Rapid effects of inhaled corticosteroids in acute asthma: an evidence-based evaluation
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CRD summary
The author concluded that inhaled corticosteroids, in addition to standard treatment, may be beneficial for acute exacerbations of asthma among adults and children. Multiple doses should be administered at least half hourly for 90 to 120 minutes. These conclusions appear to be supported by the data, but poor reporting of the review methods makes it difficult to assess their reliability.

Authors' objectives
To determine the early clinical impact and optimum regimen of inhaled corticosteroids (ICS) for acute asthma in adults and children in the emergency department setting.

Searching
MEDLINE and EMBASE (from inception to 2006) and the Cochrane CENTRAL Register (Issue 1, 2006) were searched; the search terms were provided. The reference lists of retrieved articles and the top 20 respiratory and emergency care journals were handsearched. Unpublished data were requested from primary authors as required, but unpublished studies and studies published only in abstract form were excluded from the review.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion.

Specific interventions included in the review
Studies of ICS compared with placebo or systemic corticosteroids (SCS) were eligible for inclusion. The included studies compared ICS with placebo or SCS, and ICS plus SCS with SCS; all participants also received a beta-agonist drug. The included ICS were beclamethasone, dexamethasone, flunisolide, budesonide and fluticasone, mainly delivered via a metered dose inhaler, either once or repeated at 10- to 60-minute intervals. The included SCS were oral prednisolone, intravenous or intramuscular methylprednisolone and intravenous hydrocortisone. Beta-agonists included fenoterol, salbutamol and terbutaline, in most cases administered by a nebuliser. Patients in 2 studies also received ipatropium bromide. The drug dosages varied and details of them can be found in the review.

Participants included in the review
Eligible studies included adults (age at least 18 years) or children (age 6 months to 17 years) in an emergency department or similar setting, with acute exacerbation of asthma diagnosed by an accepted criterion. Studies solely of inpatients were excluded. The majority of included studies recruited only children; the rest included only adults. Where stated, the participants showed a forced expiratory volume (FEV1) ranging from under 40 to 90% and a peak expiratory flow (PEF) of 50 to 70%, with the clinical impact ranging from moderate to severe.

Outcomes assessed in the review
The primary outcomes were hospital admission rates and emergency department discharge rates. The secondary outcomes were spirometric measures (PEF and FEV1), clinical symptoms (not specified), heart and respiratory rates, oxygen saturation and side-effects. For all outcomes, the timeframe of interest was within 1 to 4 hours of the intervention. Studies with outcomes measured solely later than 4 hours post-intervention were excluded.

How were decisions on the relevance of primary studies made?
The author did not state how the studies were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Study quality was evaluated using the Jadad scale, which measures adequacy of randomisation, blinding, and the management of withdrawals and drop-outs. Each study was awarded a score out of a maximum of 5 points. The author did not state how many reviewers performed the validity assessment, or how any discrepancies were resolved.
Data extraction
Odds ratios (ORs) with 95% confidence intervals (CIs) were calculated for dichotomous outcomes and mean differences for continuous outcomes. Study authors were contacted for unpublished information if necessary, and graphs were used to estimate data when required. The author did not state how the data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
The data were combined using a fixed-effect model. Pooled ORs with 95% CIs were calculated for dichotomous outcomes, and weighted mean differences or standardised mean differences with 95% CIs for continuous outcomes.

How were differences between studies investigated?
Statistical heterogeneity between studies was assessed using the DerSimonian and Laird Q statistic (p<0.05 value for significance) and the I-squared statistic (with 50% and 75% representing moderate and high heterogeneity, respectively). Where heterogeneity was found, it was investigated using subgroup analysis. The studies were grouped by the interventions used and the intensity of the ICS treatment (i.e. multiple or single dose). Multiple dose was defined as at least 3 doses at intervals of 30 minutes or less; single dose was defined as 2 doses or fewer at intervals of 30 minutes or less, or at least one dose at intervals of more than 30 minutes.

Results of the review
Seventeen RCTs were included (n=1,133; 470 adults and 663 children).

Jadad scores for quality ranged from 3 points (7 RCTs) to 5 points (4 RCTs) out of a possible maximum of 5. All of the trials were double-blinded.

