Intravenous and Oral Corticosteroids for the Prevention of Relapse after Treatment of Decompensated COPD*

Effect on Patients with a History of Multiple Relapses

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To determine if a regimen of intravenous and oral corticosteroids reduces the relapse rate after treatment of decompensated COPD in the ED, 30 patients were studied. Forty-five visits in which intravenous and oral corticosteroids were given (T visits) were compared with an equal number of matched visits in which they were withheld (N visits). No differences were noted between T and N visits with respect to clinical findings, laboratory results and other forms of therapy. Treatment with corticosteroids reduced the relapse rate within 24 h of discharge. At 48 h, the cumulative relapse rate for T visits (8.9 percent) was significantly lower than for N visits (33.3 percent; p = 0.005). For patients with a history of multiple relapses, a regimen consisting of intravenous and oral corticosteroids reduces the risk of relapse after ED treatment of decompensated COPD.

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The role of corticosteroids in the treatment of decompensated COPD is controversial. A randomized clinical trial† showed that hospitalized patients given intravenous methylprednisolone every 6 h had greater improvement in the FEV₁ than those given placebo. However, a more recent study‡ showed that a single dose of methylprednisolone had no effect on the FEV₁, the hospitalization rate or the 48-h relapse rate for patients treated in an ED. Since their physiologic effects may be transient, repeated doses might be necessary for corticosteroids to have an effect. The most feasible regimen for outpatients consists of a single intravenous dose of a corticosteroid given in the ED followed by a daily course of prednisone taken at home. No information is available on the types of patients who might respond to this regimen, its effect on relapse rates, or its onset and duration of action.

The purpose of this study was to determine if corticosteroids reduce the relapse rate after ED treatment for decompensated COPD. We conducted a four-year retrospective review of their effect in patients with a history of multiple relapses. The ED visits in which intravenous and oral corticosteroids were given were compared with visits in which they were withheld. Patient characteristics and other treatment factors were controlled by pairwise matching of visits using multiple criteria. We describe the clinical characteristics of this patient subset and the time-course for corticosteroid effect.

METHODS

The Albuquerque VA Medical Center is a 365-bed, acute-care hospital serving veterans in New Mexico, west Texas and southern Colorado. The Emergency Department is staffed by faculty and house officers from the University of New Mexico. Almost all of the patients who present to the medical center with exacerbations of COPD are referred to the ED. All decisions about treatment are made by the ED physician and are based on his assessment of the patient's condition. No protocols exist for the use of intravenous corticosteroids or prednisone. Patients who improve are advised to return to the ED if symptoms recur after their discharge. They are also given follow-up appointments with a walk-in clinic, a general medical clinic or the pulmonary clinic. If they require additional treatment at the time of follow-up, they are referred back to the ED.

The effect of corticosteroids was evaluated in patients with a history of multiple relapses (the relapse or R group). Patients were assigned to the R group if:

1. they had at least one recent set of baseline PFTs that showed chronic airflow obstruction,
2. they had two or more relapses between April 1, 1985, and April 30, 1989, and
3. they did not have occupational lung disease, pulmonary fibrosis or features of asthma.

A patient was considered to have asthma† if he had one or more of the following features:

1. onset of symptoms before the age of 40,
2. a history of atopic dermatitis, eczema, multiple drug allergies or aspirin sensitivity,
3. minimal dyspnea between episodes of respiratory decompensation.

Pulmonary function tests were reviewed if they were performed within three years of the patient's first visit between April 1, 1985, and April 30, 1989. They were considered diagnostic of chronic...
airflow obstruction if the FEV₁ was less than 75 percent predicted and the FEV₁/VC ratio was less than 75 percent on all baseline PFTs, both before and after inhaled bronchodilators. When multiple PFTs were performed within three years of entry, only the highest values for FEV₁ and bronchodilator response were used.

A relapse was defined as recurrent symptoms requiring treatment in the ED within two weeks of a preceding visit for respiratory distress.

The R patients were compared with another group (control or C patients) who met the same study criteria but who did not have relapses after treatment at any time during the four-year observation period.

