Glucocorticosteroid therapy in acute severe asthma - a critical review

T. Engel, J.H. Heinig

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ABSTRACT: Glucocorticosteroid (GCS) therapy is one of the corner-stones in the treatment of asthma. Its value in acute severe asthma is still open for debate. Many of the papers published on the topic are subject to methodological problems.

In 8 of 13 placebo-controlled studies, GCS therapy proved to be superior to placebo, evaluated either as result of pulmonary function, blood gas tension, or hospital admission rate. The most important point for GCS therapy in acute severe asthma seems to be frequent dosage, typically 4 times daily. Oral and intravenous administration seem to have equal efficacy.

Only 2 of 10 studies were able to prove a dose-response relationship. Both studies included very low doses of GCS. Doses of 100-200 mg of methylprednisolone for 24 h seem as effective as high doses.

A protective effect against relapses within a certain time after the GCS therapy has been demonstrated only for periods not exceeding 4 weeks, and only in children. So far, no study has been able to depict the categories of patients who may or may not benefit by the addition of GCS therapy to the symptomatic treatment of acute severe asthma.

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For the past 40 yrs, glucocorticosteroid (GCS) therapy has been applied in the treatment of asthma [1]. The value of this therapy in the maintenance treatment of chronic asthma is generally accepted [2, 3]. In acute severe asthma, GCS therapy is, however, still debated [4-7]. Data regarding the benefit of this therapy in acute asthma are conflicting, and dose-response relationships have been very difficult to achieve. Generally, GCS therapy is, however, frequently applied in the treatment of acute severe asthma [8]. We therefore found it of interest to review the published investigations on the use of GCS therapy in addition to the symptomatic treatment in the alleviation of acute, severe asthma.

An optimal evaluation of the effect of GCS therapy in acute, severe asthma should in our opinion discuss the following criteria (tables 1-4):
A. The study should be randomized and double-blind, and either be placebo-controlled or include different doses of GCS.
B. A significant number of patients should be assessable in order to offer sufficient statistical efficacy.
C. The diagnosis of asthma should be confirmed (e.g. ATS 1962 [9]) either by an investigation prior to the exacerbation or afterwards in a steady phase of the disease. Patients with exacerbations of chronic bronchitis and other chronic obstructive lung diseases should be excluded.
D. The application of long-term prophylactic treatment, including inhaled or systemic GCS prior to the exacerbation and the duration of the exacerbation before intervention with GCS.
E. Standardization of type and dose of symptomatic treatment and the patients' response to this treatment.
F. When evaluating the initial response, a period with symptomatic treatment solely should be included, in order to exclude the patients responding significantly to the symptomatic treatment alone.
G. Criteria for initiating GCS therapy, including results of pulmonary function (e.g. as % predicted) and results of arterial blood gas analysis, including arterial oxygen tension (Pao2).
H. Potency and pharmacokinetics of the applied GCS, with special reference to route of administration and duration of action should be stated.
I. Variables of efficacy for judgement of treatment failure or success should be carefully defined, and the time of judgement should be stated. Efficacy could be shown in pulmonary function values (e.g. forced expiratory volume in one second (FEV1) or peak expiratory flow (PEF)), normalization of blood gas abnormalities, hospital admission rate, or “relapse rate.” Relapse rate should be defined, if this parameter is included.
Table 1. Placebo-controlled studies in adults on the acute effect of GCS therapy in acute severe asthma

| 1st author [Ref. no.] | Design | Pat. no. | Final evaluat. | GCS | Admin. route | Dose | Dose m.p. | Effect | Effect
|-----------------------|--------|----------|----------------|-----|--------------|------|----------|--------|--------
| ARNAUD [10]           | ub, r  | 32       | 4 d            | Methylprednisolone | i.v. | 20 mg, 0.25 mg | -      | FEV₁ (+)
| FANTA [11]            | p, db, r | 20      | 24 h          | Hydrocortisone | i.v. | 14 mg·kg⁻¹ | 196 mg | FEV₁, PFC, Pao₂ (+)
| LITENBERG [12]        | p, db, r  | 97      | 4 h            | Methylprednisolone | i.v. | 125 mg | 125 mg | FEV₁, PFC, Pao₂ (+)
| LIKÉSA [13]           | p, ub, dr | 90      | 48 h          | Hydrocortisone | i.v. | 400 mg, 1200 mg | 80 mg | PEF, Pao₂, FVC (+)
| MCFADDEN [14]         | p, db, r, dr | 38    | 6 h            | Hydrocortisone | i.v. | 250 mg, 500 mg | 50 mg | PEF, Pao₂, FVC (+)
| MRC [15]              | p, db, r  | 32      | 14 d          | Cortisone | oral | 350 mg | 56 mg | 'Clin. score' (+)
| SCHNEIDER [16]        | p, db, r  | 54      |                | Methylprednisolone | i.v. | 30 mg·kg⁻¹ | 2.1 g | PEF, Pao₂, FVC (+)

