Replacement of Oral Corticosteroids With Inhaled Corticosteroids in the Treatment of Acute Asthma Following Emergency Department Discharge*

A Meta-analysis

Marcia L. Edmonds, MD, MSc; Carlos A. Camargo, Jr., MD, DrPH, FCCP; Barry E. Brenner, MD, PhD, FCCP; and Brian H. Rowe, MD, MSc

Objectives: Oral corticosteroids (CS) are standard treatment for patients discharged from the emergency department (ED) after treatment for acute asthma. Several recent, relatively small trials have investigated the replacement of CS with inhaled corticosteroids (ICS), with varied results and conclusions. This systematic review examined the effect of using ICS in place of CS on outcomes in this setting.

Methods: Only randomized controlled trials were eligible for inclusion. Studies in which patients were treated for acute asthma in the ED or its equivalent, and on discharge compared ICS therapy to standard CS therapy, were eligible for inclusion. Trials were identified using the Cochrane Airways Review Group register, searching abstracts and bibliographies, and contacting primary authors and pharmaceutical companies. Data were extracted and methodologic quality assessed independently by two reviewers, and missing data were obtained from authors.

Results: Seven trials, involving a total of 1,204 patients, compared high-dose ICS therapy vs CS therapy after ED discharge. There were no significant differences demonstrated between the treatments for relapse rates (odds ratio, 1.00; 95% confidence interval, 0.66 to 1.52) or in the secondary outcomes of β-agonist use, symptoms, or adverse events. However, the sample size was not adequate to prove equivalence between the treatments, and severe asthmatics were excluded from these trials.

Conclusions: There is some evidence that high-dose ICS therapy alone may be as effective as CS therapy when used in mild asthmatics on ED discharge; however, there is a significant possibility of a type II error in drawing this conclusion. (CHEST 2002; 121:1798–1805)

Key words: asthma; corticosteroids; emergency department; inhaled corticosteroids; prevention; relapse

Abbreviations: ARG = Cochrane Airways Review Group; CI = confidence interval; CS = oral corticosteroids; ED = emergency department; ICS = inhaled corticosteroids; PEFR = peak expiratory flow rate; PFT = pulmonary function test; WMD = weighted mean difference

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Acute asthma is a common presenting complaint to the emergency department (ED). In the United States, acute asthma accounts for nearly 2 million ED visits per year. Approximately 15 to 25% of these patients will require admission to the hospital; of those discharged from the ED after apparently successful treatment, approximately 10 to 20% will relapse within the subsequent 2 weeks. The enormity of the asthma problem overall has led to the creation of several national and international asthma guidelines.

Current practice for patients discharged after treatment in the ED usually involves the use of short-acting β-agonists and oral corticosteroids (CS) prescribed for 5 to 10 days after discharge in a majority of cases. The use of inhaled corticosteroids (ICS) in addition to or as replacement for CS in acute asthma after hospital discharge remain areas of considerable practice variation. ICS have been shown to be effective alternatives to CS in long-term asthma therapy, where they can reduce or even eliminate CS requirements. In the ED setting, addition of ICS to CS after ED discharge has been shown to reduce asthma relapses in one study, however, the pooled analysis of all trials demonstrates only a nonstatistically significant trend in favor of ICS.

There are several potential advantages of ICS compared to CS in acute asthma therapy. The direct delivery of high doses of medication to the airways may be one advantage of inhalational delivery of these drugs. As well, greater efficacy in reducing airway reactivity and edema either by direct local effects on the airways, or by systemic effects unique to certain ICS agents, may make ICS a viable alternative to CS therapy. Although short-term use of CS is generally very safe, there are concerns about possible long-term effects in asthmatics requiring frequent courses of CS, as well as rare complications, and nuisance side effects. As well, ease of use and patient acceptance are important considerations.

The possibility of replacing CS with ICS in acute asthma therapy after ED discharge has led to several recent, relatively small studies comparing the two therapies, with varied results and conclusions. This research was designed to produce summary evidence using systematic approaches and meta-analytic techniques in an attempt to generate stronger conclusions and recommendations. Using methodology defined a priori, studies comparing ICS vs CS in the treatment of acute asthma after ED discharge were eligible for inclusion in this review, when outcomes included asthma relapse (the primary outcome), symptoms, β-agonist use, or pulmonary function tests.

