on the basis of individual assessment and initial response to therapy. [B]
2. Methylxanthines should be avoided either orally or systemically since these agents may lead to side effects and have no proven efficacy in the setting of an acute exacerbation of COPD. [D]

RATIONALE

- Short-acting bronchodilators are necessary in the early treatment of dyspnea and respiratory distress in a patient with an exacerbation of COPD. Such agents act quickly (albuterol more quickly than ipratropium, but both provide relief within a few minutes (albuterol within 15 minutes; ipratropium within 30 minutes). Since albuterol acts more rapidly, it is almost always used alone or in combination with ipratropium unless there is a contraindication to the use of beta 2-agonist such as an unstable arrhythmia or angina. Of note, albuterol has more side effects including tremor, vomiting, palpitations, and transient reductions in PaO_2, and rarely abnormal cardiac rhythm and changes in the electrocardiogram. These have not been reported when ipratropium has been used alone.

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**Net Effect**	**R**
1	Ipratropium and albuterol, alone and in combination demonstrated improvement in FEV1, with no difference between therapies.	Bach et al., 2001	I	Fair	Substantial	B
2	A methyxanthine (such as aminophylline) added to ipratropium and albuterol, alone and in combination, increased side effects.	Bach et al., 2001	I	Fair	Substantial	D

QE = Quality of Evidence; Net Effect = Size of Intervention Effect; R = Strength of Recommendation (See Appendix A)

Annotation V *Is there Evidence of Respiratory Infection?*

12.2 Antibiotics

BACKGROUND

Up to half of COPD exacerbations are related to bacterial infection of the airways. Treatment of COPD exacerbations that are due to bacteria with antibiotics hastens resolution and could prevent complications. Identification of exacerbations that are more likely to be related to bacterial infection can guide appropriate antibiotic therapy. Stratification of patients with exacerbation into uncomplicated (see Table 13) and complicated patients with readily assessable clinical criteria can guide antibiotic choice.

ACTION STATEMENT

Prescribe a course of antibiotics for acute exacerbation of COPD if symptoms indicate bacterial infection; choice of antibiotic agent may be based on the degree of complication (number of exacerbations, FEV1, previous exposure to antibiotics, and cardiac disease).

RECOMMENDATIONS

1. COPD patients with acute exacerbation of COPD with at least two of the following will most likely benefit from antibiotic therapy [A]:
    a. Increased sputum purulence (change in sputum color)
    b. Increased sputum volume
    c. Increased dyspnea.
2. Choice of antibiotic agents may be determined based on local bacterial resistance patterns. [C]
3. Choice of antibiotic agents may be determined based on the frequency of exacerbations in the past 12 months, severity of underlying COPD, presence of cardiac disease, and recent (within 3 months) antibiotic exposure for each patient. [B]
4. For uncomplicated exacerbations of COPD, consider doxycycline, trimethoprim/ sulfamethoxazole, second generation cephalosporin. [C]
5. For complicated exacerbations of COPD, consider beta-lactam/beta-lactamase inhibitor or fluoroquinolone. [C]

Stratifying the patient as complicated or uncomplicated may be helpful in determining the choice of antibiotic and is summarized in Table 13.

Table 13. Determine Level of Patient Complication and Antibiotic Agents

Patient Characteristics	Antibiotic Agents
Uncomplicated Patients 1. Have experienced less than 3 exacerbations in the past 12 months 2. Have a baseline FEV1 of > 50% predicted 3. Do not have cardiac disease 4. Have not been exposed to antibiotics in the past 3 months	• Doxycycline • Trimethoprim/Sulfamethoxazole • Second or third generation cephalosporin • Extended spectrum macrolide
Complicated Patients 1. Have experienced 3 or more exacerbations in the past 12 months 2. Have a baseline FEV1 of < 50% predicted 3. Have cardiac disease 4. Have been exposed to antibiotics in the past 3 months	• Beta-lactam/beta-lactamase inhibitor • Fluoroquinolone [a]

[a] *By explicitly defining the patient that would benefit from the use of quinolone, the use of these drugs in uncomplicated exacerbations is discouraged.*

RATIONALE

- Bacterial infection is one of the major causes of COPD exacerbation. Treatment of the patient with acute exacerbation of COPD with antibiotics is helpful when evidence of bacterial infection is present. Since sputum cultures and resistance patterns are only rarely available, resistance patterns are not suggested for criteria for antibiotic choice in outpatient care. Presence of symptoms is adequate and sputum culture is not recommended for outpatient management of acute COPD exacerbation. Haemophilus influenzae, streptococcus pneumoniae, moraxella catarrhalis, pseudomonas spp, and enterobacteriaceae spp are the major bacteria causing acute exacerbation of COPD.

- The current approach to treatment of exacerbations is clearly suboptimal. Relapse rates after ambulatory treatment of acute exacerbation of COPD may be as high as 20 to 25 percent of cases. Relapses are associated with significant morbidity and increased costs. The greatest part of costs derives from therapeutic failures, particularly those that end in hospitalization (Miravitlles et al., 2002).

- Evidence indicates that the number of patients with pathogenic bacteria in respiratory secretions and the bronchial bacterial load increases during exacerbations. Furthermore, the local inflammatory response of the host parallels the increase in bacterial load. It can be speculated, that for symptoms of acute exacerbation to appear, there must be a minimal bacterial load in the airways; i.e., the threshold above which the inflammatory reaction is severe enough to elicit clinical symptoms of exacerbation. This threshold may vary from patient to patient due to different modifying factors. Some of these factors may be the recognized risk factors for relapse, such as increasing age, impairment of lung function, comorbid conditions, or frequent exacerbations in the past.

- Though not proven, it is very likely that appropriate treatment of selected patients with more effective antibiotics could actually reduce hospitalizations and costs of care. Early aggressive treatment of exacerbations as outpatients has the potential for decreasing hospitalizations, resulting in overall less in-hospital antibiotic use and emergence of resistance.

EVIDENCE STATEMENTS

- Bacterial infection results in acute exacerbation of COPD (Sethi et al., 2002).

- Randomized controlled trials (stratified on steroid use) comparing quinolones to standard antibiotic treatment (i.e., amoxicillin, clarithromycin, or cefuroximeaxetil [250 mg bid for 7 days]) (Wilson et al., 2002, 2004) have shown more rapid resolution of symptoms, less failure of treatment, less need for additional antibiotics, and less frequency of recurrent exacerbation in the subsequent 6 months of patients treated with quinolones. Several clinically relevant outcomes such as less failure of treatment, less need for additional antibiotics, and less frequency of recurrent exacerbation in the subsequent 6 months have shown superiority of the quinolones.

- Antibiotics are helpful in patients with acute exacerbation of COPD and symptoms of bacterial infection (Allegra et al., 2001; Anthonisen et al., 1987; Nouira et al., 2001; Saint et al., 1995).

- Sputum culture is not recommended for determination of bacterial infection in outpatient management of acute exacerbation of COPD (NICE, 2004).

- Sputum purulence or increased sputum production accompanied with increased dyspnea indicates responsiveness of antibiotic therapy (Anthonisen et al., 1987; Stockley et al., 2000).

- Complicated patients are more likely to have antibiotic resistant pathogens and a worse outcome of the exacerbation (Martinez et al., 2005; Miravittles et al., 2001; O'Donnell et al., 2003). The baseline characteristics of the patients such as degree of dyspnea, coexisting ischemic heart disease, and number of previous visits for respiratory problems are strongly associated with increased risk of relapse after ambulatory treatment of acute exacerbations (Miravittles et al., 2001).

- A systematic review of 11 (917 patients) RCTs estimating the value of antibiotics in the management of acute COPD exacerbations (search period 1966 – 2005) shows that in COPD exacerbations with increased cough and sputum purulence antibiotics, regardless of choice, reduce the risk of short-term mortality by 77 percent, decrease the risk of treatment failure by 53 percent and the risk of sputum purulence by 44 percent; with a small increase in the risk of diarrhea. Antibiotics did not improve arterial blood gases and peak flow. These results should be interpreted with caution due to the differences in patient selection, antibiotic choice, small number of included trials, and lack of control for interventions that influence outcome, such as the use of systemic corticosteroids and ventilatory support. Nevertheless, this review supports antibiotics for patients with COPD exacerbations with increased cough and sputum purulence who are moderately or severely ill (Ram et al., 2006).

- A trial of 369 patients was included in an intent-to-treat population (187 treated with levofloxacin and 182 treated with amoxicillin/clavulanate). A total of 175 patients were microbiologically assessable (86 treated with levofloxacin and 89 treated with amoxicillin/clavulanate). At the on-treatment visit, a significantly higher proportion of the microbiologially accessible patients in the levofloxacin group resolved purulent sputum production (57.5% vs. 35.6%; $P < 0.006$), sputum production (65.4% vs. 45.3%; $P < 0.013$), and cough (60.0% vs. 44.0%; $P < 0.045$), compared with the amoxicillin/clavulanate group. However, no significant between-group differences were observed at posttreatment (Grossman et al., 2006).

- The MOSAIC study randomized patients with acute exacerbation to moxifloxacin and three other standard antibiotic treatments. Further exploratory analyses were performed to identify prognostic factors of short- and long-term clinical outcomes. Patients were assessed 7 to 10 days after study treatment, and followed monthly until a new acute exacerbation chronic

bronchitis or for up to 9 months. The clinical cure was positively influenced by treatment with moxifloxacin (odds ratio (OR) 1.49; 95% CI 1.08 to 2.04) while cardiopulmonary disease (OR 0.59; 95% CI 0.38 to 0.90), FEV1 < 50 percent predicted (OR 0.48; 95% CI 0.35 to 0.67), and more than 4 exacerbations in the previous year (OR 0.68; 95% CI 0.48 to 0.97) predicted a poorer outcome. For clinical success, treatment with moxifloxacin had a positive influence (OR 1.57; 95% CI 1.03 to 2.41). The occurrence of the composite event was influenced by antibiotic treatment (hazard ratio=0.82) (Wilson et al., 2006).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**R**
1	Identify presence of symptoms that may indicate bacterial infection.	Anthonisen et al., 1987 Stockley et al., 2000	I	Good	A
2	Patients with COPD and acute exacerbation who have at least 2 of the following symptoms will benefit from antibiotic therapy: • Increased dyspnea • Increased sputum volume • Increased sputum purulence.	Anthonisen et al., 1987 Ram et al., 2006	I	Good	A
3	Do not perform sputum culture in primary care (outpatient) setting for establishing the bacteriological cause of COPD exacerbation.	ATS/ERS, 2004 NICE, 2004	III	Good	D
4	Start a course of antibiotics in patients with acute exacerbation of COPD and symptoms indicative of bacterial infection.	Allegra et al., 2001 Anthonisen et al., 1987 Nouira et al., 2001 Ram et al., 2006 Saint et al., 1995	I	Good	A
5	Base antibiotic choice on the local bacterial resistance patterns (if available).	ATS/ERS, 2004 Grossman et al., 2006 NICE, 2004	I	Fair	C
6	Stratify patients into uncomplicated and complicated to assist in antibiotic choice.	Martinez et al., 2005 Miravittles et al., 2001 O'Donnell et al., 2003	I	Fair	B
7	For uncomplicated exacerbations of COPD, consider the following antibiotics: • Doxycycline • Trimethoprim/sulfamethoxazole • Second generation cephalosporin • Extended spectrum macrolide ketolide.	ATS/ERS, 2004 NICE, 2004	III	Fair	C
8	For complicated exacerbations of COPD, consider the following antibiotics: • Beta-lactam/beta-lactamase inhibitor • Fluoroquinolone.	Martinez et al., 2005 Wilson et al., 2002, 2004, 2006	I	Fair	B

QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)

Annotation W *Consider Oral Glucocorticoid Treatment*

12.3 Oral Glucocorticoids

BACKGROUND

Airway inflammation is an integral part of stable COPD. Increased airway inflammation underlies exacerbations of COPD. Systemic glucocorticoids can decrease airway inflammation in exacerbations. Several placebo controlled trials in patients with exacerbations of COPD who were hospitalized or treated in the emergency department have shown significant benefit with glucocorticoids with better and more sustained clinical resolution and shorter hospitalizations.

ACTION STATEMENT

Consider a course of oral glucocorticoids in the treatment of an acute exacerbation of COPD to improve outcomes. [A]

RECOMMENDATIONS

1. A short course of oral glucocorticoids with a dose equivalent to 30 to 40 mg of prednisone per day (up to 14 days) should be considered for patients with COPD exacerbation. [A]

RATIONALE

- Oral glucocorticoids have been shown in several RCTs to be superior to placebo in the treatment of acute exacerbation.

EVIDENCE STATEMENTS

- There are 8 published clinical trials comparing systemic glucocorticoids to placebo in patients with acute exacerbation of COPD. Studies were conducted in patients who were either hospitalized or presented to the emergency department due to a COPD exacerbation. The dose and duration of glucocorticoids varied from study to study. Patients received concomitant bronchodilators +/- antibiotics.
- Use of systemic glucocorticoids resulted in greater improvement in FEV1 within the first 3 to 5 days compared to placebo in all studies except for the single-dose study by Emerman et al. (1989) (mean difference 140 mL [95%CI: 80, 200 mL]). One study found that dyspnea was improved while 2 others showed a trend favoring glucocorticoids.
- In those studies that were emergency department based, numerically fewer patients receiving glucocorticoids required hospital admission, except for the single-dose study by Emerman et al., (1989). In the studies of hospitalized patients, the duration of the hospitalization was approximately one to 2 days shorter in the glucocorticoid treated groups (Davies et al., 1999; Maltais et al., 2002; Niewoehner et al., 1999; Wood-Baker et al., 2005).
- Two studies evaluated 30-day relapse rate and found that the rate was lower in patients treated with glucocorticoids (Relative Risk=0.78; 95%CI: 0.63, 0.97) (Aaron et al., 2003; Niewoehner et al., 1999; Wood-Baker et al., 2005).
- There was no difference in mortality between glucocorticoid treated patients versus placebo (OR=0.85; 95%CI: 0.45, 1.59) (Wood-Baker et al., 2005).

- Hyperglycemia was more common in glucocorticoid treated patients compared to placebo (Albert et al., 1980; Davies et al., 1999; Maltais et al., 2002; Niewoehner et al., 1999; Wood-Baker et al., 2005).
- The optimal dose of glucocorticoids has not been clearly defined. The minimum dose used that showed benefit was prednisone 40 mg (prednisolone 30 mg) once daily.
- The optimal duration of glucocorticoid therapy has not been clearly defined. The majority of studies used a 9- to 10-day or 14-day course of therapy. One study showed there was no difference in outcomes between a 2-week versus an 8-week course of glucocorticoids (Niewoehner et al., 1999). A single-blind comparative trial (no placebo control) found that a 9-day course resulted in greater improvement in FEV1 and PaO_2 and fewer exacerbations compared to a 3-day course. There is no evidence to support the long-term use of oral glucocorticoids (Walters et al., 2005). No study has compared tapering of glucocorticoid dose to no taper. In the clinical trials, some tapered the glucocorticoid dose while others did not. Glucocorticoids were shown to be beneficial whether or not the dose was tapered.

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**R**
1	Short-term treatment (up to 14 days) with systemic glucocorticoids results in greater improvement in FEV1 compared to placebo.	Aaron et al.,2003 Albert et al., 1980 Davies et al., 1999 Maltais et al., 2002 Niewoehner et al., 1999 Walters et al., 2005 Wood-Baker et al., 2005	I	Fair	B
2	The 30-day relapse rate is lower in glucocorticoid treated patients compared to placebo.	Aaron et al., 2003 Niewoehner et al., 1999 Wood-Baker et al., 2005	I	Good	A
3	Duration of hospitalization is approximately one to 2 days shorter in glucocorticoid treated patients compared to placebo.	Davies et al., 1999 Maltais et al., 2002 Niewoehner et al., 1999 Wood-Baker et al., 2005	I	Good	A
4	There was no significant difference in mortality between glucocorticoid treated patients compared to placebo.	Wood-Baker et al., 2005	I	Good	A
5	Glucocorticoid treated patients had greater improvement in dyspnea compared to placebo.	Aaron et al., 2003 Maltais et al., 2002 Thompson et al., 1996 Wood-Baker et al., 2005	I	Good	A
6	In emergency department based studies, numerically fewer patients receiving glucocorticoids required hospital admission compared to placebo.	Aaron et al.,2003 Wood-Baker et al., 2005 Thompson et al., 1996	I	Good	A
7	Hyperglycemia was more common in patients receiving glucocorticoids compared to placebo.	Albert et al., 1980 Davies et al., 1999 Maltais et al., 2002 Niewoehner et al., 1999 Wood-Baker et al., 2005	I	Good	A

QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)

Annotation X *Arrange for Follow-Up if Needed*

13 Follow-Up

RECOMMENDATIONS

1. Patients should be instructed that if they have not improved with therapy over 48 to 72 hours or if they deteriorate at any time, they should seek attention from a healthcare provider. [I]

RATIONALE

- There are no studies that have addressed a specific schedule that is more likely to result in positive outcomes, but patients with frequent exacerbations are more likely to relapse. The continuous evaluation of a patient with COPD should resume (see Annotation O).

MODULE C: PHARMACOTHERAPY

TABLE OF CONTENTS

14 Bronchodilators

14.1 Short-Acting Bronchodilators in Patients with COPD

BACKGROUND

Patients with COPD have airflow obstruction that may be partially reversible. By reducing airflow obstruction, short-acting bronchodilators can improve pulmonary function, typically measured by FEV1, and this may or may not be associated with improved respiratory symptoms, quality of life (QOL), and COPD exacerbations. Short-acting bronchodilators are limited by the short duration of action and this can restrict their effectiveness.

ACTION STATEMENT

Consider using a maintenance short-acting anticholinergic and/or a maintenance short-acting beta 2-agonist in patients whose symptoms adequately respond to these drugs. Educate patient about the use of inhaler devices.

RECOMMENDATIONS

1. Short-acting beta 2-agonists should be used as rescue therapy as needed. [A]
2. Short-acting bronchodilators may be considered for maintenance for patients with COPD, as follows:
    a. Short-acting anticholinergics (SAAC) or short-acting beta 2-agonists (SABA) to improve FEV1 and respiratory symptoms and reduce frequency of exacerbations [B]
    b. Short-acting anticholingerics (SAAC) to improve quality of life (QOL) [B]
    c. Insufficient evidence for short-acting beta 2-agonists (SABA) to improve QOL [I].
3. Since all chlorofluorocarbons (CFC) aerosols must be phased out, ipratropium CFC has been replaced by ipratropium hydofluoroalkane (HFA). These two preparations may be considered in usual doses to improve FEV1 in patients with COPD. [B]

RATIONALE

- Patients with COPD have increased airway resistance due to mucus, inflammatory cell infiltration, airway remodeling, and loss of alveolar attachments and vagal tone. Short-acting anticholinergics can reduce the vagal tone, decrease airway resistance and thereby improve pulmonary function. Short-acting beta 2-agonists can also produce smooth muscle relaxation by stimulating cyclic adenosine monophosphate in airway smooth muscle. Reduction in bronchomotor tone, obtained either with short-acting anticholinergics or short-acting beta 2-agonists causes a much larger reduction in airway resistance in patients with COPD than normal subjects, because airway resistance is inversely related to radius to the fourth power. Empirically, patients with COPD and FEV1 of 70 percent predicted or lower have improvement in respiratory function and symptoms with inhalation of 36 µg ipratropium or 200 µg albuterol 4 times a day. Although there is no evidence to support this recommendation in patients with FEV1 greater than 70 percent or more, there is an expectation that such patients with airflow obstruction may have improvement in respiratory symptoms, if present, and therefore its use is also recommended in symptomatic patients with mild to moderate COPD.

