

Oral versus repository corticosteroid therapy after hospitalization for treatment of asthma

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Tapering regimens of oral steroids may be difficult or confusing for some patients. Repository steroids have been shown to be as effective as tapering oral doses in preventing relapse after emergency treatment. This study was undertaken to determine whether repository steroids are as effective as tapering oral steroids in preventing relapse after hospitalization for treatment of asthma. Twenty-six patients with acute exacerbations of asthma requiring treatment for 24 to 72 hours with parenteral steroids were randomized into two groups. Both groups received oral prednisone, 60 mg daily, when parenteral steroids were discontinued. At discharge, one group received intramuscular placebo and oral prednisone tapered over 8 days, and the other received 80 mg intramuscular methylprednisolone sodium acetate and oral placebo. At discharge and 2-week follow-up, patients were interviewed and examined, and spirometry results were obtained. There was little difference between groups in ratings of symptoms at discharge or follow-up. Both groups had less wheezing at follow-up than at discharge, though the improvement was significant only in the repository steroid group ($p < 0.05$). Mean forced expiratory volume in 1 second, forced vital capacity, peak expiratory flow rate improved at follow-up in both groups. No significant differences in outcome were found between the oral and repository steroid groups. (J ALLERGY CLIN IMMUNOL 1995;95:15-22.)

Key words: Asthma, corticosteroids, repository steroids

Corticosteroids have been used to treat asthma exacerbations since the 1950s. Researchers only recently have established the efficacy and optimal dosage of steroids in acute exacerbations.^{1,2} Parenteral steroids are used most frequently when patients are hospitalized for treatment of asthma, and clinicians commonly switch patients from intravenous to oral steroids once their clinical symptoms and pulmonary function improve. Patients usually are discharged while receiving tapering doses of oral corticosteroids; recent research has focused on the optimal schedule for steroid withdrawal to prevent relapse.³ Unfortunately, tapering doses of oral steroids are complicated, often involving numerous pills and frequent changes in dosage. Such a regimen can be confusing to some patients, and compliance may be difficult.

Abbreviations used

FEV ₁ :	Forced expiratory volume in 1 second
FVC:	Forced vital capacity
PEFR:	Peak expiratory flow rate

Because a single injection of a repository steroid might be a more convenient and reliable substitute for a tapering course of oral steroids, one recent study⁴ compared these two options in patients discharged from the emergency room. This study suggested that intramuscular methylprednisolone sodium acetate was as effective as oral methylprednisolone in preventing rehospitalization and more effective in preventing reappearance of symptoms in patients not ill enough to require hospitalization. No similar study has been done in patients with asthma admitted to the hospital, who generally have more severe disease. Our study was undertaken to determine whether repository steroids are as effective as tapering regimens of oral steroids in preventing asthma relapse after hospitalization.

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METHODS

Patients over age 18 who were admitted to the general medicine service at two urban teaching hospitals with acute exacerbations of asthma requiring parenteral steroid therapy were eligible for entry into the study. Asthma was defined according to the American Thoracic Society criteria.⁵ Consecutive patients were enrolled if they had no evidence of concurrent underlying disease, such as congestive heart failure, pneumonia, occupational or interstitial lung disease, or tumor; did not have chronic obstructive pulmonary disease as determined by American Thoracic Society criteria⁵; were not returning home to a known allergenic source; did not require intubation or mechanical ventilation during hospitalization; had no contraindication to steroid therapy; were not pregnant, or if female and of childbearing age, were using an acceptable method of contraception; were not dependent on oral steroid therapy before admission; and were able to comply with study requirements. Patients were considered to be steroid-dependent if they were currently taking oral steroids or had required more than one course of oral steroid therapy in the 6 months before admission. Patients provided written informed consent. Approval was obtained from the Medical College of Wisconsin Human Research Review Committee.

The study was designed as a randomized, placebo-controlled, double-blind clinical trial. All patients received intravenous steroids for 18 to 72 hours. Bronchodilators, antibiotics, and intravenous corticosteroid treatment were given at the discretion of the attending physician, and on completion of a course of parenteral steroids, patients were switched to an oral dose of 60 mg prednisone daily for 1 or 2 days until discharge.

