Low-Dose Inhaled Corticosteroid Therapy and Risk of Emergency Department Visits for Asthma

Don D. Sin, MD, MPH; S. F. Paul Man, MD

Background: Patients who visit the emergency department (ED) because of asthma frequently have a relapse. While the use of inhaled corticosteroids has been demonstrated to improve asthma symptoms and lung function, it is not clear whether their use after discharge from the ED reduces asthma relapse rates.

Objective: To determine whether inhaled corticosteroid therapy reduces ED asthma relapse rates.

Methods: We analyzed ED visit and medication data on patients 5 to 60 years of age who were enrolled in a government-sponsored drug plan and who visited an ED because of asthma between April 1, 1997, and March 31, 1999, in Alberta, Canada (N=1293). Using a Cox proportional hazards model, we determined the relative risk (RR) of relapse ED visits among users and nonusers of inhaled corticosteroids after discharge from the ED. We also compared the RR of relapse ED visits across different dose categories.

Results: Users of inhaled corticosteroids after ED discharge had 45% fewer relapse ED visits than did nonusers (adjusted RR, 0.55; 95% confidence interval [CI], 0.44-0.69). Low-, medium-, and high-dose therapies were associated with similar reductions in the risk of relapse ED visits: low-dose therapy (RR, 0.52; 95% CI, 0.39-0.68), medium-dose therapy (RR, 0.51; 95% CI, 0.34-0.76), and high-dose therapy (RR, 0.67; 95% CI, 0.47-0.94).

Conclusions: Inhaled corticosteroid therapy after ED discharge is associated with a significant reduction in the risk of subsequent ED visits. Low-dose therapy appears to be as effective as high-dose therapy. However, further studies are needed to determine the optimal dosing regimen for inhaled corticosteroid therapy for asthma.

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Asthma accounts for nearly 2 million visits to the emergency department (ED) per year, making it the leading cause of ED use among children and young adults in the United States.1 Despite the “best” in-hospital therapy, 30% of these patients will have a relapse within few weeks to months of discharge, leading to recurrent use of EDs for rescue care and necessitating frequent absenteeism from school or work.2 Moreover, once a relapse occurs, the risk of asthma-related morbidity and mortality rises sharply.3

In randomized controlled trials, inhaled corticosteroid therapy has been shown to increase lung function,4 to decrease airway hyperresponsiveness,5 to reduce the need for rescue bronchodilators,6 and to improve asthma symptoms compared with treatment with placebo.7,8 Logically, inhaled corticosteroid therapy should also decrease the risk of subsequent ED visits. However, the use of inhaled corticosteroids after ED discharge remains controversial, as the published studies to date have produced inconsistent and heterogeneous findings.7

The inconsistent findings of published studies may in part be related to small sample sizes and variable follow-up periods among these studies.7 Therefore, more data are needed to determine the utility of these medications among patients with a recent ED visit for asthma.

Information concerning the effect of different doses of inhaled corticosteroids on asthma exacerbation rates would also be useful. Recent studies suggest that these medications, while efficacious, are also fraught with certain adverse effects, including cataract formation,8,9 glaucoma,10 and bone demineralization,11 which occur in a dose-dependent fashion. Avoidance of high-dose therapy, if it is not associated with better asthma control than low-dose therapy, is desirable. A
recently completed meta-analysis suggests that low-dose therapy is as effective as high-dose therapy in reducing asthma exacerbation rates and patient symptoms. However, owing to a number of methodological problems with the primary studies included in this review, the relationship between different dosing schedules of inhaled corticosteroids and clinical outcomes in asthma remains unclear.

We used population-based data to determine whether long-term inhaled corticosteroid therapy after ED dis-
**Table 1. Dose Equivalencies for Various Inhaled Corticosteroids**

<table>
<thead>
<tr>
<th>Inhaled Corticosteroids</th>
<th>Conversion Factor to Beclomethasone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beclomethasone dipropionate</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Budesonide (Turbuhaler*)</td>
<td>1.25</td>
</tr>
<tr>
<td>Budesonide (for wet nebulization)</td>
<td>0.50</td>
</tr>
<tr>
<td>Fluticasone propionate</td>
<td>2.00</td>
</tr>
<tr>
<td>Flunisolide</td>
<td>0.50</td>
</tr>
<tr>
<td>Triamcinolone acetonide</td>
<td>0.50</td>
</tr>
</tbody>
</table>

*A dry-powder inhaler.

charge is associated with a lower risk for subsequent visits to the ED. We also sought to compare ED relapse rates among patients receiving low-, medium-, and high-dose therapies.

