



The Difficult COPD Patient: Alternative Therapeutic Regimens

With the advent of β -adrenergic drugs, the initial approach to the patient with COPD who is in respiratory distress has been simplified. What about the patient who does not respond? The lecturer will discuss the approach to the refractory COPD patient. Alternative medication choices, the use of Bi-PAP, and the indications for intubation, as well as postintubation management problems, will be discussed.

- Discuss the pathophysiology of COPD.
- Discuss current therapeutic regimens, including atropine, ipratropium, and steroids.
- Discuss Bi-PAP and its indications in the management of COPD.
- List the indications for intubation.
- Describe the postintubation management problems unique to the patient with COPD.

MO-23
Monday, October 11, 1999
5:00 PM - 5:55 PM
Room # N204
Las Vegas Convention Center

Speaker: Pfizer

FACULTY

Charles L Emerman, MD, FACEP

American College of Emergency Physicians

1999 Scientific Assembly

The Difficult COPD Patient: Alternative Therapeutic Regimens

MO-23

Instructor

Charles L. Emerman, MD

The Difficult COPD Patient: Alternative Therapeutic Regimens

MO-23

1 Hour

Instructor

Charles L. Emerman, MD

The initial approach to the COPD patient involves oxygen therapy and inhaled beta-agonists. Not every patient, however, will respond to this treatment. This course will discuss the pathophysiology, assessment, and treatment of the patient with COPD. It will also discuss the management of the patient with severe respiratory distress who is not responding to standard therapy.

Objectives

- Discuss the pathophysiology of COPD.
- Discuss current therapeutic regimens, including atropine, ipratropium, and steroids.
- Discuss Bi-PAP and its indications in the management of COPD.
- List the indications for intubation.
- Describe the postintubation management problems unique to the patient with COPD.

Chronic obstructive pulmonary disease is a leading cause of morbidity and mortality among smokers age 55 and older, affecting more than 20 million Americans¹. COPD accounts for about 150,000 hospitalizations per year in Medicare eligible patients.² Chronic obstructive pulmonary disease (COPD) is also occasionally termed chronic obstructive lung disease (COLD) is composed of three distinct entities³. C

- 1) Chronic bronchitis is a cough for at least three months out of the year for two successive years.
- 2) Most patients with COPD have central bronchial enlargement, the common manifestation of emphysema
- 3) Patients with COPD may have peripheral airways disease, manifested by chronic airway obstruction.

The majority of patients with COPD will have either a history of cigarette smoking, a history of exposure to second-hand cigarette smoke or occupational exposure. A minority of patients develop emphysema as a result of α -1-protease inhibitor deficiency or intravenous drug abuse. These patients develop emphysema earlier in life than those with the development of COPD secondary to cigarette smoke.

Chronic obstructive pulmonary disease is associated with decreased long-term survival. A number of factors are associated with the decrease in survival in patients with chronic airflow limitation⁴ but with acute respiratory failure there is an even greater risk of short-term mortality. There is an inpatient mortality rate between 10% and 30% with an ICU admission.^{4, 5} **Most patients who require intubation for COPD are successfully weaned off mechanical ventilation over the course of 7 to 14 days⁵⁻⁷.** Nevertheless, the mortality rate over the next one to two years is substantial, ranging between 40% and 60%.

Evaluation

The patient in extreme distress will require immediate therapy. The physician may wish to determine the precipitant of this particular respiratory attack when the patient is able to give a history. Infection, exposure to cigarette smoke, noxious fumes, or weather changes may all precipitate an acute attack. Other considerations include

- 1) congestive heart failure
- 2) pneumonia
- 3) pneumothorax
- 4) or myocardial infarction

Jugular venous distension, hepatic congestion, and pedal edema can occur in cor pulmonale, as well as, congestive heart failure. Pulmonary embolism can be very difficult to confirm in patients with COPD based on clinical evaluation alone.⁸ Evidence of calf swelling, tenderness, increased warmth, erythema, or the presence of a tender cord may suggest a deep venous thrombosis, which may be verified by impedance plethysmography, ultrasound or venography.