¹: design of the study; r: randomized; db: double-blind; ub: unblind; dr: dose-response; p: placebo-controlled; c: cross-over; ²: time before final evaluation; ³: type of glucocorticosteroid; ⁴: route of administration (i.v.: intravenous; i.m.: intramuscular); ⁵: cumulated dose during the first 24 h; ⁶: cumulated dose during the first 24 h, converted to the corresponding dose of methylprednisolone in a 70 kg person (adults only); ⁷: effect parameter; ⁸: statistically significant difference between the groups; ⁹: no statistically significant difference between the groups. FEV₁: forced expiratory volume in one second; FVC: forced vital capacity; Pao₂: arterial oxygen tension; PEF: peak expiratory flow; sGaw: specific airway conductance; GCS: glucocorticosteroid.

Table 2. Placebo-controlled studies in children on the acute effect of GCS therapy in acute severe asthma

| 1st author [Ref. no.] | Design | Pat. no. | Final evaluat. | GCS | Admin. route | Dose | Dose m.p. | Effect | Effect
|-----------------------|--------|----------|----------------|-----|--------------|------|----------|--------|--------
| KATTAN [17]           | p, ub, r  | 19      | 36 h          | Hydrocortisone | i.v. | 28 mg·kg⁻¹ | 5.6 mg·kg⁻¹ | PEF (+)
| LOREN [18]            | p, db, r  | 16      | 48 h          | Prednisolone | oral | 2 mg·kg⁻¹ | 1.6 mg·kg⁻¹ | PEF (+)
| PIERSO [19]           | p, db, r  | 45      | 24 h          | Dexamethasone | i.v. | 14 mg·kg⁻¹ | 2.8 mg·kg⁻¹ | FEV₁, Pao₂ (+)
| | | | | Betamethasone | i.v. | 0.6 mg·kg⁻¹ | 3.2 mg·kg⁻¹ | FEV₁, Pao₂ (+)
| SHAPIRO [20]          | p, db, r  | 28      | 14 d          | Methylprednisolone | oral | 32 mg | 32 mg | FEV₁, PFC, FEFso (+)
| STORM [21]            | p, db, r  | 140     | 48 h          | Prednisolone | oral | 30 mg | 30 mg | PEF, 'Clin. score' (+)
| YOUNGER [22]          | p, db, r  | 45      | 36 h          | Methylprednisolone | i.v. | 5 mg·kg⁻¹ | 5 mg·kg⁻¹ | FEV₁, PEF (+)

FEF = FEFso: maximal flow at 50% of vital capacity. For further abbreviations see legend to table 1.
Table 3. - Dose-response studies on the acute effect of GCS therapy in acute severe asthma

