Management of COPD Exacerbations

ANN E. EVENSEN, MD, *University of Wisconsin School of Medicine and Public Health, Verona, Wisconsin*

Exacerbations of chronic obstructive pulmonary disease contribute to the high mortality rate associated with the disease. Randomized controlled trials have demonstrated the effectiveness of multiple interventions. The first step in outpatient management should be to increase the dosage of inhaled short-acting bronchodilators. Combining ipratropium and albuterol is beneficial in relieving dyspnea. Oral corticosteroids are likely beneficial, especially for patients with purulent sputum. The use of antibiotics reduces the risk of treatment failure and mortality in moderately or severely ill patients. Physicians should consider antibiotics for patients with purulent sputum and for patients who have inadequate symptom relief with bronchodilators and corticosteroids. The choice of antibiotic should be guided by local resistance patterns and the patient's recent history of antibiotic use. Hospitalized patients with exacerbations should receive regular doses of short-acting bronchodilators, continuous supplemental oxygen, antibiotics, and systemic corticosteroids. Noninvasive positive pressure ventilation or invasive mechanical ventilation is indicated in patients with worsening acidosis or hypoxemia. (*Am Fam Physician*. 2010;81(5):607-613, 616. Copyright © 2010 American Academy of Family Physicians.)

ILLUSTRATION BY MARK LEFKOWITZ

▶ **Patient information:** A handout on COPD exacerbations, written by the author of this article, is provided on page 616.

EB CME

This clinical content conforms to AAFP criteria for evidence-based continuing medical education (EB CME).

In patients with known chronic obstructive pulmonary disease (COPD), exacerbations occur an average of 1.3 times per year.[1] Exacerbations range in severity from transient declines in functional status to fatal events. In the United States, exacerbations have contributed to a 102 percent increase in COPD-related mortality from 1970 to 2002 (21.4 to 43.3 deaths per 100,000 persons).[2] Effective management of a COPD exacerbation combines relieving acute symptoms and lowering the risk of subsequent exacerbations.

Definition and Classification

Criteria for the diagnosis of COPD have been established.[3] However, there is no validated diagnostic test or biomarker of COPD exacerbations.[4] The American Thoracic Society (ATS) and European Respiratory Society (ERS) define an exacerbation as an acute change in a patient's baseline dyspnea, cough, or sputum that is beyond normal variability, and that is sufficient to warrant a change in therapy.[5] The ATS and ERS classify COPD exacerbations as mild, moderate, or severe, based on the intensity of the medical intervention required to control the patient's symptoms *(Table 1)*.[4,5] In addition to the hallmark symptoms of a COPD exacerbation (cough, dyspnea, and increased sputum), systemic inflammation also causes extrapulmonary symptoms *(Table 2)*.[6-8] Factors that increase the risk of a severe exacerbation are listed in *Table 3*.[5-7,9-11]

Table 1. Classification of COPD Exacerbations by Severity

Severity of exacerbation	*Description*
Mild	Can be controlled with an increase in dosage of regular medications
Moderate	Requires treatment with systemic corticosteroids or antibiotics
Severe	Requires hospitalization or evaluation in the emergency department

COPD = chronic obstructive pulmonary disease.

Information from references 4 and 5.

Etiology

Infection of the tracheobronchial tree and air pollution (e.g., tobacco smoke, occupational exposures, ozone) are the most common identifiable causes of COPD exacerbations. One third of exacerbations have no identifiable cause.[6] Other medical problems, such as congestive heart failure, nonpulmonary infections, pulmonary embolism, and pneumothorax, can also prompt a COPD exacerbation.[9]

Table 2. Symptoms of COPD Exacerbation

Body system	*Symptoms*
Cardiac	Chest tightness
	Tachycardia
Musculoskeletal	Decreased exercise tolerance
Psychiatric	Confusion
	Depression
	Insomnia
	Sleepiness
Pulmonary	Change in volume, color, or tenacity of sputum
	Cough
	Dyspnea
	Tachypnea
	Wheezing
Systemic	Fatigue
	Fever
	Malaise

COPD = chronic obstructive pulmonary disease.

Information from references 6 through 8.