Visits to the ED were included in this study if (1) the visit was for increased dyspnea and (2) the patient did not have pneumonia, a pleural effusion, pneumothorax, pulmonary embolism or left ventricular failure as an explanation for his symptoms. For the R group, visits in which corticosteroids were given (treatment or T visits) were compared with visits in which they were withheld (nontreatment or N visits). For each T visit, one N visit was selected as a control. A pair of T and N visits was considered a “match” if the following conditions were met:

1. the T and N visits were made by the same patient.
2. the number of treatments with nebulized bronchodilators differed by one or less.
3. the number of doses of parenteral adrenergic drugs was the same.
4. intravenously administered aminophylline was either given or withheld for both members of the pair.

Visits were selected so that there was no difference between the T and N groups for the use of antibiotics. Visits were matched by one of the authors (G.H.M.) blinded with respect to outcome. To avoid weighting the data by including patients with several relapses, no more than two pairs of visits were allowed for any patient. When several pairs were available for a given patient, only the most closely matched pairs were used. Patients on maintenance therapy with prednisone were considered “treated” if they were given corticosteroids intravenously and their prednisone dose was increased at the time of discharge. For calculation of mean intravenous steroid dose, methylprednisolone was considered to have five times the potency of hydrocortisone.

Data were entered into a microcomputer and analyzed by a commercial statistical package (Systat). All values are expressed as mean ± SD. Differences in the proportion of nominal variables between R and C patients were examined by chi square analysis. Differences in continuous variables were analyzed by Student's unpaired t test or by the Mann-Whitney U-test. McNemar's test was used to compare the frequency of relapse for T and N visits at 24 h, 48 h and 14 days. Significance levels for this analysis were adjusted by Bonferroni's correction for multiple comparisons. Student’s paired t test or the Wilcoxon signed-rank test was used to analyze differences in continuous variables for matched visits. Confidence intervals for the difference in proportions in paired samples were derived by the method of Snedecor and Cochran.

### RESULTS

Between April 1, 1985, and April 30, 1989, 55 patients experienced multiple relapses after ED treatment for decompensated COPD. These patients (R patients) were compared with 176 subjects who had never experienced a relapse (control or C patients) (Table 1). Almost all the patients in both groups were elderly, white men. The R patients made more visits to the ED for respiratory distress and were more likely to be receiving oxygen at home. The postbronchodilator FEV₁ (percent predicted) value was higher for R patients, but the difference was small (5.4 percent).

### Table 2—Comparison of Treatment and Nontreatment Visits

<table>
<thead>
<tr>
<th>R Patients (n = 55)</th>
<th>C Patients (n = 176)</th>
<th>p Value</th>
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#### Study factors
- Duration of symptom (days) 3.59 ± 3.59 2.86 ± 3.27 NS
- Length of stay in ED (h) 2.85 ± 2.12 2.51 ± 1.24 NS
- Temperature (°C) 36.7 ± 0.62 36.5 ± 0.56 NS
- Heart rate (min⁻¹) 106 ± 13 102 ± 17 NS
- Respiratory rate (min⁻¹) 27.3 ± 6.7 25.9 ± 6.4 NS
- Pretreatment FEV₁, (L) 0.72 ± 0.32 0.75 ± 0.36 NS

#### Laboratory tests
- Serum theophylline level (mg/L) (n = 13) 12.3 ± 4.5 13.5 ± 4.5 NS
- Arterial blood gas values (room air) (n = 14)
  - pH 7.39 ± 0.06 7.39 ± 0.06 NS
  - PO₂ (mm Hg) 57.9 ± 11.1 57.4 ± 10.6 NS
  - PCO₂ (mm Hg) 39.1 ± 5.4 40.3 ± 5.8 NS
- Blood counts (n = 10)
  - Hematocrit 47.6 ± 4.0 47.0 ± 3.2 NS
  - Leukocyte count 9.32 ± 3.39 8.94 ± 3.29 NS

#### Treatment
- No. of treatments with nebulized bronchodilators 1.7 ± 0.6 1.5 ± 0.6 0.012
- Parenteral sympathomimetics 46.7% 46.7% NS
- Intravenous aminophylline 15.6% 15.6% NS
- Antibiotics 35.6% 35.6% NS

* n = number of pairs in which data was available for both T and N visits.
Thirty-nine R patients were given corticosteroids intravenously followed by prednisone given orally at least once in the ED. For 30 subjects, visits in which corticosteroids were given (T visits) were compared with matched visits in which they were withheld (N visits). The T and N visits of each pair were made by the same patient and matched for the use of nebulized bronchodilators, parenteral adrenergic drugs and intravenously administered aminophylline. Pairs were selected so that the frequency of antibiotic use was the same for each group. Forty-five pairs of visits were examined in this study. Fifteen patients contributed one matched pair, while 15 contributed two pairs. No matches could be found for the T visits of nine patients.