Pulse oximetry is an inexpensive, noninvasive way of assessing oxygen saturation. Unlike blood gas sampling, pulse oximetry is non-invasive; results are immediately and continuously available. Oximetry is accurate to within 3% to 5% at saturations greater

than 70%.⁹ The relationship between the P_{aO_2} and oxygen saturation is complex and varies depending on many factors, including the PO_2 and the acid base status. Most importantly, however, the pulse oximetry provides a relatively rapid means of categorizing the patient into mild, moderate and severe respiratory impairment. Additionally, trends in the oxygen saturation provide a clue to the efficacy of therapy.

Pulmonary function testing is a useful means for assessing ventilatory function that cannot be replicated by physical examination.¹⁰ Relatively inexpensive peak flowmeters are available that can provide a quick assessment of expiratory function. The peak expiratory flow meter is effort dependent and overestimates expiratory function compared to spirometry. Portable spirometers are also readily available and are simple to operate.

The spirometer has some advantages over the peak flow meter in that it is

- 1) easily calibrated
- 2) less effort dependent than the peak expiratory flow rate
- 3) provides a graphic output, which can be kept in the medical record.

Patients with COPD frequently have alterations of gas exchange. In general, the results of pulmonary function testing predict the presence of hypercarbia¹¹. Significant hypercarbia is unlikely to occur with patients with a FEV_1 less than 35% of predicted normal. On the other hand, patients may have severe hypoxemia even the presence of moderate airway obstruction.¹²

Significant, new abnormalities occur in about 15% of patients with acute exacerbation of COPD. The exact incidence of pneumonia in patients with obstructive lung disease is uncertain. The appearance of acute bronchitis can be difficult to differentiate from pneumonia in the patient with COPD, given that many patients have baseline radiographic abnormalities. Symptoms such as fever, sputum production, and abnormal lung sounds are common findings, regardless of whether or not the patient has pneumonia.¹³ Given the wide differential diagnosis of respiratory distress in these patients, routine chest radiography may be warranted.¹⁴

Initial Therapy

Patients in respiratory distress should receive oxygen therapy, guided by pulse-oximetry and arterial blood gases when available. Patients with COPD may have hypoxemia due to structural lung abnormalities, impairment of diffusion capacity, or ventilation perfusion mismatch. In addition, beta-agonist therapy may slightly worsen ventilation perfusion mismatch. Oxygen therapy is usually initiated by nasal cannula. Patients with hypercarbia may require controlled oxygen therapy using a Venturi mask in order to control the FiO_2 .

Beta-agonists

Most patients with COPD have some degree of reversible bronchospasm and the response to bronchodilators acutely does not help to differentiate between patients with

asthma and those with COPD. Further, in the setting of severe respiratory distress even modest improvements in ventilatory resistance may be of significant clinical benefit ¹⁵.

Inhaled beta-agonists are the first line therapy for acute exacerbation of COPD.

Beta-agonist therapy decreases dyspnea and improves pulmonary functional status in the acute exacerbation, even in the face of only modest changes in pulmonary function. Beta-agonists delivery via nebulizer is best accomplished by dilution of the drug to 2 to 3cc's, with airflow in the range of 6 to 8 liters per minute. Beta-agonists can be delivered by metered dose inhalers which have been shown to be equivalent to nebulizers as long as a spacer is used.

Many beta-agonist agents are available for use in acute exacerbation of COPD. (Table 1) In general, the onset of action of inhaled beta-agonists is rapid, on the order of ten minutes. The various beta-agonist agents vary in terms of duration of action and relative beta-2 agonist selectivity.

BETA-AGONISTS	MDI	AEROSOL
Albuterol (Proventil, Ventolin)	Yes	Yes
Bitolterol (Tornalate)	Yes	Yes
Isoetharine (Bronkosol)	Yes	Yes
Isoproterenol (Isuprel)	Yes	Yes
Metaproterenol (Alupent, Metaprel)	Yes	Yes
Pirbuterol (Maxair)	Yes	No
Terbutaline (Brethaire)	Yes	No
From Ref 16		

The timing and optimal dose of inhaled beta-agonists is not firmly established in COPD. At one time these agents were administered every hour but there has been a trend toward increasing frequency and size of dosing for inhaled beta-agonists. One study failed to demonstrate a significant advantage to giving albuterol more often than every 60 minutes¹⁷. Recommendations for management in patients with asthma are to give an agent such as albuterol in a dose of 2½ -5 mg every 20 minutes but there is little evidence to guide this in the patient with COPD.