EVIDENCE STATEMENTS

- A Cochrane meta-analysis and two recent RCTs of nebulized albuterol (Donohue et al., 2006; Nair et al., 2005) support the use of maintenance short-acting beta 2-agonists as therapy for patients with COPD, as it improved FEV1, respiratory symptoms, and exacerbations (Sestini et al., 2002).

- Four studies of ipratropium (Dahl et al., 2001; Mahler et al., 1999; Rennard et al., 2001; Wadbo et al., 2002) compared to placebo and one (Friedman et al., 1999) compared to maintenance albuterol provide support for improvement in FEV1, respiratory symptoms, and QOL. The studies provide inconsistent evidence for a reduction in exacerbations with a trend in some studies and a significant reduction in a post-hoc analysis.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	Net Effect	R
1	Ipratropium improved FEV1 and respiratory symptoms compared to placebo. When placebo was used, a short-acting inhaled beta 2-agonist was used as rescue therapy.	Dahl et al., 2001 Mahler et al., 1999 Wadbo et al., 2002	I	Good	Substantial for FEV1 Moderate for symptoms	B
2	Ipratropium improved QOL compared to placebo or maintenance albuterol.	Dahl et al., 2001 Friedman et al., 1999 Mahler et al., 1999 Rennard et al., 2001	I	Good	Moderate	B
3	Ipratropium was equivalent to maintenance albuterol for FEV1.	Friedman et al., 1999	I	Good	Substantial	C
4	Short-acting beta 2-agonists improve FEV1, respiratory symptoms, and reduce exacerbations.	Donohue et al., 2006 Nair et al., 2005 Sestini et al., 2002	I	Good	Moderate	B
5	HFA ipratropium is equivalent to CFC for FEV1.	Brazinsky et al., 2003 Taylor et al., 2001	I	Fair	Substantial	B

QE = Quality of Evidence; Net Effect = Size of Intervention Effect; R = Strength of Recommendation (See Appendix A)

14.2 Long-Acting Inhaled Beta 2-Agonists in Patients with COPD

BACKGROUND

Long-acting beta 2-agonists (LABA) act by increasing cyclic adenosine monophosphate in airway smooth muscle, thereby causing bronchodilation. LABAs are used as maintenance treatment only. The 2 available LABAs have different actions. Salmeterol has a slow onset and prolonged duration of action. Formoterol has a rapid onset and a prolonged duration of action. There have been no long-term head-to-head trials comparing the 2 available LABAs in COPD.

Studies have examined the effect of LABAs on FEV1, an increase of which is a measure of physiological reversibility, and on patient-related outcomes such as symptoms, QOL, and COPD exacerbations.

The FDA issued an alert notifying manufacturers of Advair Diskus, Foradil Aerolizer, and Serevent Diskus to update their existing product labels with new warnings and a Medication Guide for patients to alert healthcare professionals and patients that these medicines may increase the chance of severe asthma episodes, and death when those episodes occur. All of these products contain long-acting beta2-adrenergic agonists (LABA). Even though LABAs decrease the frequency of asthma episodes, these medicines may make asthma episodes more severe when they occur. A Medication Guide with information about these risks will be given to patients when a prescription for a LABA is filled or refilled [see Public Health Advisory November, 2005].

ACTION STATEMENT

Consider using a long-acting inhaled beta 2-agonist (LABA) to improve QOL or respiratory symptoms such as dyspnea [A], and to reduce exacerbations [C]. Educate patient about the use of inhaler devices

RECOMMENDATIONS

1. Long-acting inhaled beta 2-agonists (LABA) should be considered for patients with COPD with an FEV1 70 percent predicted or less to:
    a. Improve FEV1 [B]
    b. Improve persistent respiratory symptoms such as dyspnea, or impaired health-related quality of life (QOL) [A]
    c. Reduce exacerbations in patients who have had at least one exacerbation in the previous year and required glucocorticoids, antibiotics, or hospitalization [C].
2. In general, a long-acting inhaled beta 2-agonist (LABA) should not be substituted for a short-acting anticholinergic (SAAC) with the expectation of improving respiratory symptoms, quality of life (QOL), or exacerbations. [B]

RATIONALE

- Compared to no maintenance bronchodilator therapy, LABAs improve pulmonary function, respiratory symptoms, and QOL and inconsistently reduce the frequency of exacerbations. The improvement in QOL is most consistent in studies of one year duration. The reduction in exacerbations has been most consistent in patients who have had a previous history of at least one exacerbation in the past year. However, there is no proven outcome benefit when a LABA is compared to short-acting anticholinergic used as maintenance therapy. The studies to date have only examined patients with an FEV1 70 percent predicted or less.

EVIDENCE STATEMENTS

- Two systematic reviews supported the benefit of salmeterol for improvement in health-related QOL, reduction in symptoms, consistent reduction in exacerbations and lung function. They also provided qualified support for similar outcomes for formoterol (Appleton et al., 2006a; Stockley et al., 2006b). There was no evidence of tachyphylaxis to salmeterol over 12 months (Stockley et al., 2006b).

- Six 12-week studies of a LABA compared to placebo plus as-needed short-acting beta 2-agonist collectively supported significant improvement in FEV1 and respiratory symptoms and a trend toward improvement in QOL (Aalbers et al., 2002; Dahl et al., 2001; Mahler et al., 1999; Rennard et al., 2001; van Noord et al., 2000; Wadbo et al., 2002). Mahler and colleagues (1999) had a reduction in time to first exacerbation, but the other studies did not support a consistent reduction in exacerbations.

- Four of these studies (Dahl et al., 2001; Mahler et al., 1999; Rennard et al., 2001; Wadbo et al., 2002) compared a LABA to ipratropium. Collectively, these studies had a trend toward improvement of FEV1 by the LABA, but respiratory symptoms and QOL were essentially the same between treatments. One study had a reduction in time to first exacerbation, but the other studies did not support this finding.

- Three studies comparing salmeterol to placebo for 6 months supported improvement in FEV1 and respiratory symptoms; however, no consistent reduction in exacerbations (Brusasco et al., 2003; Hanania et al., 2003; Mahler et al., 2002). Two studies for 12 months supported significant improvement in FEV1 and respiratory symptoms (Calverley et al., 2003b; Stockley et al., 2006a,b).

- Four studies that followed patients for one year supported significant improvement in FEV1, symptoms, and QOL (Calverley et al., 2003a; Rossi et al., 2002; Szafranski et al., 2003).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	Net Effect	R
1	LABA (formoterol or salmeterol) improved FEV1 compared to placebo.	Aalbers et al., 2002 Appleton et al., 2006a Brusasco et al., 2003 Calverley et al., 2003a; 2003b Dahl et al., 2001 Hanania et al., 2003 Mahler et al., 1999; 2002 Rennard et al., 2001 Rossi et al., 2002 Stockley et al., 2006a, 2006b Szafranski et al., 2003 van Noord et al., 2000 Wadbo et al., 2002	I	Fair	Substantial	B
2	LABA (formoterol or salmeterol) improved respiratory symptoms compared to placebo.	Aalbers et al., 2002 Brusasco et al., 2003 Calverley et al., 2003a; 2003b Dahl et al., 2001 Hanania et al., 2003 Mahler et al., 1999 Rossi et al., 2002 Stockley et al., 2006a, 2006b Szafranski et al., 2003 van Noord et al., 2000 Wadbo et al., 2002	I	Good	Substantial	A
3	Formoterol improved QOL.	Calverley et al., 2003a Dahl et al., 2001 Rossi et al., 2002 Szafranski et al., 2003	I	Good	Substantial	A
4	Salmeterol improved QOL and reduced exacerbations.	Appleton et al., 2006a Mahler et al., 1999 Calverley et al., 2003b Stockley et al., 2006a, 2006b	I	Good	Small	C
5	Formoterol or salmeterol inconsistently improved FEV1, QOL, and respiratory symptoms compared to ipratropium, with little or no improvement in exacerbations.	Dahl et al., 2001 Mahler et al., 1999 Rennard et al., 2001 Wadbo et al., 2002	I	Good	Small	C

QE = Quality of Evidence; Net Effect = Size of Intervention Effect; R = Strength of Recommendation; (See Appendix A)

14.3 Long-Acting Inhaled Anticholinergics in Patients with COPD

BACKGROUND

Long-acting anticholinergics (LAAC) act by blocking the constricting effect of acetylcholine on airway smooth muscle. These bronchodilators are used as maintenance treatment only. Studies have examined the effect of a LAAC on FEV1and on patient-related outcomes such as symptoms, QOL, COPD exacerbations, exercise capacity, and hospitalizations.

ACTION STATEMENT

Consider using a long-acting inhaled anticholinergic (LAAC) in patients with COPD to improve respiratory symptoms and QOL or reduce moderate to severe exacerbations [A]; or to improve FEV1 or reduce hospitalizations [B].

RECOMMENDATIONS

1. Long-acting anticholinergics (LAAC), compared to placebo or maintenance short-acting anticholinergic (SAAC), should be considered for patients with COPD and an FEV1 65 percent predicted or less to:
    a. Improve persistent respiratory symptoms such as dyspnea or impaired quality of life (QOL) [A]
    b. Reduce moderate to severe COPD exacerbations (i.e., exacerbations requiring antibiotics and/or oral or systemic glucocorticoids) [A]
    c. Reduce COPD-related hospitalizations [B].
2. When a long-acting anticholinergic (LAAC) is used to improve patient outcomes in patients taking a short-acting anticholinergic (SAAC), the SAAC should be discontinued. [I] However, the use of a short-acting beta 2-agonist (SABA) as needed for rescue therapy should be continued.
3. In choosing long-acting bronchodilators, both long-acting anticholinergics (LAAC) and long-acting beta 2-agonists (LABA) provide similar benefits; however, there may be more modest improvement in FEV1 with LAAC. [B]

RATIONALE

- Compared to placebo plus a SABA used as-needed or to placebo plus maintenance anticholinergic, a LAAC improves pulmonary function and patient-related outcomes such as dyspnea, QOL, and frequency of exacerbations and hospitalizations. However, while there is a modest improvement in FEV1, there is no other proven outcome benefit when a LAAC is compared to a LABA. LAAC has been shown to have the same degree of improvement in the FEV1 after one year. The studies to date have only examined patients with an FEV1 lower than 65 percent predicted.

EVIDENCE STATEMENTS

- A review of the available published literature (Barr et al., 2005) of RCTs of a LAAC compared to placebo and ipratropium provides evidence for significant and substantial improvement in FEV1, exacerbations, respiratory symptoms, and COPD-related QOL. There is a substantial trend to a reduction in hospitalizations compared to placebo and ipratropium (Niewoehner et al., 2005). More recent RCTs support these conclusions (Dusser et al., 2006). There is a significant substantial improvement in FEV1 and cycle ergometer exercise capacity with tiotropium compared to placebo in one study (O'Donnell et al., 2004).

- A Cochrane review of the available published literature (Barr et al., 2005) and a more recent systematic review (Barr et al., 2006) provide evidence for a significant, moderate improvement in post-dose FEV1 of tiotropium compared to a LABA. There is a small, nonsignificant trend to improvement in trough FEV1, dyspnea, exacerbations, hospitalizations, and COPD-related QOL compared to salmeterol (Briggs et al., 2005). More recent RCTs support these conclusions (Oostenbrink et al., 2005). There is a small

nonsignificant trend to improvement in trough FEV1 compared to formoterol (Van Noord et al., 2005).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	Net Effect	R
1	Tiotropium improved QOL, dyspnea, or exacerbations compared to placebo and maintenance ipratropium.	Barr et al., 2005 Barr et al., 2006 Dusser et al., 2006 Niewoehner et al., 2005	I	Good	Substantial	A
2	Tiotropium improved FEV1, or hospitalizations compared to placebo and maintenance ipratropium.	Barr et al., 2005 Niewoehner et al., 2005	I	Fair	Moderate	B
4	Tiotropium improved FEV1 compared to salmeterol or formoterol.	Barr et al., 2005 Briggs et al., 2005 Van Noord et al., 2005	I	Fair	Small	C
5	Tiotropium did not significantly improve dyspnea, QOL, exacerbations, or hospitalizations compared to salmeterol.	Barr et al., 2005 Barr et al., 2006 Briggs et al., 2005 Oostenbrink et al., 2005	I	Fair	Small	C

QE = Quality of Evidence; Net Effect = Size of Intervention Effect; R = Strength of Recommendation (See Appendix A)

15 Combination of Inhaled Bronchodilators

BACKGROUND

The 3 classes of bronchodilators used in the treatment of COPD include beta 2-agonists, anticholinergics, and theophylline. Each drug class affects airway caliber through different mechanisms of action. In addition, it appears that beta 2-agonists target the smaller airways and anticholinergics, the larger airways. When single-agents do not provide adequate control, combining agents from different therapeutic classes may result in added efficacy. At this time, the following combinations have been studied: short-acting beta-agonist (SABA) and short-acting anticholinergic (SAAC); long-acting beta-agonist (LABA) and SAAC; LABA and long-acting anticholinergic (LAAC); theophylline with a SABA and a SAAC; and theophylline and a LABA.

ACTION STATEMENT

Combination bronchodilator therapy may be considered for patients with inadequate response to single agents to improve FEV1 and to reduce symptoms and/or exacerbations. [B]

RECOMMENDATIONS

1. When response to therapy with a short-acting beta-agonist (SABA) is inadequate, consider the use of regularly scheduled combination SABA + short-acting anticholinergic (SAAC) to improve FEV1 and reduce exacerbations compared to treatment with the individual components. [B]

2. When response to regularly scheduled SAAC or combination of SABA + SAAC is inadequate, consider the use of combination SAAC + long-acting beta 2-agonist (LABA) to improve FEV1 and symptoms and reduce exacerbations compared to treatment with the individual components. [B]
3. When response to a LABA + SAAC or a long-acting anticholinergic (LAAC) alone is inadequate, consider the use of combination LABA + LAAC to improve FEV1. [B]
4. Consider the use of theophylline in addition to short-acting bronchodilators to improve FEV1. [B]
5. Consider the use of theophylline in addition to LABA to improve FEV1, symptoms, and quality of life (QOL) compared to therapy with the individual components. [B]
6. There is insufficient evidence to recommend that certain combinations are superior to other combinations, monotherapy with LAAC, or regimens including an inhaled glucocorticoid. Therefore, treatment selection should be based on patient-specific variables. [I]

RATIONALE

- Combination bronchodilators are often used when single agents do not provide adequate symptomatic control. While several studies have evaluated combination therapy, only one has been conducted in the setting of patients having had inadequate response to prior therapy. Nevertheless, drugs with different mechanisms and possibly different sites of action suggest a clinical rationale for combination therapy.

EVIDENCE STATEMENTS

- Four studies suggested that a combination of SABA and SAAC compared to the use of a single agent leads to improvement in FEV1, decrease in exacerbation, and little change in respiratory symptoms. Two of these studies, which were large RCTs, used meter dose inhalers (Campbell, 1999; COMBIVENT, 1994). A post-hoc analysis by Freidman et al. (1999) suggested that ipratropium containing combinations may reduce exacerbations. The other 2 studies compared a combination of SABA and SAAC given by nubulizers to each agent alone (COMBIVENT, 1997; Gross et al., 1998).

- Three studies suggested that a combination of a LABA and a SAAC appear to have some increased benefit in FEV1, symptoms scores, and HRQL over a SAAC and SABA (Chapman et al., 2002; D'Urzo et al., 2001; van Noord et al., 2000).

- One randomized 3-way crossover study (6-weeks per arm) compared the combination of formoterol 12 µg + tiotropium 18 µg once daily versus formoterol 12 µg BID or tiotropium 18 µg once daily in 71 stable patients with COPD. Average FEV1 after the morning dose using the combined agent were significantly greater compared to either agents alone (van Noord et al., 2000; 2006).

- Combination LABA and theophylline provided greater improvement in pulmonary function, HRQL, and dyspnea than either agent alone. The combination reduced exacerbations compared to placebo and there was a trend towards reduced exacerbations compared to the LABA alone (ZuWallack et al., 2001).

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	Net Effect	R
1	Combination SABA + SAAC improved FEV1 and decreased exacerbations.	Campbell, 1999 COMBIVENT, 1994 COMBIVENT,1997 Friedman et al., 1999 Gross et al., 1998	I	Fair	Moderate	B
2	Combination LABA + SAAC caused improvement in FEV1and a trend in decreased exacerbations and improved symptoms.	Appleton et al., 2006a Chapman et al., 2002 D'Urzo et al., 2001 van Noord et al., 2000	I	Fair	Moderate	B
3	Combination LABA + LAAC provided greater improvement in pulmonary function than either agent alone.	van Noord et al., 2000 van Noord et al., 2006	I	Fair	Moderate	B
4	Combination short-acting agents and theophylline provided greater improvement in pulmonary function than either agent alone.	Nishimura et al., 1993 Nishimura et al.; 1995	I	Fair	Moderate	B
5	Combination LABA and theophylline improved FEV1.	ZuWallack et al., 2001	I	Good	Moderate	B

QE = Quality of Evidence; Net Effect = Size of Intervention Effect ; R = Strength of Recommendation (See Appendix A)

16 Inhaled Glucocorticoids

BACKGROUND

COPD is associated with a progressive decline in lung function and QOL. Exacerbations of COPD that require treatment with systemic glucocorticoids, antibiotics, or hospitalization are major determinants of the QOL and are associated with an increase in the rate of decline in QOL and, possibly, lung function. Exacerbations tend to be more frequent and have larger impact on the patient when the COPD is more severe. Furthermore, exacerbations, particularly if associated with hospitalization, are costly. Therefore, a reduction in exacerbation rate in addition to improvements in spirometry, symptoms, and QOL are desirable.

There is good evidence that treatment with inhaled glucocorticoids in patients with severe COPD (FEV1 < 50% predicted) AND with frequent exacerbations reduces the rate of exacerbations. Inhaled glucocorticoids may also cause a small increase in FEV1 and reduce the rate of deterioration in health status. Furthermore, LABAs improve FEV1 and symptoms in patients with COPD. Therefore, it has been postulated that the combination of an inhaled glucocorticoid and a LABA may have a larger effect on FEV1, symptoms, exacerbation, and QOL in patients with COPD than administration of either of these components alone.

There are also theoretical reasons for postulating such an additive effect. Studies in asthma have suggested synergistic action between inhaled glucocorticoids and LABAs. In COPD, a similar effect may exist.

Smoking and COPD in itself are risk factors for the development of osteoporosis. Chronic use of oral glucocorticoids in the treatment of COPD places patients at risk for, or potentially worsens, existing osteoporosis. There is concern that the chronic use of inhaled glucocorticoids in the treatment of COPD leads to an increased loss of bone mineral density and the development of osteoporosis and bone fractures.