### Materials and Methods

A priori, a protocol was developed, including a search strategy for identifying trials, explicit criteria for how trials would be selected for inclusion into the review, and how the data would be analyzed.

#### Literature Search and Identification of Trials

Five strategies were employed in a comprehensive search for potential studies. The Cochrane Airways Review Group (ARG) has developed an “Asthma and Wheez* RCT” register through a standardized, comprehensive search of EMBASE, MEDLINE, and CINAHL. In addition, hand searching of 20 respiratory care journals with the highest yield for respiratory publications has been completed, and trials have been added to the register. Finally, the register is updated with searches of CENTRAL, the Cochrane Collaboration’s clinical trials register. The ARG register contains studies published in a variety of foreign languages, and we did not exclude trials on the basis of language. The current systematic review includes ARG register updates to October 2001.

Search of this register was completed using the following terms: Emerg* OR acute OR status AND dexe* OR dexe* OR fluticasone OR Flovent OR beclomethasone OR Becloforte OR budesonide OR Pulmicort OR flunisolide OR Aerobid OR Bronalide OR triamcinolone OR Beclovent OR Azmacort OR Vanceril OR Becotide OR Flixotide OR Aerobec.

Additional efforts to locate potential trials included searching reference lists of all primary studies and review articles, contacting authors of the primary studies and other asthma researchers regarding the existence of other published or unpublished research in the area, and contacting the scientific advisors of the pharmaceutical companies known to manufacture ICS. Hand searching of abstracts from the last three years of the Society for Academic Emergency Medicine (published in Academic Emergency Medicine), the last 5 years of the American College of Chest Physicians (published in CHEST) and the British Thoracic Society (published in Thorax) was completed. Abstracts from the 1997–1999 abstracts-on-disk from the American Thoracic Society (published in the American Journal of Respiratory and Critical Care Medicine) meetings also were searched.

#### Study Selection

Criteria for considering trials included: (1) randomized controlled clinical trials conducted after discharge from an ED setting or equivalent (such as an unscheduled outpatient clinic visit for acute asthma); (2) unprovoked asthma exacerbations in children or adults (ie, not simulated asthma attacks such as those induced by allergen or histamine challenges in a laboratory setting); and (3) ICS therapy compared with CS therapy after discharge from the ED. The primary outcome considered was acute asthma relapse; other outcomes included PFTs, symptoms, β-agonist use, and side effects.

Each citation (title and abstract) identified through the search strategies was reviewed by two reviewers for potential relevance. The complete article of citations identified as being relevant were retrieved and reviewed by the same two reviewers for final inclusion. Disagreement between reviewers was resolved by
consensus. Where possible, the authors of the primary trials were contacted to verify study methodology and data abstracted from the trials.

**Methodologic Quality**

Trials were then assessed for methodologic quality independently by two reviewers using two methods. First, concealment of allocation was graded on a scale from A (adequate) to C (clearly inadequate). Second, the methodologic quality of studies was also assessed using the criteria of Jadad et al. This scale evaluates the quality of randomization and blinding, and reasons for withdrawal, on a score of 0 (worst) to 5 (best). Interobserver reliability was measured for both quality scales by using the κ statistic.

**Data Abstraction**

All primary investigators of the trials were contacted and provided confirmation of data extracted from the trials, and some were able to provide additional information for the review.

**Statistical Considerations**

This meta-analysis was performed using Review Manager (version 4.0.4; Update Software; Oxford, UK). For continuous variables, a weighted mean difference (WMD) and 95% confidence interval (CI) was calculated for each study, and a pooled WMD and 95% CI was calculated for similar studies, with weights based on the inverse of the variance. Heterogeneity among pooled estimates was tested using the DerSimonian and Laird method. The use of the WMD is common in many systematic reviews and is the difference between the experimental and control group outcomes, when similar units of measure are used. For dichotomous variables, an odds ratio with 95% CI was calculated for individual studies. Odds ratios for similar studies were pooled using the DerSimonian and Laird method, and this method was also used to estimate the absolute risk reduction and the number needed to treat. For pooled effects, heterogeneity was tested using the Breslow-Day test; p < 0.1 was considered statistically significant.