Table 3. Factors that Increase Risk of Severe COPD Exacerbations

Altered mental status
At least three exacerbations in the previous 12 months
Body mass index of 20 kg per m^2 or less
Marked increase in symptoms or change in vital signs
Medical comorbidities (especially cardiac ischemia, congestive heart failure, pneumonia, diabetes mellitus, or renal or hepatic failure)
Poor physical activity levels
Poor social support
Severe baseline COPD (FEV_1/FVC ratio less than 0.70 and FEV_1 less than 50 percent of predicted)
Underutilization of home oxygen therapy

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; FVC = forced vital capacity.

Information from references 5 through 7, and 9 through 11.

Initial Evaluation

The initial evaluation of patients with a suspected COPD exacerbation should include a history of baseline and current symptoms, such as limitations in activities of daily living. If available, previous chest radiographs, arterial blood gas measurements, and spirometry results can help establish the baseline lung function and illustrate a typical exacerbation. Because increasing confusion is a hallmark of respiratory compromise, the physical examination should include a mental status evaluation, as well as heart and lung examinations.

Recommended diagnostic evaluation of an exacerbation depends on its severity (*Table 4*).[5,8,9,12,13] Pulse oximetry should be performed in all patients. Chest

Table 4. Diagnostic Evaluation of Patients with Suspected COPD Exacerbation

Test	*Potential diagnosis*
Perform routinely	
Pulse oximetry	Hypoxemia
Perform if hospitalized	
Arterial blood gas measurement	Hypercarbia
	Hypoxemia
	Respiratory acidosis
Chest radiography	Alternate sources of dyspnea
Complete blood count	Anemia
	Leukocytosis
	Polycythemia
Electrocardiography	Cardiac arrhythmias
	Cardiac ischemia
Metabolic panel	Electrolyte disturbances
	Hypo- or hyperglycemia
	Metabolic acid-base changes
Consider performing, especially if patient is not responding to conventional exacerbation treatment	
Brain natriuretic peptide measurement	CHF (one third of dyspnea in chronic lung disease may be attributable to CHF)
Cardiac enzyme measurement	Cardiac ischemia (myocardial infarction is underdiagnosed in patients with COPD)

CHF = congestive heart failure; COPD = chronic obstructive pulmonary disease.

Information from references 5, 8, 9, 12, and 13.

radiography is appropriate in hospitalized patients and can guide treatment by revealing comorbid conditions such as congestive heart failure, pneumonia, and pleural effusion. A room air arterial blood gas (ABG) measurement should be obtained at the time of hospital admission to quantify hypercarbia and hypoxemia. Measurement of brain natriuretic peptide and serial cardiac enzyme levels should be considered in hospitalized patients, because cardiac ischemia and congestive heart failure are common comorbidities in patients with COPD.[5,12,13]

Other physical examination maneuvers, laboratory tests, and assessments of cardiac function have not been proven beneficial in the treatment of COPD exacerbations.[9]

Indications for Hospitalization

About 50 percent of COPD exacerbations are not reported to physicians, suggesting that many exacerbations are mild.[14] The risk of death from an exacerbation increases with the development of respiratory acidosis, the presence of significant comorbidities, and the need for ventilatory support.[5] Patients with symptoms of respiratory distress and those at risk of distress should be admitted to the hospital to provide access to critical care personnel and mechanical ventilation. Inpatient mortality for COPD exacerbations is 3 to 4 percent.[9] Patients admitted to the intensive care unit have a 43 to 46 percent risk of death within one year after hospitalization.[9]

Nonambulatory patients should receive routine prophylaxis for deep venous thrombosis. Because COPD is a progressive and often fatal illness, physicians should consider discussing and documenting the patient's wishes concerning end-of-life care.

Oxygenation and Ventilation

Oxygen supplementation should be titrated to an oxygen saturation level of at least 90 percent. High-flow oxygen devices deliver oxygen more reliably than nasal prongs, but nasal prongs may be better tolerated. Noninvasive positive pressure ventilation (NIPPV) is indicated if adequate oxygenation or ventilation cannot be achieved using a high-flow mask.[15] Patients requiring NIPPV should be monitored continuously for decompensation.

If the patient cannot be adequately oxygenated, complications, such as pulmonary embolism or edema, should be considered.[6] Carbon dioxide retention is possible in moderately and severely ill patients; therefore, ABG should be measured 30 to 60 minutes after initiating oxygen supplementation.