ACTION STATEMENT

Consider adding inhaled glucocorticoids to optimize bronchodilator therapy in patients with COPD who have both severe disease (FEV1 < 50 percent predicted) and who have had at least one exacerbation in the prior year, to reduce the frequency of exacerbations. [A]

Alternatively, consider adding inhaled glucocorticoids in patients with severe COPD (FEV1 < 50 percent predicted) to improve FEV1, respiratory symptoms, and QOL. [B]

RECOMMENDATIONS

1. Inhaled glucocorticoids are not recommended in patients with mild to moderate COPD (FEV1 ≥ 50 percent predicted) as there is little evidence of efficacy. [D]
2. Combination of a long-acting beta 2-agonist (LABA) and inhaled glucocorticoid may be considered in patients with severe COPD and at least one COPD exacerbation in the prior year to decrease the incidence of COPD exacerbations compared to therapy with the individual components. [A]
3. Combination of a long-acting beta 2-agonist (LABA) and inhaled glucocorticoid can be used in symptomatic patients with severe COPD to improve FEV1(approximately 0 to 100 ml), symptoms, and/or quality of life (QOL). [B]
4. There is insufficient evidence to recommend a specific choice or optimal dose when starting treatment with inhaled glucocorticoids. The doses used in efficacy trials (fluticasone proprionate 500 µg bid, budesonide 400 µg bid) or equivalent dosages are recommended. [I]
5. Once treatment with inhaled glucocorticoids has been initiated, it is recommended to use caution when stopping the medication, as discontinuation may lead to COPD exacerbation. [B]
6. Patients should be informed about the potential side effects of inhaled glucocorticoids (oral candidiasis, bruising, adrenal suppression, cataracts, and osteoporosis). [B]
7. Treatment with inhaled glucocorticoids does not significantly affect the rate of decline in FEV1. [C]
8. Patients with COPD who are receiving oral or inhaled glucocorticoids should be evaluated for bone loss and considered for prevention or treatment of osteoporosis. [I]
9. The risks of long-term treatment with glucocorticoids should be discussed with the patient. [I]

RATIONALE

- Airway inflammation is an integral component in the pathogenesis of COPD. In patients with mild to moderate disease (FEV1 greater than 50 percent predicted) the airway inflammation is

predominantly neutrophilic. Glucocorticoids are generally not effective against neutrophils. However, in patients with severe disease (FEV1 < 50 percent predicted) there is a mixture of inflammatory cells. This mixture, which includes lymphoid follicles, may be the result of repeated exacerbations and contains cells that are glucocorticoid responsive. Consequently, the effects of inhaled glucocorticoids on lung function, symptoms, exacerbations, and mortality has been investigated in patients with COPD. As there is less systemic absorption with inhaled glucocorticoids compared to oral glucocorticoids, side effects are expected to be reduced.

EVIDENCE STATEMENTS

- The literature on the effect of inhaled glucocorticoids on lung function, exacerbations, symptoms, and QOL in patients with COPD is complex and highly contentious. Study designs have been variable. As results and conclusions are also dependent on disease severity, the evidence is presented for patients with mild to moderate disease and for those with moderate to severe disease.

  Mild to moderate COPD: Three large, long (3-year) trials have been performed in patients with mild to moderate COPD. In 2 of these trials, budesonide was compared to placebo (Pauwels et al., 1999; Vestbo et al., 1999) and in the remaining one triamcinolone was compared to placebo (The Lung Health Study Research Group, 2000).

  These studies in this population demonstrated that: (1) the rate of decline in FEV1 was not significantly affected by inhaled glucocorticoids; (2) a small initial improvement in FEV1 may occur with inhaled glucocorticoids (Pauwels et al., 1999), but this observation was not uniform (The Lung Health Study Research Group, 2000; Vestbo et al., 1999); and (3) reductions in exacerbations and symptoms may occur with inhaled glucocorticoids (The Lung Health Study Research Group, 2000), but these results also were inconsistent (Vestbo et al., 1999).

  A systematic review of 13 RCTs and 11 observational studies concluded that existing evidence does not indicate a treatment benefit for patients with mild COPD (Gartlehner et al., 2006).

  Moderate to severe COPD: Studies of inhaled glucocorticoids in patients with moderate to severe COPD vary widely in design. Studies vary in size, duration, disease severity, comparators (the selected glucocorticoid vs. placebo and/or LABA), inclusion criteria (smokers, reversibility, existence of prior exacerbations), presence of systemic glucocorticoid run-in phase, definition of exacerbation and its severity, symptoms studied, and QOL measures. These factors complicate interpretation of results.

  To summarize these individual studies: inhaled glucocorticoids appear to have no substantial effect on rate of decline in FEV1, may cause a small improvement in FEV1, may decrease exacerbations, and may improve symptoms and QOL.

  The above studies in patients with moderate and severe COPD and the studies in patients with mild to moderate COPD and several additional small studies have been combined and reviewed in detail (Alsaedi et al., 2002). This review, encompassing 3,976 patients, showed an overall decrease in exacerbation rate with inhaled glucocorticoids compared to placebo (RR=0.70, 95%CI: 0.58-0.84) (Alsaedi et al., 2002). In a further review of these randomized trials, it was shown the greatest reduction in exacerbations occurred in the patients with the lowest FEV1 (Sin et al., 2003). The pooled RR for COPD exacerbations among trials enrolling patients with a mean FEV1 of 2.0 L or less was 0.75 (95%CI: 0.71-0.80). Similar conclusions were drawn from a post hoc analysis (Jones et al., 2003) of the data obtained in the

Isolde study (Burge et al., 2003). In the Isolde study, fluticasone reduced the overall exacerbation rate by 25 percent from 1.32/year on placebo to 0.99/year on fluticasone ($p < 0.026$). When reanalyzed according to disease severity (Jones et al., 2003), it was shown that fluticasone only had a significant effect in reduction on exacerbations in the moderate to severe group (1.75 vs. 1.47, $p < 0.022$) and that there was no significant reduction in the mild group (0.92 vs. 0.67, $p=0.45$). Thus, efficacy of inhaled glucocorticoids in reducing exacerbations increases as disease severity increases (Sin et al., 2003).

Comparison between placebo, inhaled glucocorticoid, LABA and the combination of inhaled glucocorticoid and LABA. (For details on all arms of the study, see the combination long-acting beta 2-agonist and inhaled glucocorticoid section.)

The focus here is only on the comparisons of the inhaled glucocorticoid and placebo arms of those studies. Five such studies have been performed: 3 with the salmeterol fluticasone combination (Calverley et al., 2003b; Mahler et al., 2002; Hanania et al., 2003), and 2 with the budesonide formoterol combination (Szafranski et al., 2003; Calverley et al., 2003b).

To summarize these studies: inhaled glucocorticoids may cause a small improvement in FEV1, decrease exacerbations, and improve symptoms and QOL.

Individual studies (see above) showed no effect of inhaled glucocorticoids on the rate of decline in FEV1. One meta-analysis (Sutherland et al., 2003) using pooled data from 8 trials lasting more than 2 years and encompassing 3,715 subjects with moderate to severe COPD showed a reduction in rate of decline of FEV1 of 7.7 ml/year (95%CI: 1.3-14.2 ml/year, $p=0.02$) with inhaled glucocorticoids – a statistically significant but clinically very small effect. However, another more recent meta-analysis (Highland et al., 2003) using pooled data from 6 trials, encompassing 3,571 subjects found an increase in rate of decline of FEV1 of 5.0 ml/year (95%CI: -1.2 to 11.2 ml/year) with inhaled glucocorticoids. As these results are opposite, conflicting, and small in magnitude, it appears that inhaled glucocorticoids have a clinically insignificant effect, if any, on rate of decline in FEV1.

A post hoc analysis suggests that the response to inhaled glucocorticoids cannot be predicted from the response to a short course of oral glucocorticoids (Burge et al., 2003).

As the randomized studies (see above) have been performed with a variety of inhaled glucocorticoids and different dosages (e.g., fluticasone proprionate 500 µg bid, budesonide 400 µg bid, triamcinolone acetonide 600 µg bid), no inhaled glucocorticoid can be recommended over any other and there is no information on the optimal or minimally efficacious dose.

Little or no effect of inhaled glucocorticoids on mortality was found in the randomized studies (Alsaedi et al., 2002; Bourbeau et al., 1998; Burge et al., 2003; Paggiaro et al., 1998; Pauwels et al., 1999; Sin et al., 2003; The Lung Health Study Research Group, 2000; Vestbo et al., 1999; Weir et al., 1999), and the three year large study that measured mortality as the primary outcome (Calverley et al., 2007). This is in contrast to retrospective epidemiological data that suggested that initiation of inhaled glucocorticoids after hospitalization for an exacerbation may decrease mortality (Kiri et al., 2005; Sin et al., 2001) that were reported as having methodological problems (Suissa, 2003 & 2004).

Inhaled glucocorticoids are associated with increased oral candidiasis and skin bruising and decreased cortisol levels, but effects on cataracts, bone mineral density

and osteoporosis have been variable and inconclusive in these 3 years, but still relatively short term, studies (Burge et al., 2003; Pauwels et al., 1999; The Lung Health Study Research Group, 2000; Vestbo et al., 1999).

Cessation of inhaled glucocorticoids can lead to an increase of exacerbations (van der Valk et al., 2002; Wouters et al., 2005).

In the first study (van der Valk et al., 2002), 244 patients (mean FEV1 approximately 57 percent predicted) on fluticasone proprionate 1,000 µg/day for 4 months were randomized to continue fluticasone or placebo for another 5 months. Less patients in the fluticasone group developed exacerbation than in the placebo group (47 percent vs. 57 percent) with a hazard ratio for first exacerbation of 1.5 (95%CI: 1.05-2.1) in the placebo compared to the fluticasone group. Symptoms and health-related QOL were also significantly better in the fluticasone than placebo groups.

In the second study (Wouters et al., 2005), 497 patients (mean FEV1 approximately 49 percent predicted) treated with fluticasone-salmeterol 500/50 µg bid for 3 months were randomized over one year to remain on fluticasone-salmeterol or receive salmeterol. The mean annual exacerbation rates for moderate to severe exacerbations in the salmeterol group was 1.6 and in the salmeterol plus fluticasone group was 1.3 (p=0.15). For mild exacerbations the rates were 1.3 in the salmeterol group and 0.6 in the salmeterol plus fluticasone group (p=0.02). These studies suggest that withdrawal of inhaled glucocorticoids once started can lead to disease deterioration.

Adverse effects of glucocorticoids:

- Oral glucocorticoids produce many side-effects especially osteoporosis, peripheral myopathy, and cataracts.
- Data on the effect of inhaled glucocorticoids on bone mineral density is contradictory, with evidence of significant reductions in femoral neck mineralization after use of triamcinolone (The Lung Health Study Research Group, 2000) but no change in bone density after budesonide (Pauwels et al., 1999).
- One long-term study showed no effect of budesonide on bone density and fracture rate (Johnell et al., 2002; Pauwels et al., 1999), while another study showed that treatment with triacinolone acetonide was associated with a decrease in bone density (The Lung Health Study Research Group, 2000).
- Spontaneous skin bruising is a common finding that has been noted to occur with inhaled glucocorticoids more frequently than in patients randomized to placebo medication in the one clinical trial where it has been assessed.
- Topical side effects due to pharyngeal deposition are well recognized and include oropharyngeal candiasis and hoarse voice.

EVIDENCE TABLE

	Evidence	Source	QE	Overall Quality	Net Effect	R
1	In moderate to severe COPD, inhaled glucocorticoids decrease exacerbations (~20 to 30 percent) and can cause a small increase in FEV1 (< 100 ml) and improve symptoms and QOL.	Alsaedi et al., 2002 Bourbeau et al., 1998 Burge et al., 2003 Calverley et al., 2003a, 2003b, 2007 Hanania et al., 2003 Jones et al., 2003 Kardos et al., 2007 Lofdahl et al., 2005 Mahler et al., 2002 Paggiaro et al., 1998 Pauwels et al., 1999 Sin et al., 2003 Szafranski et al., 2003 The Lung Health Study Research Group, 2000 Vestbo et al., 1999 Weir et al., 1999	I	Good	Substantial decrease in exacerbations Moderate improvement in FEV1 Improvement in symptoms and QOL	A C
2	Inhaled glucocorticoids have no effect on exacerbation rate in mild to moderate COPD.	Alsaedi et al., 2002 Gartlehner et al., 2006 Jones et al., 2003 Pauwels et al., 1999 Sin et al., 2003 The Lung Health Study Research Group, 2000 Vestbo et al., 1999	I	Good	Negligible	D
3	Withdrawal of inhaled glucocorticoids can lead to exacerbations.	Van der Valk et al., 2002 Wouters et al., 2005	I	Good	Moderate	B
4	Glucocorticoids produce many side effects.	The Lung Health Study Research Group, 2000	I	Good	Moderate	B
5	Inhaled glucocorticoids do not significantly affect the rate of decline in FEV1.	Highland et al., 2003 Sutherland et al., 2003	I	Good	Negligible	C

QE = Quality of Evidence; Net Effect = Size of Intervention Effect; R = Strength of Recommendation; (See Appendix A)

17 Theophylline

BACKGROUND

Methylxantines include theophylline, aminotheophylline, and its derivates. Theophylline has a narrow therapeutic index, with the potential for dose-related adverse reactions that include insomnia, anxiety, nausea, vomiting, tremor, arrhythmias, delirium, seizures, and death. The narrow therapeutic margin and complex pharmacokinetics make their use difficult; however, the slow release preparation has improved the use and had lead to a more stable plasma level throughout the day. Many theophylline preparations are available, but sustained release

formulations may provide longer control and better benefit for nocturnal dyspnea. Because of potential toxicity and significant interactions with other drugs, theophylline is no longer considered initial empirical treatment. When reference is made to theophylline, it is to the long-acting/slow release formulations, unless otherwise stated.

ACTION STATEMENT

Theophylline can be added to improve pulmonary function, symptoms, or activities in patients with COPD who do not achieve adequate symptom control with inhaled bronchodilators. [A]

RECOMMENDATIONS

1. Patients with COPD who do not achieve adequate symptom control with inhaled bronchodilators may be considered for adding theophylline therapy with an initial dose of 400 to 600 mg/day and a therapeutic target of blood level in the range 5 to 12 µg/ml. [A]
2. Blood levels should be carefully measured after initiation or change in dose. [I]
3. After the initial stability, repeat levels should be obtained when symptoms change, acute illness develops, potentially interacting drugs are added, noncompliance is suspected, dose adjustments are made, or symptoms suggestive of toxicity develop. [I]
4. If benefit has been demonstrated with a higher blood level (15 µg/ml of theophylline), careful monitoring is required. The risk-to-benefit ratio increases above a concentration of 12 µg/ml, especially in older patients. [B]
5. Drug interactions with theophylline are common and may either increase or decrease theophylline metabolism. All changes in medical regimens should be evaluated for potential impact on theophylline levels. [C]
6. Theophylline should be continued only in patients who demonstrate a symptomatic benefit, such as improved dyspnea or exercise tolerance. The improvement in function from theophylline may not be evident in pulmonary function testing. However, therapy should be discontinued in patients who demonstrate no subjective or objective improvement after several weeks of theophylline therapy. [D]

RATIONALE

- Methylxantines are nonspecific phosphodiesterase inhibitors that increase intracellular cyclic adenosine monophosphate within airway smooth muscle. The bronchodilator effects of these drugs are best seen at high doses where there is also a higher risk of toxicity. Theophylline is metabolized through the cytochrome P450 pathway. Medications metabolized through this pathway are associated with significant food and medication interactions. Theophylline, as adjunctive therapy with beta-antagonists or anticholinergics, can alleviate shortness of breath symptoms, reduce exacerbations, and improve exercise tolerance compared to individual agents alone in patients with stable COPD.

EVIDENCE STATEMENT

- Theophylline was also significantly more effective at increasing FEV1 than placebo at every time point and for each visit (all $p < 0.005$) in the study by Rossi et al. (2002) and the difference was clinically relevant at 5-, 7-, 8-, 10-, 11-, and 12-hours. The study included 844 patients with inhaled formoterol, 12 µg bid, vs. 24 µg bid, vs. oral theophylline, vs. placebo. Formoterol, 12 µg, improved FEV1 compared to placebo and theophylline but did not reduce moderate to severe exacerbations. Formoterol, 24 µg bid, improved FEV1 compared to

placebo but was inferior to 12 µg at 12 months. Formoterol, 24 µg, reduced moderate to severe exacerbations. Formoterol at both doses improved health-related QOL. Both formoterol doses were superior to theophylline (Rossi et al., 2002).

- A meta-analysis of 4 studies of 169 patients for acute treatment of COPD exacerbations indicated no benefit and increased side effects from methylxanthines, such as theophylline (Barr et al., 2003).

Theophylline Combination Therapy

- In a controlled trial, clinically used oral doses of theophylline (target theophylline level of 10 to 20 µg) combined with inhaled salmeterol increased FEV1 more and reduced dyspnea better than either alone, and the combination reduced COPD exacerbations more compared to either alone. However, this difference was significant ($p < 0.05$) compared to theophylline but not to salmeterol ($p = 0.07$). Drug-related adverse events were greater with theophylline-containing regimens (ZuWallack et al., 2001).

- Ram and colleagues analyzed 20 RCTs evaluating theophylline either alone or in combination with other COPD bronchodilators and inhaled glucocorticoids. There was a statistically significant modest improvement in FEV1 and FVC in favor of the theophylline group compared to placebo, and slight improvement in arterial blood gases (Ram et al., 2002). Patients also preferred treatment with theophylline when compared with placebo. The benefits of theophylline have to be weighed against the risk of adverse effects (Ram, 2006).

- Oxitropium bromide (not available in the U.S.) in combination with theophylline provided a greater improvement in evening post-dosing peak expiratory flow rate and improved the QOL alone or in combination with theophylline (Bellia et al., 2002).

EVIDENCE TABLE

	Evidence	**Source**	**QE**	**Overall Quality**	**R**
1	Improvement in FEV1 and FVC and symptoms in favor of the theophylline group compared to placebo.	Chen et al., 2005 Ram et al., 2002 Ram, 2006 Rossi et al., 2002 Zhou et al., 2006	I	Good	B
2	Combination treatment with salmeterol + theophylline increased FEV1 and reduced dyspnea better than either alone, but is associated with an increased incidence of gastrointestinal side effects.	ZuWallack et al., 2001	I	Good	B
3	Theophylline may prevent exacerbations.	Rossi et al., 2002	I	Good	B
4	Theophylline has no benefit in treatment of COPD exacerbations and increased adverse effects.	Barr et al., 2003	I	Fair	D

QE = Quality of Evidence; R = Strength of Recommendation (See Appendix A)

APPENDICES

APPENDIX A

GUIDELINE DEVELOPMENT PROCESS

The update of the VA/DoD Clinical Practice Guideline for Management of COPD was initiated in summer of 2005. The development process followed the steps described in "Guideline for Guidelines," an internal working document of the VA/DoD Evidence Based Practice Working Group, that requires an ongoing review of the work in progress. The Working Group of the VA/DoD was charged to update the evidence-based action recommendations whenever possible; hence, major clinical randomized controlled trials (RCTs) and observational studies published from 2000 through November 2006 in the areas of COPD were used.

Guideline Development Process

The Offices of Quality and Performance and Patient Care Services, in collaboration with the network Clinical Managers, the Deputy Assistant Under Secretary for Health, and the Medical Center Command of the DoD identified clinical leaders to champion the guideline development process. During a preplanning conference call, the clinical leaders defined the scope of the guideline and identified a group of clinical experts from the VA and DoD that formed the Management of COPD Working Group. Working Group members included representatives of the following specialties: Pulmonology, Internal Medicine, Primary Care, Physiotherapy, Nursing, and Pharmacology.

As a first step, the Working Group defined a set of clinical questions within the area of the guideline. This ensured that the guideline development work outside the meeting focused on issues that practitioners considered important and produced criteria for the search and the protocol for systematic review and, where appropriate, meta-analysis.

The Working Group participated in an initial face-to-face meeting to reach consensus about the guideline algorithm and recommendations and to prepare a draft document. The draft continued to be revised by the Working Group at-large through numerous conference calls and individual contributions to the document. Following the initial effort, an editorial panel of the Working Group convened to further edit the draft document. Recommendations for the performance or exclusion of specific procedures or services were derived through a rigorous methodological approach that included the following:

- Determining appropriate criteria, such as effectiveness, efficacy, population benefit, or patient satisfaction
- Reviewing literature to determine the strength of the evidence in relation to these criteria
- Formulating the recommendations and grading the level of evidence supporting the recommendation

Experts from the VA and DoD in the areas of pulmonology reviewed the final draft and their feedback was integrated into the final draft document. This document will be updated every 3 years, or when significant new evidence is published to ensure that Department of Veterans Affairs (VA) and Department of Defense (DoD) healthcare delivery remain on the cutting edge of the latest medical research.

