Rapid Effects of Inhaled Corticosteroids in Acute Asthma: An Evidence-Based Evaluation

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Rapid Effects of Inhaled Corticosteroids in Acute Asthma*
An Evidence-Based Evaluation

Gustavo J. Rodrigo, MD

Background: Current reviews on the use of inhaled corticosteroids (ICS) for acute asthma underestimated their early (minutes) clinical impact and produced conclusions of questionable validity.

Objective: The analysis of the best evidence available on the early (1 to 4 h) clinical impact of ICS for patients with acute asthma in the emergency department (ED) setting.

Methods: Published (from 1966 to 2006) randomized controlled trials were retrieved using different databases (MEDLINE, EMBASE, Cochrane Controlled Trials Register), bibliographic reviews of primary research, review articles, and citations from texts. Primary outcome measures were admission and ED discharge rates.

Results: Seventeen studies met criteria for inclusion in the review (470 adults and 663 children and adolescents). After 2 to 4 h of protocol, a greater reduction in admission rate was observed with trials that used multiple doses of ICS (odds ratio [OR], 0.30; 95% confidence interval [CI], 0.16 to 0.55), especially when they were compared with placebo. Patients treated with ICS also displayed a faster clinical improvement compared with placebo or systemic corticosteroids (SCS), increasing the probability of an early ED discharge (OR, 4.70; 95% CI, 2.97 to 7.42; p = 0.0001). The advantage of the use of ICS was also demonstrated in spirometric and clinical measures as early as 60 min. These benefits were obtained only when patients received multiple doses of ICS along with β-agonists compared with placebo or SCS.

Conclusions: Data suggests that ICS present early beneficial effects (1 to 2 h) when they were used in multiple doses administered in time intervals < 30 min over 90 to 120 min. The nongenomic effect is a possible candidate by covering the link between molecular pathways and the clinical effects of corticosteroids.

Key words: acute asthma treatment; beclomethasone; budesonide; flunisolide; fluticasone; inhaled corticosteroids; nongenomic effects

Abbreviations: CI = confidence interval; CS = corticosteroids; ED = emergency department; ICS = inhaled corticosteroids; MDI = metered-dose inhaler; OR = odds ratio; PEF = peak expiratory flow; SCS = systemic corticosteroids; WMD = weighted mean difference

All patients with asthma are at risk for exacerbations characterized by a progressive increase in shortness of breath, cough, wheezing, or chest tightness, and by a decrease in expiratory airflow that can be quantified by simple measures of pulmonary function.1 Progressive airway narrowing due to airway inflammation, edema, and increased bronchiolar smooth-muscle tone is the hallmark of an asthma attack. Acute asthma is a medical emergency that must be diagnosed and treated urgently. The severity of asthma exacerbations determines the treatment administered. The goals may be summarized as maintenance of adequate arterial oxygen saturation with supplemental oxygen, relieve airflow obstruction with repetitive administration of rapid-acting inhaled bronchodilators (β-agonists and anticholinergics) and reduce airway inflammation, and to

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prevent future relapses with early administration of systemic corticosteroids (SCS).2

SCS should be considered in the management of all but the mildest exacerbations of asthma.1,2 These agents are extremely effective in reducing airway inflammation present in virtually all asthmatics. Despite controversy about their efficacy, route of delivery, and dosage, data summarized in two systematic reviews3,4 suggest the following: (1) SCS require 4 to 24 h to improve pulmonary function and reduce hospitalizations; (2) IV and oral corticosteroids (CS) appear to have equivalent effects in most patients with acute asthma; (3) while precise dose-response relationships are not well described, there is a tendency toward greater and more rapid improvement in pulmonary function with medium (parenteral hydrocortisone, 100 mg q6h) and high doses (200 mg q6h), although these effects likely plateau without additional benefit at very high dosing.5 The time delay observed between administration and improvement in lung function or hospital admissions is consistent with belief that the beneficial effect of CS result from changes in gene transcription and altered protein synthesis6 (genomic effect). Opposed, inhaled corticosteroids (ICS) have been considered ineffective in treatment of acute exacerbations of asthma. Nevertheless, many studies published in the last 15 years have showed therapeutic early effects (after minutes of its administration) suggesting a different mechanism of action of topical character (nongenomic effect).7 However, state-of-the-art and systematic reviews8–10 have analyzed the evidence without distinguish both effects. Thus, they were considered neither the temporary course of these effects nor their relation with the dose administered. For example, in a systematic review,8 the authors pooled the admission rates of different trials with protocol durations ranging from 2 to 12 h. As a result, these reviews have underestimated the immediate clinical impact of ICS and have produced conclusions of questionable validity.