Invasive mechanical ventilation is needed if the patient cannot tolerate NIPPV; has worsening hypoxemia, acidosis, confusion, or hypercapnia despite NIPPV; or has severe comorbid conditions, such as myocardial infarction or sepsis.[6] Worsening hypercarbia and acidosis herald respiratory failure. A pH of less than 7.36 and an arterial partial pressure of carbon dioxide of more than 45 mm Hg indicate the need for mechanical ventilation.

Therapeutic Options

SHORT-ACTING BRONCHODILATORS

Inhaled short-acting bronchodilators include beta agonists (e.g., albuterol, levalbuterol [Xopenex]) and anticholinergics (e.g., ipratropium [Atrovent]). These agents improve dyspnea and exercise tolerance.[6,9] The first step in treating a COPD exacerbation is increasing the dosage of albuterol delivered via metered dose inhaler or nebulizer.[9] Levalbuterol is more expensive than albuterol but has similar benefits and adverse effects.[16] If the patient is not already taking ipratropium, it can be added to the treatment regimen.[5] Fixed-dose albuterol/ipratropium (Combivent) is available.

CORTICOSTEROIDS

Short courses of systemic corticosteroids increase the time to subsequent exacerbation, decrease the rate of treatment failure, shorten hospital stays, and improve hypoxemia and forced expiratory volume in one second (FEV_1).[1,6,7,9,17-20] Administration of oral corticosteroids early in an exacerbation decreases the need for hospitalization.[21] A randomized controlled trial (RCT) of patients with COPD compared eight weeks of corticosteroids, two weeks of corticosteroids, and placebo; participants in the treatment groups had fewer treatment failures than those in the control group.[17] Treatment failure rates were the same for long and short courses of corticosteroids.

High-dosage corticosteroid regimens (methylprednisolone [Solu-Medrol], 125 mg intravenously every six hours) and low-dosage regimens (prednisolone, 30 mg orally daily) decrease the length of hospitalization and improve FEV_1 compared with placebo.[17,19] An RCT comparing oral and intravenous prednisolone in equivalent dosages (60 mg daily) showed no difference in lengths of hospitalization and rates of early treatment failure.[22]

Because oral corticosteroids are bioavailable, inexpensive, and convenient, parenteral corticosteroids should be reserved for patients with poor intestinal absorption or comorbid conditions that prevent safe oral intake (e.g., decreased mental status, vomiting).[5,6] Inhaled corticosteroids have no role in the management of an acute exacerbation.[8]

ANTIBIOTICS

One half of patients with COPD exacerbations have high concentrations of bacteria in their lower airways.[6,23] Cultures often show multiple infectious agents, including *Streptococcus pneumoniae*, *Haemophilus influenzae*, *Moraxella catarrhalis*, *Mycoplasma pneumoniae*, and viruses.[6,23]

The use of antibiotics in moderately or severely ill

Table 5. Treatment Options for Acute COPD Exacerbations

Therapy	*Outpatient management*	*Inpatient management*	*Benefits*
Antibiotic, broad spectrum (e.g., amoxicillin/clavulanate [Augmentin], macrolides, second- or third-generation cephalosporins, quinolones)	Consider if sputum is purulent or after treatment failure Use if local microbial patterns show resistance to narrow-spectrum agents	Use if local microbial patterns show resistance to narrow-spectrum agents	Decreases risk of treatment failure and mortality compared with narrow-spectrum agents
Antibiotic, narrow spectrum (e.g., amoxicillin, ampicillin, trimethoprim/sulfamethoxazole [Bactrim, Septra], doxycycline, tetracycline)	Consider if sputum is purulent or after treatment failure Use if local microbial patterns show minimal resistance to these agents and if patient has not taken antibiotics recently	Use if local microbial patterns show minimal resistance to these agents and if patient has not taken antibiotics recently	Believed to decrease mortality risk, but has not been tested in placebo-controlled trials
Anticholinergic, short acting (e.g., ipratropium [Atrovent])	May add to beta agonist; if patient is already taking an anticholinergic, increase dosage	May add to beta agonist; if patient is already taking an anticholinergic, increase dosage	Improves dyspnea and exercise tolerance
Beta agonist, short acting (e.g., albuterol, levalbuterol [Xopenex])	Increase dosage	Increase dosage	Improves dyspnea and exercise tolerance
Corticosteroid	Consider using oral corticosteroids in moderately ill patients, especially those with purulent sputum	Use oral corticosteroids if patient can tolerate; if not suitable for oral therapy, administer intravenously	Decreases risk of subsequent exacerbation, rate of treatment failures, and length of hospital stay Improves FEV_1 and hypoxemia
Mechanical ventilation	NA	Use if patient cannot tolerate NIPPV; has worsening hypoxemia, acidosis, confusion, or hypercapnia despite NIPPV; or has comorbid conditions such as myocardial infarction or sepsis	Decreases short-term mortality risk in severely ill patients
NIPPV	NA	Use in patients with worsening respiratory acidosis and hypoxemia when oxygenation via high-flow mask is inadequate	Improves respiratory acidosis and decreases respiratory rate, breathlessness, need for intubation, mortality, and length of hospital stay
Oxygen supplementation	NA	Use in patients with hypoxemia (PaO_2 less than 60 mm Hg)	Decreases mortality risk