**RESULTS**

**Search**

Three hundred fifty-two articles were identified in the computer search, of which 187 were original citations. From these, a total of 12 articles were identified as being potentially relevant, with moderate agreement (κ = 0.57) between the two reviewers. An additional 20 studies were identified from hand searching, review of the reference lists, contact with authors, update searches, and contact with the pharmaceutical industry. Thirty-two full articles were reviewed for inclusion. Full texts were obtained for published articles; further information was sought about unpublished studies from the authors. From these 32 studies, 7 studies were identified by both reviewers for inclusion, with complete agreement (κ = 1.0). This search is considered updated to October 2001.

**Description of Studies**

Seven studies compared ICS alone to CS alone; two studies were unpublished at the time of this writing (Tables 1, 2). All seven studies compared high-dose ICS (≥ 2 mg/d of beclomethasone dipropionate or equivalent) vs oral prednisolone or prednisone, and “ICS” will be used to refer to “high-dose ICS” throughout the article.

Cointerventions included various inhaled β-agonists in all studies. The studies allowed concurrent medications, including theophylline, ipatropium bromide, and long-acting β-agonists to be continued, although they were infrequently used in all but one study where approximately 57% of the patients were receiving oral β-agonists and 55% were receiving xanthines.

Only one of the four pediatric studies reported asthma relapse rates as an outcome, while it was reported in all three adult studies. One of the three adult studies used change in FEV₁ as the primary outcome, and one of the adult studies used asthma relapse rates as the primary outcome. The third adult study used “treatment failure” as the primary outcome. Patients were categorized as a treatment failure if: (1) peak expiratory flow rate (PEFR) fell to

<table>
<thead>
<tr>
<th>Source</th>
<th>Location, Year</th>
<th>Total Sample</th>
<th>Age Group, Range</th>
<th>PEFR (Mean)</th>
<th>PEFR (% Predicted)</th>
<th>Prior ICS Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fitzgerald et al</td>
<td>Canada, 2000</td>
<td>175 Adults</td>
<td>Adults</td>
<td>407</td>
<td>NR</td>
<td>Low dose only (35%)</td>
</tr>
<tr>
<td>Francis et al</td>
<td>UK, 1999</td>
<td>56 Children, 6 mo–4 yr</td>
<td>NR</td>
<td>NR</td>
<td>75</td>
<td>No</td>
</tr>
<tr>
<td>Levy et al</td>
<td>UK, 1996</td>
<td>513 Adults</td>
<td>Adults</td>
<td>175</td>
<td>NR</td>
<td>78% already receiving ICS</td>
</tr>
<tr>
<td>Manjra et al</td>
<td>UK/South Africa/Singapore, 2000</td>
<td>321 Children, 4–16 yr</td>
<td>194</td>
<td>NR</td>
<td>FEV₁ 64%</td>
<td>35% previously receiving ICS</td>
</tr>
<tr>
<td>Nana et al</td>
<td>Thailand, 1999</td>
<td>84 Adults</td>
<td></td>
<td>NR</td>
<td>FEV₁ 64%</td>
<td>&lt; 1% previously receiving ICS</td>
</tr>
<tr>
<td>Verona et al</td>
<td>UK, 1999</td>
<td>143 Children, 3–15 yr</td>
<td>194</td>
<td>NR</td>
<td>79</td>
<td>No</td>
</tr>
<tr>
<td>Volovitz et al</td>
<td>Israel, 1998</td>
<td>22 Children, 6–16 yr</td>
<td></td>
<td>248</td>
<td>79</td>
<td></td>
</tr>
</tbody>
</table>

*NR = not reported, PEFR = peak expiratory flow rate.
< 60% of the best/predicted value on two consecutive occasions, (2) a symptom score of 3 (indicating the symptoms were the same or worse than on entry to the study) was recorded on ≥ 3 consecutive days, or (3) the patient withdrew because of uncontrolled symptoms or an adverse event related to asthma. This outcome was pooled with the data for asthma relapse from other studies in the analyses.

Length of treatment and follow-up in five studies was 7 days, although two of these studies also recorded 21-day pulmonary function outcomes. Two other studies followed up patients for 16 days and 24 days.