Patients were randomized by means of computer-generated numbers into one of two groups. At discharge, the oral steroid group received an intramuscular injection of placebo and a prescription for tapering doses of oral prednisone, from 40 mg to 0 mg, decreasing by 5 mg daily over 8 days. The repository steroid group received an intramuscular injection of methylprednisolone sodium acetate (80 mg) at the time of discharge and a prescription for tapering doses of oral placebo to be taken over 8 days. The oral placebo was indistinguishable from the oral steroid. Methylprednisolone sodium acetate is a repository steroid with a half-life of approximately 69 hours. Both groups received prescriptions at discharge for their usual medications, including theophylline. They were told to use their nonsteroid inhalers as needed.

Before discharge, subjects were interviewed regarding history of asthma, smoking, allergies, and asthma medications. A standardized questionnaire was used during the interview to determine degree of symptoms of cough, wheeze, shortness of breath, and chest tightness on a scale of 1 (most) to 5 (least). Physical findings, including vital signs and results of chest examination for presence of wheezing, were recorded. Theophylline levels and spirometry results were also obtained.

Follow-up was accomplished by a return visit 10 to 14

days after the patient's discharge. Once again, patients were interviewed regarding symptoms of cough, wheeze, shortness of breath, and chest tightness. They were also questioned about drug compliance, inhaler usage, recurrent symptoms, and rehospitalization. Patients were asked whether they had experienced any side effects from their medications and then were questioned specifically about the occurrence of any gastrointestinal symptoms or the appearance of pain, redness, or swelling at the injection site. Theophylline levels were obtained. Physical examination and spirometry were again performed.

Fisher's exact test (two-tailed), Student's *t* test (unpaired), and Pearson's chi square analysis were used as appropriate to compare the characteristics and subjective response variables of the two groups. Calculations were performed with Statworks Version 1.1 (Cricket Software, Inc., Philadelphia, Pa.). A *p* value of less than 0.05 was considered significant. Spirometry data for forced expiratory volume in 1 second (FEV₁) and forced vital capacity (FVC) were analyzed as mean percent of predicted value^{6,7} to eliminate confounding caused by possible differences between groups in patient age, sex, race, or height. Improvement in spirometry data from time of discharge to time of follow-up was calculated for each group, and 95% confidence intervals were calculated for the difference between groups. Ninety-five percent confidence intervals were also calculated for the difference between groups as to presence of expiratory wheezing at discharge versus follow-up.

RESULTS

Thirty-five patients were eligible for enrollment into the study. Of these, 28 agreed to complete the study protocol. Two patients in the repository group were rehospitalized (one for treatment of hepatitis and one for treatment of asthma) and had to be dropped, because follow-up data were not available. The remaining 26 patients constitute the study group.

Characteristics of the study patients are shown in Table I. There were no significant differences between groups with regard to sex, race, age, duration of asthma, or smoking history.

Study groups were compared in terms of duration of hospital stay and duration of parenteral steroid use while hospitalized. Mean hospital stay in the oral steroid group was 3.93 days, versus 4.18 days in the repository group (*p* = 0.50). There was no significant difference in duration of intravenous steroid treatment, 40 hours in the oral steroid group versus 37 hours in the repository group (*p* = 0.63). Similarly, there was no significant difference in total dose of intravenous (*p* = 0.73) or oral (*p* = 0.15) steroids given before hospital discharge.

Figs. 1 and 2 show the results from the standard-

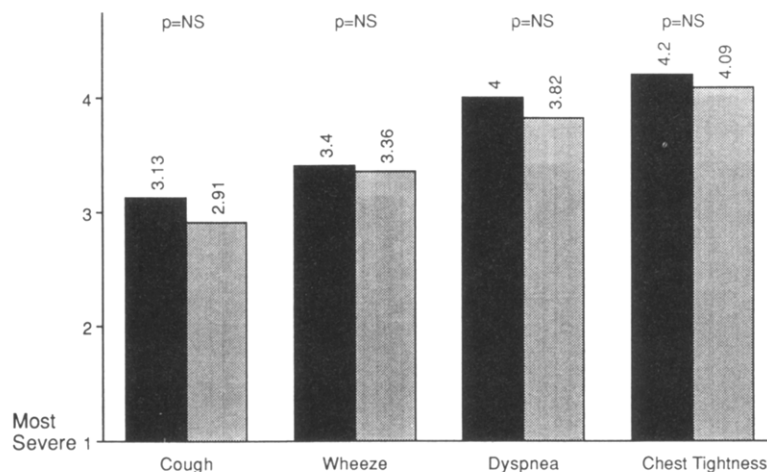


FIG. 1. Patient ratings of symptoms of cough, wheeze, dyspnea, and chest tightness on a scale of 1 (most severe) to 5 (least severe) at the time of discharge.