Genomic Effects of CS

The mechanisms of action of CS on the inflammatory process are complex. The classic antiinflammatory effects implicate the activation or repression of multiple genes involved in the inflammatory process. Thus, CS produce their effects on cells by activating glucocorticoid receptors that alter transcription through direct DNA binding or transcription factor inactivation.11,12 As a consequence, CS increase the synthesis of antiinflammatory proteins, or inhibit the synthesis of many inflammatory proteins through suppression of the genes that encode them. This effect is also denominated genomic because it implies the participation of cellular genome. The length of time between CS entry into the cell and the production of new proteins is in order of hours or still days. This fact is in concordance with clinical evidence that shows a 4 to 12 h delay to be able to detect beneficial effects of SCS.3,4

Rapid Nongenomic Effects of CS

Although the major part of the investigation has been performed in the last decade, already in 1942 Hans Selye13 observed that some CS-induced effects (anesthesia) only minutes after their application, constituting the first notification of a nongenomic effect of CS. Two decades later, acute cardiovascular effects of aldosterone (after 5 min of its administration) were reported in humans.14 Lately, CS have also been shown to acutely decrease nasal itching in allergic rhinitis patients.15 These rapid effects are initiated by specific interactions with membrane-bound or cytoplasmic CS receptors, or nonspecific interactions with the cell membrane,16,17 and the responses are much more rapid (seconds or minutes). Membrane receptor inactivation has been shown to induce rapid effects on a variety of second messenger systems.7 In addition, CS could bind other receptors, ion channels, enzymes, or transporters.

More recently, research16–20 has been focused in the nongenomic effects of ICS on airway smooth-muscle tone, and particularly in the study of the mucosal blood flow of asthmatic and healthy people. Thus, membrane binding sites for CS have been demonstrated in smooth-muscle cells isolated from human airway blood vessels.21 Studies16–20 also show that asthmatics present a significant increase in airway mucosal blood flow in comparison with healthy subjects (24 to 77% higher in asthmatics), and that inhalation of fluticasone (880 µg) or budesonide (400 µg) decreases blood flow in both groups. This effect is transient, reaching a maximum approximately 30 min after inhalation, and returning to basal values at 60 to 90 min (Fig 1). This blood flow decrease is dose dependent, with a greater effect in asthmatics than in healthy subjects. Finally, it was not specific for fluticasone or budesonide, and also it was demonstrated for beclomethasone. However, fluticasone and budesonide cause greater effect than beclomethasone.18 Evidence suggests that CS decrease airway blood flow by modulating sympathetic control of vascular tone, potentiating noradrenergic neurotransmission in the airway vasculature.19,20 After release from sympathetic terminals, norepinephrine must be taken up by postsynaptic cells from
inactivation by intracellular enzymes (Fig 2). Because uptake of noradrenaline is inhibited by CS, this could lead to an increased norepinephrine concentration at the neuromuscular junction explaining the CS-induced vasoconstriction. Furthermore, this decrease of airway blood flow is likely to enhance the action of inhaled bronchodilators by diminishing their clearance from the airway.\textsuperscript{23} Thus, simultaneous administration of ICS and bronchodilators could be of clinical significance.

In summary, CS can show two different effects on acute asthma patients (Table 1): (1) the classic antiinflammatory or genomic action, involving the modification of gene expression, that occurs with a time lag of hours or days; and (2) the nongenomic action, with a rapid onset (minutes), is reversible (short duration), and is dose dependent. Finally, a direct relationship was observed between the ICS-induced airway blood flow decrease and predrug airway blood flow.\textsuperscript{16} These vascular effects of ICS on airway blood can be expected to have therapeutic implications in the management of acute asthma, and its characteristics are fundamental to establish the optimum dose and timing of administration in the emergency department (ED) setting. Accordingly, ICS would have to be administered simultaneously with bronchodilators in high and repeated or sequential doses as a way to obtain and maintain the effect throughout the time. Since ICS induce vasoconstriction peaks between 30 and 60 min after drug...
administration, their use in intervals not > 30 min seems adequate. The objective of this review was the analysis of the best evidence available on the early clinical impact of ICS for acute asthma patients.