Anticholinergics

Anticholinergic therapy has been studied as an adjunct with beta-agonists in the treatment of acute exacerbation of COPD. Most studies using anticholinergic agents have used one of the quaternary ammonium compounds since they have a better safety profile than nebulized atropine. Several studies found a beneficial effect of combination treatment

with glycopyrrolate and either albuterol or metaproterenol^{18,19,20}. In combination with metaproterenol, glycopyrrolate leads to greater peak effect, with maximum action at around 2-3 hours¹⁸. . Ipratropium is available both as a metered dose inhaler and as a solution for inhalation. In patients with stable COPD, there is a clear role for the use of ipratropium in chronic management^{21,22,23,24}. The role of ipratropium in patients with an acute exacerbation is less clear.

Corticosteroids

There may be some role for steroids in the patient with an exacerbation of COPD. Almost twenty years ago Alpert found an improvement in pulmonary function among patients admitted for acute exacerbation of COPD when given methylprednisolone at a dose of .5 mg per kilogram²⁵. Another study however, found that the administration of steroids did not lead to a change in the short course of treatment in the emergency department²⁶. Several studies have suggested that patients with an acute exacerbation of COPD should receive steroids for outpatient therapy^{27,28}. A more recent study of hospitalized VA patients demonstrated that a two week tapering course of prednisone decreased the rate of treatment failure for up to three months²⁹. Among patients with stable COPD, the addition of inhaled steroids seems to result in improved pulmonary function and decreased beta-agonist use in about 25% of patients³⁰.

Theophylline

Aminophylline is still used in the treatment of COPD, but it's role remains controversial. Relatively few studies have been performed on the clinical effect of theophylline in acute exacerbation of COPD. Of the two larger studies that have been performed, the results were contradictory³¹. A theophylline level should be measured prior to administering theophylline in patients on chronic therapy. **In general, each milligram per kilogram of aminophylline will raise the theophylline level by two micrograms/cc.** There is inadequate evidence at this time to make a judgment on whether aminophylline has any role in the ED management of acute exacerbation of COPD. Its use may be considered in patients who are unresponsive to other agents.

Magnesium

One recent study demonstrated a significant improvement in pulmonary function for patients given magnesium during an acute exacerbation of COPD³². Given in a dose of 1.2g over 20 minutes magnesium significantly improved peak expiratory flow, although there was a nonsignificant decrease in the hospitalization rate. At these doses, magnesium is relatively safe but adverse effects can include flushing sensation, transient hypotension, and at higher doses, cardiac conduction delays.

Heliox

Helium oxygen mixtures have been found to decrease dyspnea in patients with COPD by minimizing the risks of gas flow, since helium is only 14% as dense as nitrogen. There

are no large-scale studies evaluating the use of helium oxygen mixtures in patients with acute exacerbation of COPD. Its use should probably be limited to experimental studies or as a last alternative for patients in extremis.

Ventilatory Assistance

Despite appropriate and aggressive treatment some patients with COPD may require assisted ventilation. As discussed above, in the past there may have been a reluctance to intubate these patients because of fear that once intubated, patients become ventilator dependent. Most patients with COPD will survive an initial episode of acute respiratory failure although the mortality rate over the next several years is very high. On average, patients who survive their episode of acute respiratory failure are intubated for an average of ten days. Patients with extreme dyspnea, discordant breathing, fatigue, inability to speak, or deteriorating mental status in the face of adequate therapy may require ventilatory assistance. Hypoxemia that does not respond to oxygen therapy or worsening of acid base status in spite of controlled oxygen therapy may also indicate the need for ventilatory assistance. Once intubated, care should be taken to avoid precipitous drops in the PCO_2 since this may lead to severe respiratory alkalosis. A concept of “permissive hypercapnia” has been advocated for patients with respiratory failure allowing slight increases in the PCO_2 so long as the pH remains above 7.26 with maintenance of adequate oxygenation. Invasive ventilation can be associated with significant complications before, during and after tube placement. This includes adverse events during intubation such as airway trauma, cardiac arrhythmias, transient hypoxemia, and aspiration of gastric contents. Post intubation the patient is at risk for tracheal stenosis, sinusitis, nosocomial pneumonia, and inadvertent extubation.