This update of the COPD Guideline is the product of many months of diligent effort and consensus building among knowledgeable individuals from the VA, DoD, academia, as well as guideline facilitators from the private sector. An experienced moderator facilitated the multidisciplinary Working Group. The list of participants is included in Appendix E.

Formulation of Questions

The Working Group developed researchable questions and associated key terms after orientation to the scope of the guideline and to goals that had been identified by the Working Group. The questions specified (adapted from the Evidence-Based Medicine toolbox, Center for Evidence-Based Medicine, (http://www.cebm.net):

- **P**opulation – Characteristics of the target patient population
- **I**ntervention – Exposure, diagnostic, or prognosis
- **C**omparison – Intervention, exposure, or control used for comparison
- **O**utcome – Outcomes of interest.

These specifications served as the preliminary criteria for selecting studies. Research questions focused on the following areas of inquiry:

1. Does treatment based on **symptoms** compared to treatment based on **spirometry (FEV1)** lead to better outcomes?
2. Do **inhaled and/or oral bronchodilators** improve outcomes (quality of life [QOL], dyspnea, frequency of COPD exacerbations, lung function [i.e., FEV1 and/or lung volumes] and exercise) compared to placebo or other comparators?
3. Does a **combination of 2 or more bronchodilator** agents compared to a single agent or other combination improve outcomes (QOL, dyspnea, frequency of COPD exacerbations, lung function [i.e., FEV1 and/or lung volumes], and exercise)?
4. Do **inhaled glucocorticoids** in patients who have mild to moderate COPD (FEV1 of 50 percent predicted or more) lead to improved outcomes (QOL, dyspnea, frequency of COPD exacerbations, lung function [i.e., FEV1 and/or lung volumes] and exercise) compared to placebo?
5. In COPD patients who are on a long-acting inhaled beta 2-agonist (LABA), does **adding an inhaled glucocorticoid** improve outcomes (QOL, dyspnea, frequency of COPD exacerbations, lung function [i.e., FEV1 and/or lung volumes] and exercise)?
6. Does early (as initial treatment) **intervention with glucocorticoids** lead to better outcomes in patients with COPD (QOL, dyspnea, frequency of COPD exacerbations, lung function [i.e., FEV1 and/or lung volumes] and exercise) compared to later (delayed treatment)?
7. Does a **combination of a long-acting beta 2-agonist plus an inhaled glucocorticoid** lead to better outcomes (QOL, dyspnea, frequency of COPD exacerbations, lung function [i.e., FEV1 and/or lung volumes] and exercise) than the individual components (i.e., LABA or inhaled glucocorticoid) or placebo?
8. In COPD patients, does **one inhaler**, vs. inhaled glucocorticoids with a long-acting beta 2-agonist in **separate inhalers**, improve outcomes (QOL, dyspnea, frequency of COPD exacerbations, lung function [i.e., FEV1 and/or lung volumes] and exercise)?
9. Should COPD patients, who are not qualified to use supplemental oxygen continuously, use **oxygen** during periods of exercise or nocturnal hypoxemia to improve outcomes (dyspnea, QOL, exercise tolerance, nocturnal pulmonary hypertension and/or survival)?
10. Does adding a brief **pulmonary rehabilitation** program affect long-term (> one year) outcome (mortality, hospitalizations, QOL, dyspnea, or exercise capacity) in moderate to severe COPD (on optimized bronchodilator therapy)?
11. What is the impact of **pulmonary rehabilitation** on health-related QOL, dyspnea, and exercise capacity in patients with COPD?

Selection of Evidence

The evidence selection was designed to identify the best available evidence to address each key question and ensured maximum coverage of studies at the top of the hierarchy of study types. Published, peer-reviewed RCTs, as well as meta-analyses and systematic reviews that include randomized controlled studies were considered to constitute the strongest level of evidence in support of guideline recommendations. This decision was based on the judgment that RCTs provide the clearest, scientifically sound basis for judging comparative efficacy. The Working Group made this decision recognizing the limitations of RCTs, particularly considerations of generalizability with respect to patient selection and treatment quality. When available, the search sought out critical appraisals already performed by others that described explicit criteria for deciding what evidence was selected and how it was determined to be valid. The sources that have already undergone rigorous critical appraisal include Cochrane Reviews, Best Evidence, Technology Assessment, and AHRQ systematic evidence reports.

In addition to Medline/PubMed, the following databases were searched: Database of Abstracts of Reviews of Effectiveness (DARE) and Cochrane Central Register of Controlled Trials. For Medline/PubMed searches, limits were set for language (English), and type of research (RCT, systematic reviews and meta-analysis).

As a result of the literature reviews, articles were identified for possible inclusion. These articles formed the basis for formulating the guideline recommendations. The following inclusion criteria were used for selecting randomized controlled trial studies:

- English language only
- Full articles only
- Age limited to adults greater than 18 years
- Randomized controlled trials or prospective studies
- Key outcomes cited.

Preparation of Evidence Tables (Reports) and Evidence Rating

The results of the search were organized and evidence reports as well as copies of the original studies were provided to the Working Group for further analysis. Each reference was appraised for scientific merit, clinical relevance, and applicability to the populations served by the Federal healthcare system. Recommendations were based on consensus of expert opinions and clinical experience only when scientific evidence was unavailable.

A group of research analysts read and coded each article that met inclusion criteria. The articles have been assessed for methodological rigor and clinical importance.

The information was synthesized and reported in a brief summary of the critical appraisal of each article that included the following components:

- Description of patient population
- Interventions
- Comparisons
- Outcomes
- Summary of results
- Analysis of findings
- Evidence appraisal
- Clinical significance.

Recommendation and Overall Quality Rating

Evidence-based practice involves integrating clinical expertise with the best available clinical evidence derived from systematic research. The Working Group received an orientation and tutorial on the evidence USPSTF 2001 rating process, reviewed the evidence and independently formulated Quality of Evidence ratings (see Table A-1), a rating of Overall Quality (see Table A-2), and a Strength of Recommendation (see Table A-3).

Table A-1: Quality of Evidence (QE)	
I	At least one properly done RCT
II-1	Well-designed controlled trial without randomization
II-2	Well-designed cohort or case-control analytic study, preferably from more than one source
II-3	Multiple time series evidence with/without intervention, dramatic results of uncontrolled experiment
III	Opinion of respected authorities, descriptive studies, case reports, and expert committees

Table A-2: Overall Quality	
Good	High grade evidence (I or II-1) directly linked to health outcome
Fair	High grade evidence (I or II-1) linked to intermediate outcome; *or* Moderate grade evidence (II-2 or II-3) directly linked to health outcome
Poor	Level III evidence or no linkage of evidence to health outcome

Table A-3: Net Effect of the Intervention	
Substantial	More than a small relative impact on a frequent condition with a substantial burden of suffering; *or* A large impact on an infrequent condition with a significant impact on the individual patient level.
Moderate	A small relative impact on a frequent condition with a substantial burden of suffering; *or* A moderate impact on an infrequent condition with a significant impact on the individual patient level.
Small	A negligible relative impact on a frequent condition with a substantial burden of suffering; *or* A small impact on an infrequent condition with a significant impact on the individual patient level.
Zero or Negative	Negative impact on patients; *or* No relative impact on either a frequent condition with a substantial burden of suffering; or an infrequent condition with a significant impact on the individual patient level.

Table A-4: Final Grade of Recommendation

	The net benefit of the intervention			
Quality of Evidence	**Substantial**	**Moderate**	**Small**	**Zero or Negative**
Good	A	B	C	D
Fair	B	B	C	D
Poor	I	I	I	I

Evidence Rating System

A	A strong recommendation that the clinicians provide the intervention to eligible patients. *Good evidence was found that the intervention improves important health outcomes and concludes that benefits substantially outweigh harm.*
B	A recommendation that clinicians provide (the service) to eligible patients. *At least fair evidence was found that the intervention improves health outcomes and concludes that benefits outweigh harm.*
C	No recommendation for or against the routine provision of the intervention is made. *At least fair evidence was found that the intervention can improve health outcomes, but concludes that the balance of benefits and harms is too close to justify a general recommendation.*
D	Recommendation is made against routinely providing the intervention to asymptomatic patients. *At least fair evidence was found that the intervention is ineffective or that harms outweigh benefits.*
I	The conclusion is that the evidence is insufficient to recommend for or against routinely providing the intervention. *Evidence that the intervention is effective is lacking, or poor quality, or conflicting, and the balance of benefits and harms cannot be determined.*

Lack of Evidence – Consensus of Experts

Where existing literature was ambiguous or conflicting, or where scientific data was lacking on an issue, recommendations were based on the clinical experience of the Working Group. These recommendations are indicated in the evidence tables as based on "Working Group Consensus."

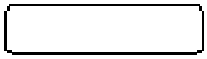
Algorithm Format

The goal in developing the guideline for management of COPD was to incorporate the information into a format which would maximally facilitate clinical decision-making. The use of the algorithm format was chosen because of the evidence that such a format improves data collection, diagnostic and therapeutic decision-making and changes patterns of resource use. However, few guidelines are published in such a format.

The algorithmic format allows the provider to follow a linear approach to critical information needed at the major decision points in the clinical process, and includes:

- An ordered sequence of steps of care
- Recommended observations
- Decisions to be considered
- Actions to be taken

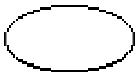
A clinical algorithm diagrams a guideline into a step-by-step decision tree. Standardized symbols are used to display each step in the algorithm (Society for Medical Decision-Making Committee, 1992). Arrows connect the numbered boxes indicating the order in which the steps should be followed.



Rounded rectangles represent a clinical state or condition.

Hexagons represent a decision point in the guideline, formulated as a question that can be answered Yes or No. A horizontal arrow points to the next step if the answer is YES. A vertical arrow continues to the next step for a negative answer.

Rectangles represent an action in the process of care.



Ovals represent a link to another section within the guideline.

A letter within a box of an algorithm refers the reader to the corresponding annotation. The annotations elaborate on the recommendations and statements that are found within each box of the algorithm. Included in the annotations are brief discussions that provide the underlying rationale and specific evidence tables. Annotations indicate whether each recommendation is based on scientific data or expert opinion. A complete bibliography is included in the guideline.

REFERENCES

Agency for Health Care Policy and Research (AHCPR). Manual for conduction systematic review. Draft. August 1996. Prepared by Steven H. Woolf.

Harris RP, Helfand M, Woolf SH, Lohr KN, Mulrow CD, Teutsch SM, Atkins D; Methods Work Group, Third US Preventive Services Task Force Current methods of the U.S. Preventive Services Task Force: a review of the process. Am J Prev Med 2001 Apr;20(3 Suppl):21-35.

Society for Medical Decision-Making Committee (SMDMC). Proposal for clinical algorithm standards,

SMDMC on Standardization of Clinical Algorithms. Med Decis Making 1992 Apr-Jun;12(2):149-54.

United States Preventive Service Task Force (USPSTF). Guide to clinical preventive services. 2nd edition. Washington, DC: US Department of Health and Human Services, Office of Disease Prevention and Health Promotion, 1996.

Woolf SH. Practice guidelines, a new reality in medicine II. Methods of developing guidelines. Arch Intern Med 1992 May;152(5):946-52.

APPENDIX B

STRUCTURED EXERCISE TRAINING PROGRAM

Components: Rehabilitation focuses primarily on patients with COPD with exertional symptoms. As exercise in these patients is limited by dyspnea and/or muscle fatigue, these patients avoid exercise, which results in progressive cardiovascular and peripheral muscle deconditioning.

The major goal of an exercise program is to recondition the cardiovascular system and peripheral muscles. Reconditioning will reduce exertional dyspnea and muscle fatigue. Consequently, the patient's behavior will change from a sedentary to a more active lifestyle with an improvement in health status. The reconditioning is achieved by **both cardiovascular training and skeletal muscle training**. Cardiovascular training may be achieved with treadmill walking and/or cycling and skeletal muscle training with weight training. The optimal type of training, its optimal length, duration, frequency and intensity, as well as the necessary follow-up training required to maintain improvements, have not yet been precisely determined.

The exercise portion of a rehabilitation program is usually under the direct supervision of a physiotherapist. Critical appraisals of such programs from a physiotherapy perspective have been published (The Chartered Society of Physiotherapy, 2003). Components of rehabilitation programs are also available elsewhere (Lacasse et al., 1997).

Course duration and frequency: The program duration is recommended to be from 8 to 12 weeks (Lacasse et al., 1997). Although measurable physiologic effects of training can be shown to be present within 4 weeks, the behavioral changes required to go from a sedentary to a more active lifestyle take longer (Troosters et al., 2005). Programs of even longer duration (such as 6 months) show better long-term effects than shorter ones, especially in patients with very severe COPD. Supervised training sessions of 3 to 5 times per week with session durations of 30 to 45 minutes are recommended. Principles of exercise training programs in COPD are postulated to be similar to those that apply to normal subjects (American College of Sports Medicine, 1998; Gosselink et al., 1997; Sneed & Paul, 2003).

Cardiovascular training: The maximal work rate may be estimated from a preliminary incremental exercise test. It should be noted that the magnitude of the increments in the rate of work during an incremental test affect the obtained maximal work rate (smaller increments result in lower estimated maximal work rate as the exercise duration is longer). Exercise intensity at 60 to 80 percent of the obtained maximal work can be maintained for sufficiently long periods and can be used as an initial endurance training target (Lacasse et al., 1997). The lower numbers may be more applicable to cycle ergometry, whereas the higher numbers may be more applicable for treadmill walking. However, dependent on the patient's symptomatic response, the initial training targets may have to be adjusted up or down. Thereafter, intensity targets may be increased on a weekly basis. Whereas heart rate is a poor predictor of work intensity in COPD, the modified Borg dyspnea scale can be used to guide intensity increments. A score of 4 to 6 is thought to indicate adequate training intensity (Pollock et al., 1977). In general, the higher the training intensity is, the higher the physiologic benefit. Patients with very severe disease, profound muscle weakness, or a very substantial ventilatory limitation may be unable to comfortably achieve exercise levels of sufficient intensity to achieve a physiologic training effect. Salutary cardiovascular effects may be achieved with endurance training at 3 to 5 days per week for periods of 30 minutes or longer.

Strength training: Weight (resistance) training is not accompanied by the same level of dyspnea as endurance training. Hence, higher relative work rates can be achieved briefly and improvements in both upper and lower extremity strength can be made. Typically, 2 to 3 sets of 8 repetitions each at about 70 percent of the one repetition maximum are used to increase strength of various muscle groups. Targets can be adjusted on a weekly basis. Lower extremity strength training can improve endurance in walking, whereas upper extremity training will only improve arm function.

Oxygen during exercise: Supplemental oxygen administration may improve exercise tolerance and thereby increase achievable training intensity (Horowitz et al., 1996). However, as no significant other benefits have been shown, it is not routinely recommended. If clinically important desaturation (SaO_2 < 90 percent) occurs during the initial maximal incremental exercise test, it is recommended that oxygen be administered during exercise training as well as during exercise at home (in accordance with the oxygen administration guideline).

REFERENCES

American College of Sports Medicine Position Stand. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. Med Sci Sports Exerc 1998 Jun;30(6):975-91.

Gosselink R, Troosters T, Decramer M. Exercise training in COPD patients: the basic questions. Eur Respir J 1997 Dec;10(12):2884-91.

Horowitz MB, Littenberg B, Mahler DA. Dyspnea ratings for prescribing exercise intensity in patients with COPD. Chest 1996 May;109(5):1169-75.

Lacasse Y, Guyatt GH, Goldstein RS. The components of a respiratory rehabilitation program: a systematic overview. Chest 1997 Apr;111(4):1077-88.

Pollock M, Ward A, Ayres JJ. Cardiorespiratory fitness response to differing intensities and duration of training. Arch Phys Med Rehab 1977 Nov;58(11):467-73.

Sneed NV, Paul SC. Readiness for behavioral changes in patients with heart failure. Am J Crit Care 2003 Sep; 12(5):444-53.

The Chartered Society of Physiotherapy. The effectiveness of pulmonary rehabilitation: evidence and implications for physiotherapists. March 2003. Available from:http://www.csp.org.uk/uploads/documents/evidencebrief_pulmonary_EB05.pdf (Retrieved October 2006).

Troosters T, Casaburi R, Gosselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005 Jul 1;172(1):19-38.

APPENDIX C

PHARMACOTHERAPY

Metered dose inhalers (MDIs)

Currently, the propellants used in MDIs are chlorofluorocarbons (CFCs) or hydofluoroalkanes (HFAs). Because of environmental concerns, the use of CFC will eventually be phased out. Products containing CFC and HFA have been shown to be clinically comparable.

Use of MDIs requires coordination of actuation with inhalation. Add-on spacer devices may be used for patients whose technique using MDIs is inadequate. Spacers may also improve drug deposition into the lung and lessen side effects due to oropharyngeal deposition (e.g., oral candidiasis with inhaled glucocorticoids).

MDIs do not have a dosage indicator.

Dry powder inhalers (DPIs)

Dry powder inhalers (DPIs) are available as single-dose or multi-dose inhalers. DPIs are breath-activated and do not require coordination of inhalation with actuation. DPIs also eliminate the uncertainty of the number of doses remaining, as may occur with the MDIs. For most products, the active medication is combined with lactose so that the patient can "taste" that they have inhaled the dose. Directions for use differ from device to device; therefore, patients must be instructed on proper use.

- Single-dose DPIs require that the patient load the drug into the accompanying device. The drug is in a capsule formulation and is packaged in individual foil blister packs. Patients must be instructed not to swallow the capsules. The delivery device that is specific for the drug should be used. Do not interchange devices from other single-dose DPIs.

- For multi-dose DPIs, the drug is preloaded in the device. A dosage indicator allows patients to know the number of doses remaining. Multi-dose DPIs may be easier to use for individuals who have visual or dexterity limitations.

Use of inhalers and nebulizers for obstructive lung disease

Currently, inhaled bronchodilators can be delivered by a metered dose inhaler (MDI) using a propellant such as HFA or CFC, by a dry powder inhaler (DPI) either multi-dose or single-dose, or by generally, a wet aerosol from one of several available handheld, generally small volume nebulizers using a compressor to power the aerosol. Most MDIs can be used with a spacer to improve patient coordination, prevent some deposition in the upper airway and reduce wastage of the respirable portion of the inhaled bronchodilator. While efficacious delivery can be achieved with all devices, each device has advantages and disadvantages and a single-device or mode of bronchodilator delivery that is suitable for all patients is not currently available. This was emphasized in an evidence-based review of device delivery of inhaled bronchodilators (Dolovich et al., 2005) which concluded the following:

> Devices used for the delivery of bronchodilators can be equally efficacious. When selecting an aerosol delivery device for patients with asthma and COPD, the following should be considered: device/drug availability; clinical setting; patient age and the ability to use the selected device

correctly; device use with multiple medications; cost and reimbursement; drug administration time; convenience in both outpatient and inpatient settings; and physician and patient preference.

However, in general, the use of an MDI (with or without a spacer) or a DPI is more convenient, more portable, less time consuming, and less costly than a nebulizer. However, other considerations should be taken into account in prescribing a nebulizer for inhaled bronchodilator delivery, including an inability to coordinate with the MDI or DPI, an inability to use the MDI or DPI (e.g., from arthritis or poor vision), or the need to have an attendant deliver the bronchodilator to a patient who is not able to fully cooperate. In some cases, a nebulized bronchodilator, rather than one delivered by an MDI or DPI, may be necessary for rescue use in patients who suffer frequent or severe exacerbations. The reason for this approach is unclear but may result from a patient's severe shortness of breath, inability to take a deep breath, or for other undefined but clinically documented reasons.