**Materials and Methods**

The main component of an evidence-based review that distinguishes it from the traditional narrative or state-of-the-art reviews is an extensive, structured, and explicit search strategy targeted at identification of all relevant studies. Initially, we need to develop a well-defined, clinically relevant, and concise question. In view of previous considerations, we formulated the question as follows: In children and adults with acute asthma, does the addition of ICS to a standard treatment of β2-agonists decrease the likelihood of hospital admissions or discharge rates during the first 4 h of ED treatment? Additionally, what are the optimum dose and timing of administration?

The search was conducted using five strategies to identify potentially relevant trials without language restriction: (1) MEDLINE (1966 to February 2006), and EMBASE (1974 to February 2006) databases were searched using the following MeSH, full text, and key word terms: [emergency OR acute asthma OR status asthmaticus OR severe asthma OR wheeze] AND [inhaled corticosteroids OR beclomethasone OR dexamethasone OR flunisolide OR fluticasone OR budesonide OR triamcinolone]; (2) an advanced search of the Cochrane Controlled Trials Register (first quarter 2006) was completed using the above search strategy to identify any additional trials; (3) references from included studies, reviews, and texts were searched for citations; (4) hand searching of the top 20 respiratory and emergency care journals was completed; and (5) unpublished data were requested from the primary authors when necessary. Trials published solely in abstract form were excluded.

Included studies met the following criteria: (1) target population: children (6 months to 17 years old) and adults (≥18 years old) with acute exacerbations of asthma; all study participants had a clinical diagnosis of acute asthma exacerbation according to an accepted criterion; (2) design: randomized controlled trials conducted in an ED or equivalent care setting; studies involving only admitted patients were excluded; (3) intervention: ICS compared to placebo or SCS; and (4) primary outcomes: admission and ED discharge rates. Secondary outcomes were spirometric measures (peak expiratory flow [PEF] or FEV₁), clinical symptoms, heart and respiratory rates, oxygen saturation, and side effects, all measured from 1 to 4 h of protocol. Studies with outcomes measured only after 4 h were excluded (long-term studies). In some cases, information was estimated from graphs. The methodologic quality of each trial was evaluated using the 5-point scale (0 = worst to 5 = best) described by Jadad et al.

**Results**

A total of 50 articles were identified in the initial search. Of these, there were 24 articles potentially eligible. Reasons for subsequent exclusion were studies on chronic asthma (n = 1) and long-term studies (n = 6). Finally, 17 studies (6 studies including adults and 11 studies including children) were selected. All eligible reports were described as randomized, double-blind, placebo-controlled trials. Data for 1,133 subjects (470 adults and 663 children) were available for analysis. There were three types of protocols (Table 2): (1) ICS compared with placebo (eight studies including adults and 11 studies including children); (2) ICS plus SCS compared with SCS (three studies); and (3) ICS compared with SCS (six studies). The ICS used were beclomethasone (three studies), dexamethasone (one study), flunisolide (two studies), budesonide (eight studies), and fluticasone (three studies). In agreement with the fact that ICS-induced vasoconstriction peaks approximately 30 min after drug administration, trials were grouped according to the intensity of the ICS treatment. Thus, we defined as “multiple dose” those protocols that administered three or more doses of ICS at ≤ 30-
Table 2—Characteristics of Included Studies*