A significantly lower rate of hospital admission was reported in patients treated with ICS than those receiving placebo or SCS (OR 0.55, 95% CI: 0.35, 0.88; 7 studies), but there was evidence of significant statistical heterogeneity (p=0.005; I-squared 67.7%). A greater reduction in admission rate, favouring the ICS group, was reported for trials using multiple doses of ICS (OR 0.30, 95% CI: 0.16, 0.55; 5 studies); no statistical heterogeneity was reported. When the analysis was restricted to studies comparing ICS versus SCS, the results were mixed: 2 studies comparing multiple doses of ICS with SCS reported no statistically significant difference between the groups (OR 0.43, 95% CI: 0.14, 1.28), while a third study using a single dose of ICS reported statistically significant results favouring the SCS group (OR 3.91, 95% CI: 1.31, 11.71). The author speculated that the heterogeneity between these studies was due to differences in dosing (single versus multiple) and the timing of the outcome measure.

Significantly more patients treated with ICS were discharged from the emergency department compared with those who received placebo or SCS (OR 4.70, 95% CI: 2.97, 7.42; 6 studies); there was no evidence of statistical heterogeneity.

A statistically significant improvement in PEF was noted in patients treated with ICS compared with those who received placebo (p<=0.0001) or SCS (p<=0.001), with pooled results (7 studies) showing weighted mean differences of 25, 35 and 46 L/minute at 1, 2 and 3 hours, respectively. There was a dose-response relationship, with greater benefit in patients receiving multiple doses of ICS. These results had low to moderate heterogeneity (I-squared: 0 to 38%). Measures of FEV1 produced similar results, with statistically significant benefits in the ICS group versus either placebo or SCS at the 2 and 3 hour time points (p<=0.001). However, the results for outcomes at 1 hour were mixed, with a high level of heterogeneity (I-squared: 82 to 95%).

All studies reported that there were no serious side-effects among the participants.

Further analyses were reported in the review.

Authors' conclusions
The evidence suggests that ICS, in conjunction with standard treatment, may be beneficial for the early treatment of acute exacerbations of asthma among adults and children. Multiple doses should be administered at least half hourly for 90 to 120 minutes.
CRD commentary
The review question was clear, and several relevant sources and strategies were used in the literature search. However, only published trials were included, which raises the potential for publication bias. It is difficult to assess the risk of reviewer error and bias with regard to the study selection, assessment of studies and extraction of data, owing to the poor reporting of the study methods. However, since this article is a single author review, it seems likely that only one reviewer was involved. It should also be noted that the review author also appears to have been the author of 3 of the 17 included studies. Adequate details of the primary studies were provided and the meta-analysis of studies appears appropriate. Statistical heterogeneity was assessed and there was some attempt to investigate potential sources of heterogeneity. Overall, the author's conclusions appear to be supported by the data, but the potential for reviewer error and bias make it difficult to assess their reliability.

Implications of the review for practice and research
Practice: The author stated that inhaled fluticasone or budesonide should be administered to adults and children with acute exacerbations of asthma at minimum doses of 500 microg every 15 minutes or 800 microg every 30 minutes, respectively, via a metered-dose inhaler and spacer or nebuliser for 90 to 120 minutes. Higher doses and more prolonged periods of administration might generate larger benefits.

Research: The author stated that future studies should investigate the relationship between the ICS dose administered, acute asthma severity and treatment response.

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Other publications of related interest
This additional published commentary may also be of interest.
Boulet L.P. Review: inhaled corticosteroids reduce hospital admission and increase discharge rate during the first 4 hours in the emergency department for acute asthma. Evid Based Med 2007;12:75.

Indexing Status
Subject indexing assigned by NLM

MeSH
Acute Disease; Administration, Inhalation; Adolescent; Adrenal Cortex Hormones /administration & dosage /therapeutic use; Adult; Aged; Asthma /drug therapy /physiopathology; Child; Child, Preschool; Dose-Response Relationship, Drug; Drug Administration Schedule; Humans; Infant; Middle Aged; Randomized Controlled Trials as Topic; Reproducibility of Results; Time Factors; Treatment Outcome

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This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.