TABLE I. Patient demographics

	Oral steroid group (n = 15)	Repository steroid group (n = 11)	p Value
Sex			
Male	3	6	0.10*
Female	12	5	
Race/ethnic group			
Black	11	9	0.67†
White	3	2	
Hispanic	1	0	
Mean age in years (range)	38 (20-69)	43 (20-68)	0.40‡
Duration of asthma in years (range)	16 (04-49)	20 (00-50)	0.40‡
Smokers	5 (33%)	6 (55%)	0.43*

*Fisher's exact test (two-tailed).

†Pearson's chi square analysis.

‡Student's *t* test (unpaired).

ized symptom questionnaire in graphic form. There was no significant difference between the groups in their ratings of symptoms of cough, wheezing, chest tightness, or dyspnea at the time of discharge. At follow-up, only the symptom of cough was rated significantly different by the two groups, with the repository steroid group rating their symptom of cough as more severe, at 3.09, than the oral steroid group, who gave cough a mean rating of 4.07. However, the repository group's rating of cough reflected improvement from 2.91 at the time of discharge to 3.09 at the time of follow-up.

Ratings for each group in every symptom category but one stayed the same or improved between discharge and follow-up. The oral steroid group

rated dyspnea as being more severe at follow-up (3.53) than at discharge (4.00), though the difference was not statistically significant.

Because patients were told at the time of discharge to use their β -agonist inhalers as needed, inhaler usage was evaluated as an end point. Twelve patients in the oral steroid group (80%) used their inhalers, compared with 10 (91%) in the repository group ($p = 0.61$). Frequency of usage by those who reported using inhalers was also similar between groups, 1.73 times daily in the oral steroid group versus 1.36 times daily in the repository group ($p = 0.29$).

Presence of expiratory wheezing on physical examination is shown in Fig. 3. The percent of patients with wheezing at discharge in the reposi-

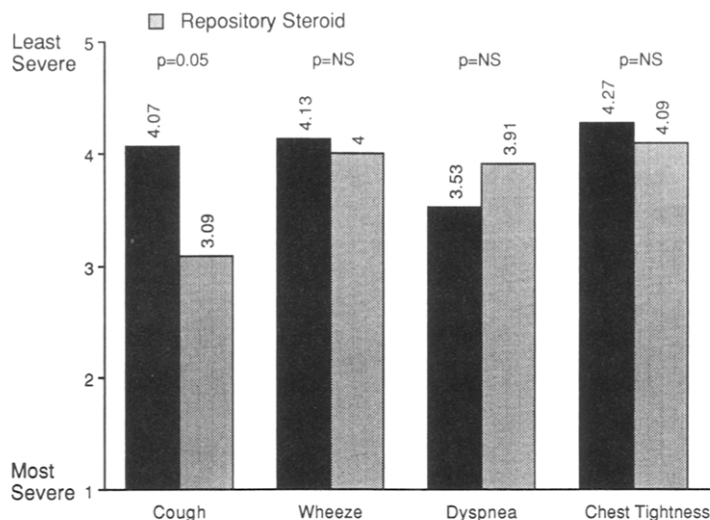


FIG. 2. Patient ratings of symptoms of cough, wheeze, dyspnea, and chest tightness on a scale of 1 (most severe) to 5 (least severe) at the time of follow-up visit.

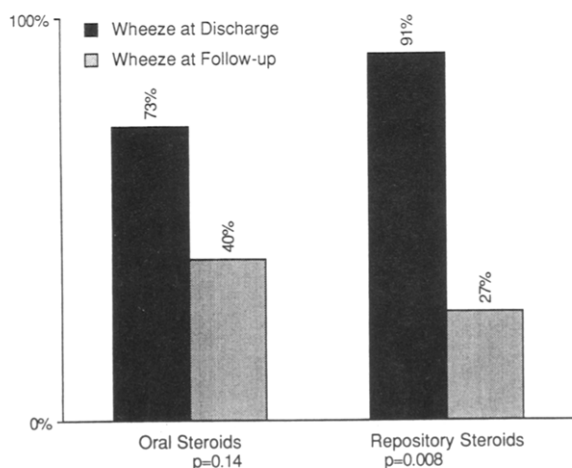


FIG. 3. A comparison of the presence of wheezing as determined by physical examination at the time of discharge and at the 2-week follow-up visit in patients who received oral steroids compared with those who received repository steroids.

tory steroid group was higher, 91%, and decreased to 27% at follow-up, a statistically significant decrease ($p = 0.008$). We compared the difference in percentage of improvement in wheezing between groups by calculating 95% confidence intervals as shown in Fig. 4.