<table>
<thead>
<tr>
<th>Studies</th>
<th>Population</th>
<th>Protocols</th>
<th>Jadad Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pansegrove et al</td>
<td>40 adults (18-70 yr old); FEV1 &lt; 70%</td>
<td>F 400 μg plus BE 200 μg MDI 1 × 1 vs F 400 μg</td>
<td>3</td>
</tr>
<tr>
<td>Rodrigo and Rodrigo</td>
<td>94 adults (18-50 yr old); FEV1 &lt; 50%</td>
<td>S 400 μg plus FLU 1 mg MDI every 10 min during 3 h vs S 400 μg every 10 min during 3 h</td>
<td>4</td>
</tr>
<tr>
<td>Afilalo et al</td>
<td>54 adults (&gt; 18 yr old); FEV1 40 to 59%</td>
<td>S 2.5 mg nebulizer × 1 plus BE 1 mg MDI (30 min, 1 h, 2h, 4h) vs S 2.5 mg nebulizer × 1</td>
<td>4</td>
</tr>
<tr>
<td>Singhi et al</td>
<td>60 children (3 to 13 yr old); PEF 50 to 70%</td>
<td>S 0.15 mg/kg nebulizer plus BUD 400 μg MDI every 30 min × 3 vs S 0.15 mg/kg nebulizer × 2</td>
<td>3</td>
</tr>
<tr>
<td>Tsai et al</td>
<td>24 children (6 to 17 yr old); PEF 100 L/min</td>
<td>TE 0.1 mg/kg nebulizer q6h × 2 plus BUD 0.05 mg/kg nebulizer × 1 vs TE 0.1 mg/kg nebulizer q6h × 2</td>
<td>3</td>
</tr>
<tr>
<td>Rodrigo and Rodrigo</td>
<td>116 adults (18 to 50 yr old); FEV1 &lt; 50%</td>
<td>S 400 μg plus BI 84 μg MDI every 10 min during 3 h vs FLU 1 mg MDI every 10 min during 3 h vs S 400 μg plus BI 84 μg MDI every 10 min during 3 h</td>
<td>5</td>
</tr>
<tr>
<td>Estrada-Reyes et al</td>
<td>100 children (&gt; 5 yr old); PEF 70%</td>
<td>S 30 μL/kg nebulizer every 15 min × 3 plus FLUT 500 μg nebulizer every 15 min × 3</td>
<td>3</td>
</tr>
<tr>
<td>Sekerel et al</td>
<td>67 children (6 to 15 yr old); FEV1 70 to 90%</td>
<td>S 0.15 mg/kg nebulizer 60 min × 3 plus BUD 1 mg nebulizer 60 min × 3 vs S 0.15 mg/kg nebulizer every 60 min × 3</td>
<td>5</td>
</tr>
<tr>
<td>Sung et al</td>
<td>44 children (6 mo to 18 yr old); CI moderate to severe</td>
<td>PRED 1 mg/kg po × 1 plus S 0.15 mg/kg nebulizer every 30 min × 3 plus BUD 2 mg nebulizer × 1 vs PRED 1 mg/kg po × 1 plus S 0.15 mg/kg nebulizer every 30 min × 3</td>
<td>4</td>
</tr>
<tr>
<td>Guttman et al</td>
<td>60 adults (&gt; 18 yr old); FEV1 &lt; 40%</td>
<td>S 2.5 mg nebulizer 0.5, 1, 2, 4, 6, 8, and 10 h plus MET 80 mg IV q6h × 2 plus BE 1 mg MDI 0.5, 1, 2, 4, 6, 8, and 10 h vs S 2.5 mg nebulizer 0.5, 1, 2, 4, 6, 8, 10 h plus MET 80 mg IV q6h × 2 vs S 2.5 mg nebulizer × 2</td>
<td>3</td>
</tr>
<tr>
<td>Nuhoglu et al</td>
<td>26 children (5 to 15 yr old); CI moderate</td>
<td>S 0.15 mg/kg nebulizer × 3 plus MET 1 mg/kg IM plus BUD 1 mg nebulizer × 1 vs S 0.15 mg/kg nebulizer × 1 vs MET 1 mg/kg IM</td>
<td>4</td>
</tr>
<tr>
<td>Scarfone et al</td>
<td>105 children (1 to 17 yr old); CI moderate</td>
<td>S 0.15 mg/kg nebulizer every 30 min × 3 plus DE 1.5 mg/kg nebulizer every 30 min × 3 vs S 0.15 mg/kg nebulizer every 30 min × 3 plus PRED 2 mg/kg po</td>
<td>4</td>
</tr>
<tr>
<td>Volovitz et al</td>
<td>22 children (6 to 16 yr old); PEF 35 to 75%</td>
<td>TE 5 mg nebulizer × 1 plus BUD 1.6 mg Turbuhaler1 × 1 vs TE 5 mg nebulizer × 1 plus PREDN 2 mg/kg po</td>
<td>3</td>
</tr>
<tr>
<td>Devidayal et al</td>
<td>80 children (2 to 12 yr old); PEF 63%</td>
<td>S 0.15 mg/kg nebulizer every 30 min × 3 plus BUD 800 μg mdn every 30 min × 3 vs S 0.15 mg/kg nebulizer every 30 min × 3 plus PREDN 2 mg/kg po</td>
<td>3</td>
</tr>
<tr>
<td>Schuh et al</td>
<td>101 children (5 to 18 yr old); FEV1 &lt; 60%</td>
<td>S 0.15 mg/kg nebulizer every 20 min × 6 plus FLUT 2 mg MDI 1 × 1 vs S 0.15 mg/kg nebulizer every 20 min × 6 plus FLUT 2 mg/kg po</td>
<td>5</td>
</tr>
<tr>
<td>Milan et al</td>
<td>34 children (2 to 7 yr old); CI moderate to severe</td>
<td>S 0.15 mg/kg nebulizer plus BUD 2 mg nebulizer × 1 vs S 0.15 mg/kg nebulizer plus PRED 1 mg/kg po</td>
<td>3</td>
</tr>
<tr>
<td>Rodrigo et al</td>
<td>106 adults (18 to 50 yr old); FEV1 &lt; 50%</td>
<td>S 400 μg plus BI 84 μg MDI every 10 min during 3 h vs FLUT 500 μg every 10 min during 3 h vs S 400 μg plus BI 84 μg MDI every 10 min during 3 h vs HYD 500 mg IV</td>
<td>5</td>
</tr>
</tbody>
</table>