Noninvasive Ventilation

One of the dramatic developments in the treatment of acute exacerbation of COPD over the last few years has been the acceptance of noninvasive nasal bilevel positive airway pressure (BiPAP). Noninvasive ventilation leads to improvement in respiratory rate, tidal volume, and minute ventilation. Mask ventilation can be complicated by local skin irritation, aerophagia with subsequent emesis and reduced cardiac output at high pressures. The advantages, however, are that patients are able to talk, swallow, and expectorate. Noninvasive ventilation is successful in about 2/3 of patients³³ and decreases ICU stay and overall mortality rate.

Nasal BiPAP requires a cooperative patient. The technique cannot be used in the apneic or comatose patient. Nasal BiPAP is initiated with an explanation of the procedure to the patient. Typically the therapy is initiated with

- 1) Expiratory pressure levels beginning around 3 cm H_2O
- 2) Inspiratory pressures of around 8 cm of H_2O
- 3) IPAP is increased in 2-cm increments to titrate the PCO_2
- 4) EPAP is increased to titrate the PO_2
- 5) IPAP must be maintained above the EPAP.
- 6) Expiratory and inspiratory pressures are increased rapidly over the course of 15 minutes to achieve targeted oxygenation and CO_2 level.

If a patient does not improve within one to two hours of initiation of nasal BiPAP then intubation may be required.³⁴

Disposition

A number of factors are utilized to decide on the disposition of patients treated with an acute exacerbation of COPD. These include the patients respiratory status post treatment with assessment of respiratory rate, respiratory effort, oxygen saturation, and pulmonary function. In addition, factors such as the patients home living conditions, mental status, and concomitant illnesses may play a factor in the decision to admit or discharge a patient. There is a high rate of relapse following ED discharge, ranging from 15-30%^{35,36}.

On discharge from the emergency department, several adjustments to the patients outpatient medical therapy may be considered. First, patients with a severe chronic obstructive pulmonary disease may be eligible for home oxygen therapy. Although this is generally not initiated out of the emergency department, patients may benefit from referral for consideration for home oxygen therapy.

Patients should be discharged on bronchodilators beginning with either inhaled beta-agonists or inhaled anticholinergics. Anticholinergics should probably be used for routine maintenance in most patients with COPD. Patients should be taught the proper means of using metered dose inhalers. Many patients will benefit from the use of a spacer device.

Technique for Using a Metered-Dose Inhaler

1. Invert inhaler so that opening is downward after shaking briskly.
2. Hold inhaler about four finger-widths in front of open mouth.
3. Exhale normally to functional residual capacity.
4. Activate inhaler at beginning of inspiration.
5. Inhale slowly and deeply to total lung capacity
6. Hold breath for 10 seconds
7. Exhale slowly.

Theophylline does have dose related effects on pulmonary function in patients with stable chronic obstructive pulmonary disease. This drug may be used for patients who can not or will not use meter dose inhalers, patients who are not responding to otherwise maximal therapy, or patients who have prominent nighttime symptoms. Therapy is usually initiated at a dose of 300 mg twice a day with monitoring of the theophylline level.

About 25% of patients with COPD will respond to oral steroids. Patients with a significant degree of reversibility of pulmonary function on base line testing are most likely to respond to steroids³⁷. It seems reasonable to give a two week trial of oral steroids to patients with COPD. Limited studies indicate that there may be a role for inhaled corticosteroids in patients with chronic obstructive pulmonary disease.

While most episodes of acute exacerbation of COPD are related to viral infection, the weight of evidence seems to indicated that patients may respond to oral antibiotics. Signs

of acute bronchitis include fever, increase in sputum production, or change in the color of sputum production. Patients with a greater risk of respiratory failure are more likely to benefit from antibiotic therapy. This would include patients of advanced age and patients with significant lung impairment, impairment due to other co-morbid conditions, frequent exacerbations, or steroid use.

