

## **Evidence Based Medicine: Inhaled Steroids for Acute Asthma Following Emergency Department Discharge**

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### **Abstract**

The source for this systematic review abstract is: Edmunds ML, Camargo CA, Brenner BE, Rowe BH. Inhaled steroids for acute asthma following emergency department discharge (Cochrane Review). In: *The Cochrane Library*, Issue 4, 2005

**MeSH Words:** Asthma, corticosteroids, inhaled, emergency department, evidence based medicine relapse, admission.

### **Objective**

To assess the effects of inhaled corticosteroids (ICS) on the treatment of discharged asthmatics from the emergency department.

### **Search Strategy**

The primary source was the Cochrane Airways Review Group registry, which consists of randomized controlled trials (RCT) found in EMBASE, MEDLINE, and CINAHL databases as well as manual searches of 20 respiratory

journals. Also, conference abstracts were reviewed, primary authors and pharmaceutical companies were contacted, and bibliographies from prior studies, reviews, and texts were searched for published or unpublished studies.

### **Study Selection**

RCT's or quasi RCT's (e.g. allocation by days of the week) involving both pediatric and adult patients who have been treated and discharged from an Emergency Department or its equivalent. Patients randomized to receive ICS

treatment following discharge either in addition to or as a substitute for standard oral corticosteroid (CS) therapy were included in the review. The primary outcome was acute asthma relapse (defined as an unscheduled visit for worsening asthma).

### Data Extraction

Two reviewers independently examined all selected studies. For continuous variables, a weighted mean difference (WMD) or standardized mean difference (SMD) and 95% confidence intervals (CI) were calculated for each study and pooled with similar studies. For dichotomous variables, an odds ratio (OR) with 95% CI was calculated for each study and pooled with similar studies. The DerSimonian and Laird method was used to pool similar studies, to estimate the absolute risk reduction and the number needed to treat (NNT), and to evaluate the heterogeneity among pooled estimates ( $p < 0.05$  was considered statistically significant).

### Main Results

Two separate comparisons were performed: one comparing ICS plus CS vs CS alone, the other comparing ICS alone vs CS alone.

#### 1. ICS plus CS to CS alone

Three studies compared ICS plus CS to CS alone, all involving adults. There were a total of 909 patients: 455 treated with ICS plus CS, and 454 treated with CS alone. Patients were excluded if currently using ICS or had recently used CS. In all three trials, patients were considered moderate to severe disease at presentation with mean peak flows of 40-55% predicted. ICS were administered for 20-24 days in doses ranging from moderate to high. All patients received a 5-7 day course of oral prednisone.

#### Primary Outcomes

Relapse rates were the primary outcome in all three trials, and there were no statistically significant differences between the two groups. Relapse rates were calculated as intention-to-treat. There was a trend towards a benefit of ICS at both 7-10 (OR: 0.72; 95% CI: 0.48-1.10) and 20-24 day (OR: 0.68; 95% CI: 0.46-1.02) follow up. Because of the marked difference in rate of

follow-up between the trials, the analyses were repeated excluding all the patients who were lost to follow-up. The results were similar to those in the primary analysis, with no statistically significant differences between the groups

#### Secondary Outcomes

Hospital admission rates were only reported in two studies and there were no statistically significant differences between the groups (OR: 0.99; 95% CI: 0.39-2.52), although the overall admission rate was low (2%). Two studies recorded peak expiratory flow rates (PEFR), and there were no differences between the groups in either absolute or predicted PEFR. Beta-agonist use was studied and there was no difference between the groups at 7-10 days (WMD: 0.5 inhalations/day, 95% CI: -0.4-1.5) and 20-24 days, (random effects model WMD: 0.1 inhalations/day; 95% CI: -2.3-2.1). Pooled results of the asthma-quality of life questionnaire (AQLQ) in two trials did not show a significant effect of ICS at 7-10 days (WMD = 0.19, 95% CI: -0.01 to 0.39) or at 20-24 days (using the random effects model WMD = 0.33, 95% CI: -0.4 to 1.0). Two studies recorded data on asthma symptoms (cough, dyspnea, and wheezing) using the seven-point Likert scale. At 7-10 days and at 20-24 days, using the random effects model and pooling of the results, there were no statistically significant differences between the groups in any of the symptoms.