*All studies were randomized, double blind, and placebo controlled. BE = beclomethasone; BI = budesonide; BI = budesonide; DE = dexamethasone; F = fenoterol; FLU = flumisolide; FLUT = fluticasone; HYD = hydrocortisone; MET = methylprednisolone; PRED = prednisone; PREDN = prednisolone; S = salbutamol; TE = terbutaline.

†AstraZeneca, Lund, Sweden.

min intervals,30,32,36,37,40,42,44 and “single dose” as those that administered two or fewer doses of ICS at ≤ 30-min intervals, or one or more doses at > 30-min intervals.29,31,33–35,38,39,41,43,45

Admission Rate

Seven studies32,33,36–38,40,44 accumulating 601 children, adolescents, and adults reported hospital admissions from 2 to 4 h of the protocol (Fig 3). Trials were stratified by protocol and intensity of ICS treatment. At the end of treatment (2 to 4 h), the overall weighted OR showed a significantly lower admission rate in patients treated with ICS; however, this effect was statistically heterogeneous. However, a greater reduction was observed when all trials32,36,37,40,44 that used multiple doses were pooled.

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(OR, 0.30; 95% CI, 0.16 to 0.55; I² = 0%), especially when ICS were compared with placebo. The number of patients needed to treat was 10 (95% CI, 7 to 21), indicating that 10 patients needed to be treated with ICS to prevent one hospital admission. Also, there was a trend toward a decrease in hospital admissions in the two studies that compared multiple doses of ICS with SCS. On the contrary, only one study showed a superiority of SCS over ICS. When this study was excluded, the other six studies were homogeneous and had a significant pooled OR (0.34; 95% CI, 0.19 to 0.62; I² = 0%). In that case, the superiority of SCS on ICS could be explained on the basis of two factors: (1) a single-dose ICS protocol was used, and (2) the decision to hospitalize patients was made after 4 h of the protocol. So we cannot exclude the beginning of the antiinflammatory or genomic effects.

**Discharge Rate**

Six studies (545 patients) examined the discharge rates after 2 to 3 h of treatment. Pooled analysis showed that at that time, a significantly greater proportion of ICS-treated patients were discharged from the ED compared with either placebo or with SCS (Fig 4). Patients who received multiple doses of ICS had 4.7 times greater odds to be discharged (95% CI, 2.97 to 7.42). This effect was statistically homogeneous, which accepts the null hypothesis of similar treatment effects.

**Spirometry**

Seven trials examined the response to treatment in children and adults with acute asthma using spirometry. Data were documented between 60 and 180 min of treatment. When we pooled the studies that reported PEF (liters per minute) stratified by time, protocol, and intensity of ICS treatment (single vs multiple doses), homogeneity was achieved, and a significant improvement in PEF favoring ICS treatment was found (Table 3). There was a dose-response relationship; the greater benefit was obtained when patients were treated with multiple doses of ICS. Patients treated with ICS showed pooled WMD in PEF of 25, 35, and 46 L/min at 60, 120, and 180 min respectively. Similar results were obtained for FEV₁ (liters) [Table 4]. Pooled WMDs in FEV₁ were 0.12, 0.16, and 0.24 L at 60, 120, and 180 min, respectively. In this case, there was a significant heterogeneity between trials;
however, significant improvements in FEV₁ favoring ICS treatment compared with placebo were found at 120 min and 180 to 240 min (WMD, 0.2 L; 95% CI, 0.0 to 0.3; I² = 0%; and WMD, 0.3 L; 95% CI, 0.1 to 0.5; I² = 0%, respectively).