REFERENCES

Dolovich MB, Ahrens RC, Hess DR, Anderson P, Dhand R, Rau JL, Smaldone GC, Guyatt G; American College of Chest Physicians; American College of Asthma, Allergy, and Immunology. Device selection and outcomes of aerosol therapy: Evidence-based guidelines American College of Chest Physicians/American College of Asthma, Allergy, and Immunology. Chest 2005 Jan;127(1):335-71.

RECOMMENDED DOSAGE FOR SELECTED COPD DRUG THERAPY

Table C1: Inhaled Bronchodilators [a]

Drug	Dosage form	Dosage	Maximum dose	Nebulizer dosage
Short-acting beta 2-agonists Albuterol 90 µg	MDI	1-2 puffs q4-6 h [b]	12 puffs/day [c]	2.5 mg administered 3-4 times daily
Metaproterenol 0.65 mg	MDI	2-3 puffs q 3-4 h [b]	12 puffs/day [c]	10-15 mg administered 3-4 times daily
Pirbuterol 200 µg	MDI	1-2 puffs q 4-6 h	12 puffs/day	Not available
Levalbuterol 45 µg	MDI	1-2 puffs q 4-6 h	12 puffs/day	0.63–1.25 mg administered 3 times daily
Long-acting beta 2-agonists Formoterol 12 µg	DPI (capsules)	12 µg q 12 h	12 µg q 12 h	Not available
Salmeterol 50 µg [d]	DPI	50 µg q 12 h	50 µg q 12 h	Not available
Short-acting anticholinergics Ipratropium 18 µg	MDI	2 puffs q 6 h [b]	12 puffs/day [c]	0.25–0.5 mg q 6-8 h
Long-acting anticholinergics Tiotropium 18 µg	DPI (capsules)	18 µg once daily	18 µg once daily	Not available
Combination bronchodilators Albuterol 90 µg + ipratropium 18 µg	MDI	2 puffs q 6 h	12 puffs/day	2.5 mg/0.5 mg administered 4 times daily

[a] Dosing information obtained from AHFS Drug Information 2005 and product package inserts
[b] These are usual recommended **maintenance** doses, although they may be modified in particular clinical circumstances
[c] Maximum doses per manufacturer's recommendations, although higher doses have been used clinically
[d] Also available in the following combination products: fluticasone 100 µg/salmeterol 50 µg; fluticasone 250 µg/salmeterol 50 µg; fluticasone 500 µg/salmeterol 50 µg

Table C2: Oral Beta-Adrenergic Agonists

Drug	Oral dose	Precautions
Albuterol Immediate release Sustained release Metaproterenol Terbutaline	 2-4 mg tid qid 4-8 mg q 12 h 20 mg bid tid 2.5-5 mg tid qid	• Instruct patient to report palpitations, tachycardia, chest pain, muscle tremors, dizziness, headache, flushing, difficult urination, or breathing difficulty • Oral agents should be reserved for patients unable to use inhaled dosage forms as the risk of adverse effects significantly increase with the oral beta 2-agonists

Dosing information obtained from AHFS Drug Information 2005

Table C3: Inhaled Glucocorticoids [a-b]

Inhaled Glucocorticoid	Dosage forms	Usual dosing interval	Low dose µg/day	Medium dose µg/day	High dose µg/day	Maximum dose per MFR (µg/day)
Beclomethasone 40 µg 80 µg	MDI	Q 6-8h or Q 12h	100-250 (2-6 puffs) (1-3 puffs)	250-500 (6-10 puffs) (3-5 puffs)	> 500 (> 10 puffs) (> 5 puffs)	640
Budesonide 200 µg [c]	DPI	Q 12h	200-600 (1-3 inhalations)	600-1000 (3-5 inhalations)	> 1000 (> 5 inhalations)	1600
Flunisolide 250 µg	MDI	Q 12h	500-1000 (2-4 puffs)	1000-2000 (4-8 puffs)	> 2000 (> 8 puffs)	2000
Fluticasone [d] 44 µg 110 µg 220 µg	MDI	Q 12h	88-264 (2-6 puffs) - -	264-660 (6-15 puffs) (2-6 puffs) (1-3 puffs)	> 660 (> 15 puffs) (> 6 puffs) (> 3 puffs)	1760
Mometasone 220 µg	DPI	Q 24h or Q 12h	200-400	400-800	> 800	880
Triamcinolone 100 µg	MDI with built-in spacer	Q 6-8h or Q 12h	400-1000 (4-10 puffs)	1000-2000 (10-20 puffs)	> 2000 (> 20 puffs)	1600

[a] Not approved by the FDA for COPD. Beclomethasone, budesonide, fluticasone, and triamcinolone have been studied in clinical trials in COPD. The combination of fluticasone and salmeterol is approved by the FDA for COPD.
[b] Dosing adapted from Global Initiative for Asthma 2005 and Global Strategy for Asthma Management and Prevention 2004 update
[c] Also available in a formulation for use with a jet nebulizer (currently indicated for pediatric asthma)
[d] Also available in the following combination products: fluticasone 100 µg/salmeterol 50 µg; fluticasone 250 µg/salmeterol 50 µg; fluticasone 500 µg/salmeterol 50 µg

Table C4: Theophylline

<table>
<tr><th></th><th colspan="2">Starting dose</th><th>Maintenance dose</th></tr>
<tr><td>Adults (16-60 years) Without Risk Factors for Impaired Clearance</td><td>Initial dose 400 mg/day</td><td rowspan="2">If using prompt release tablets, divide daily dose q 6-8 hours

Dosing may also be initiated with the 12-hour extended release products

In general, once daily products (e.g., Uniphyl or Theo-24) should not be used when initiating theophylline</td><td rowspan="2">If serum concentration < 5 µg/ml and symptoms are not controlled, increase daily dose by 25%

If serum concentration 5–12 µg/ml and symptoms are controlled and dosage tolerated, maintain dose. If symptoms are not controlled, increase dose by 25%. In general, serum concentrations should not exceed 15 µg/ml</td></tr>
<tr><td>Patients with risk factors for impaired clearance, (e.g., age > 60 years, patients with liver disease or congestive heart failure, or those in whom it is not feasible to monitor serum theophylline concentrations)</td><td>Initial dose should not exceed 300 mg/day</td></tr>
</table>

Dosage increases should be made only if the previous dose has been tolerated and at intervals no less than 3 days. For extended release products, serum concentration should be measured approximately 8 hours post-dose.

Table C5: Factors That Can Affect Theophylline Levels [a]

Drugs or factors decreasing theophylline clearance	Drugs or factors increasing theophylline clearance
Cimetidine, ciprofloxacin, clarithromycin, disulfiram, enoxacin, erythromycin, mexiletine, pentoxifylline, propranolol, ticlopidine, troleandomycin, zileuton, allopurinol (≥ 600 mg/day), fluvoxamine, interferon, propafenone, tacrine, verapamil Congestive heart failure, cor pulmonale, elderly (> 60 years), hepatic insufficiency [b] (cirrhosis, acute hepatitis, cholestasis), fever (> 24 hours)	Charcoal broiled food; low carbohydrate, high protein diet Smoking (tobacco or marijuana); henobarbital; phenytoin; rifampin, carbamazepine; isoniazid; moricizine

[a] List is not intended to be inclusive of all potential drug interactions
[b] Theophylline clearance has been decreased by 50 percent or more

Table C6: Caution and Special Instruction for Selected COPD Drug Therapy

Drug class	Cautions
Beta 2-agonists	• May cause palpitations, chest pain, rapid heart rate, increased blood pressure, tremor, nervousness • Decreases in potassium levels have occurred • Short-acting beta 2-agonists are used for acute treatment of bronchospasm • Long-acting beta 2-agonists are not to be used for acute treatment of bronchospasm • Formoterol: capsules are for oral inhalation only; not to be taken by mouth; administer using supplied inhalation device (Aerolizer) only
Anticholinergics	• Use with caution in patients with narrow angle glaucoma, prostatic hyperplasia, or bladder neck obstruction • Caution patient to getting product in eyes; temporary blurred vision may result • For relief of dry mouth, suggest use of saliva substitute, practice of good oral hygiene, rinsing of mouth after inhalation; instruct patient to take sips of water frequently, suck on ice chips or sugarless hard candy, or chew sugarless gum • Not indicated for initial treatment of acute episodes of bronchospasm • Tiotropium: capsules are for oral inhalation only; not to be taken by mouth; administer using supplied inhalation device (HandiHaler) only
Inhaled glucocorticoids	• Localized fungal infections with Candida albicans or Aspergillus niger have occurred in the mouth, pharynx, and occasionally the larynx • Advise patients to rinse mouth after inhalation • Rare instances of glaucoma, increased intraocular pressure, and cataracts have been reported • Risk of skin thinning and bruising may be increased • Decreased bone density may occur with long-term use in patients with COPD
Theophylline	• Carefully monitor patients with history of arrhythmias, seizures, peptic ulcer, or gastroesophageal reflux • Monitor theophylline levels; the usual therapeutic range is 7 to 20 µg/mL but some toxicity may be noted at the upper end of this range • Common adverse reactions include stomach upset, nausea, insomnia, tremors, palpitations, exfoliative dermatitis, and urticaria • Instruct patient not to take extra doses of theophylline for acute asthma attack • Sustained-release products should not be crushed or chewed • Scored tablets may be split without affecting absorption characteristics

APPENDIX D

ACRONYM LIST

AAT	Alpha l-Antitrypsin
ACIP	The Advisory Committee on Immunization Practices
ATS	American Thoracic Society
BMI	Body Mass Index
BODE	The Body Mass Index Airflow Obstruction, Dyspnea, Exercise Performance Index
CFC	Chlorofluorocarbons
COPD	Chronic Obstructive Pulmonary Disease
CRDQ	Chronic Respiratory Disease Questionnaire
CRQ	Chronic Respirator Questionnaire
DM	Dyspnea Self-Management
DPI	Dry Powder Inhaler
ERS	European Respiratory Society
FEV1	Forced Expiratory Volume in One Second
FVC	Forced Vital Capacity
HFA	Hydofluoroalkane
HRQOL	Health-Related Quality of Life
LAAC	Long-Acting Anticholinergic
LABA	Long-Acting Inhaled Beta 2-Agonist
LTOT	Long-Term Oxygen Therapy
LVRS	Long Volume Reduction Surgery
MDI	Metered Dose Inhalers
MMRC	Modified Medical Research Council
MRC	Medical Research Council
NAC	N-Acetycysteine
OR	Odds Ratio
PPV	Pneumococcal Polysaccharide Vaccine
QOL	Quality of Life
QWB	Quality of Well-Being Scale
RR	Risk Ratio
SAAC	Short-Acting Anticholinergic
SABA	Short-Acting Beta 2-Agonist
6MWD	Six-Minute Walk Distance
SOBQ	Shortness of Breath Questionnaire
TORCH	Towards a Revolution in COPD Health
UPLIFT	Understanding Potential Long-Term Impacts on Function with Tiotropium
USPSTF	U.S. Preventive Services Task Force
VC	Vital Capacity

APPENDIX E

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APPENDIX F

BIBLIOGRAPHY

Aalbers R, Ayres J, Backer V, Decramer M, Lier PA, Maqvar P, Malolepazy J, Ruffin R, Sybrecht GW. Formoterol in patients with chronic obstructive pulmonary disease: a randomized, controlled, 3-month trial. Eur Respir J 2002;19(5): 936-43.

Aaron SD, Vandemheen KL, Hebert P, Dales R, Stiell IG, Ahuja J, Dickinson G, Brison R, Rowe BH, Dreyer J, Yetisir E, Cass D, Wells G. Outpatient oral prednisone after emergency treatment of chronic obstructive pulmonary disease. N Engl J Med 2003 Jun 26;348(26):2618-25.

ACCP/ACCVPR – see Pulmonary rehabilitation: joint ACCP/AACVPR evidence based guidelines. ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel.

Agostoni P, Doria E, Galli C, Tamborini G, Guazzi MD. Nifedipine reduces pulmonary pressure and vascular tone during short- but not long-term treatment of pulmonary hypertension in patients with chronic pulmonary disease. Am Rev Respir Dis 1989 Jan;139(1)120-5.

Albert RK, Martin TR, Lewis S. Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. Ann Intern Med 1980 Jun;92(6):753-8.

Alfageme I, Vazquez R, Reyes N, Munoz J, Fernandez A, Hernandez M, Merino M, Perez J, Lima J. Clinical efficacy of anti-pneumococcal vaccination in patients with COPD. Thorax 2006; 61 (3):189-95.

Allegra L, Blasi F, de Bernardi B, Cosentini R, Tarsia P. Antibiotic treatment and baseline severity of disease in acute exacerbations of chronic bronchitis: a re-evaluation of previously published data of a placebo-controlled randomized study. Pulm Pharmacol Ther 2001;14(2):149-55.

Alpha-1-Antitrypsin Deficiency Registry Study Group. Survival and FEV1 decline in individuals with severe deficiency of alpha1-antitrypsin. Am J Respir Crit Care Med 1998;158:49-59.

Alsaedi A, Sin DD, Mc Alister FA. The effects of inhaled corticosteroids in chronic obstructive pulmonary disease: a systematic review of randomized placebo-controlled trials. Am J Med 2002;113:59-65.

American College of Sports Medicine. The recommended quantity and quality of exercise for developing and maintaining cardiorespiratory and muscular fitness, and flexibility in healthy adults. Med Sci Sports Exerc 1998;30:975-91.

American Thoracic Society/European Respiratory Society (ATS/ERS) statement standards for the diagnosis and management of individuals with alpha-1-antitrypsin deficiency. Am J Respir Crit Care Med 2003;168:818-900.

Anthonisen NR, Connett JE, Kiley JP, Altose MD, Bailey WC, Buist AS, Conway WA Jr, Enright PL, Kanner RE, O'Hara P. Effects of smoking intervention and the use of inhaled anticholinergic bronchodilator on the rate of decline of FEV1. JAMA 1994 Nov:272(19):1497-505.

Anthonisen NR, Manfreda J, Warren CP, Hershfield ES, Harding GK, Nelson NA. Antibiotic therapy in exacerbations of chronic obstructive pulmonary-disease. Ann Intern Med 1987 Feb;106(2):196-204.

Anthonisen NR, Skeans MA, Wise RA, Manfreda J, Kanner RE, Connett JE, for the Lung Health Study Reasearch Group. The effects of smoking cessation intervention on 14.5 – year mortality. Ann Intern Med 2005; 142(4):233-9.

Anthonisen NR, Wright EC, Hodgkin JE, The IPPB Trial Group. Prognosis in chronic obstructive pulmonary disease. Am Rev Respir Dis 1986;133:14-20.

Appleton S, Jones T, Poole P, Pilotto L, Adams R, Lasserson TJ, Smith B, Muhammad J. Ipratropium bromide versus long-acting beta-2 agonists for stable chronic obstructive pulmonary disease. Cochrane Database Syst

2006a Rev 3: CD006101.

Appleton S, Poole P, Smith B, Veale A, Lasserson TJ, Chan MM. Long-acting beta2-agonists for poorly reversible chronic obstructive pulmonary disease. Cochrane Database Syst 2006b Rev 3:CD001104.

Arcasoy SM, Kotloff RM. Lung transplantation. N Engl J Med 1999;340:1081-91.

ATS/ERS 2004 – See Celli et al., 2004.

Bach PB, Brown C, Gelfand SE, McCrory DC; American College of Physicians-American Society of Internal Medicine; American College of Chest Physicians. Management of acute exacerbations of chronic obstructive pulmonary disease: a summary and appraisal of published evidence. Ann Intern Med 2001 Apr;134(7):600-20.

Ball P, Harris JM, Lowson D, Tillotson G, Wilson R. Acute infective exacerbations of chronic bronchitis. QJM 1995 Jan;88:61-68.

Bando K, Paradis IL, Keenan RJ, Yousem SA, Komatsu K, Konishi H, Guilinger RA, Masciangelo TN, Pham SM, Armitage JM, et al.. Comparison of outcomes after single and bilateral lung transplantation for obstructive lung disease. J Heart Lung Transplant 1995;14:692-98.

Barbera JA, Peinado VJ, Santos S. Pulmonary hypertension in chronic obstructive pulmonary disease. Eur Respir J 2003 May;21(5):892-905.

Barr RG, Bourbeau J, Camargo CA, Ram FS. Inhaled tiotropium for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005 Apr 18;(2):CD002876.

Barr RG, Bourbeau J, Camargo CA, Ram FS. Tiotropium for stable chronic obstructive pulmonary disease: A meta-analysis. Thorax 2006;61(10):854-62.

Barr RG, Rowe BH, Camargo CA Jr. Methylxanthines for exacerbations of chronic obstructive pulmonary disease: meta-analysis of randomized trials. BMJ 2003 Sept;327(7416):643.

Bellia V, Foresi A, Blanco S, Grassi V, Olivieri D, Bensi G, Volante M, BREATH Italian Study Group. Efficacy and safety of oxitropium bromide, theophylline and their combination in COPD patients: a double-blind, randomized, multicenter study. Respir Med 2002;96(11):881-9.

Berger RL, Wood KA, Cabral HJ, Goodnight-White S, Ingenito EP, Gray A, Miller J, Springmeyer SC. Lung volume reduction surgery: a meta-analysis of randomized clinical trials. Treat Respir Med 2005;4(3):201-9.

Bernard S, Whittom F, LeBlanc P, Jobin J, Belleau C, Carrier G, Maltais F. Aerobic and strength training in patients with chronic obstructive pulmoanary disease. Am J Respir Crit Care Med 1999;159:896-901.

Bestall JC, Paul EA, Garrod R, Garnham R, Jones PW, Wedzicha JA. Usefulness of the Medical Research Council (MRC) dyspnoea scale as a measure of disability in patients with chronic obstructive pulmonary disease. Thorax 1999;54:581-6.

Bestall JC, Paul EA, Garrod R, Garnham R, Jones RW, Wedzicha JA. Longitudinal trands in exercise capacity and health status after pulmonary rehabilitation in patients with COPD. Respir Med 2003 Feb;97:173-80.

Biernacki W, Flenley DC, Muir AL, MacNee W. Pulmonary hypertension and right ventricular function in patients with COPD. Chest 1988;94:1169-75.

Borson S, McDonald GJ, Gayle T, Deffebach M, Lakshminarayan S, VanTuinen C. Improvement in mood, physical symptoms, and function with nortriptyline for depression in patients with chronic obstructive pulmonary disease. Psychosomatics 1992 Spring;33(2):190-201.

Bourbeau J, Ernst P, Cockcoft D, Suissa S. Inhaled corticosteroids and hospitalisation due to exacerbation of COPD. Eur Respir J 2003 Aug;22(2):286-9.

Bourbeau J, Rouleau MY, Boucher S. Randomised controlled trial of inhaled corticosteroids in patients with chronic obstructive pulmonary disease. Thorax 1998;53:477-82.

Bradley JM, O'Neill B. Short-term ambulatory oxygen for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005 Oct 19;(4):CD004356.

Bratel T, Hedenstierna G, Nyquist O, Ripe E. Long-term treatment with new calcium antagonist, felodipine, in chronic obstructive pulmonary disease. Eur Respir J 1986 May;68(5):351-61.

Brazinsky SA, Lapidus RJ, Weiss LA, Ghafouri M, Fagan NM, Witek TJ, The ATROVENT HFA Study Group. One-year evaluation of the safety and efficacy of ipratropium bromide HFA and CFC inhalation aerosols in patients with chronic obstructive pulmonary disease. Clin Drug Investigation 2003;Vol.23(3):181-91.