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second; MDI = metered dose inhaler; NA = not applicable; NIPPV = noninvasive positive pressure ventilation; PaO_2 = arterial partial pressure of oxygen.

**—Spacer can be used with MDI to improve delivery.*

Information from references 5, 6, 8, 9, 18, and 25.

patients with COPD exacerbations reduces the risk of treatment failure and death.[24] Antibiotics may also benefit patients with mild exacerbations and purulent sputum.[5] The optimal choice of antibiotic and length of use are unclear. Increasing microbial resistance has prompted some physicians to treat exacerbations with broad-spectrum agents, such as second- or third-generation cephalosporins, macrolides, or quinolones. One meta-analysis showed a lower risk of treatment failure with broad-spectrum antibiotics compared with narrow-spectrum antibiotics (odds ratio = 0.51; 95% confidence interval, 0.34 to 0.75), but no change in mortality rates.[25] Another meta-analysis showed no difference in clinical cure rates when broad-spectrum antibiotics were administered for at least five days versus less than five days.[26] There is no comparable study of narrow-spectrum antibiotics. The decision to use antibiotics and the choice of antibiotic should be guided by the patient's symptoms (e.g., presence of purulent sputum), recent antibiotic use, and local microbial resistance patterns.[18,23,25] Prophylactic, continuous use of antibiotics does not improve outcomes in patients with COPD.[6]

Disadvantages/common adverse effects	*Typical dosage*
Antibiotic resistance, diarrhea, yeast vaginitis; side effects specific to the antibiotic prescribed	Amoxicillin/clavulanate: 875 mg orally twice daily or 500 mg orally three times daily for 5 days Levofloxacin (Levaquin): 500 mg daily for 5 days
Antibiotic resistance, diarrhea, yeast vaginitis; side effects specific to the antibiotic prescribed	Amoxicillin: 500 mg orally three times daily for 3 to 14 days Doxycycline: 100 mg orally twice daily for 3 to 14 days
Dry mouth, tremor, urinary retention	Ipratropium: 500 mcg by nebulizer every 4 hours as needed; alternatively, 2 puffs (18 mcg per puff) by MDI every 4 hours as needed*
Headache, nausea, palpitations, tremor, vomiting	Albuterol: 2.5 mg by nebulizer every 1 to 4 hours as needed, or 4 to 8 puffs (90 mcg per puff) by MDI every 1 to 4 hours as needed*
Gastrointestinal bleeding, heartburn, hyperglycemia, infection, psychomotor disturbance, steroid myopathy	Oral prednisone: 30 to 60 mg once daily Intravenous methylprednisolone (Solu-Medrol): 60 to 125 mg 2 to 4 times daily
Aspiration, cardiovascular complications, need for sedation, pneumonia	Titrate to correct hypercarbia and hypoxemia
Expensive, poorly tolerated by some patients	Titrate to correct hypercarbia and hypoxemia
Hypercarbia	Titrate to Pa_{O_2} > 60 mm Hg or oxygen saturation ≥ 90 percent

OTHER TREATMENT OPTIONS

Parenteral methylxanthines, such as theophylline, are not routinely recommended for the treatment of COPD exacerbations.[27] These agents are less effective and have more potentially adverse effects than inhaled bronchodilators.