Spirometry results are shown in Table II. Groups had comparable values at the time of discharge for FEV₁ and FVC. Mean peak expiratory flow rate (PEFR) was somewhat higher at the time of discharge in the oral steroid group, at 4.6 L/sec, than in the repository group, in which mean PEFR at dis-

charge was 3.5 L/sec. However, the difference did not reach statistical significance ($p = 0.08$).

FEV₁, FVC, and PEFR improved in both groups between discharge and follow-up. Although there was greater improvement in all three parameters in the repository group, the differences did not achieve statistical significance.

One patient in each group sought additional medical care between the time of discharge and follow-up; again there was no significant difference between groups ($p = 1.00$). One patient enrolled in the repository steroid group was readmitted to another hospital with a reexacerbation of asthma and had to be excluded from the data analysis because follow-up data could not be obtained. Concern that the exclusion of this patient might bias our results led us to reevaluate the data, assuming a worst case scenario for that patient. Giving this patient the worst scores for shortness of breath, chest tightness, or wheezing, we still found no significant difference between the groups at follow-up. Assuming this patient had no wheezing as determined by physical examination at discharge and had wheezing at follow-up, there was still a significant decrease in wheezing in the group overall ($p < 0.05$).

Table III shows the incidence of adverse reactions. The repository steroid group reported a 55% incidence of pain and/or swelling at the injection site, compared with 7% of the oral steroid group ($p < 0.05$). Complaints pertaining to fluid retention were more common in the oral steroid group (33% vs 0%, $p = 0.27$). There was a higher

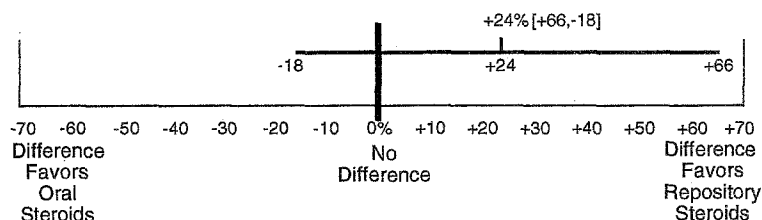


FIG. 4. Difference in percent of patients whose wheezing resolved between time of discharge and follow-up in patients who received oral steroids compared with those who received repository steroids.

TABLE II. Spirometry results

Measurement	Oral steroid group	Repository steroid group	<i>p</i> Value*
% Predicted FEV ₁ at discharge	67 ± 14	57 ± 23	0.17
% Predicted FEV ₁ at follow-up	73 ± 18	71 ± 36	0.83
Change in % predicted FEV ₁	+6 ± 14	+14 ± 29	0.36
% Predicted FVC at discharge	72 ± 13	70 ± 22	0.80
% Predicted FVC at follow-up	73 ± 14	84 ± 32	0.24
Change in % predicted FVC	+1 ± 10	+14 ± 22	0.06
Mean PEFR (L/sec) at discharge	4.6 ± 1.6	3.5 ± 1.3	0.08
Mean PEFR (L/sec) at follow-up	4.9 ± 2.1	4.3 ± 1.6	0.46
Change in PEFR (L/sec)	0.5 ± 1.4	0.9 ± 1.8	0.56

Values are expressed as means ± SD.

*Student's *t* test.

TABLE III. Incidence of side effects

	Oral steroid group (<i>n</i> = 15)	Repository steroid group (<i>n</i> = 11)	<i>p</i> Value*
Gastrointestinal (nausea, vomiting, diarrhea)	53%	27%	0.25
Edema (fluid retention, puffiness)	33%	0%	0.27
Injection site (pain, swelling, redness)	7%	55%	0.02
Miscellaneous†	67%	55%	1.00
Overall	87%	82%	1.00

*Fisher's exact test (two-tailed).