<table>
<thead>
<tr>
<th>1st author [Ref. no.]</th>
<th>Design</th>
<th>Patients</th>
<th>Age no.</th>
<th>Final evaluat.</th>
<th>GCS</th>
<th>Admin. route</th>
<th>Dose</th>
<th>Dose6 m.p.</th>
<th>Effect7 param.</th>
<th>Effect8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Britton [23]</td>
<td>ub, dr</td>
<td>Adults 26</td>
<td>6 d</td>
<td>Hydrocortisone</td>
<td>i.v.</td>
<td>280 mg</td>
<td>120 mg</td>
<td>PEF 0</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prednisolone</td>
<td>oral</td>
<td>80 mg</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Hydrocortisone</td>
<td>i.v.</td>
<td>1120 mg</td>
<td>224 mg</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Methylprednisolone</td>
<td>i.v.</td>
<td>700 mg</td>
<td>700 mg</td>
<td></td>
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</tr>
<tr>
<td>Engel [24]</td>
<td>db, r, dr</td>
<td>Adults 18</td>
<td>14 d</td>
<td>Prednisolone</td>
<td>oral</td>
<td>50 mg</td>
<td>40 mg</td>
<td>FEV1 0</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Methylprednisolone</td>
<td>i.v.</td>
<td>1 g</td>
<td>1 g</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Harfi [25]</td>
<td>db, r, dr</td>
<td>Children 21</td>
<td>-</td>
<td>Methylprednisolone</td>
<td>i.v.</td>
<td>30 mg·m⁻²</td>
<td>30 mg·m⁻²</td>
<td>PEF 0</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prednisolone</td>
<td>i.v.</td>
<td>75 mg</td>
<td>60 mg</td>
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<tr>
<td>Harrison [26]</td>
<td>db, r, dr</td>
<td>Adults 47</td>
<td>24 h</td>
<td>Prednisolone</td>
<td>oral</td>
<td>75 mg</td>
<td>60 mg</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prednisolone</td>
<td>oral</td>
<td>12 mg·kg⁻¹</td>
<td>228 mg</td>
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<td></td>
</tr>
<tr>
<td>Haskell [27]</td>
<td>db, r, dr</td>
<td>Adults 24</td>
<td>72 h</td>
<td>Methylprednisolone</td>
<td>i.v.</td>
<td>60 mg</td>
<td>60 mg</td>
<td></td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prednisolone</td>
<td>i.v.</td>
<td>160 mg</td>
<td>160 mg</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Prednisolone</td>
<td>i.v.</td>
<td>500 mg</td>
<td>500 mg</td>
<td></td>
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</tr>
<tr>
<td>Lueksza [13]</td>
<td>p, ub, dr</td>
<td>Adults 90</td>
<td>48 h</td>
<td>Hydrocortisone</td>
<td>i.v.</td>
<td>400 mg</td>
<td>80 mg</td>
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<td></td>
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<td></td>
<td></td>
<td>i.v.</td>
<td>1200 mg</td>
<td>240 mg</td>
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<tr>
<td>McFadden [14]</td>
<td>p, db, r, dr</td>
<td>Adults 38</td>
<td>6 h</td>
<td>Hydrocortisone</td>
<td>i.v.</td>
<td>250 mg</td>
<td>50 mg</td>
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<td></td>
<td></td>
<td></td>
<td>i.v.</td>
<td>500 mg</td>
<td>100 mg</td>
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<td></td>
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<td></td>
<td></td>
<td>i.v.</td>
<td>1 g</td>
<td>200 mg</td>
<td></td>
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<tr>
<td>Raimondi [28]</td>
<td>ub, dr</td>
<td>Adults 40</td>
<td>5 d</td>
<td>Hydrocortisone</td>
<td>i.v.</td>
<td>6 mg·kg⁻¹</td>
<td>84 mg</td>
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<td></td>
<td></td>
<td>i.v.</td>
<td>80 mg·kg⁻¹</td>
<td>1.12 g</td>
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</tr>
<tr>
<td>Ratto [29]</td>
<td>ub, dr</td>
<td>Adults 70</td>
<td>72 h</td>
<td>Methylprednisolone</td>
<td>oral</td>
<td>160 mg</td>
<td>160 mg</td>
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<td></td>
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<td></td>
<td></td>
<td>i.v.</td>
<td>320 mg</td>
<td>320 mg</td>
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<td></td>
<td>i.v.</td>
<td>500 mg</td>
<td>500 mg</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>i.v.</td>
<td>1 g</td>
<td>1 g</td>
<td></td>
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<tr>
<td>Tanaka [30]</td>
<td>db, r, dr</td>
<td>Adults 10</td>
<td>10 d</td>
<td>Methylprednisolone</td>
<td>i.v.</td>
<td>80 mg</td>
<td>80 mg</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td>i.v.</td>
<td>500 mg</td>
<td>500 mg</td>
<td></td>
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</tr>
<tr>
<td>Webs [31]</td>
<td>db, r, dr, c</td>
<td>Adults 10</td>
<td>14 d</td>
<td>Prednisolone</td>
<td>oral</td>
<td>0.2 mg·kg⁻¹</td>
<td>11.2 mg</td>
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<td></td>
<td></td>
<td></td>
<td>oral</td>
<td>0.4 mg·kg⁻¹</td>
<td>2.4 mg</td>
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<td></td>
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<td></td>
<td></td>
<td>oral</td>
<td>0.6 mg·kg⁻¹</td>
<td>3.6 mg</td>
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</tbody>
</table>

For abbreviations see legend to table 1.

J. Before evaluation, a sufficient period of time, probably not less than 12 h, should be allowed for the GCS therapy to exert its effect.

K. Number and severity of side-effects from GCS.

We have reviewed 24 published controlled studies on GCS therapy in acute severe asthma in humans, all fulfilling one or more of the above mentioned criteria [10-33] (tables 1-4).