Other Outcomes

Eight trials reported a significant reduction of clinical scores after ICS treatment compared with placebo and SCS. This reduction was dose related (WMD, −0.40; 95% CI, −0.60 to −0.20; p = 0.0001, I² = 12%; and WMD, −0.51; 95% CI, −0.71 to −0.31; p = 0.0001; I² = 40%, at 60 min and 120 to 180 min, respectively). Finally, all studies reported that there were no serious side effects.

**Discussion**

The purpose of this systematic review was the analysis of the best evidence available on the early clinical impact of ICS for patients with acute asthma. In agreement with previous studies, asthmatic patients present a significant increase in airway mucosal blood flow, and ICS would decrease it by modulating sympathetic control of vascular tone. This nongenomic action might reduce the airway obstruction, improving clinical and spirometric parameters in a short period of time. Nevertheless, in addition with its early onset (minutes), this effect is reversible (short duration), dose dependent, and correlated with baseline airway blood flow. Furthermore, the decrease of airway blood flow is likely to enhance the action of inhaled bronchodilators by diminishing their clearance from the airway and, thus, simultaneous administration of ICS and bronchodilators could have clinical significance. Consequently, the rational use of ICS in the treatment of the asthmatic exacerbations would have to consider these characteristics.

It is certain that there is no direct proof to support the involvement of either nongenomic pathways or airway blood flow responses in the observed clinical or spirometric responses. However, because is not possible to use genomic pathway inhibitors in clinical trials, a short-time frame (minutes) is one of the strongest pieces of evidence in favor of a nongenomic effect. Also, previous published basic trials did not show acute improvements in airway conductance or other lung functional parameters in connection with airway blood flow responses. However, in these trials spirometry was measured 60 min after the inhalation of single doses of ICS, just when airway blood flow was returning toward baseline values. Additionally, asthmatic patients studied showed only mild-to-moderate airway obstruction in the stable state. Consequently, this topical effect is a good candidate by covering the link between molecular pathways and the clinical effects of CS actions, and it is unlikely that early clinical effects (seen as early as 60 min) are due to a genomic mechanism.

The analysis of evidence confirmed that those clinical trials that used repeated doses of ICS in short
time intervals (three or more doses administered in ≤ 30-min intervals over 90 to 120 min) showed early benefits (1 to 2 h) in terms of clinical and spirometric variables. Thus, ICS lead to a reduction in admission rates at 2 to 4 h, as much in children as in adults. The pooled analysis of all trials that used multiple doses showed a significant reduction in admission rate, with only 10 subjects needed to be treated to prevent a hospitalization. This effect was evident particularly when ICS were compared with placebo. This is a very relevant finding since hospital admissions count for the largest part of direct health costs for asthma.

Regarding spirometric testing, significant early differences favoring the use of ICS were observed in trials in both children and adults. There was a dose-response relationship; the greater benefit was obtained when patients were treated with multiple doses of ICS along with β-agonists compared with placebo or SCS. Finally, data showed a significant reduction of different clinical scores after ICS treatment compared with placebo and SCS. Therapy with ICS produced clinically significant improvements in terms of PEF (> 18 L/min), FEV1 (> 0.23 L), and clinical score (≥ 0.31 points).46

### Strengths and Limitations

This study met most of the methodologic criteria suggested for scientific reviews.47 Similar to all systematic reviews, this analysis is limited by the quality and quantity of existing research and how data are reported. A comprehensive search of the published literature for potentially relevant studies was conducted using a systematic strategy to avoid bias. All of the 17 trials were randomized and double blind,