†Miscellaneous side effects included headache, nervousness, dizziness, fatigue, blurred vision, and pruritus.

incidence of gastrointestinal side effects in the oral steroid group (53% vs 27%, *p* = 0.25). However, many of these patients were receiving multiple medications, so it was not clear which drug was responsible for side effects. When data from only patients who were not taking antibiotics were examined, the incidence of nausea, vomiting, diarrhea, or flatulence was still lower in the repository group, 0 of 4 (0%) versus 3 of 8 (38%) in the oral steroid group. Overall, the incidence of side effects was similar in the two groups. Four patients in the oral steroid group and one patient in the repository steroid group did not finish taking the study medication. Two of these patients, both in the oral

steroid group, discontinued the study drug because of side effects they attributed to the drug. One of these patients had vomiting and constipation and discontinued trimethoprim/sulfamethoxazole and theophylline, as well as the study drug. The other complained of nausea, diarrhea, tinnitus, nervousness, shakiness, and low back pain. A theophylline level was in therapeutic range, and prednisone was discontinued at the advice of a physician. The patient was also taking amoxicillin.

Theophylline levels before discharge were in the low therapeutic range in both groups, 12.39 mg/L in the oral steroid group and 12.97 mg/L in the repository steroid group (*p* = 0.79). Levels

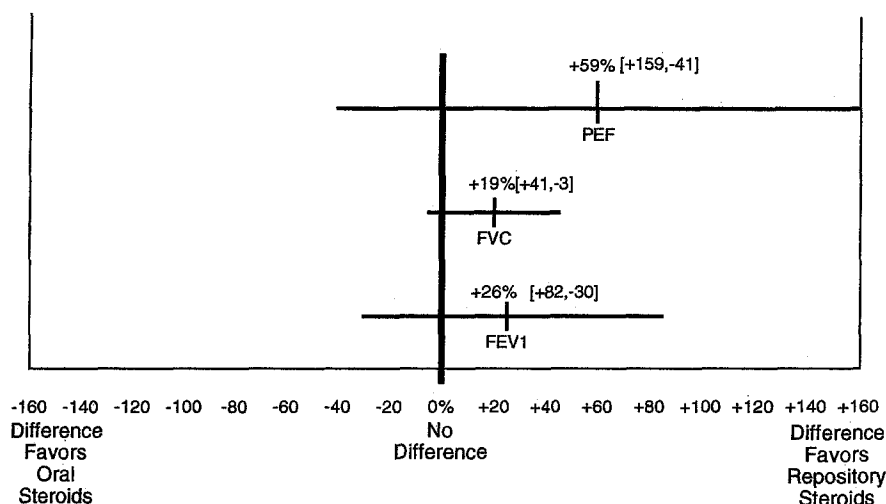


FIG. 5. Difference in percent improvement in results of pulmonary function tests from time of discharge to follow-up in oral versus repository steroid groups (percent improvement repository minus percent improvement oral).

dropped to subtherapeutic ranges in both groups after discharge, 7.12 mg/L in the oral group and 5.17 mg/L in the repository group ($p = 0.44$).

DISCUSSION

Use of high-dose triamcinolone for 3 days along with oral prednisone has been shown to significantly decrease emergency room visits and total oral steroid doses needed in patients with severe, steroid-dependent asthma.⁸ Parenteral steroids have been shown to be effective in treating acute exacerbations of asthma and are widely used both in the emergency room setting and during hospitalization for treatment of asthma. Jonsson et al.⁹ found that oral administration of steroids was as effective as intravenous use in hospitalized patients with moderate exacerbations of airway obstruction. Chapman et al.¹⁰ showed that a short course of oral prednisone reduced early relapse rates after emergency room treatment of acute asthma.

Because of potential problems with compliance in patients sent home with prescriptions for tapering doses of oral prednisone, repository steroids might offer an advantage over oral steroids in preventing relapse of asthma after exacerbation. Hoffman and Fiel⁴ compared use of oral steroids with a single injection of repository steroids on discharge from the emergency room and found intramuscular methylprednisolone to be as effective as oral methylprednisolone in preventing rehospitalization. Use of oral versus repository steroids to prevent relapse in patients hospitalized for treatment of asthma exacerbations, who may have

more severe disease, has not previously been studied. Our results show no significant differences in outcome between the two treatment groups.