Brenes GA. Anxiety and chronic obstructive pulmonary disease: prevalence, impact, and treatment. Psychosom Med 2003 Nov-Dec;65(6):963-70.

Briggs DD Jr, Covelli H, Lapidus R, Bhattycharya S, Kesten S, Cassino C. Improved daytime spirometric efficacy of tiotropium compared with salmeterol in patients with COPD. Pulm Pharmacol Ther 2005;18(6):397-404.

Brijker F, Heijdra YF, van den Elshout FJ, Folgering HT. Discontinuation of furosemide decreases $PaCO_2$ in patients with COPD. Chest 2002 Feb;121(2):377–82.

British Thoracic Society. COPD Guidelines Group of the Standards of Care Committee of the BTS. BTS guidelines for the management of chronic obstructive pulmonary disease. Thorax 1997;52:S1-28.

Brown SE, Pakron FJ, Milne N, Linden GS, Stanbury DW, Fischer CE. Effects of digoxin on exercise capacity and right ventricular function during exercise in chronic airflow obstruction. Chest 1984;85:187-91.

Brusasco V, Hodder R, Miravitlles M, Korducki L, Towse L, Kesten S. Health outcomes following treatment for six months with once daily tiotropium compared with twice daily salmeterol in patients with COPD. Thorax 2003;58(5):399-404.

Bullard MJ, Liaw SJ, Tsai YH, Min HP. Early corticosteroid use in acute exacerbations of chronic airflow obstruction. Am J Emerg Med 1996;14:139-43.

Burge PS, Calverley PMA, Jones PW, Spencer S, Anderson JA. Prednisolone response in patients with chronic obstructive pulmonary disease: results from the ISOLDE study. Thorax 2003;58:1-5.

Calverley PM, Anderson JA, Celli B, Ferguson GT, Jenkins C, Jones PW, Yates JC, Vestbo J; TORCH investigators. Salmeterol and fluticasone propionate and survival in chronic obstructive pulmonary disease. N Engl J Med. 2007 Feb 22;356(8):775-89.

Calverley PM, Boonsawat W, Cseke Z, Zhong N, Peterson S, Olsson H. Maintenance therapy with budesonide and formoterol in chronic obstructive pulmonary disease. Eur Respir J 2003a Dec;22(6):912-9.

Calverley PM, Pauwels R, Vestbo J, Jones P, Pride N, Gulsvik A, Anderson J, Maden C; TRial of Inhaled STeroids ANd long-acting beta2 agonists study group. Combined salmeterol and fluticasone in the treatment of chronic obstructive pulmonary disease: a randomised controlled trial. Lancet 2003b Feb 8;361(9356):449-56.

Campbell S. For COPD a combination of ipratropium bromide and albuterol sulfate is more effective than albuterol base. Arch Intern Med 1999 Jan 25;159(2):156-60.

Carrieri-Kohlman V, Nguyen HQ, Donesky-Cuenco D, Demir-Deviren S, Neuhaus J, Stulbarg MS. Impact of brief or extended exercise training on the benefit of a dyspnea self-management program in COPD. J Cardiopulm Rehabil 2005 Sep-Oct;25(5):275-84.

Casaburi R, Bhasin S, Cosentino L, Porszasz J, Somfay A, Lewis MI, Fournier M, Storer TW. Anabolic effects of testosterone replacement and strength training in men with COPD. Am J Respir Crit Care 2004;170:870-78.

Casaburi R, Patessio A, Ioli F, Zanaboni S, Donner CF, Wasserman K. Reductions in exercise lactic acidosis and ventilation as a result of exercise training in patients with obstructive lung disease. Am Rev Respir Dis 1991 Jan;143(1):9-18.

Celli B, MacNee W: ATS/ERS Task Force. Standards for the Diagnosis and Management of Patients with COPD: a

summary of the ATS/ERS position paper. Eur Respir J 2004; 23(6):932-46. Available from: www.thoracic.org /copd/ (Retrieved August 3, 2005).

Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca M, Mendez RA, Pinto Plata V, Cabral HJ. The body mass index, airflow obstruction, dyspnea, exercise performance index in chronic obstructive pulmonary disease. New Engl J Med 2004 Mar;350(10):1005-12.

Celli BR, Cote CG, Marin JM, Casanova C, Montes de Oca, Mendez RA, Pinto Plata V, Cabral HJ. The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med 2004;350:1005–12.

Chaouat A, Weitzenblum E, Kessler R, Charpentier C, Enrhart M, Schott R, Levi-Valensi P, Zielinski J, Delaunois L, Comudella R, Moutinho dos Santos J. A randomized trial of nocturnal oxygen therapy in chronic obstructive pulmonary disease patients. Eur Respir J 1999;14: 997–9.

Chapman KR, Arvidsson P, Chuchalin AG, Dhillon DP, Faurschou P, Goldstein RS, Kuipers AF; International study group. The addition of salmeterol 50mcg BID to anticholinergic treatment in patients with COPD: a randomized, placebo controlled trial. Can Respir J 2002;9:178-85.

Charman SC, Sharples LD, McNeil KD, Wallwork J. Assessment of survival benefit after lung transplantation by patient diagnosis. J Heart Lung Transplant 2002;21:226–232.

Chen CY, Yang KY, Lee YC, Perng PP. Effect of oral aminophylline on pulmonary function improvement and tolerability in different age groups of COPD patients. Chest 2005;128(4):2088-92.

Christensen CC, Ryg M, Refvem OK, Skjonsberg OH. Development of severe hypoxemia in chronic obstructive pulmonary disease patients at 2438 m (8000 ft) altitude. Eur Resp J 2000;15:635-9.

Clark CJ, Cochrane L, Mackay E. Low intensity peripheral muscle conditioning improves exercise tolerance and breathlessness in COPD. Eur Respir J 1996;9:2590-6.

Cochrane Database Syst Rev., 2006 – see Wood-Baker et al., 2006.

Cohen CA, Zagelbaum G, Gross D, Roussos, Macklem PT. Clinical manifestations of respiratory muscle fatigue. Am J Med 1982;73(3):308-16.

COMBIVENT inhalation aerosol study group. In chronic obstructive pulmonary disease, the combination of ipratropium and albuterol is more effective than either agent alone. An 85-day multicenter trial. Chest 1994;105:1411-9.

COMBIVENT inhalation solution study. Routine nebulized ipratropium and albuterol together are better than either agent alone in COPD. Chest 1997;112:1514-21.

Conaty S, Watson L, Dinnes J, Waugh N. The effectiveness of pneumonococcal polysaccharide vaccines in adults: a systematic review of observational studies and comparison with results from randomized controlled trials. Vaccine 2004;22:3214-24.

Cooper CB. Exercise in chronic pulmonary disease: aerobic exercise prescription. Med Science Sports Med 2001;33:S671-S679.

Cornu C, Yzebe D, Leophonte P, Gaillat J, Boissel JP, Cucherat M. Efficacy of pneumococcal polysaccharide vaccine in immunocompetent adults: a meta-analysis of randomized trials. Vaccine 2001 Sep 14;19(32):4780-90.

Cranston JM, Crockett AJ, Moss JR, Alpers JH. Domiciliary oxygen for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005 Oct 19;(4):CD001744.

D'Urzo AD, De Salvo MC, Ramirez-Rivera A, Almeida J, Sichletidis L, Rapatz G, Kottakis J; FOR-INT-03 Study Group. In patients with COPD, treatment with a combination of formoterol and ipratropium is more effective than a combination of salbutamol and ipratropium. Chest 2001;119:1347-56.

Dahl R, Greefhorst LA, Nowak D, Nonikov V, Byrne AM, Thomson MH, Till D, Cioppa G;Formoterol in Chronic Obstructive Pulmonary Disease I Study Group. Inhaled formoterol dry powder versus ipratropium bromide in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;164(5):778-84.

Dal Nogare AR, Rubin LJ. The effects of hydralazine on exercise capacity in pulmonary hypertension secondary to chronic obstructive pulmonary disease. Am Rev Respir Dis 1986 Mar;133(3):385-9.

Davies L, Angus RM, Calvery PMA. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomized controlled trial. Lancet 1999 Aug;354(9177):456-60.

Davis AL, Aranda CP, Schiffman G, Christianson LC. Pneumococcal infection and immunologic response to pneumococcal vaccine in chronic obstructive pulmonary disease. A pilot study. Chest 1987 Aug;92(2):204-12.

Decramer M, Rutten-van Mölken M, Dekhuijzen PNR, Troosters T, van Herwaarden C, Pellegrino R, van Schayck CP, Olivieri D, Del Donno M, De Backer W, Lankhorst I, Ardia A. Effects of N-acetylcysteine on outcomes in chronic obstructive pulmonary disease (Bronchitis Randomized onNAC Cost-Utility Study, BRONCUS): a randomised placebo controlled trial. Lancet 2005 Apr-May;365(9470):1552–60.

Dewan N, Rafique S, Kanwar B, Satpathy H, Ryschon K, Tillotson GS, Niederman MS. Acute exacerbation of COPD: factors associated with poor treatment outcome. Chest 2000; 117: 662-671.

Dillard T, Moores LK, Bilello KL, Phillips YY. The preflight evaluation: a comparison of the hypoxia inhalation test with hypobaric exposure. Chest 1995;107(2):352-357.

Dillard TA, Beninati WA, Berg BW. Air travel in patients with chronic obstructive pulmonary disease. Arch Intern Med 1991 Sep;151:1793-5.

Dillard TA, Berg B, Rajagopal K, Dooley JW, Rajagopal KR. Hypoxemia during air travel in patients with chronic obstructive pulmonary disease. Ann Int Med 1989;111:362-7.

Dillard TA, Rosenberg AP, Berg BW. Hypoxemia during altitude exposure. A meta-analysis of chronic obstructive pulmonary disease. Chest 1993 Feb;103(2):422-5.

Dirksen A, Dijkman JH, Madsen F, Stoel B, Hutchison DC, Ulrik CS, Skovgaard LT, Kok-Jensen A, Rudolphus A, Seersholm N, Vrooman HA, Reiber JH, Hansen NC, Heckscher T, Viskum K, Stolk J. A randomized clinical trial of alpha-1-antitrypsin augmentation therapy. Am J Respir Crit Care Med 1999 Nov;160:1468-72.

Donohue JF, Parsey MV, Andrews C, D'Urzo T, Sharma S, Schaefer K, Claus R, Baumgarten RA. Evaluation of the efficacy and safety of levalbuterol in subjects with COPD. COPD 2006;3(3):125-32.

Dusser D, Bravo ML, Iacono P. The effect of tiotropium on exacerbations and airflow in patients with COPD. Eur Respir J 2006;27(3):547-55.

Eaton T, Garrett JE, Young W, Fergusson W, Kolbe J, Rudkin S, Whyte KL. Ambulatory oxygen improves quality of life of COPD patients: a randomised controlled study. Euro Resp J 2002;20:306-12.

Eller J, Ede A, Schaberg T, Niederman MS, Mauch H, Lode H. Infective exacerbations of chronic bronchitis: relation between bacteriologic etiology and lung function. Chest 1998;113:1542-8.

Emanuel EJ, Fairclough DL, Slutsman J, Alpert H, Baldwin D, Emanuel LL. Assistance from family members, friends, paid care givers, and volunteers in the care of terminally ill patients. N Engl J Med 1999;341:956-63.

Emerman CL, Connors AF, Lukens TW, May ME, Effron D. A randomized, controlled trial of methylprednisolone in the emergency treatment of acute exacerbations of COPD. Chest 1989 Mar;95(3):563-67.

Emerman CL, Cydulka RK. Evaluation of high-yield criteria for chest radiography in acute exacerbation of chronic obstructive pulmonary disease. Ann Emerg Med 1993 Apr;22(4):680-4.

Ferreira IM, Brooks D, Lacasse Y, Goldstein RS. Nutritional support for individuals with COPD: a meta-analysis. Chest 2000;117:672-8.

Ferrer M, Alonso J, Morera J, Marrades RM, Khalaf A, Aguar MC, Plaza V, Prieto L, Anto JM. Chronic obstructive pulmonary disease and health related quality of life. The Quality of Life Chronic Obstructive Pulmonary Disease Study Group. Ann Int Med 1997;127:1072-9.

Fiore MC, Bailey WC, Cohen SJ, Dorfman SF, Goldstein MG, Gritz ER, Heyman RB, Jaen CR, Kottle TE, Lando HA et al. Treating Tobacco Use and Dependence. Rockville, MD: U.S. Department of Health and Human Services. Public Health Service. October 2000. Available from: http://www.surgeongeneral.gov/tobacco/treating_tobacco_use.pdf (Retrieved November 2006).

Fishman A, Martinez F, Naunheim K, Piantadosi S, Wise R, Ries A, Weinmann G, Wood DE; National Emphysema Treatment Trial Research Group. A randomized trial comparing lung-volume-reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003 May 22;348(21):2059-73.

Fletcher C, Peto R. The natural history of chronic airflow obstruction. Br Med J. 1977 Jun 25;1(6077):1645–8.

Fletcher EC, Luckett RA, Goodnight-White SA, Miller CC, Qian W, Costarangos-Galarza C. A double-blind trial of nocturnal supplemental oxygen for sleep desaturation in patients with chronic obstructive pulmonary disease and a daytime PaO2 above 60 mm Hg. Am Rev Resp Dis 1992;145(5):1070-6.

Friedman M, Serby CW, Menjoge SS, Wilson JD, Hilleman DE, Witek TJ Jr. Pharmacoeconomic evaluation of a combination of ipratropium plus albuterol compared with ipratropium alone and albuterol alone in COPD. Chest 1999:115(3);635-41.

Fujimoto K, Matsuzawa Y, Yamaguchi S, Koizumi T and Kubo K. Benefits of oxygen on exercise performance and pulmonary hemodynamics in patients with COPD with mild hypoxemia. Chest 2002;122:457-63.

Gadoury MA, Schwartzman K, Rouleau M, Maltais F, Julien M, Beaupre A, Renzi P, Begin R, Nault D, Bourbeau J; Chronic Obstructive Pulmonary Disease axis of the Respiratory Health Network, Fonds de la recherche en sante du Quebec (FRSQ). Self-management reduces both short- and long-term hospitalisation in COPD. Eur Respir J 2005 Nov;26(5):853-7.

Gallefoss F, Bakke PS. Patient satisfaction with healthcare in asthmatics and patients with COPD before and after patient education. Respir Med 2000 Nov;94(11):1057-64.

Garrod R, Paul EA, Wedzicha JA. Supplemental oxygen therapy during pulmonary rehabilitation in patients with COPD and exercise hypoxaemia. Thorax 2000;55:539-43.

Gartlehner G, Hansen RA, Carson SS, Lohr KN. Efficacy and safety of inhaled corticosteroids in patients with COPD: a systematic review and meta-analysis of health outcomes. Ann Fam Med 2006 May-Jun;4(3):253-62.

George CF, Bayliff CD. Management of insomnia in patients with chronic obstructive pulmonary disease. Drugs 2003;63:379-87.

Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. (Based on an April 1998 NHLBI/WHO Workshop, updated 2004). Available from:http://goldcopd.com/GuidelineList.asp? (Retrieved November 2006).

GOLD, 2001 – See Pauwels, 2001

GOLD, 2005 ─ Available from: http://goldcopd.com

Goldstein RS, Todd TR, Guyatt G, Keshavjee S, Dolmage TE, van Rooy S, Krip B, Maltais F, LeBlanc P, Pakhale S, Waddell TK. Influence of lung volume reduction surgery (LVRS) on health related quality of life in patients with chronic obstructive pulmonary disease. Thorax 2003 May;58(5):405-10.

Gong H. Air travel and oxygen therapy in cardiopulmonary patients. Chest 1992; 101:1104-13.

Gorecka D, Gorzelak K, Sliwinski P, Tobiasz M, Zielinsli J. Effect of long-term oxygen therapy on survival in patients with chronic obstructive pulmonary disease with moderate hypoxaemia. Thorax 1997;52(8):674-9.

Grandjean EM, Berthet P, Ruffmann R, Leuenberger P. Efficacy of oral long term N=acetylcysteine in chronic

bronchopulmonary disease: a meta-analysis of published double-blind, placebo-controlled clinical trials. Clin Therapeut 2000;22:209-21.

Granger R, Walters J, Poole P, Lasserson T, Mangtani P, Cates CJ, Wood-Baker R. Injectable vaccines for preventing pneumococcal infection in patients with chronic obstructive pulmonary disease. Cochrane database Syst Rev 2006(4):CD001390.

Gray Donald K, Gibbons L, Shapiro SH, Macklem PT, Martin JG. Nutritional status and mortality in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1996;153:961-6.

Green LH, Smith TW. The use of digitalis in patients with pulmonary disease. Ann Intern Med 1977;87:459-65.

Griffiths TL, Burr ML, Campbell IA, Lewis-Jenkins V, Mullins J, Shiels K, Turner-Lawlor PJ, Payne N, Newcombe RG, Ionescu AA, Thomas J, Tunbridge J. Results at 1 year of outpatient multidisciplinary pulmonary rehabilitation: a randomised controlled trial. Lancet 2000 Jan 29;355(9201):362-8.

Gross N, Tashkin D, Miller R, Oren J, Coleman W, Linberg S. Inhalation by nebulization of albuterol-ipratropium combination (Dey combination) is superior to either agent alone in the treatment of chronic obstructive pulmonary disease. Dey Combination Solution Study Group. Respiration 1998;65(5):354-62.

Grossman RF, Ambrusz ME, Fisher AC, Khashab MM, Kahn JB. Levofloxacin 750 mg QD for five days versus amoxicillin/clavulanate 875 mg/125 mg BID for ten days for treatment of acute bacterial exacerbation of chronic bronchitis: a post hoc analysis of data from severely ill patients. Clin Ther 2006;28(8):1175-80.

Guell R, Casan P, Belda J, Sangenis M, Morante F, Guyatt GH, Sanchis J. Long-term effects of outpatient rehabilitation of COPD: A randomized trial. Chest 2000 Apr;117(4):976-83.

Hamilton AL, Killian KJ, Summers E, Jones NL. Muscle strength, symptom intensity, and exercise capacity in patients with cardiorespiratory disorders. Am J Respir Crit Care Med 1995;152:2021-31.

Hanania NA, Darken P, Horstman D, Reisner C, Lee B, Davis S, Shah T. The efficacy and safety of fluticasone propionate (250 microg)/salmeterol (50 microg) combined in the Diskus inhaler for the treatment of COPD. Chest 2003;124(3):834-43.

Hedlund J, Christenson B, Lundbergh P, Ortqvist A. Effects of a large-scale intervention with influenza and 23-valent pneumococcal vaccines in elderly people: a 1-year follow-up. Vaccine 2003;21:3906-11.

Heffner JE, Fahy B, Hilling L, Barbieri C. Attitudes regarding advance directives among patients in pulmonary rehabilitation. Am J Respir Crit Care Med 1996;154:1735-40.

Heng D, Sharples LD, McNeil K, Stewart S, Wreghitt T, Wallwork J. Bronchiolitis obliterans syndrome: incidence, natural history, prognosis, and risk factors. J Heart Lung Transplant 1998;17:1255–1263.

Highland KB, Strange C, Heffner JE. Long-term effects of inhaled corticosteroids on FEV1 in patients with chronic obstructive pulmonary disease. A meta-analysis. Ann Intern Med 2003;969-73.

Hosenpud JD, Bennett LE, Keck BM, Boucek MM, Novick RJ. The Registry of the International Society for Heart and Lung Transplantation: eighteenth Official Report-2001. J Heart Lung Transplant 2001;20:805–815.

Hosenpud JD, Bennett LE, Keck BM, Edwards EB, Novick RJ. Effect of diagnosis on survival benefit of lung transplantation for end-stage lung disease. Lancet 1998;351:24-27.