Several therapies lack adequate evidence for routine use in the treatment of COPD exacerbations, including mucolytics (e.g., acetylcysteine [formerly Mucomyst]), nitric oxide, chest physiotherapy, antitussives, morphine, nedocromil, leukotriene modifiers, phosphodiesterase IV inhibitors (drug class not available in the United States), and immunomodulators (e.g., OM-85 BV, AM3 [neither drug available in the United States]).[6,7] *Table 5* summarizes the treatment options for acute COPD exacerbations.[5,6,8,9,18,25]

Preparation for Hospital Discharge

To qualify for discharge, a patient should have stable clinical symptoms and a stable or improving arterial partial pressure of oxygen of more than 60 mm Hg for at least 12 hours. The patient should not require albuterol more often than every four hours. If the patient is stable and can use a metered dose inhaler, there is no benefit to using nebulized bronchodilators.[28] Patient education may improve the response to future exacerbations[29]; suggested topics include a general overview of COPD, available medical treatments, nutrition, advance directives, and advice about when to seek medical help. In-home support, such as an oxygen concentrator, nebulizer, and home health nurse services, should be arranged before discharge.

SORT: KEY RECOMMENDATIONS FOR PRACTICE

Clinical recommendation	*Evidence rating*	*References*	*Comments*
Noninvasive positive pressure ventilation improves respiratory acidosis and decreases respiratory rate, breathlessness, need for intubation, mortality, and length of hospital stay.	A	6, 9, 15, 18	—
Inhaled bronchodilators (beta agonists, with or without anticholinergics) relieve dyspnea and improve exercise tolerance in patients with COPD.	A	6, 9	—
Short courses of systemic corticosteroids in patients with COPD increase the time to subsequent exacerbation, decrease the rate of treatment failure, shorten hospital stays, and improve FEV_1 and hypoxemia.	A	1, 6, 7, 9, 17-20	—
Low-dosage corticosteroid regimens are not inferior to high-dosage regimens in decreasing the risk of treatment failure in patients with COPD.	B	17, 19	—
Oral prednisolone is equivalent to intravenous prednisolone in decreasing the risk of treatment failure in patients with COPD.	B	22	Because they are bioavailable, inexpensive, and convenient, oral corticosteroids are recommended in patients who can safely swallow and absorb them.
Antibiotics should be used in patients with moderate or severe COPD exacerbations, especially if there is increased sputum purulence or the need for hospitalization.	B	6, 9, 18, 24	—
The choice of antibiotic in patients with COPD should be guided by symptoms (e.g., presence of purulent sputum), recent antibiotic use, and local microbial resistance patterns.	C	18, 23, 25	There is limited evidence that broad-spectrum antibiotics are more effective than narrow-spectrum antibiotics.
Smoking cessation reduces mortality and future exacerbations in patients with COPD.	A	6, 7, 30	—
Long-term oxygen therapy decreases the risk of hospitalization and shortens hospital stays in severely ill patients with COPD.	B	7, 32	—

COPD = chronic obstructive pulmonary disease; FEV_1 = forced expiratory volume in one second.

A = consistent, good-quality patient-oriented evidence; B = inconsistent or limited-quality patient-oriented evidence; C = consensus, disease-oriented evidence, usual practice, expert opinion, or case series. For information about the SORT evidence rating system, go to http://www.aafp.org/afpsort.xml.

Preventing Future Exacerbations

Smoking cessation, immunization against influenza and pneumonia, and pulmonary rehabilitation have been shown to improve function and reduce subsequent COPD exacerbations.[6,7,30] Long-term oxygen therapy decreases the risk of hospitalization and shortens hospital stays in severely ill patients with COPD.[7,31,32] The indications for long-acting inhaled bronchodilators and inhaled corticosteroids to improve symptoms and reduce the risk of exacerbations in patients with stable COPD are reviewed elsewhere.[5,7,33-38]

The author thanks Brian Earley, DO, for assistance in the preparation of the manuscript.

The Author

ANN E. EVENSEN, MD, FAAFP, is an assistant professor in the Department of Family Medicine at the University of Wisconsin School of Medicine and Public Health, Verona.

Address correspondence to Ann E. Evensen, MD, FAAFP, University of Wisconsin School of Medicine and Public Health, 100 N. Nine Mound Rd., Verona, WI 53593 (e-mail: ann.evensen@uwmf.wisc.edu). Reprints are not available from the author.

Author disclosure: Nothing to disclose.