Intravenously administered methylprednisolone was given in 13 T visits and hydrocortisone in 32. The mean dose was 365 ± 235 mg of hydrocortisone or its equivalent. Prednisone was the only oral preparation given during T visits. The mean discharge dose was 42.4 ± 12.3 mg, and the rate at which it was tapered varied widely.

T and N visits are compared in Table 2. No differences were noted in the duration of symptoms, length of stay in the ED, vital signs, pretreatment FEV₁, value, theophylline level or arterial blood gas values. The number of treatments with nebulized bronchodilators was slightly higher for T than N visits (mean difference = 0.2 ± 0.6 per visit). No other treatment differences were found.

Figure 1 shows the cumulative relapse rates for T and N visits as a function of time. The relapse rate was much lower for T than for N visits at 24 h (2.2 vs 20.0 percent; \( p = 0.011 \)) and at 48 h (8.9 vs 33.3 percent; \( p = 0.005 \)). At 14 days, the rate for T visits (35.6 percent) was less than for N visits (55.6 percent), but the difference was not significant (\( p = 0.11 \)). The 95 percent confidence intervals for the difference in relapse rates are shown in Figure 2. No correlation could be found between the rate of steroid tapering and risk of relapse because of the varied regimens used.

Patients used inhaled corticosteroids on 55 percent of T and 51 percent of N visits. Corticosteroids may have had little effect on patients who were not steroid-dependent. To exclude this possibility, we analyzed the subset of visits (22 pairs) for patients who were not receiving prednisone at the time of presentation. A significant reduction in the 48-h relapse following T visits was observed in this group (10.7 vs 39.3 percent; \( p = 0.011 \)).

The 48-h relapse rate was reexamined using pairs of visits in which the numbers of treatments with nebulized bronchodilators were equal. Administration of corticosteroids significantly reduced the risk of relapse for this subset of 29 paired visits (3.4 vs 24.1 percent; \( p = 0.014 \)). When matched visits were limited to one pair per patient, a similar reduction in the 48-h relapse rate was observed (10.0 vs 33.3 percent; \( p = 0.035 \)).

**DISCUSSION**

Chronic obstructive pulmonary disease is difficult to manage in the outpatient setting. Respiratory decompensation occurs in an unpredictable manner, is difficult to reverse and often recurs for reasons that are not apparent. In 1987, nearly 7 percent of patients discharged from VA Medical Centers with the diagnosis of COPD required readmission within two weeks. (Patient Treatment file, VA Central Office, 1987 statistics). The average rate for other diagnoses was 4 percent. In a previous report, we showed that 30 percent of the visits to an ED for respiratory distress resulted in admission to the hospital. Of the patients who were treated and released, 28 percent...
developed recurrent symptoms within 14 days. These observations suggest that more effective strategies are needed for the prevention of relapse in patients who respond to initial treatment.

Corticosteroids have many properties that could be of benefit to patients with decompensated COPD. They modify the inflammatory response, stimulate the biosynthesis of catecholamines, inhibit catecholamine metabolism, prevent tachyphylaxis to chronic adrenergic stimulation and reduce the activity of tissue phosphodiesterase. Despite these properties, it has been difficult to prove that patients with stable or decompensated COPD benefit from steroid treatment. No information is available about the optimal regimen for treating decompensated COPD in the outpatient setting and the types of patients who benefit from treatment.

The purpose of this study was to determine if corticosteroids reduce the relapse rate after ED treatment of decompensated COPD. We restricted our analysis to patients who are the most likely candidates for such therapy—those with a history of multiple relapses. The regimen consisted of a single intravenous dose of a corticosteroid followed by orally administered prednisone, which is the only practical alternative to the repetitive doses of intravenously administered corticosteroids previously shown to be beneficial. To control for confounding variables, we compared visits in which steroids were given (T visits) to closely matched visits in which they were withheld (N visits).