Summary

Assessment of the patient with acute exacerbation of COPD should include an attempt to distinguish between many of the entities that have a similar clinical picture including heart disease, pulmonary embolism, pneumonia and pneumothorax. Once the diagnosis is verified then a brief search for the exacerbating agent should be undertaken. Therapy should be initiated with oxygen and beta-agonists while other therapies such as anticholinergic agents, theophylline, steroids, or magnesium should be considered only in patients with impending respiratory failure or possibly in patients being admitted. Patients with unresponsive respiratory failure may be considered for a trial of nasal BiPAP before invasive ventilation. Patients eligible for discharge may require modification of their outpatient regimen to include anticholinergic agents and beta-agonists by meter dose inhalers, antibiotics in the appropriate setting, and possibly corticosteroids.

1. Statistics VaH. Current Estimates from the National Health Interview Survey. *NHS Publication*. 1990:1643.
2. Cydulka R, McFadden E, Emerman C, Sivinski L, Pisanelli W, Rimm A. Patterns of Hospitalization in Elderly Patients with Asthma and Chronic Obstructive Pulmonary Disease. *Am J Respir Crit Care Med*. 1997;156:1807-1812.
3. Celli BR, Snider GL, Heffner J. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *Am J Respir Crit Care Med*. 1995;152:S77-120.
4. Kanner RE, Renzetti AD, Jr., Stanish WM, Barkman HW, Jr., Klauber MR. Predictors of survival in subjects with chronic airflow limitation. *Am J Med*. 1983;74:249-55.
5. Seneff MG, Wagner DP, Wagner RP, Zimmerman JE, Knaus WA. Hospital and 1-year survival of patients admitted to intensive care units with acute exacerbation of chronic obstructive pulmonary disease. *Jama*. 1995;274:1852-7.
6. Connors AF, Jr., Dawson NV, Thomas C, et al. Outcomes following acute exacerbation of severe chronic obstructive lung disease. The SUPPORT investigators (Study to Understand Prognoses and Preferences for Outcomes and Risks of Treatments) [published erratum appears in *Am J Respir Crit Care Med* 1997 Jan;155(1):386]. *Am J Respir Crit Care Med*. 1996;154:959-67.
7. Fuso L, Incalzi RA, Pistelli R, et al. Predicting mortality of patients hospitalized for acutely exacerbated chronic obstructive pulmonary disease. *Am J Med*. 1995;98:272-7.
8. Lesser BA, Leeper KV, Jr., Stein PD, et al. The diagnosis of acute pulmonary embolism in patients with chronic obstructive pulmonary disease [see comments]. *Chest*. 1992;102:17-22.
9. Wiedemann H, McCarthy K. Noninvasive monitoring of oxygen and carbon dioxide. *Clin Chest Med*. 1989;10:239-254.
10. Emerman CL, Lukens TW, Effron D. Physician estimation of FEV1 in acute exacerbation of COPD. *Chest*. 1994;105:1709-12.
11. Emerman CL, Cydulka RK. Use of peak expiratory flow rate in emergency department evaluation of acute exacerbation of chronic obstructive pulmonary disease [see comments]. *Ann Emerg Med*. 1996;27:159-63.
12. Emerman CL, Connors AF, Lukens TW, Effron D, May ME. Relationship between arterial blood gases and spirometry in acute exacerbations of chronic obstructive pulmonary disease. *Ann Emerg Med*. 1989;18:523-7.
13. Sherman S, Skoney JA, Ravikrishnan KP. Routine chest radiographs in exacerbations of chronic obstructive pulmonary disease. Diagnostic value. *Arch Intern Med*. 1989;149:2493-6.
14. Emerman CL, Cydulka RK. Evaluation of high-yield criteria for chest radiography in acute exacerbation of chronic obstructive pulmonary disease. *Ann Emerg Med*. 1993;22:680-4.