REFERENCES

1. Singh JM, Palda VA, Stanbrook MB, Chapman KR. Corticosteroid therapy for patients with acute exacerbations of chronic obstructive pulmonary disease: a systematic review. *Arch Intern Med*. 2002;162(22):2527-2536.
2. Jemal A, Ward E, Hao Y, Thun M. Trends in the leading causes of death in the United States, 1970-2002. *JAMA*. 2005;294(10):1255-1259.
3. Stephens MB, Yew KS. Diagnosis of chronic obstructive pulmonary disease. *Am Fam Physician*. 2008;78(1):87-92.
4. Cazzola M, MacNee W, Martinez FJ, et al., for the American Thoracic Society, European Respiratory Society Task Force on Outcomes of COPD. Outcomes for COPD pharmacological trials: from lung function to biomarkers. *Eur Respir J*. 2008;31(2):416-469.
5. American Thoracic Society, European Respiratory Society Task Force. Standards for the Diagnosis and Management of Patients with COPD. Version 1.2. New York, NY: American Thoracic Society; 2004. http://www.thoracic.org/go/copd. Accessed January 11, 2010.
6. Rabe KF, Hurd S, Anzueto A, et al., for the Global Initiative for Chronic Obstructive Lung Disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med*. 2007;176(6):532-555.
7. Decramer M, Nici L, Nardini S, et al. Targeting the COPD exacerbation. *Respir Med*. 2008;102(suppl 1):S3-S15.
8. Snow V, Lascher S, Mottur-Pilson C, for the Joint Expert Panel on COPD of the American College of Chest Physicians and the American

College of Physicians/American Society of Internal Medicine. The evidence base for management of acute exacerbations of COPD: clinical practice guideline, part 1. *Chest*. 2001;119(4):1185-1189.