### RESULTS

**STUDY POPULATION**

We identified 1293 patients between 5 and 60 years of age who had at least 1 ED visit for their asthma during the study period. Of these patients, 499 (38.6%) were men, and 156 (12.2%) were hospitalized during the index ED visit. Only 20 (1.5%) patients had a Charlson comorbidity score of 1 or more. The mean±SD age of the cohort was 30.8±17.7 years.

**inhaled corticosteroid use**

Overall, 658 patients (50.9%) did not receive any inhaled corticosteroids during the follow-up period; 241 (18.6%) received low-dose therapy; 96 (7.4%) received medium-dose therapy; and 122 (9.4%) received high-dose therapy. We could not calculate an average daily dose for 176 patients (13.6%) because they received only 1 dispensing of inhaled corticosteroids during the follow-up period. The baseline characteristics of those who did and did not receive inhaled corticosteroids after ED discharge are shown in Table 2. Users of inhaled corticosteroids were older and more likely to have received other asthma medications, including oral corticosteroids, theophyllines, and ipratropium, during the first 100 days of follow-up. Since these medications are generally reserved for treating those with moderate to severe disease, it is likely that users of inhaled corticosteroids had greater disease severity than nonusers.

**RISK OF SUBSEQUENT ED VISITS**

During the follow-up period, 462 patients (35.7%) had a subsequent ED visit for asthma. Crudely, inhaled corticosteroids were associated with a 36% (relative risk [RR], 0.64; 95% confidence interval [CI], 0.52-0.79) reduction in the risk for a subsequent ED visit. After adjustment for all factors in our model, users of inhaled corticosteroids after ED discharge had a 45% (RR, 0.55; 95% CI, 0.44-0.69) reduction in the risk for a subsequent ED visit compared with nonusers of inhaled corticosteroids (Figure). Patients who received low-dose therapy had 48% (RR 0.52; 95% CI, 0.39-0.68) fewer subsequent ED emergency visits compared to nonusers. Those receiving medium- and high-dose therapy also had fewer subsequent ED visits (RR for medium dose, 0.51; 95% CI, 0.34-0.76; RR for high-dose 0.67; 95% CI, 0.47-0.94). Those in the indeterminate-dose group did not experience any significant changes in their risk for subsequent ED visits compared with nonusers (RR, 1.01; 95% CI, 0.78-1.32) (Table 3).

To determine the robustness of the relationship between inhaled corticosteroid therapy and risk of a subsequent ED visit, we conducted a series of subgroup analyses. Among those who received at least 1 dispensing of a bronchodilator (ie, β₂-adrenergics, ipratropium, or oral...
demonstrate. Because prior research has focused on less important outcomes such as ED readmission rates that impact of inhaled corticosteroid therapy on clinically significant benefits for patients with asthma.19 In our study, users of inhaled corticosteroids were 45% less likely to experience a subsequent ED visit than nonusers (RR, 0.55; 95% CI, 0.43-0.70). In this subgroup of patients, low- (RR, 0.53; 95% CI, 0.39-0.72), medium- (RR, 0.48; 0.31-0.74), and high- (RR, 0.67; 95% CI, 0.46-0.98) dose therapy were all associated with significant reductions in the risk for subsequent ED visits. A similar pattern was observed when we restricted the analysis to patients who received oral corticosteroid therapy within the first 100 days of the index ED visit. We found that low- (RR, 0.41; 95% CI, 0.26-0.64), medium- (RR, 0.46; 95% CI, 0.25-0.85), and high- (RR, 0.55; 95% CI, 0.34-0.88) dose therapy were all associated with significant reductions in the risk for subsequent ED visits.