**Quality Scoring**

Overall, the methodologic quality of the seven trials was high. Using the method of Jadad et al, all seven studies were rated as “strong,” with five studies receiving a score of 5, and two studies receiving a score of 4. Using the Cochrane methodology, all seven studies were rated as having blinded allocation (after confirmation with the authors in several cases). Compliance was measured in five of the seven studies, but information on compliance was only available in two studies, where the compliance with both regimens was reported to be > 90%.

**Outcomes**

**Relapse Rates:** Only four of seven studies reported asthma relapse rates, and one of these studies had no patients who relapsed. At 7 to 10 days, there was no demonstrated difference in asthma relapse between the groups (odds ratio, 1.0; 95% CI, 0.66 to 1.52; Fig 1). There was no significant heterogeneity between the studies (p = 0.88). Only two studies followed up patients beyond 10 days, one of which had no relapses; at a 16-day follow-up, there was no significant difference in relapse rates between the groups (odds ratio, 1.26; 95% CI, 0.80 to 1.99). Overall, relapse rates were relatively low (pooled relapse rate, 106 of 684 patients [15%]).

**Admission Rates:** Hospital admissions were defined as relapses resulting in subsequent need for hospitalization, and these would be considered a measure of the severity of the relapse. Only two studies reported hospital admission, and there were no hospital admissions in either of these studies, in either of the treatment groups.

**PFTs:** Six studies reported absolute PEFR at 7 to 10 days, and four studies at 16 to 21 days, while only two studies reported percent-predicted PEFR at both times. At 7 to 10 days, the difference in absolute PEFR between the two groups was not statistically significant, with the PEFR in the ICS-treated group 10 L/min (95% CI, 6 to 26 L/min) higher than in the CS-treated group. At 20 to 24 days, there was a statistically significant but clinically nonsignificant improvement in PEFR in the ICS-treated group of 15 L/min (95% CI, 2 to 29 L/min). There was no

### Table 2—Study Design*

<table>
<thead>
<tr>
<th>Source</th>
<th>Type of ICS</th>
<th>ICS Regimen</th>
<th>Control Regimen</th>
<th>Reported Outcomes</th>
<th>Overall Conclusion</th>
<th>Jadad Quality Score</th>
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<tr>
<td>Fitzgerald et al</td>
<td>Budesonide by dry-powder inhaler</td>
<td>600 µg qid for 7–10 d</td>
<td>Prednisone, 40 mg/d for 7 d</td>
<td>Relapse, PFTs, AQLQ, symptoms, side effects</td>
<td>Equivalent</td>
<td>5</td>
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<td>Fluticasone by nebulizer</td>
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<td>Prednisolone, 2 mg/kg for 4 d then 1 mg/kg for 3 d</td>
<td>Symptoms, clinical index, β-agonist use</td>
<td>Equivalent</td>
<td>4</td>
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<tr>
<td>Levy et al</td>
<td>Fluticasone by MDI with spacer</td>
<td>1 mg bid for 16 d</td>
<td>Prednisolone, 40 mg/d tapering over 16 d</td>
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<td>Budesonide by dry-powder inhaler</td>
<td>1,600 µg qid tapering over 24 d</td>
<td>Prednisolone, 2 mg/kg/d tapering over 8 d</td>
<td>PEFR, symptoms, side effects, relapse, β-agonist use</td>
<td>ICS at least as effective as CS</td>
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*MDI = metered-dose inhaler; AQLQ = asthma quality-of-life questionnaire.

**< 60% of the best/predicted value on two consecutive occasions, (2) a symptom score of 3 (indicating the symptoms were the same or worse than on entry to the study) was recorded on ≥ 3 consecutive days, or (3) the patient withdrew because of uncontrolled symptoms or an adverse event related to asthma.**

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statistically significant heterogeneity (7 to 10 days, p = 0.19; 20 to 24 days, p = 0.41). There was no significant difference between the groups for percent-predicted PEFR at either time interval, with the point estimates for the difference being very small (< 1% predicted).