9. McCrory DC, Brown C, Gelfand SE, Bach PB. Management of acute exacerbations of COPD: a summary and appraisal of published evidence. *Chest*. 2001;119(4):1190-1209.
10. Kessler R, Faller M, Fourgaut G, Mennecier B, Weitzenblum E. Predictive factors of hospitalization for acute exacerbation in a series of 64 patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1999;159(1):158-164.
11. Garcia-Aymerich J, Monsó E, Marrades RM, et al., for the EFRAM Investigators. Risk factors for hospitalization for a chronic obstructive pulmonary disease exacerbation. *Am J Respir Crit Care Med*. 2001; 164(6):1002-1007.
12. Mueller C, Laule-Kilian K, Frana B, et al. Use of B-type natriuretic peptide in the management of acute dyspnea in patients with pulmonary disease. *Am Heart J*. 2006;151(2):471-477.
13. Brekke PH, Omland T, Smith P, Søyseth V. Underdiagnosis of myocardial infarction in COPD—Cardiac Infarction Injury Score (CIIS) in patients hospitalised for COPD exacerbation. *Respir Med*. 2008;102(9):1243-1247.
14. Seemungal TA, Donaldson GC, Bhowmik A, Jeffries DJ, Wedzicha JA. Time course and recovery of exacerbations in patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2000;161(5):1608-1613.
15. Ram FS, Picot J, Lightowler J, Wedzicha JA. Non-invasive positive pressure ventilation for treatment of respiratory failure due to exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2004;(3):CD004104.
16. Donohue JF, Hanania NA, Ciubotaru RL, et al. Comparison of levalbuterol and racemic albuterol in hospitalized patients with acute asthma or COPD: a 2-week, multicenter, randomized, open-label study. *Clin Ther*. 2008;30(spec no):989-1002.
17. Niewoehner DE, Erbland ML, Deupree RH, et al. Effect of systemic glucocorticoids on exacerbations of chronic obstructive pulmonary disease. Department of Veterans Affairs Cooperative Study Group. *N Engl J Med*. 1999;340(25):1941-1947.
18. Quon BS, Gan WQ, Sin DD. Contemporary management of acute exacerbations of COPD: a systematic review and metaanalysis. *Chest*. 2008;133(3):756-766.
19. Davies L, Angus RM, Calverley PM. Oral corticosteroids in patients admitted to hospital with exacerbations of chronic obstructive pulmonary disease: a prospective randomised controlled trial. *Lancet*. 1999;354(9177):456-460.
20. Walters JA, Gibson PG, Wood-Baker R, Hannay M, Walters EH. Systemic corticosteroids for acute exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2009;(1):CD001288.
21. Wilkinson TM, Donaldson GC, Hurst JR, Seemungal TA, Wedzicha JA. Early therapy improves outcomes of exacerbations of chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 2004; 169(12):1298-1303.
22. de Jong YP, Uil SM, Grotjohan HP, Postma DS, Kerstjens HA, van den Berg JW. Oral or IV prednisolone in the treatment of COPD exacerbations: a randomized, controlled, double-blind study. *Chest*. 2007; 132(6):1741-1747.
23. Sethi S, Evans N, Grant BJ, Murphy TF. New strains of bacteria and exacerbations of chronic obstructive pulmonary disease. *N Engl J Med*. 2002;347(7):465-471.
24. Ram FS, Rodriguez-Roisin R, Granados-Navarrete A, Garcia-Aymerich J, Barnes NC. Antibiotics for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2006;(2):CD004403.
25. Dimopoulos G, Siempos II, Korbila IP, Manta KG, Falagas ME. Comparison of first-line with second-line antibiotics for acute exacerbations of chronic bronchitis: a metaanalysis of randomized controlled trials. *Chest*. 2007;132(2):447-455.
26. El Moussaoui R, Roede BM, Speelman P, Bresser P, Prins JM, Bossuyt PM. Short-course antibiotic treatment in acute exacerbations of chronic bronchitis and COPD: a meta-analysis of double-blind studies. *Thorax*. 2008;63(5):415-422.
27. Barr RG, Rowe BH, Camargo CA. Methylxanthines for exacerbations of chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2003;(2):CD002168.
28. Jenkins SC, Heaton RW, Fulton TJ, Moxham J. Comparison of domiciliary nebulized salbutamol and salbutamol from a metered-dose inhaler in stable chronic airflow limitation. *Chest*. 1987;91(6):804-807.
29. Turnock AC, Walters EH, Walters JA, Wood-Baker R. Action plans for chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2005;(4):CD005074.
30. Au DH, Bryson CL, Chien JW, et al. The effects of smoking cessation on the risk of chronic obstructive pulmonary disease exacerbations. *J Gen Intern Med*. 2009;24(4):457-463.
31. Poole PJ, Chacko E, Wood-Baker RW, Cates CJ. Influenza vaccine for patients with chronic obstructive pulmonary disease. *Cochrane Database Syst Rev*. 2006;(1):CD002733.
32. Drummond MB, Dasenbrook EC, Pitz MW, Murphy DJ, Fan E. Inhaled corticosteroids in patients with stable chronic obstructive pulmonary disease: a systematic review and meta-analysis [published correction appears in *JAMA*. 2009;301(10):1024]. *JAMA*. 2008;300(20):2407-2416.
33. Singh S, Amin AV, Loke YK. Long-term use of inhaled corticosteroids and the risk of pneumonia in chronic obstructive pulmonary disease: a meta-analysis. *Arch Intern Med*. 2009;169(3):219-229.
34. Ernst P, Gonzalez AV, Brassard P, Suissa S. Inhaled corticosteroid use in chronic obstructive pulmonary disease and the risk of hospitalization for pneumonia. *Am J Respir Crit Care Med*. 2007;176(2):162-166.
35. Tashkin DP, Celli B, Senn S, et al., for the UPLIFT Study Investigators. A 4-year trial of tiotropium in chronic obstructive pulmonary disease. *N Engl J Med*. 2008;359(15):1543-1554.
36. Singh S, Loke YK, Furberg CD. Inhaled anticholinergics and risk of major adverse cardiovascular events in patients with chronic obstructive pulmonary disease: a systematic review and meta-analysis. *JAMA*. 2008;300(12):1439-1450.
37. Rabe KF, Timmer W, Sagkriotis A, Viel K. Comparison of a combination of tiotropium plus formoterol to salmeterol plus fluticasone in moderate COPD. *Chest*. 2008;134(2):255-262.
38. Aaron SD, Vandemheen KL, Fergusson D, et al., for the Canadian Thoracic Society/Canadian Respiratory Clinical Research Consortium. Tiotropium in combination with placebo, salmeterol, or fluticasone-salmeterol for treatment of chronic obstructive pulmonary disease: a randomized trial. *Ann Intern Med*. 2007;146(8):545-555.