#### 2. ICS alone vs. CS alone

Seven studies were included that compared ICS alone to CS alone, including two unpublished studies. A total of 1204 patients; 612 received ICS, and 592 were treated with CS. Patients presenting with severe acute asthma were excluded.

#### Primary Outcomes

Only four studies reported relapse rates. At 7-10 days, there was no statistically significant difference in relapse rates between the groups (OR: 1.0; 95% CI: 0.66 to 1.52). Only two studies followed patients beyond 10 days and there was no statistically significant difference in relapse rates at 16 days (OR: 1.26; 95% CI: 0.80 to 1.98).

### Secondary Outcomes

Only two studies reported hospital admissions, and there were no admissions in either study. Six studies reported on absolute PEF. At 7-10 days, the absolute PEF in the ICS treatment group was 11.0 L/min higher than the control group, which was not statistically significant (95% CI: -1 to 23). At 20-24 days, there was a statistically significant improvement in the ICS treated group (15.2 L/min higher; 95% CI: 2 to 29). In both beta-agonist use and quality of life data, there was no significant difference between the groups.

### Author's Conclusion

The authors of this report feel there is insufficient evidence that the addition of ICS to standard CS therapy benefits discharged asthmatic from ED. There is some evidence that high dose ICS may be as effective as CS therapy in mild asthmatics.

### Commentary: Clinical Implications

Asthma is a common disease with a prevalence of 4% to 8%.<sup>1</sup> The current trend shows that hospitalization, death rates and prevalence continue to rise.<sup>2,3,4,5</sup> Acute exacerbations are responsible for almost 2 million ED visits per year in the United States.<sup>6</sup> This amounts to a large medical and economic burden on an already stressed health care system. In 1998, direct and indirect expenditures exceeded US\$12 billion in the United States.<sup>7</sup> Asthma primarily affects children, but the burden of the disease is spread across all age groups. Prevalence rates are higher for the inner city poor, many of whom are racial and ethnic minorities, who are at increased risk for morbidity and mortality.<sup>8</sup>

The pathophysiology of an acute asthma exacerbation is well understood. Airway inflammation leads to increased mucus production which, in turn, leads to bronchoconstriction. The end result is obstruction of both small and large airways. Treatment of acute asthma is also well-established and is driven by understanding of the underlying pathophysiology. Bronchodilation is achieved with short-acting beta-adrenergic agonists (albuterol) and anticholinergics (ipratropium bromide). Systemic or inhaled

corticosteroids act to reduce the inflammatory response.

The dose and route of administration for corticosteroids is less well-established. The evidence for oral CS (CS) for treatment of acute asthma is strong.<sup>9</sup> The standard of care for asthmatics being discharged from the ED is a 5-10 day fixed-dose "burst" of CS. Patients may be put on a tapering dose if they have received a course of CS recently or there are other contraindications to burst therapy. Inhaled corticosteroids (ICS) have an established role in the outpatient setting as suppressive therapy, however the evidence for their role in the management of acute asthma following ED discharge is inconsistent. Potential advantages to the use of ICS in the acute setting include reduced systemic side-effects, direct delivery into the airways and improved reduction of airway edema and reactivity.<sup>10</sup>

This review examined 10 studies in which CS were compared to ICS alone or ICS plus CS. The reviewers had hoped to comment on the efficacy of ICS in men vs women, children vs adults and moderate vs severe asthma, however due to variations in study design, there was only enough data to comment on the first group.

### ICS plus CS Vs CS

This arm of the review included 3 studies involving 909 patients: 455 treated with ICS plus CS and 454 treated with OCS alone. All patients received a fixed-dose of 5-7 days of oral prednisone. Pooled results failed to demonstrate a statistically significant difference in the primary outcome, asthma relapse, although there was a trend in favor of ICS at both 7-10 (OR: 0.72; 95% CI: 0.48 to 1.10) and 20-24 days (OR: 0.68; 95% CI: 0.46 to 1.02). The number needed to treat based on a baseline relapse rate of 10-20% is 22-39 patients at 7-10 days and 19-34 patients at 20-24 days. There was no benefit in the secondary outcomes of hospital admission or pulmonary function tests. Interpretations of the other outcomes were limited because not all studies reported the same outcomes. One study demonstrated a statistically and clinically important gender difference; however it did not reach statistical significance in the meta analysis. The authors point out that this is a possible area for future research.