**β-Agonist Use:** This information was only available in two studies, at 7 to 10 days only. There was no significant difference between the treatment groups in β-agonist use (WMD, 0.1 more puffs per day in the ICS-treated group; 95% CI, −0.4 to 0.7 puffs per day).

**Quality of Life:** Only two studies reported quality-of-life information. There was no significant difference between the groups in quality of life (WMD, −0.1; 95% CI, −0.7 to 0.5).

**Asthma Symptoms and Side Effects:** Due to insufficient and varied reporting, there was insufficient information to determine the effect of treatment on asthma symptoms and adverse effects of treatment. However, the rate of side effects was low and balanced in each study.

**Discussion**

This systematic review examined the best available evidence for the use of ICS in place of CS in the management of asthmatics on discharge from the ED or other acute care settings. Despite an exhaustive search and the existence of recommendations supporting the use of ICS in outpatient treatment of acute asthma, only seven trials were identified, many of which were small, and there were marked variations in the study protocols. Clearly this is an area where further research is required before clarity will emerge.

The results of this review are based on seven studies: five published studies and two unpublished studies. A total of 1,204 patients have been enrolled in these studies; 612 patients were treated with ICS, and 592 patients were treated with CS. Unfortunately, despite the relatively large number of patients included in these studies, the studies reported different outcomes. Consequently, smaller numbers of patients contribute to each of the individual outcomes.

There was no statistically significant difference between the treatments for asthma relapse, at either 7 to 10 days or 16 to 21 days. The important question to be answered is whether or not there is sufficient information to conclude these two treatments are equivalent. At 7 to 10 days, the odds ratio for relapse was 1.0 (95% CI, 0.66 to 1.52). This range in the 95% CI includes the possibility that the use of ICS in place of CS may prevent one asthma relapse for every 20 patients treated, or that it may cause one additional relapse for every 19 patients treated. Only one study contributed data to the 16-day outcome, with an odds ratio for relapse of 1.26 (95% CI, 0.80 to 1.99). This corresponds to one extra relapse for every 24 patients treated with ICS instead of CS (95% CIs: one extra relapse per 8 people treated, to one less relapse for every 26 patients treated). Based on these wide CIs for the primary analysis, equivalence cannot be claimed.

These studies also included only patients with relatively mild asthma, as evidenced by the inclusion criteria and relapse rates (15% overall). For example, one of the studies defined relapse as the failure of symptoms or peak flow to improve, a definition at variance with other studies included in this review. This definition would likely include less “severe” relapses, and it is not clear if this is an appropriate surrogate outcome for relapses resulting in an additional acute care visit. This was the largest study contributing to this outcome (403 of 684 total patients), and were its data not included, the range of uncertainty for the overall treatment effect would be much larger (and the overall relapse rate would fall to 10%).

Despite the clinical importance of relapse outcomes to physicians and quality-of-life outcomes to patients, it was surprising that several studies used absolute PEFR as their primary outcome. Furthermore, even in trials comparing CS to placebo after discharge, poor psychometric properties of PFTs as an outcome provide contradictory results. Consequently, smaller numbers of patients contribute to each of the individual outcomes.
quent, many investigators suggest that this outcome is a poor one to select for these types of studies.20–26

There was a small, statistically significant improvement in PEFR in the group treated with ICS at 20 to 24 days, with an improvement of 15 L/min compared with the CS-treated group. The minimum difference in PFTs that is considered clinically significant has been infrequently studied in this setting. In the adult population, a minimum improvement of approximately 30 L/min in PEFR,29 or a 10 to 12% predicted rise in PEFR,26 is likely necessary to demonstrate a clinically important difference. The small improvement in peak flow demonstrated here would be unlikely to be important to patients, particularly in the absence of any other demonstrated benefits of ICS therapy. As well, there was no difference between the groups in percent-predicted PEFR at the same time interval, suggesting that the absolute PEFR difference was more likely due to imbalances between the groups in age, gender, and/or height.

Other outcomes, including quality of life, asthma symptoms scores, and side effects, were infrequently recorded and reported in diverse ways, with little information that was amenable to pooling. Many of the trials17–19,21 used new scales with questionable validity for measuring these outcomes. In addition, the information for several of the trials was reported incompletely, precluding the incorporation of these results in the meta-analyses.