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Protocols</th>
<th>Studies</th>
<th>Totals</th>
<th>WMD (95% CI)</th>
<th>p Value</th>
<th>F², %</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>ICS vs placebo (SD)</td>
<td>Afilalo et al35, Tsai et al50</td>
<td>Subtotal</td>
<td>2.7 (~ 55.8 to 61.2)</td>
<td>0.32</td>
<td>0</td>
</tr>
<tr>
<td></td>
<td>ICS vs placebo (MD)</td>
<td>Rodrigo and Rodrigo32, Rodrigo and Rodrigo40</td>
<td>Subtotal</td>
<td>28.9 (~ 3.0 to 60.8)</td>
<td>48.5 (~ 15.9 to 81.0)</td>
<td>0.32</td>
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<tr>
<td></td>
<td>ICS vs SCS (SD)</td>
<td>Guttman et al31, Nuhoglu et al43</td>
<td>Subtotal</td>
<td>23.5 (~ 95.6 to 48.6)</td>
<td>29.6 (~ 8.8 to 68.0)</td>
<td>0.32</td>
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<tr>
<td>120</td>
<td>ICS vs placebo (SD)</td>
<td>Afilalo et al35</td>
<td>Subtotal</td>
<td>6.3 (~ 66.0 to 53.4)</td>
<td>0.0003</td>
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<td></td>
<td>ICS vs placebo (MD)</td>
<td>Rodrigo and Rodrigo32, Rodrigo and Rodrigo40</td>
<td>Subtotal</td>
<td>49.9 (14.9 to 84.8)</td>
<td>39.5 (6.0 to 73.0)</td>
<td>0.0003</td>
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<td></td>
<td>ICS vs SCS (SD)</td>
<td>Guttman et al31, Nuhoglu et al43</td>
<td>Subtotal</td>
<td>22.9 (~ 94.0 to 42.8)</td>
<td>40.5 (13.1 to 68.4)</td>
<td>0.0003</td>
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<td>180</td>
<td>ICS vs placebo (SD)</td>
<td>Tsai et al50</td>
<td>Subtotal</td>
<td>32.6 (~ 2.6 to 67.8)</td>
<td>51.2 (23.4 to 78.9)</td>
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<td></td>
<td>ICS vs placebo (MD)</td>
<td>Rodrigo and Rodrigo32, Rodrigo and Rodrigo40</td>
<td>Subtotal</td>
<td>44.5 (16.2 to 72.7)</td>
<td>49.9 (28.1 to 67.7)</td>
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<td>ICS vs SCS (SD)</td>
<td>Rodrigo44</td>
<td>Subtotal</td>
<td>52.7 (21.4 to 84.0)</td>
<td>52.7 (21.4 to 84.0)</td>
<td>0.0001</td>
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<td></td>
<td>ICS vs SCS (MD)</td>
<td>Rodrigo44</td>
<td>Subtotal</td>
<td>46.2 (31.1 to 61.3)</td>
<td>46.2 (31.1 to 61.3)</td>
<td>0.0001</td>
</tr>
</tbody>
</table>

*MD = multiple dose (protocols that administered three or more doses of ICS at ≤ 30-min intervals); SD = single dose (those that administered two or fewer doses of ICS at ≤ 30-min intervals, or one or more doses at > 30-min intervals).
and we limited the confusion between genomic and nongenomic effects selecting only trials with outcomes measured at ≤4 h of protocol; thus, our conclusions were based exclusively on early changes. However, the selected studies were quite homogeneous in terms of acute asthma baseline severity (moderate to severe). Finally, in 10 studies ICS were delivered by nebulization; however, this method could be insufficient for patients with acute severe asthma. More rapid and profound bronchodilatation with fewer side effects and less time in the ED can be achieved when adequate doses of β-agonists are administered using metered-dose inhalers (MDIs) and valved spacers than when conventional doses are administered with a jet nebulizer.48,49

**Implications for Practice and Research**

As previously mentioned, the goals of acute asthma treatment may be summarized as maintenance of adequate arterial oxygen saturation with supplemental oxygen, relieve airflow obstruction with repetitive administration of rapid-acting inhaled bronchodilators, and reduce airway inflammation, and to prevent future relapses with early administration of SCS.1,2 This review clearly supports the use of ICS for the treatment of children and adults with asthma exacerbations. Even though SCS remain the treatment of choice for acute asthma, this early and probably nongenomic early effect may be significant in the treatment of most severe cases.50 Thus, on the basis of this evidence, the use of inhaled fluticasone or budesonide through an MDI and spacer or nebulization every 10 to 30 min could be recommended. Although there was an important variation between studies, the evidence suggests that the minimum effective nebulized doses for fluticasone and budesonide would be 500 μg every 15 min, and 800 μg every 30 min, respectively. The use of 400 μg every 30 min of budesonide via an MDI and spacer was also effective, and greater doses (fluticasone 500 μg every 10 min by MDI) generated larger benefits. These doses would have to be administered during a minimum of 90 min, although more prolonged periods of administration could generate a greater benefit. Nevertheless, future studies will have to clarify the relationship between the dose administered, acute asthma severity, and response to treatment.