Placebo-controlled studies in adults

We have reviewed 7 placebo-controlled studies on the effects of GCS therapy in adults with acute severe asthma [10-16] (table 1).
Table 4. — Studies of relapse rate following GCS therapy in acute severe asthma

<table>
<thead>
<tr>
<th>1st author</th>
<th>Design1</th>
<th>Patients</th>
<th>Age</th>
<th>Final2 eval.</th>
<th>GCS3</th>
<th>Admin.4 route</th>
<th>Dose5</th>
<th>Dose6 m.p.</th>
<th>Effect7</th>
<th>Effect8</th>
</tr>
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<tr>
<td>ENOEL</td>
<td>db, r</td>
<td>Adults</td>
<td>18</td>
<td>12 wks</td>
<td>Prednisolone</td>
<td>oral</td>
<td>50 mg</td>
<td>40 mg</td>
<td>FEV1 0</td>
<td>PEF 0</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td>Methyl-</td>
<td>i.v.</td>
<td>1 g</td>
<td>1 g</td>
<td>Relapse</td>
<td>0</td>
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<td></td>
<td></td>
<td>prednisolone</td>
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<td>+</td>
</tr>
<tr>
<td>FERL</td>
<td>p, db</td>
<td>Adults</td>
<td>76</td>
<td>1 wk</td>
<td>Methyl-</td>
<td>i.v.</td>
<td>4 mg·kg⁻¹</td>
<td>280 mg</td>
<td>Relapse</td>
<td>0</td>
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<td></td>
<td></td>
<td>prednisolone</td>
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<td></td>
<td>+</td>
</tr>
<tr>
<td>HOFFMAN</td>
<td>db, r</td>
<td>Adults</td>
<td>18</td>
<td>1 wk</td>
<td>Methyl-</td>
<td>i.v.</td>
<td>4 mg·kg⁻¹</td>
<td>360 mg</td>
<td>Relapse</td>
<td>0</td>
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<td></td>
<td>prednisolone</td>
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<td>+</td>
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<td></td>
<td></td>
<td>Methyl-</td>
<td>i.v.</td>
<td>4 mg·kg⁻¹</td>
<td>344 mg</td>
<td>Relapse</td>
<td>0</td>
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<td>prednisolone</td>
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<td></td>
<td>+</td>
</tr>
<tr>
<td>MRC</td>
<td>p, db</td>
<td>Adults</td>
<td>32</td>
<td>12 wks</td>
<td>Cortisone</td>
<td>oral</td>
<td>350 mg</td>
<td>56 mg</td>
<td>Relapse</td>
<td>0</td>
</tr>
<tr>
<td>YOUNGERS</td>
<td>p, db</td>
<td>Children</td>
<td>45</td>
<td>4 wks</td>
<td>Methyl-</td>
<td>i.v.</td>
<td>5 mg·kg⁻¹</td>
<td>5 mg·kg⁻¹</td>
<td>Relapse</td>
<td>+</td>
</tr>
</tbody>
</table>

For abbreviations see legend to table 1.

Three other papers did not find that GCS therapy resulted in a faster increase in parameters of ventilatory capacity than placebo. However, no standardized measurements of pulmonary function were included.

Three other papers did not find that GCS therapy resulted in a faster increase in parameters of ventilatory capacity than placebo [12-14]. The GCS therapy was given as either an intravenous bolus of 125 mg of methylprednisolone [12], or different doses of hydrocortisone [14], or as repeated intravenous injections of hydrocortisone [13]. In two studies, however, evaluation was made after a mean observation period of only 4–6 h [12, 14], and one study was neither randomized nor double-blind [13].

One study [10] indicated that the addition of β₂-agonists is necessary for the bronchodilating effect of GCS therapy. Treatment with intravenous β₂-agonists alone or methylprednisolone plus adrenocorticotropic hormone (ACTH) alone resulted in poorer bronchodilatation as compared with the combination.

In one study [11], no difference in PaO₂ was demonstrated between intravenous hydrocortisone and placebo.

Out-patients receiving GCS therapy for acute severe asthma, have been shown to require hospital admission to a significantly lesser degree than patients receiving placebo treatment [12, 16]. Evaluation was made after a mean observation period of only 4 h [12] and 6 h [16] after medication with an intravenous bolus of either methylprednisolone or placebo.

**Placebo-controlled studies in children**

Four of 6 randomized, placebo-controlled studies in children (table 2) demonstrated a significant benefit of GCS therapy on pulmonary function [18, 20-22], as compared with placebo.

Six-hourly treatment with oral prednisolone resulted in a significant improvement in PEF, which was measurable 12-48 h after the start of medication [18]. After single, oral doses of prednisolone or placebo in 140 children, PEF was significantly higher in the prednisolonetreated group 6–8 h after medication [21]. The difference disappeared eight hours after medication. A once-daily tapering schedule of oral methylprednisolone in moderately severe asthmatic children resulted in identical...
improvement in FEV₁ in both the active and the placebo-treated groups 1, 7 and 14 days after start of treatment [20]. Forced mid-expiratory flow (FEF₂⁰₋₇₅) was, however, significantly higher in the methylprednisolone group on day 7, as compared with placebo.