In the conclusions for six of the seven trials, it was stated that ICS therapy may be substituted for CS therapy after an acute asthma attack, as there were no significant differences demonstrated between the treatments. Five of these trials (two of which were published in abstract form only) did not present a power calculation or mention the possibility of type II error in drawing these conclusions. Four of the trials based their conclusions on a lack of significant differences in PFTs between the treatment groups. Two trials found small (< 30 L/min) differences in absolute PEFR at some time intervals in favor of ICS therapy, but no apparent corresponding improvement in other PFTs measured including FEV₁ and forced expiratory flow between 25% and 75% of FVC. However, PFTs may not be an appropriate outcome to use in assessing clinical equivalence, as they have not been shown to be responsive to treatment with inhaled steroids.20–22 Despite improvements in other clinical markers. The sixth trial presented a post hoc sample size calculation that demonstrated that very large differences (200% relative difference in hospital admission rates) would have been necessary to demonstrate a statistically significant difference between the treatments.23 One trial concluded they were unable to show important differences between the treatments, and did present an a priori sample size calculation. However, the investigators were unable to accrue the required number of patients in the trial and had a calculated power of only 57% to demonstrate a clinically significant difference in relapse rates.18

It is not surprising that these studies, and a meta-analysis of them, failed to generate conclusive results, as the trials were relatively small, and the reported outcomes diverse. As the trials were relatively small, and the reported outcomes diverse. For asthma relapse, if baseline asthma relapse rates were 10%, to show a 50% reduction in the risk of relapse (5% absolute risk reduction), 621 patients would be required in each arm of a trial to demonstrate this difference with a power of 80% and α level of 5%. If the goal were to demonstrate a 25% relative risk reduction (2.5% absolute risk reduction), 2,764 patients would be needed in each group (for a total sample size of 5,528 patients). Clearly, more research using larger numbers of patients is required to reach these numbers of included patients.

While these studies provide some evidence that ICS therapy alone may be effective in patients with mild asthma exacerbations after ED discharge, there is insufficient evidence at this point to support the use of ICS, rather than CS, as the standard of care. Moreover, the cost differences between the two are also an important consideration (with an approximate cost of $0.10/d for prednisone, vs $1 to $2/d for inhaled steroids). If further trials in this area support a conclusion of equivalence between these therapies, there would need to be evidence of other compelling reasons to use ICS in place of CS therapy, such as side effect profile, symptom control, or compliance, which were not evident in this systematic review. As well, the patients included in these studies had relatively mild asthma exacerbations, with low relapse rates and better PFTs than might be anticipated for the “average” ED asthma patient. This may be a result of including studies of patients from outpatient clinics, or due to the inclusion criteria of several studies limiting the participants to those with less severe exacerbations. This may limit the applicability of these results to typical ED patients who often have more severe asthma exacerbations. As the most severe asthmatics were excluded from all of these studies, these results cannot be extrapolated to this population.

As with any systematic review, several possible limitations must be reviewed. There is a possibility of publication bias in this meta-analysis. By missing unpublished negative trials, we may be missing trials that would add more support to the conclusion that ICS are as efficacious as CS in mild asthmatics. However, a comprehensive search of the published

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literature was conducted, and attempts to include non-English language studies was made. Finally, efforts to identify unpublished trials were made by corresponding with authors and the pharmaceutical companies that manufacture ICS. Three of the seven trials included in this review were unpublished; however, we recognize that more unpublished trials may exist. The decision to include unpublished research is common to many systematic reviews and is an attempt to decrease the effect of publication bias on the results of the review. The merits of including unpublished research have been previously studied.33,34

There is also a possibility of selection bias. However, two independent reviewers selected studies for inclusion, and criteria for study inclusion and exclusion were explicitly specified. Finally, as this is a rapidly evolving area, it will be important to reevaluate this topic area in future.

Many questions remain unanswered regarding the use of ICS in the treatment of acute asthma after ED discharge. There is some evidence that ICS therapy may substitute for CS in mild asthma exacerbations on ED discharge; there is no evidence for this practice in moderate or severe asthma exacerbations. Further research in this area should focus on clearly defined, clinically important outcomes, with clear, a priori definitions of equivalence, and adequate sample sizes to address these questions.

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