Corticosteroids dramatically reduced the relapse rate for this group of patients. Large differences between T and N visits were noted within 24 h of treatment. There was no bias in patient selection because each subject served as his own control. Clinical features and laboratory findings at the time of treatment were similar for both types of visits. The T and N visits also were matched for the use of inhaled bronchodilators, parenteral adrenergic drugs and intravenously administered aminophylline. Although inhaled bronchodilators were used more frequently in T visits, it is unlikely that the difference (0.2 treatments per visit) could explain the persistent reduction in the relapse rate. In the subset of visits in which these treatments were equal, the use of corticosteroids was still associated with a significantly lower relapse rate. Since this study was not blinded or placebo-controlled, we cannot exclude a placebo effect. However, the fourfold reduction in the 48-h relapse rate makes this possibility unlikely.

Our results differ from those reported by Emerman and associates, who showed that 100 mg of intravenously administered methylprednisolone had no effect on the 48-h relapse rate for patients treated in an ED. However, they gave corticosteroids to random patients with decompensated COPD. In a previous report, we showed that relapses were observed in only a small proportion of COPD patients. By using a history of multiple relapses, we selected patients with a poor prognosis and were more likely to detect a treatment effect.

It is unclear why the R patients had such a poor prognosis. There were no significant differences between R and C patients with respect to demographic characteristics, severity of baseline airflow obstruction or bronchodilator response. Despite the apparent similarity between these groups, R patients had five times as many episodes of respiratory decompensation during the observation period, and their 48-h relapse rate was 33 percent in the absence of corticosteroid therapy. Regardless of the explanation, our study shows that there are major differences in the risk of relapse for patients with decompensated COPD and that randomized clinical trials in this disease should be stratified by prognosis.

Sixteen patients with multiple relapses were not included in this study because they were never given intravenously administered corticosteroids during episodes of respiratory distress. However, 11 of these subjects were given prednisone on multiple occasions. It is unclear if they would have benefited from an intravenously administered preparation. Another nine patients received combined therapy but were excluded because no suitable matches could be found for their T visits. Since pairwise matching was based on four criteria and visits were group-matched on a fifth (antibiotic use), it is not surprising that a proportion of T visits could not be evaluated. Nevertheless, it should be noted that intravenously and orally administered corticosteroids were shown to be beneficial for most, but not all, of the patients in whom they were given.

The clinical relapse was chosen as the endpoint in this study because it is the most practical measure of treatment effect in the outpatient setting. It also is the most relevant outcome with respect to patient satisfaction, hospital cost and physician time. It could be argued that clinical improvement is difficult to interpret in the absence of more objective measures of respiratory function. Physiologic endpoints, such as an improvement in FEV1, may not have been affected by treatment. However, there often is poor correlation between symptoms, exercise tolerance and expiratory flow rates in COPD. It is unclear which of these parameters is an important measure of corticosteroid effect. The patients in our study had a better prognosis when they were given corticosteroids than when they were not. Although the mechanism for this effect could not be determined from our data, corticosteroids prevented most of the relapses that would have occurred within the first 24 h after treatment.
multiple allergies, early onset of symptoms or episodic dyspnea. No patient had an FEV$_1$ (percent predicted) or FEV$_1$/VC ratio greater than 75 percent, either before or after use of bronchodilators. On the average, FEV$_1$ increased 20 percent after the administration of inhaled bronchodilators on baseline spirometry. Nevertheless, it is possible that some of the patients in this study had asthma. Patients with long-standing asthma can develop irreversible airway obstruction associated with narrowing of small airways. It is therefore difficult to be certain of the diagnosis in some patients with obstructive lung disease. We showed that corticosteroids had a beneficial effect on patients selected on the basis of history and baseline PFTs, not by diagnosis. The distinction between asthma and COPD is therefore of more theoretical than practical significance.

In summary, intravenously and orally administered corticosteroids reduce the relapse rate after treatment for decompensated COPD in patients with a history of multiple relapses. The effect of corticosteroids occurs within 24 h of treatment, but the mechanism is unknown. Such a regimen should be used for patients with a poor prognosis if the benefits of corticosteroid therapy outweigh the risks.

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