Jackson LA, Neuzil KM, Yu O, Benson P, Barlow WE, Adams AL, Hanson CA, Mahoney LD, Shay DK, Thompson WW; Vaccine Safety Datalink. Effectiveness of pneumococcal polysaccharide vaccine in older adults. N Engl J Med 2003 May;348(18):1747-55.

Jefferson T, Rivetti D, Rivetti A, Rudin M, Di Pietrantonj C, Demicheli V. Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. Lancet 2005;366:1165-74.

Jennings B, Callahan D, Caplan AL. Ethical challenges of chronic illness. Hastings Cent Report 1988 May;18(1):S1-16.

Johnell O, Prauwels R, Lofdahl CJ, Laitinen LA, Postma DS, Pride NB, Ohlsson SV. Bone mineral density in patients with chronic obstructive pulmonary disease treated with budesonide Turbuhaler. Eur Resp J 2002 Jun; 19(6):1058-63.

Jones PW, Willis LR, Burge PS, Calverley PM; Inhaled Steroids in Obstructive Lung Disease in Europe study investigators. Disease severity and the effect of fluticasone proprionate on chronic obstructive pulmonary disease exacerbations. Eur Respir J 2003 Jan;21(1):68-73.

Jonsonn JS, Gislason T, Gislason D, Siqurdsson JA. Acute bronchitis and clinical outcome 3 years later; prospective cohort study. BMJ 1998 Nov;317(7170):1433.

Kardos P, Wencker M, Glaab T, Vogelmeier C. Impact of salmeterol/fluticasone propionate versus salmeterol on exacerbations in severe chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2007;175(2):144-9.

Kimura H, Suda A, Sakuma T, Tatsumi K, Kawakami Y, Kuriyama T. Nocturnal oxyhemoglobin desaturation and prognosis in chronic obstructive pulmonary disease and late sequelae of pulmonary tuberculosis. Intern Med 1998;37:354–9.

Kiri VA, Bettoncelli G, Testi R, Viegi G. Inhaled corticosteroids are more effective in COPD patients when used with LABA than with SABA. Respir Med 2005 Sep;99(9):1115-24.

Klink M, Quan SF. Prevalence of reported sleep disturbances in a general adult population and their relationship to obstructive airways diseases. Chest 1987 Apr;91(4):540-6.

Knauft E, Nielson E, Engelberg R, Patrick D, Curtis J. Barriers and facilitators to end-of- life care communication for patients with COPD. Chest 2005(6):2188-96.

Kunik ME, Roundy K, Veazey C, Souchek J, Richardson P, Wray NP, Stanley MA. Surprisingly high prevalence of anxiety and depression in chronic breathing disorders. Chest 2005 Apr;127(4):1205-11.

Kupferberg DH, Kaplan RM, Slymen DJ, Ries AL. Questionnaire. J Cardiopulm Rehabil 2005 Nov-Dec;25(6):370-7.

Kutty K. Sleep and chronic obstructive pulmonary disease. Curr Opin Pulm Med 2004 Mar;10:104-12.

Lacasse Y, Brosseau L, Milne S, Martin S, Wong E, Guyatt GH, Goldstein RS, White J. Pulmonary Rehabiliatation for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2002;(3). [Recent update – July, 2005]

Lacasse Y, Brosseau L, Milne S, Martin S, Wong E, Guyatt GH, Golstein RS. Pulmonary rehabilitation for Chronic Obstructive Pulmonary Disease. Cochrane Database Syst Rev 2002;(3):CD003793.

Lacasse Y, Guyatt GH, Goldstein RS. The components of a respiratory rehabilitation program: a systematic overview. Chest 1997;111:1077-88.

Leech JA, Gervais A, Ruben FL. Efficacy of pneumococcal vaccine in severe chronic obstructive pulmonary disease. CMAJ 1987 Feb;136(4):361-5.

Leuenberger P, Schwartz J, Ackerman-Liebrich U, Blaser K, Bolognini G, Bongard JP, Brandi O, Braun P, Bron C, Brutche M, et al. Passive smoking exposure in adults and chronic respiratory symptoms (SAPALDIA Study). Swiss Study on Air Pollution and Lung Diseases in Adults, SAPALDIA Team. Am J Respir Crit Care Med 1994; 150: 1222-8.

Lofdahl CG, Ericsson A, Svensson K, Andreasson E. Cost effectiveness of budesonide/formoterol in a single inhaler for COPD compared with each monocomponent used alone. Pharmacoeconomics 2005;23(4):365-75.

Lotters F, van Tol B, Kwakkel G, Gosselink R. Effects of controlled inspiratory muscle training in patients with COPD: a meta analysis. Eur Respir J 2002;20:570-6.

Lynn and Goldstein. (2003) Advance care planning for fatal chronic illness: avoiding commonplace errors and unwanted suffering. Annals Int Med 2003;138:812-18.

MacNee W, Morgan AD, Wathen CG, Muir AL, Flenley DC. Right ventricular performance during exercise in

chronic obstructive pulmonary disease. The effects of oxygen. Respiration 1985;48(3):206-15.

MacNee W. State of the art: Pathophysiology of cor pulmonale in chronic obstructive pulmonary disease. Part One, Am J Respir Crit Care Med 1994 Sep;150(3):833-52.

Mahler DA, Wire P, Horstman D, Chang CN, Yates J, Fischer T, Shah T. Effectiveness of fluticasone propionate and salmeterol combination delivered via the Diskus device in the treatment of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002 Oct:166(8):1084-91.

Mahler DA., Donohue JF, Barbee RA, Goldman MD, Gross NJ, Wisniewski ME, Yancey SW, Zakes BA, Rickard KA, Anderson WH. Efficacy of salmeterol xinafoate in the treatment of COPD. Chest 1999 Apr:115(4):957-65.

Mal H, Sleiman C, Jebrak G, Messian O, Dubois F, Darne C, Duchatelle JP, Mollo JL, Fournier M, Kitzis M, et al. Functional results of single-lung transplantation for chronic obstructive lung disease. Am J Respir Crit Care Med 1994;149:1476–1481.

Maltais F, LeBlanc P, Jobin J. Intensity of training and physiological adaptation in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1997;155:555-61.

Maltais F, Ostinelli J, Bourbeau J, Tonnel AB, Jacquemet N, Haddon J, Rouleau M, Boukhana M, Martinot JB, Duroux P. Comparison of nebulized budesonide and oral prednisolone with placebo in the treatment of acute exacerbations of chronic obstructive pulmonary disease: a randomized controlled trial. Am J Respir Crit Care Med 2002 Mar 1;165(5):698-703.

Management of Asthma. Washington, DC: VA/DoD Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs and Health Affairs, Department of Defense, August 1999.

Management of Chronic Obstructive Pulmonary Disease in Primary Care. Washington, DC: VA/DoD Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs and Health Affairs, Department of Defense, August 1999. Office of Quality and Performance publication 10Q-CPG/COPD-00. Available from:http://www.oqp.med.va.gov/cpg/COPD/COPD_Base.htm (Retrieved November 2006)

Management of Major Depressive Disorder in Adults. Washington, DC: VA/DoD Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs and Health Affairs, Department of Defense May 2000. Office of Quality and Performance publication 10Q-CPG/MDD-00. Available from:http://www.oqp.med.va.gov/cpg/MDD/MDD_Base.htm (Retrieved November 2006)

Management of Tobacco Use. Washington, DC: VA/DoD Clinical Practice Guideline Working Group, Veterans Health Administration, Department of Veterans Affairs and Health Affairs, Department of Defense, December 1999 (Update 2004). Office of Quality and Performance publication 10Q-CPG/TUC-04. Available from: http://www.oqp.med.va.gov/cpg/TUC3/TUC_Base.htm (Retrieved November 2006)

Marquis K, Debigare R, Lacasse Y, LeBlanc P, Jobin J, Carrier G, Maltais F. Midthigh muscle cross-sectional area is a better predictor of mortality than body mass index in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002 Sep;166(6):809-13.

Martinez FJ, Grossman RF, Zadeikis N, Fisher AC, Walker K, Ambruzs ME, Tennenberg AM. Patient stratification in the management of acute bacterial exacerbation of chronic bronchitis: the role of levofloxacin 750 mg. Eur Respir J 2005 Jun;25(6):1001-10.

Maurer JR, Frost AE, Estenne M, Higenbottam T, Glanville AR. International guidelines for the selection of lung transplant candidates. The International Society for Heart and Lung Transplantation, the American Thoracic Society, the American Society of Transplant Physicians, the European Respiratory Society. Transplantation 1998; 66:951-6.

McDonald CF, Blyth CM, Lazarus MD, Marschner I, Barter CE. Exertional oxygen of limited benefit in patients with chronic obstructive pulmonary disease and mild hypoxemia. Am J Respir Crit Care Med 1995;152:1616-9.

Miravitlles M, Espinosa C, Fernandez-Laso E, Martos JA, Maldonado JA, Gallego M. Relationship between

bacterial flora in sputum and functional impairment in patients with acute exacerbations of COPD. Study Group of Bacterial Infection in COPD. Chest 1999;116:40-6.

Miravitlles M, Murio C, Guerrero T, Gisbert R, DAFNE Study Group. Decisions sober antibioticoterapia y farmacoeconomia en la EPOC. Pharmacoeconomic evaluation of acute exacerbations of chronic bronchitis and COPD. Chest 2002 May;121(5):1449-55.

Miravitlles M, Murio C, Guerrero T. Factors associated with relapse after ambulatory treatment of acute exacerbations of chronic bronchitis. DAFNE Study Group. Eur Respir J 2001;17:928-33.

Monninkhof E, van der Valk P, van der Palen J, van Herwaarden C, Partridge MR, Zielhuis G. Self-management education for patients with chronic obstructive pulmonary disease: a systematic review. Thorax 2003 May;58(5):394-8.

Moore RA, Wiffen PJ, Lipsky BA. Are the pneumococcal polysaccharide vaccines effective? Meta-analysis of the prospective trials. BMC Fam Pract 2000;1:1.

Moser KM, Bokinsky GE, Savage RT, Archibald CJ, Hansen PR. Results of a comprehensive rehabilitation program. Physiologic and functional effects on patients with chronic obstructive pulmonary disease. Archiv Intern Med 1980 Dec;140(12):1596-601.

MRC Working Party. 1981 Report of the Medical Research Council working party. Long-term domiciliary oxygen therapy in chronic hypoxic cor pulmonale complicating chronic bronchitis and emphysema. Lancet 1981;1:681-5.

Nair S, Thomas E, Pearson SB, Henry MT. A randomized controlled trial to assess the optimal dose and effect of nebulized albuterol in acute exacerbations of COPD. Chest 2005;128(1):48-54.

National Emphysema Treatment Trial (NETT) Research Group. A randomized trial comparing lung-volume reduction surgery with medical therapy for severe emphysema. N Engl J Med 2003;348:2059-73.

National Emphysema Treatment Trial (NETT) Research Group. Patients at high risk of death after lung-volumereduction surgery. N Engl J Med 2001;345:1075-83.

Naunheim KS, Wood DE, Mohsenifar Z, Sternberg AL, Criner GJ, DeCamp MM, Deschamps CC, Martinez FJ, Sciurba FC, Tonascia J, Fishman AP. Long-term follow-up of patients receiving lung-volume-reduction surgery versus medical therapy for severe emphysema by the National Emphysema Treatment Trial Research Group. Ann Thorac Surg 2006 Aug;82(2):431-43.

NHANES III -Third national Health and Nutrition Examination Survey (NHANES III). Available from: http://www.cdc.gov/nchs/products/elec_prods/subject/nhanes3.htm (Retrieved November 2006).

NICE. Chronic Obstructive Pulmonary Disease. CG012, 2004 Available from: http://www.nice.org.uk/guidance/CG12 (Retrieved November 2006)

Nichol KL, Baken L, Nelson A. Relation between influenza vaccination and outpatient visits, hospitalization, and mortality in elderly person with chronic lung disease. Ann Intern Med 1999 Mar;130(5):397-403.

Nichol KL, Baken L, Wuorenma J, Nelson A. The health and economic benefits associated with pneumococcal vaccination of elderly persons with chronic lung disease. Arch Intern Med 1999b Nov;159(20):2437-42.

Niewoehner DE, Erbland ML, Deupree RH, Collins D, Gross NJ, Light RW, Anderson P. Morgan NA Effect of systemic glucocorticoids on exacerbation of chronic obstructive pulmonary disease. N Engl J Med 1999 June; 340(25):1941-7.

Niewoehner DE, Rice K, Cote C, Paulson D, Cooper JA Jr, Korducki L, Cassino C, Kesten S. Prevention of exacerbations of chronic obstructive pulmonary disease with tiotropium, a once-daily inhaled anticholinergic bronchodilator: a randomized trial. Ann Intern Med 2005;143:317-26.

Nishimura K, Izumi T, Tsukino M, Oga T. Dyspnea is better predictor of 5-year survival than airway obstruction in patients with COPD. Chest 2002 May;121(5):1434-40.

Nishimura K, Koyama H, Ikeda A, Izumi T. Is oral theophylline effective in combination with both inhaled anticholinergic agent and inhaled beta 2-agonist in the treatment of stable COPD? Chest 1993 Jul;104(1):179-84.

Nishimura K, Koyama H, Ikeda A, Sugiura N, Kawakatsu K, Izumi T. The additive effect of theophylline on a high-dose combination of inhaled salbutamol and ipratropium bromide in stable COPD. Chest 1995 Mar;107(3): 718-23.

Nocturnal oxygen therapy trial group (NOTT). Continuous or nocturnal oxygen therapy in hypoxemic chronic obstructive lung disease. Ann Intern Med 1980 Sep;93(3):391-8.

Nouira S, Marghli S, Belghith M, Besbes L, Elatrous S, Abroug F. Once daily oral ofloxacin in chronic obstructive pulmonary disease exacerbation requiring mechanical ventilation: a randomised placebo- controlled trial. Lancet 2001 Dec;358:2020-5.

O'Donnell DE, Fluge T, Gerken F, Hamilton A, Webb K, Aguilaniu , Make B, Magnussen H. Effects of tiotropium on lung hyperinflation, dyspnoea and exercise tolerance in COPD Eur Respir J 2004 Jun;23(6):832-40.

O'Donnell DE, Hernandez P, Aaron S, Bourbeau J, Marciniuk D, Hodder R, Balter M, Ford G, Gervaia A, Goldstein R, et al. Canadian Thoracic Society COPD Guidelines: summary of highlights for family doctors. Can Respir J 2003 Nov-Dec;10(8):463-6.

O'Donnell DE, McGuire M, Samis L, Webb KA. General exercise training improves ventilatory and peripheral muscle strength and endurance in chronic airflow limitation. Am J Respir Crit Care Med 1998 May;157(5 Pt 1):1489-97.

Oh EG. The effects of home-based pulmonary rehabilitation in patients with chronic lung disease. Int J Nurs Stud 2003 Nov;40(8):873-9.

Oostenbrink JB, Rutten-van Molken MP, Monz BU, FitzGerald JM. Probabilistic Markov model to assess the cost-effectiveness of bronchodilator therapy in COPD patients in different countries. Value Health 2005;8(1):32-46.

Orens JB, Estenne M, Arcasoy S, Conte JV, Corris P, Egan JJ, Egan T, Keshavjee S, Knoop C, Kotloff R, Martinez FJ, Nathan S, Palmer S, Patterson A, Singer L, Snell G, Studer S, Vachiery JL, Glanville AR. Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. International guidelines for the selection of lung transplant candidates: 2006 update--a consensus report from the Pulmonary Scientific Council of the International Society for Heart and Lung Transplantation. J Heart Lung Transplant 2006;25:745-55.

Ortega F, Toral J, Cejudo P, Villagomez R, Sanchez H, Castillo J, Montemayor T. Comparison of effects of strength and endurance training in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2002 Sep;166(5):669-74.

Oswald-Mammosser M, Weitzenblum E, Quoix E, Moser G, Chaouat A, Charpentier C, Kessler R. Prognostic factors in COPD patients receiving long-term oxygen therapy. Importance of pulmonary artery pressure. Chest 1995 May;107(5):1193-8.

Paggiaro PL, Dahle R, Bakran I, Frith L, Hollingworth K, Efthimiou J. Multicentre randomized placebo-controlled trial of inhaled fluticasone proprionate in patients with chronic obstructive pulmonary disease. Lancet 1998 Mar;351(9105):773-80.

Patterson GA, Maurer JR, Williams TJ, Cardoso PG, Scavuzzo M, Todd TR. Comparison of outcomes of double and single lung transplantation for obstructive lung disease. The Toronto Lung Transplant Group. J Thorac Cardiovasc Surg 1991; 101: 623–631; discussion 631–632.

Pauwels RA, Buist AS, Ma P, Jenkins CR, Hurd SS; GOLD Scientific Committee. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: National Heart, Lung, and Blood Institute and World Health Organization Global Initiative for Chronic Obstructive Lung Disease (GOLD): executive summary. Respir Care 2001;46:798-825.

Pauwels RA, Lofdahl CG, Laitinen LA, Schouten JP, Postma DS, Pride NB, Ohlsson SV.Long-term treatment with inhaled budesonide in persons with mild chronic obstructive pulmonary disease who continue smoking. Europena Respiratory Society Study on Chronic Obstructive Pulmonary Disease. N Engl J Med 1999;340(25):1948-53.

Pellegrino R, Viegi G, Brusasco V, Crapo RO, Burgos F, Casaburi R, Coates A, van der Grinten CP, Gustafsson P, Hankinson J, Jensen R, Johnson DC, MacIntyre N, McKay R, Miller MR, Navajas D, Pedersen OF, Wanger J. Interpretative strategies for lung function tests. Eur Respir J 2005 Nov;26(5):948-68.

Pien LC, Grammer LC, Patterson R. Minimal complications in a surgical population with severe asthma receiving prophylactic corticosteroids. J Allergy Clin Immunol 1988; 82: 696-700.

Pollock M, Ayres J, Ward A. Cardiorespiratory fitness response to differing intensities and duration of training. Arch Phys Med Rehab 1977;58:467-73.

Poole PJ, Black PN. Mucolytic agents for chronic bronchitis in chronic obstructive pulmonary disease.Cochrane Database Syst Rev 2003 July;3:CD001287.

Poole PJ, Black PN. Mucolytic agents for chronic bronchitis or chronic obstructive pulmonary disease.[update of Cochrane Database Syst Rev. 2003;(2):CD00128.] Cochrane Database of Systematic Reviews 2006.

Poole PJ, Chacko E, Wood-Baker RWB, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. Cochrane Database Syst Rev. 2006 Jan;(1):CD002733.

Prescott E, Almdal T, Mikkelsen KL, Tofteng CL, Vestbo J, Lange P. Prognostic value of weight change in chronic obstructive pulmonary disease: results from the Copenhagen City Heart Study. Eur Respir J 2002;20:539-44.

Pulmonary rehabilitation: joint ACCP/AACVPR evidence based guidelines. ACCP/AACVPR Pulmonary Rehabilitation Guidelines Panel. American College of Chest Physicians. American Association of Cardiovascular and Pulmonmary Rehabilitation. Chest 1997 Nov;112(5):1363-96.

Ram FS, Jones PW, Castro AA, De Brito JA, Atallah AN, Lacasse Y, Mazzini R, Goldstein R, Cendon S. Oral theophylline for chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2002;(4):CD003902.

Ram FS, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC. Antibiotics for exacerbations of chronic obstructive pulmonary disease. Cochrane Database of Systematic Reviews 2006 Apr 19;(2):CD004403.

Ram FS. Use of theophylline in chronic obstructive pulmonary disease: examining the evidence. Current Opinion in Pulmonary Med 2006;12(2):132-9.