**References**


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**Table 4—Pooled WMD in FEV1, Stratified by Time, Protocol, and Intensity of ICS Treatment**

<table>
<thead>
<tr>
<th>Time, min</th>
<th>Protocols</th>
<th>Studies</th>
<th>Totals</th>
<th>WMD (95% CI)</th>
<th>p Value</th>
<th>I², %</th>
</tr>
</thead>
<tbody>
<tr>
<td>60</td>
<td>ICS vs placebo (SD)</td>
<td>Pansegrouw38</td>
<td>Afilalo et al35</td>
<td>1.2 (0.7 to 1.6)</td>
<td>0.01</td>
<td>95</td>
</tr>
<tr>
<td></td>
<td>ICS vs placebo (MD)</td>
<td>Rodrigo and Rodrigo32</td>
<td>Rodrigo and Rodrigo40</td>
<td>−0.1 (−0.4 to 0.2)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ICS vs placebo (SD)</td>
<td>Rodrigo and Rodrigo32</td>
<td>Rodrigo and Rodrigo40</td>
<td>0.0 (−0.1 to 0.2)</td>
<td>0.1 (−0.1 to 0.3)</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>ICS vs SCS (SD)</td>
<td>Guttman et al31</td>
<td>Rodrigo44</td>
<td>0.1 (−0.1 to 0.3)</td>
<td>0.0 (−0.3 to 0.3)</td>
<td>0.37</td>
</tr>
<tr>
<td></td>
<td>ICS vs SCS (MD)</td>
<td>Guttman et al31</td>
<td>Rodrigo44</td>
<td>0.1 (−0.1 to 0.3)</td>
<td>0.0 (−0.3 to 0.3)</td>
<td>0.37</td>
</tr>
<tr>
<td>120</td>
<td>ICS vs placebo (SD)</td>
<td>Afilalo et al35</td>
<td>Rodrigo and Rodrigo32</td>
<td>−0.1 (−0.2 to 0.5)</td>
<td>0.2 (0.0 to 10.4)</td>
<td>0.1 (−0.1 to 0.4)</td>
</tr>
<tr>
<td></td>
<td>ICS vs placebo (MD)</td>
<td>Rodrigo and Rodrigo32</td>
<td>Rodrigo and Rodrigo40</td>
<td>0.2 (0.0 to 10.4)</td>
<td>0.1 (−0.1 to 0.4)</td>
<td>0.001</td>
</tr>
<tr>
<td></td>
<td>ICS vs SCS (SD)</td>
<td>Guttman et al31</td>
<td>Rodrigo44</td>
<td>0.1 (−0.1 to 0.3)</td>
<td>0.0 (−0.3 to 0.3)</td>
<td>0.3 (−0.6 to 0.6)</td>
</tr>
<tr>
<td></td>
<td>ICS vs SCS (MD)</td>
<td>Guttman et al31</td>
<td>Rodrigo44</td>
<td>0.1 (−0.1 to 0.3)</td>
<td>0.0 (−0.3 to 0.3)</td>
<td>0.3 (−0.6 to 0.6)</td>
</tr>
<tr>
<td>180–240</td>
<td>ICS vs placebo (SD)</td>
<td>Afilalo et al35</td>
<td>Rodrigo and Rodrigo32</td>
<td>−0.1 (−0.5 to 0.2)</td>
<td>0.4 (0.1 to 0.7)</td>
<td>0.3 (0.1 to 0.5)</td>
</tr>
<tr>
<td></td>
<td>ICS vs placebo (MD)</td>
<td>Rodrigo and Rodrigo32</td>
<td>Rodrigo and Rodrigo40</td>
<td>0.4 (0.1 to 0.7)</td>
<td>0.3 (0.1 to 0.5)</td>
<td>0.0002</td>
</tr>
<tr>
<td></td>
<td>ICS vs SCS (SD)</td>
<td>Guttman et al31</td>
<td>Rodrigo44</td>
<td>0.1 (−0.4 to 0.2)</td>
<td>0.4 (0.1 to 0.7)</td>
<td>0.1 (−0.4 to 0.2)</td>
</tr>
<tr>
<td></td>
<td>ICS vs SCS (MD)</td>
<td>Guttman et al31</td>
<td>Rodrigo44</td>
<td>0.1 (−0.4 to 0.2)</td>
<td>0.4 (0.1 to 0.7)</td>
<td>0.1 (−0.4 to 0.2)</td>
</tr>
</tbody>
</table>

*See Table 3 for expansion of abbreviations.
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