Since inhaled corticosteroid therapy before the index ED visit could be a marker of more severe disease, we performed a subgroup analysis in patients who did not receive any inhaled corticosteroids within 200 days before the index ED date. In this “steroid-naive” group (n=975), those who received these medications after ED discharge had 49% fewer subsequent ED visits than the nonusers (RR, 0.51; 95% CI, 0.32-0.76). Low, medium, and high doses were associated with a 51% (RR, 0.49; 95% CI, 0.34-0.71), 44% (RR, 0.56; 95% CI, 0.34-0.92), and 48% (RR, 0.52; 95% CI, 0.31-0.89) reduction in the risk for ED readmissions, respectively, in this subgroup of patients. Similar findings were present in those who had used inhaled corticosteroids before the index ED date (RR, 0.49; 95% CI, 0.39-0.68).

Our findings are consistent with a large body of evidence that inhaled corticosteroid therapy produces clinical benefits for patients with asthma.19 In our study, users of inhaled corticosteroids had 45% fewer subsequent ED visits than nonusers, after adjustment for various factors. However, we did not observe a dose-response relationship. Rates of subsequent ED visits were similar among low-, medium-, and high-dose therapy groups over a 2-year follow-up period.

Our findings provide new insights concerning the impact of inhaled corticosteroid therapy on clinically important outcomes such as ED readmission rates that prior randomized controlled trials have not been able to demonstrate. Because prior research has focused on less sick asthmatic populations, risk of subsequent visits to EDs could not be obtained. First, by targeting a sicker group of patients, we were able to show an impressive benefit of inhaled corticosteroids in reducing relapses to EDs, a finding that is consistent with the known effects of these medications on lung mechanics and health outcomes of asthmatics.19 Second, owing to our large sample size and comprehensive follow-up of patients, we were able to explore a dose-response relationship between the use of inhaled corticosteroids and ED relapse rates. In the absence of clear clinical data, some physicians may believe that “more is better” when it comes to the use of inhaled corticosteroids in asthma. Our data, on the other hand, suggest that even low doses are effective in lowering ED relapse rates among persons with asthma.

Our findings are consistent with those of Hummel and Lehtonen,20 who showed that high-dose therapy offered no significant advantages over low-dose therapy in reducing asthma symptoms, in the use of on-demand rescue medications, or in improvement of lung function. These results have been further supported by a recent meta-analysis that demonstrated only marginal improvements in airway hyperresponsiveness but no appreciable benefits on asthma symptoms or exacerbation rates with high-dose therapy (over low-dose therapy).13

Because our study is observational in nature, relying on information from administrative databases, confounding by indication is of concern. However, users and nonusers of inhaled corticosteroids had similar rates of hospitalization for their asthma (Table 2), suggesting that there were no significant dissimilarities in disease severity between these 2 groups. Moreover, users of inhaled corticosteroids were more likely to be using bronchodilators and oral corticosteroids after discharge from the ED than nonusers. Since these medications are markers of increased asthma severity,21,22 it is highly unlikely that confounding by indication could explain away our findings.

Based on our data, we cannot be certain on what the “optimal” dose of inhaled corticosteroids ought to be. However, they do provide some assurances for the practicing clinicians that in most cases low-dose inhaled corticosteroid therapy could be used for long-term asthma control in patients who have recently been discharged from EDs. Future randomized trials are required to confirm our findings and to determine “best” doses of inhaled corticosteroids for reducing asthma-related morbidity and mortality in this high-risk group of patients.

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Table 3. Relationship Between Subsequent Emergency Department (ED) Visits and Inhaled Corticosteroid Therapy

<table>
<thead>
<tr>
<th>Inhaled Corticosteroids</th>
<th>Total No. of Patients</th>
<th>Subsequent ED Visits, No. (%)</th>
<th>Adjusted RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not dispensed</td>
<td>658</td>
<td>256 (38.9)</td>
<td>1.00 (Reference)</td>
</tr>
<tr>
<td>Indeterminate</td>
<td>176</td>
<td>75 (42.6)</td>
<td>1.01 (0.78-1.32)</td>
</tr>
<tr>
<td>Low dose</td>
<td>241</td>
<td>63 (26.1)</td>
<td>0.52 (0.39-0.68)</td>
</tr>
<tr>
<td>Medium dose</td>
<td>96</td>
<td>27 (28.1)</td>
<td>0.51 (0.34-0.76)</td>
</tr>
<tr>
<td>High dose</td>
<td>122</td>
<td>41 (33.6)</td>
<td>0.67 (0.47-0.94)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, use of antiasthma medications, comorbidities, and hospitalization (see “Patients and Methods” section for details). RR indicates risk ratio; CI, confidence interval.
REFERENCES


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