The minor differences between groups in ratings of symptoms were of such small degree that they probably are not clinically significant. The repository steroid group fared slightly better than the oral steroid group with regard to expiratory wheezing. As shown in Fig. 4, the percent of patients whose wheezing resolved in the repository steroid group was higher than in the oral steroid group, though the 95% confidence interval includes 0, indicating no significant difference. Improvements in FEV₁, FVC, and PEF were much greater in the repository group than in the oral group (Table II), though because of high variability the difference did not achieve statistical significance.

Because of the relatively small sample size, the possibility of type II (β) error is great. To address this issue, we calculated the confidence intervals for the difference between the mean change in pulmonary function test results in the oral steroid group versus that in the repository steroid group. The 95% confidence intervals are shown in Fig. 5. The confidence intervals include "0" or no difference between groups, yet despite the wide confidence interval seen, it is clear that the trend favors repository steroids. The graph shows that it is very unlikely that a true difference would favor the oral steroids. Hence, in objective measurements by physical examination and spirometry, we believe it is safe to conclude that there is no significant difference between the groups; if anything, there is

a trend toward superiority of repository steroid treatment.

One explanation for the apparently superior results obtained in the repository group might be that the oral group was comprised of patients with more severe disease. However, using National Institutes of Health criteria to classify patients as to severity of asthma, we found that nearly all patients fell into the category of moderately severe disease ($p = 0.04$). Indeed, our data suggest that the repository group may have been more ill at the time of discharge.

Another explanation for the apparent superiority of the repository group might be that the intramuscular dose they received may have been more potent than the oral tapering regimen used. However, when calculating comparable doses for oral and intramuscular methylprednisolone, the manufacturer recommends multiplying the daily oral dose by 7 to arrive at the appropriate dose for a weekly intramuscular injection and suggests that a single injection of a given dose is roughly comparable to the same oral dose when given as a temporary substitute. Thus our patients given the oral steroid tapering doses received 180 mg total of methylprednisolone, compared with only 80 mg given by intramuscular injection.

One reason physicians may be reluctant to use intramuscular injection is the perception that side effects might be a problem. Dermal atrophy can occur at the site of steroid injections, but if care is taken to give the intramuscular injection in the gluteal area, avoiding leakage of solution into the dermis, the risk of subcutaneous atrophy is minimal. Though 55% of our patients had some pain or swelling at the injection site, this was not believed to be severe enough to discourage use of the intramuscular route. One patient in the oral steroid group stopped taking the study medication because of side effects; none of the patients in the repository group exhibited evidence of a steroid reaction.

The Expert Panel of the National Asthma Education Program¹¹ suggests that inhaled corticosteroids may be initiated at the first follow-up visit or at the time of hospital discharge after treatment with parenteral steroids for an asthma exacerbation. To rule out bias in the study secondary to differences in treatment with steroid inhalers, we compared use of steroid inhalers and found that two patients in each group used steroid inhalers after discharge ($p = 1.00$). On the basis of current recommendations, we would advocate initiating treatment with inhaled steroids at the time of

discharge along with administration of a repository steroid injection. In addition, we would stress the importance of scheduling a follow-up visit after discharge to minimize chances of relapse and rehospitalization by reinforcing instructions and making any necessary medication adjustments.

It is noteworthy that theophylline levels were similar and dropped to subtherapeutic levels in both groups. By self-report, 5 of 26 (19%) patients did not finish taking their study medication as prescribed. Previous work¹²⁻¹⁴ has suggested that self-report correlates well with other methods of assessing compliance. Compliance with oral medication prescriptions was clearly a problem in this group of patients. In broader-based studies of compliance, noncompliance rates of 25% to 50% have been reported.¹⁵ For this reason, we believe a repository injection may offer an advantage in keeping patients well after they have been hospitalized for treatment of asthma exacerbation.

In summary, previous data⁴ suggested that repository steroids were as effective as an oral tapering regimen in preventing relapse of asthma after emergency treatment. Our data confirm and extend this conclusion to patients with more severe disease, that is, those requiring hospitalization for treatment of asthma exacerbations. There were no significant differences in outcome between the two groups. Though larger studies would be useful to confirm our results, repository steroid injections appear to be as effective as tapering oral doses in preventing relapse after hospitalization for treatment of asthma exacerbation. The single repository injection is less complicated than an oral tapering regimen, which may be confusing or inconvenient for patients. Use of repository steroids simplifies treatment and eliminates potential problems with compliance.

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Oral methylprednisolone (Orasone) and oral placebo supplied courtesy of Reid-Rowell.

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