Based on the results, it seems as though there is no benefit to adding ICS to CS for the treatment of acute asthma. However, it may be appropriate to start patients on ICS who are poorly controlled as outpatients on inhaled bronchodilators and would otherwise be candidates for such therapy. This may provide more long-term benefits even though it won't reduce the rate of relapse over the short term.

Additionally, there were marked variations in the designs of the 3 studies in this arm of the review. The resultant heterogeneity may obscure a subgroup of patients for whom the addition of ICS therapy would be beneficial. Further research is needed to examine these variables. For example, high dose ICS may show a benefit when compared to moderate or low dose.

#### ICS alone Vs CS alone

This arm of the study included 7 studies, a total of 1204 patients 612 treated with ICS and 592 treated with CS. There was no statistically significant difference between the treatments in terms of asthma relapse at 7-10 or 16-21 days.

There were many variations in study designs that led to the inability of the meta analysis to generate conclusive results. First, the studies included different end points and defined common end points such as relapse in different terms. Next, several studies reported statistically significant reductions in endpoints, such as PEF, that were not clinically significant. Other outcomes were recorded and reported in different ways that made pooling results impossible. Lastly, most of the trials were relatively small and thus were insufficiently powered to detect a difference between the treatment groups if it existed.

Based upon the data from this arm of the study, there is insufficient evidence to suggest a benefit of ICS over oral CS in the outpatient management of acute asthma. The authors even question if there is enough data to suggest the two treatments are equivalent. Although the results are compatible with equivalent efficacy, none of the studies included enough patients to prove equivalence. Even if the two therapies can be shown to be equivalent, the daily cost of ICS is roughly 8 times that of prednisone. Thus a more convincing reason for the use of ICS such as lower side effect profile would need to emerge

through further investigation to mandate a change in current practice.

#### *Summary*

At this point, there is insufficient evidence to suggest the addition of ICS to standard CS therapy will reduce the rates of asthma relapse, admission or improve pulmonary function tests. These results do not apply to children as none of these studies included this age group. ICS alone does not appear to be inferior to CS alone, but there is insufficient evidence to say they are equivalent. Therefore, a 5-10 day course of oral CS should remain the standard of care until further research can be done. ICS can be added to the outpatient regimen in patients who are poorly controlled on their current outpatient regimen. Although the meta analysis did not reveal a treatment benefit for ICS, one of its strengths is that it did outline areas for potential future study. Perhaps there is a population of patients who will benefit from ICS use in the acute setting.

#### **References**

1. Brenner BE, Powell KA. The acute asthmatic in the emergency department. In: Brenner BE, ed. *Emergency Asthma*. New York, NY: Marcel-Dekker; 1999:489-503.
2. Weiss KB, Wagener DK. Asthma surveillance in the United States. A review of current trends and knowledge gaps. *Chest*. 1990; 98:179S.
3. Asthma--United States, 1982-1992. *MMWR Morb Mortal Wkly Rep*. 1995; 43:952.
4. Mannino DM, Homa DM, Akinbami LJ, et al. Surveillance for asthma--United States, 1980-1999. *MMWR Surveill Summ* 2002; 51:1.
5. Weiss KB, Gergen PJ, Crain EF. Inner-city asthma: The epidemiology of an emerging US public health concern. *Chest*. 1992; 101:362S.
6. Mannino DM, Homa DM, Pertowski CA, et al. Surveillance for asthma-United States, 1960-1995. *MMWR Morb Mortal Wkly Rep*. 1998;47 (No. SS-1):1-28.

7. Weiss KB, Sullivan SD. The health economics of asthma and rhinitis. I. Assessing the economic impact. *J Allergy Clin Immunol.* 1001; 107:3-8.

8. Asthma mortality and hospitalization among children and young adults--United States, 1980-1993. *MMWR Morb Mortal Wkly Rep.* 1996; 45:350.

9. Rowe, BH; Spooner, CH; Ducharme, FM; Bretzlaff, JA; Bota, GW. Corticosteroids for preventing relapse following acute exacerbations of asthma [Systematic Review] Cochrane Airways Group Cochrane Database of Systematic Reviews. 4, 2005.

10. Rodrigo G, Rodrigo C. Inhaled flunisolide for acute severe asthma. *Am J Respir Crit Care Med.* 1998;157:698-703.

**Competing Interests:** None Declared

**Funding:** Dr. Diner is a recipient of grant funding from the CDC Foundation.

This manuscript has been peer reviewed

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