Rautalahti M, Virtamo J, Haukka J, Heinonen OP, Sundvall J, Albanes D, Huttunen JK. The effect of alpha-tocoferol and beta-carotene supplementation on COPD symptoms. Am J Respir Crit Care Med 1997 Nov;156(5):1447-52.

Rennard S, Anderson W, ZuWallack R, Broughton J, Bailey W, Friedman M, Wisniewski M, Richard K. Use of a long-acting inhaled beta2-adrenergic agonist, salmeterol xinafoate, in patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2001;163(5):1087-92.

Ries AL, Kaplan RM, Limberg TM, Prewitt LM. Effects of pulmonary rehabilitation on physiologic and psychosocial outcomes in patients with chronic obstructive pulmonary disease. Ann Int Med 1995 Jun;122:823-32.

Ries AL, Kaplan RM, Myers R, Prewitt LM. Maintenance after pulmonary rehabilitation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2003 Mar;167(6):880-8.

Ries AL, Make BJ, Lee SM, Krasna MJ, Bartels M, Crouch R, Fishman AP; National Emphysema Treatment Trial Research Group. The effects of pulmonary rehabilitation in the national emphysema treatment trial. Chest 2005 Dec;128(6):3799-809.

Rooyackers JM, Dekhuijzen PN, Van Herwaarden CL, Folgering HT. Training with supplemental oxygen in patients with COPD and hypoxaemia at peak exercise. Eur Respir J 1997 Jun;10(6):1278–84.

Rose C, Wallace L, Dickson R, Ayres J, Lehman R, Searle Y, and Burge PS. The most effective psychologically-based treatments to reduce anxiety and panic in patients with chronic obstructive pulmonary disease (COPD): a systematic review. Patient Educ Couns 2002 Aug:47(4):311-8.

Rossi A, Kristufek P, Levine BE, Thomson MH, Till D, Kottakis J, Della Cioppa G; Formoterol in Chronic Obstructive Pulmonary Disease (FICOPD) II Study Group. Comparison of the efficacy, tolerability, and safety of formoterol dry powder and oral, slow-release theophylline in the treatment of COPD. Chest 2002 Apr; 121(4):1058-69.

Sahebjami H, Doers JT, Render ML, Bond TL. Anthropometric and pulmonary function test profiles of outpatients with stable chronic obstructive pulmonary disease. Am J Med 1993 May;94(5):469-74.

Saint S, Bent S, Vittinghoff E, Grady D. Antibiotics in chronic obstructive pulmonary disease exacerbations. A meta-analysis. JAMA 1995;273:957-96.

Salman GF, Mosier MC, Beasley BW, Calkins DR. Rehabilitation for patients with chronic obstructive pulmonary disease: meta-analysis of randomized controlled trials. J Gen Intern Med 2003 Mar;18(3):213-21.

Salpeter S, Ormiston T, Salpeter E. Cardioselective beta-blockers for chronic obstructive pulmonary disease. [update of Cochrane Database Syst Rev. 2002;(2):CD003566. Cochrane Database of Systematic Reviews 2005;(4):CD003566.

Scharf SM, Iqbal M, Keller C, Criner G, Lee S, Fessler HE; national Emphysema Treatment Trial (NETT) Group. Hemodynamic characterization of patients with severe emphysema. Am J Respir Crit Care Med 2002 Aug;16693):314-22.

Schols AM, Slangen J, Volovics L, Wouters EF. Weight loss is a reversible factor in the prognosis of chronic obstructive pulmonary disease. Am J Respir Crit Care Med 1998;157:1791–7.

Schols AM, Soeters P, Dingemans M, Mostert R, Frantzen P and Wouters E. Prevalence and characteristics of nutritional depletion in patients with stable COPD eligible for pulmonary rehabilitation. Am Rev Respir Dis 1993;147:1151-6.

Sestini P, Renzoni E, Robinson S, Poole P, Ram FS. Short-acting beta2-agonists for stable chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2002;(4)CD001495.

Sethi S, Evans N, Grant BJ, Murphy TF. New Strains of Bacteria and Exacerbations of Chronic Obstructive Pulmonary Disease. N Engl J Med 2002 Aug;34797):465-71.

Sherman S, Skoney JA, Ravikrishnan KP. Routine chest radiographs in exacerbations of chronic obstructive pulmonary disease. Diagnostic value. Arch Intern Med 1989 Nov;149(11):2493-6.

Simpson K, Killian K, McCartney N, Stubbing DG, Jones NL. Randomized controlled trial of weightlifting exercise in patients with chronic airflow limitation. Thorax 1992 Feb;47(2):70-5.

Sin DD, McAlister FA, Paul Man SF, Anthonison NR. Contemporary management of chronic obstructive pulmonary disease – Scientific review. JAMA 2003;290:2301-13.

Sin DD, Tu JV. Inhaled corticosteroids and the risk of mortality and readmission in elderly patients with chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2001 Aug 15;164(4):580-4.

Singh H, Ebejer MJ, Higgens DA, Henderson AH, Campbell IA. Acute hemodynamic effects of nifedipine at rest and during maximal exercise in patients with chronic cor pulmonale. Thorax 1985 Dec;40(12):910-4.

Smith K, Cook D, Guyatt GH, Madhavan J, Oxman AD. Respiratory muscle training in chronic airflow limitation: a meta-analysis. Am Rev Respir Dis 1992 Mar;145(3):533-9.

Soler N, Torres A, Ewig S, Gonzalez J, Celis R, El-Ebiary M, Hernandez C, Rodriguez-Roisin R. Bronchial

microbial patterns in severe exacerbations of COPD requiring mechanical ventilation. Am J Resp Crit Care Med 1998 May;157(5 Pt 1):1498-505.

Speizer FE, Fay ME, Dockery DW, Ferris BG Jr. Chronic obstructive pulmonary disease mortality in six U.S. cities. Am Rev Respir Dis 1989 Sep;140(3 Pt 2):S49-55.

Spruit MA, Gosselink R, Troosters T, De Paepe K, Decramer M. Resistance versus endurance training in patients with COPD and skeletal muscle weakness. Eur Respir J 2002 Jun;19(6):1072-8.

Stein DA, Bradley BL, Miller WC. Mechanisms of oxygen effects on exercise in patients with chronic obstructive pulmonary disease. Chest 1982 Jan; 81(1):6-10.

Stey C, Steurer J, Bachmann S, Medici TC, Tramer MR. The effect of oral N-acetylcysteine in chronic bronchitis: a quantitative systematic review. Eur Respir J 2000;16(2):253-62.

Stirling GR, Babidge WJ, Peacock MJ, Smith JA, Matar KS, Snell GI, Colville DJ, Maddern GJ. Lung volume reduction surgery in emphysema: a systematic review. Ann Thorac Surg 2001 Aug;72(2):641-8.

Stockley RA, Chopra N, Rice L. Addition of salmeterol to existing treatment in patients with COPD: a 12 month study. Thorax 2006a 61 (2): 122-8.

Stockley RA, O'Brien C, Pye A, Hill SL. Relationship of sputum color to nature and outpatient management of acute exacerbations of COPD. Chest 2000 Jun;117(6):1638-45.

Stockley RA, Whitehead PJ, Williams MK. Improved outcomes in patients with chronic obstructive pulmonary disease treated with salmeterol compared with placebo/usual therapy: results of a meta-analysis. Respir Res 2006b 7: 147.

Stoller JK, Abboussouan LS. Alpha1-antitrypsin deficiency. Lancet 2005 Jun25-Jul 1;365(9478):2225-36.

Suissa S. Effectiveness of inhaled corticosteroids in chronic obstructive pulmonary disease: immortal time bias in observational studies. Am J Respir Crit Care Med 2003 Jul 1;168(1):49-53.

Suissa S. Inhaled steroids and mortality in COPD: bias from unaccounted immortal time. Eur Respir J 2004; 23(3):391-5.

Sutherland ER, Allmers H, Ayas NT, Venn AJ, Martin RJ. Inhaled corticosteroids reduce the progression of airflow limitation in chronic obstructive pulmonary disease: a meta-analysis. Thorax 2003 Nov;58911):937-41.

Szafranski W, Cukier A, Ramirez A, Menga G, Sansores R, Nahabedian S, Peterson S, Olsson H. Efficacy and safety of budesonide/formoterol in the management of chronic obstructive pulmonary disease. Eur Respir J 2003 Jan:21(1):74-81.

Tarhan S, Moffitt EA, Sessler AD, Douglas WW, Taylor WF. Risk of anesthesia and surgery in patients with chronic bronchitis and chronic obstructive pulmonary disease. Surgery 1973;74:720-6.

Taylor J, Kotch A, Rice K, Ghafouri M, Kurland CL, Fagan NM, Witek TJ Jr. Ipratropium Bromide HFA Study Group. Ipratropium bromide hydrofluoroalkane inhalation aerosol is safe and effective in patients with COPD. Chest 2001;120(4):1253-61.

Teno JM, Clarridge BR, Casey V, Welch LC, Wetle T, Shield R, Mor V. Family perspectives on end-of-life care at the last place of care. JAMA 2004;291(1):88-93.

The ATBC Cancer Prevention Study Group. The alpha-tocopherol, beta-carotene lung cancer prevention study: design, methods, participant characteristics and compliance. Ann Epidemiol 1994 Jan;4(1):1-10.

The chartered society of physiotherapy. The effectiveness of pulmonary rehabilitation: evidence and implications for physiotherapists. 2003 Available from: www.csp.org.uk (Retrieved November 2006).

The effect of Vitamin E and beta carotene on the incidence of lung cancer and other cancers in male smokers. The Alpha-Tocopherol, Beta Carotene Cancer Prevention Study Group. N Engl J Med 1994 Apr;330(15):1029-35.

The lung health study research group, Altose MD, Redline S, Deitz CD, Quinlan KJ, Eichenhorn MS, Conway WA, Jentons RL, Braden K, Ketchum M, Wise RA, et al. Effect of inhaled triamcinilone on the decline in pulmonary function in chronic obstructive pulmonary disease. N Engl J Med 2000 Dec;343(26):1902-9.

Theodore J, Lewiston N. Lung transplantation comes of age. N Engl J Med 1990; 322:772-4.

Thompson WH, Nielson CP, Carvalho P, Charan NB, Crowley JJ. Controlled trial of oral prednisone in outpatients with acute COPD exacerbation. Am J Respir Crit Care Med 1996 Aug; 154(2 Pt 1):407-12.

Timms RM, Khaja FU, Williams GW. Hemodynamic response to oxygen therapy in chronic obstructive pulmonary disease. Ann Intern Med 1985;102:29-36.

Tiong LU, Davies R, Gibson PG, Hensley MJ, Hepworth R, Lasserson TJ, Smith B. Lung volume reduction surgery for diffuse emphysema. Cochrane Database Syst Rev 2006 Oct 18;(4):CD001001.

Trayner E Jr, Celli BR. Postoperative pulmonary complications. Med Clin North Am 2001; 85:1129-39.

Treating Tobacco Use and Dependence (Quick Guide for Clinicians): Available from: http://www.surgeongeneral.gov/tobacco/tobaqrg.pdf (Retrieved November 2006).

Troosters T, Casaburi R, Gooselink R, Decramer M. Pulmonary rehabilitation in chronic obstructive pulmonary disease. Am J Respir Crit Care Med 2005 Jul;172(1):10-38.

Troosters T, Gosselink R, Decramer M. Exercise training in COPD: how to distinguish responders from nonresponders. J Cardiopulm Rehab 2001 Jan-Feb;21(1):10-7.

Tsai TW, Gallagher EJ, Lombardi G, Gennis P, Carter W. Guidelines for the selective ordering of admission chest radiography in adult obstructive airway disease. Ann Emerg Med 1993;22:1854-8.

van der Valk, P, Monninkhof E, van der Palen J, Zielhuis G, van Herwaarden C. Effect of discontinuation of inhaled corticosteroids in patients with chronic obstructive pulmonary disease: the COPE study. Am J Respir Crit Care Med 2002 Nov;166(10):1358-63.

van Noord JA, Aumann JL, Janssens E, Smeets JJ, Verhaert J, Disse B, Mueller A, Cornelissen PJ. Comparison of tiotropium once daily, formoterol twice daily and both combined once daily in patients with COPD. Eur Respir J 2005 Aug 26(2):214-22.

van Noord JA, Aumann JL, Janssens E, Verhaert J, Smeets JJ, Mueller A, Cornelissen PJ. Effects of tiotropium with and without formoterol on airflow obstruction and resting hyperinflation in patients with COPD. Chest 2006;129(3):509-17.

van Noord JA, de Munck DR, Bantje TA, Hop WC, Akveld M, Bommer AM. Long-term treatment of chronic obstructive pulmonary disease with salmeterol and the additive effect of ipratropium. Eur Respir J 2000 May; 15(5):878-85.

van Shayck CP. Detecting patients at high risk of developing COPD in general practice; cross sectional case finding study. BMI 2002;324:1370-4.

Vestbo J, Sorenson T, Lange P, Brix A, Torre P, Viskum A. Long-term effect of inhaled budesonide in mild and moderate chronic obstructive pulmonary disease: a randomized controlled trial. Lancet 1999;353(9167):1819-23.

Vila-Corcoles A, Ochoa-Gondar O, Hospital I, Ansa X, Vilanova A, Rodriguez T, Llor C; EVAN Study Group. Protective effects of the 23-valent pneumococcal polysaccharide vaccine in the elderly population: the EVAN-65 study. Clin Infect Dis 2006 Oct 1;43(7):860-8. Epub 2006 Aug 21.

Vu T, Farish S, Jenkins M, Kelly H. A meta-analysis of effectiveness of influenza vaccine in persons aged 65 years and over living in the community. Vaccine 2002; 20:1831-36.

Wadbo M, Lofdahl CG, Larsson K, Skoogh BE, Tornling G, Arwestrom E, Bengtsson T, Strom K; Swedish Society of Respiratory Medicine. Effects of formoterol and ipratropium bromide in COPD: a 3-month placebo-

controlled study. Eur Respir J 2002 Nov;20(5):1138-46.

Walters JA, Walters EH, Wood-Baker R. Oral corticosteroids for stable chronic obstructive pulmonary disease. Cochrane Database of Syst Rev 2005;(3):CD005374.

Warner MA, Offord KP, Warner ME, Lennon RL, Conover MA, Jansson-Schumacher U. Role of preoperative cessation of smoking and other factors in postoperative pulmonary complications: a blinded prospective study of coronary artery bypass patients. Mayo Clin Proc 1989 June;64(6):609-16

Watson L, Wilson BJ, Waugh N. Pneumococcal polysaccharide vaccine: a systematic review of clinical effectiveness in adults. Vaccine 2002 May;20(17-18):2166-73.

Wedzicha JA, Bestall JC, Garrod R, Garnham R, Paul EA, Jones PW. Randomized controlled trial of pulmonary rehabilitation in severe chronic obstructive pulmonary disease patients, stratified with the MRC dyspnoea scale. Eur Respir J 1998 Aug;12(2):363-9.

Weir DC, Bale GA, Bright P, Sherwood Burge P. A double-blind placebo-controlled study of the effect of inhaled beclomethasone diproprionate for 2 years in patients with nonasthmatic chronic obstructive pulmonary disease. Clin Exp Allergy 1999 Jun;29 Suppl 2:125-8.

Weissman DE. (2004) Decision making at a time of crisis near the end of Life. JAMA 2004;292:1738-43.

Weitzenblum E, Sautegeau A, Ehrhart M, Mammosser M, Hirth C, Roegel E. Long-term course of pulmonary arterial pressure in chronic obstructive pulmonary disease. Am Rev Respir Dis 1984 Dec;130(6):993-8.

Weitzenblum E, Sautegeau A, Ehrhart M, Mammosser M, Pelletier A. Long-term oxygen therapy can reverse the progression of pulmonary hypertension in patients with chronic obstructive pulmonary disease. Am Rev Respir Dis 1985 Apr;131(4):493-9.

Wiedemann HP, Matthay RA. Cor pulmonale in chronic obstructive pulmonary disease: circulatory pathophysiology and management. Clin Chest Med 1990 Sep:11(3):523-45.

Williams TJ, Grossman RF, Maurer JR. Long-term functional follow-up of lung transplant recipients. Clin Chest Med 1990; 11: 347–358.

Wilson R, Allegra L, Huchon G, Izquierdo JL, Jones P, Schaberg T, et al. Short-term and long-term outcomes of moxifloxacin compared to standard antibiotic treatment in acute exacerbations of chronic bronchitis. Chest 2004;125:953-64.

Wilson R, Jones P, Schaberg T, Arvis P, DupratLomon I, Sagnier PP, Group MS. Antibiotic treatment and factors influencing short and long term outcomes of acute exacerbations of chronic bronchitis. Thorax 2006;61(4):337-42.

Wilson R, Schentag JJ, Ball P, Mandell L. A comparison of gemifloxacin and clarithromycin in acute exacerbations of chronic bronchitis and long-term clinical outcomes. Clin Ther 2002;24:639-52.

Wilt TJ, Niewoehner D, Kim C-B, Kane RL, Linabery A, Tacklind J, MacDonald R, Rutks I. Use of Spirometry for Case Finding, Diagnosis, and Management of Chronic Obstructive Pulmonary Disease (COPD). Evidence Report/Technology Assessment No. 121 (Prepared by the Minnesota Evidence-based Practice Center under Contract No. 290-02-0009.) AHRQ Publication No. 05-E017-2. Rockville, MD. Agency for Healthcare Research and Quality. September 2005.

Wongsurakiat P, Maranetra KN, Wasi C, Kositanont U, Dejsomritutai W, Charoenratanakul S. Acute respiratory illness in patients with COPD and the effectiveness of influenza vaccination. Chest 2004 Jun;125(6): 2011-20.

Wood-Baker R, Gibson P, Hannay M, Walterss EH, Walters JA. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. Cochrane Database Syst Rev 2005 Jan;(1):CD001288.

Wouters EF, Postma DS, Fokkens B, Hop WC, Prins J, Kuipers AF, Pasma HR, Hensing CA, Creutzberg EC; Cosmic (COPD) and Serentide: a Multi-Center Intervention and Characterization) Study Group. Withdrawal of fluticasone propionate from combined salmeterol/fluticasone treatment in patients with COPD causes

immediate and sustained disease deterioration: a randomised controlled trial. Thorax 2005 Jun; 60(6):480-7.

Wouters EF, Schols AM. Prevalence and pathophysiology of nutritional depletion in chronic obstructive pulmonary disease. Respir Med 1993 Aug;87 Suppl B:45-7.

You Can Quit Smoking: Available from: http://www.surgeongeneral.gov/tobacco/5daybook.pdf (Retrieved November 2006).

Youngner SJ, Lewandowsky W, McClish DK, Juknialis MA, Coulton C, Bartlett ET. "Do not resuscitate" orders: incidence and implications in a medical intensive care unit. J Am Med Assoc 1985 Jan;253(1):54-7.

Zhou Y, Wang X, Zeng X, Qiu R, Xie J, Liu S, Zheng J, Zhong N, Ran P. Positive benefits of theophylline in a randomized, double-blind, parallel-group, placebo-controlled study of low-dose, slow-release theophylline in the treatment of COPD for 1 year. Respirology 2006;11(5):603-10.

ZuWallack RL, Mahler DA, Reilly D, Church N, Emmett A, Rickard K, Knobil K. Salmeterol plus theophylline combination therapy in the treatment of COPD. Chest 2001 Jun;11996):1661-70.

ZuWallack RL, Patel K, Reardon J, Clark BA 3rd, Normandin EA. Predictors of improvement in the 12-minute walking distance following a 6-week outpatient pulmonary rehabilitation program. Chest 1991 Apr;99(4):805-8.