15. Kuhl DA, Agiri OA, Mauro LS. Beta-agonists in the treatment of acute exacerbation of chronic obstructive pulmonary disease. *Ann Pharmacother.* 1994;28:1379-88.
16. Emerman CL; CHRONIC OBSTRUCTIVE PULMONARY DISEASE NEW THOUGHTS ABOUT THE MANAGEMENT OF THE ACUTE EXACERBATION. EMERGENCY MEDICINE REPORTS: OCTOBER, 1999, IN PRESS.
17. Emerman CL, Cydulka RK. Effect of different albuterol dosing regimens in the treatment of acute exacerbation of chronic obstructive pulmonary disease. *Ann Emerg Med.* 1997;29:474-8.
18. Tzelepis G, Komanapoli S, Tyler D, Vega D, Fulambarker A. Comparison of nebulized glycopyrrolate and metaproterenol in chronic obstructive pulmonary disease. *Eur Respir J.* 1996;9:100-3.
19. Shrestha M, O'Brien T, Haddox R, Gourlay HS, Reed G. Decreased duration of emergency department treatment of chronic obstructive pulmonary disease exacerbations with the addition of ipratropium bromide to beta-agonist therapy. *Ann Emerg Med.* 1991;20:1206-9.
20. Cydulka RK, Emerman CL. Effects of combined treatment with glycopyrrolate and albuterol in acute exacerbation of chronic obstructive pulmonary disease. *Ann Emerg Med.* 1995;25:470-3.
21. Colice GL. Nebulized bronchodilators for outpatient management of stable chronic obstructive pulmonary disease. *Am J Med.* 1996;100:11S-18S.
22. Gross NJ, Petty TL, Friedman M, Skorodin MS, Silvers GW, Donohue JF. Dose response to ipratropium as a nebulized solution in patients with chronic obstructive pulmonary disease. A three-center study [see comments]. *Am Rev Respir Dis.* 1989;139:1188-91.
23. Karpel JP, Kotch A, Zinny M, Pesin J, Alleyne W. A comparison of inhaled ipratropium, oral theophylline plus inhaled beta-agonist, and the combination of all three in patients with COPD. *Chest.* 1994;105:1089-94.
24. Braun SR, McKenzie WN, Copeland C, Knight L, Ellersieck M. A comparison of the effect of ipratropium and albuterol in the treatment of chronic obstructive airway disease [published erratum appears in Arch Intern Med 1990 Jun;150(6):1242]. *Arch Intern Med.* 1989;149:544-7.
25. Albert RK, Martin TR, Lewis SW. Controlled clinical trial of methylprednisolone in patients with chronic bronchitis and acute respiratory insufficiency. *Ann Intern Med.* 1980;92:753-8.
26. 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;95:563-7.
27. Murata GH, Gorby MS, Chick TW, Halperin AK. Intravenous and oral corticosteroids for the prevention of relapse after treatment of decompensated COPD. Effect on patients with a history of multiple relapses [see comments]. *Chest.* 1990;98:845-9.
28. 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;154:407-12.

29. Niewoehner D, Erbland M, Deupree R, et al. Effect of Systemic Glucocorticoids on Exacerbations of Chronic Obstructive Pulmonary Disease. *The New England Journal of Medicine*. 1999;340:1941-1947.
30. Weiner P, Weiner M, Azgad Y, Zamir D. Inhaled budesonide therapy for patients with stable COPD [see comments]. *Chest*. 1995;108:1568-71.
31. Rice KL, Leatherman JW, Duane PG, et al. Aminophylline for acute exacerbations of chronic obstructive pulmonary disease. A controlled trial. *Ann Intern Med*. 1987;107:305-9.
32. Skorodin MS, Tenholder MF, Yetter B, et al. Magnesium sulfate in exacerbations of chronic obstructive pulmonary disease. *Arch Intern Med*. 1995;155:496-500.
33. Brochard L, Mancebo J, Wysocki M, et al. Noninvasive ventilation for acute exacerbations of chronic obstructive pulmonary disease [see comments]. *N Engl J Med*. 1995;333:817-22.
34. Poponick JM, Renston JP, Bennett RP, Emerman CL; Use of a ventilatory support system (BiPAP) for acute respiratory failure in the emergency department. *Chest* 1999 Jul;116(1):166-71
35. Emerman CL, Effron D, Lukens TW. Spirometric criteria for hospital admission of patients with acute exacerbation of COPD. *Chest*. 1991;99:595-9.
36. Murata G, Gorby M, Chick T, Halperin A. Treatment of Decompensated Chronic Obstructive Pulmonary Disease in the Emergency Department-Correlation Between Clinical Features and Prognosis. *Ann Emerg Med*. 1991;20:125-129.
37. Chanez P, Vignola AM, O'Shaugnessy T, et al. Corticosteroid reversibility in COPD is related to features of asthma. *Am J Respir Crit Care Med*. 1997;155:1529-34.