A statistically significantly faster increase in FEF₂⁰₋₇₅ as compared with placebo, was also demonstrated by Younger et al. [22] who treated 45 children with methylprednisolone or placebo. The children were evaluated 12-hourly for 36 h (fig. 2). No significant effect on FEV₁, PEF or forced vital capacity (FVC) was demonstrated in this study, which only included children with asthma not responding to a standardized treatment with β₂-agonists.

Two studies failed to demonstrate any significant improvement in pulmonary function values after therapy with GCS, as compared with placebo: in an open, randomized trial comprising 19 children, who had experienced exacerbations of asthma for at least 24 h, six-hourly intravenous injections of hydrocortisone or placebo resulted in identical improvements in PEF and clinical scoring during a 36 h observation period [17]. In 45 children presenting with status asthmaticus and treated with an intravenous bolus followed by continuous infusion for 24 h of either hydrocortisone, dexamethasone, betamethasone, or placebo [19], no significant differences in FEV₁ were demonstrated. Prior to inclusion into the study, all children had received repeated injections of epinephrine without improving. The study was randomized and double-blind. Due to deterioration, half of the children initially allocated to the placebo group were decoded and reassigned to one of the active treatment groups three hours after medication.

In GCS-treated children, a significant improvement in Pao₂ was demonstrated in one study [19], whereas another study found no significant difference between children treated with methylprednisolone 5 mg·kg⁻¹ or placebo up to 36 h after medication [22].

Dose-response relationships

Ten dose-response studies of GCS therapy in acute severe asthma in adults [14, 23, 24, 26–31] and one in children [25] have been reviewed (table 3). The dose of GCS varied conceivably from 40 to 1,120 mg during the initial 24 h, when converted to the corresponding dose of methylprednisolone in a 70 kg person. Most studies were either not double-blind [13, 23, 28, 29], did not include a placebo-treated group [23, 24, 27–31], or were not randomized [13, 23]. Two studies used sequential inclusion in the study [28, 29]. In the only study fulfilling all three criteria (double-blind, placebo-controlled and randomized), evaluations were made only 6 h after the administration of GCS [14], and the study showed no significant dose-response relationship.

Intravenous methylprednisolone six-hourly resulted in a significant dose-response relationship in FEV₁ (fig. 3) [27]. Only patients not responding to standardized emergency room therapy and with an FEV₁ less than 50% predicted were included. After 24 h, patients in the high-dose group (receiving a total of 500 mg of methylprednisolone 24 h⁻¹) had shown significant improvement in FEV₁. At the final evaluation after 72 h all patients in the medium-dose (receiving 160 mg of methylprednisolone 24 h⁻¹) and high-dose groups had improved, and only 5 of the 8 patients receiving the lower dose (60 mg of methylprednisolone 24 h⁻¹) had improved.

A triple cross-over study [31] in 10 patients receiving three different doses of oral prednisolone (0.2, 0.4, and 0.6 mg·kg⁻¹, respectively) during three consecutive deterioration episodes of asthma also demonstrated a significant dose-responsereleationship.

The remaining studies all failed to demonstrate any dose-response relationship in the acute alleviation of asthma, evaluated by results of pulmonary function within the first 6 h [14], the first days [13, 26, 29], or within the first week [23, 24, 28, 30]. Likewise, no differences between oral and intravenous GCS therapy during 24 h [26], 72 h [29], or 7 days [24, 30] were found. Hospital admission rates or arterial oxygen tensions were not evaluated in any of these studies.
In children, different doses of intravenous methylprednisolone (30 and 300 mg·m²·24 h⁻¹) failed to produce any dose-response relationship with regard to PEF or Ÿao₂ [25].

Relapse rate

We have been able to trace only two investigations reporting the application of GCS therapy as treatment of the acute attack of asthma, and investigating the long-term protection against new exacerbations [15, 24] (table 4).

In 1956, the Medical Research Council reported the results of the first randomized double-blind study of cortisone therapy in acute severe asthma [15]. Patients were followed for 12 weeks, and no protection against relapses was demonstrated. A recently published study [24] failed to demonstrate any superiority of high-dose intravenous methylprednisolone pulse therapy compared with an 18 day tapering course of oral prednisolone for the protection against relapses during the 12 weeks following the treatment.

Short-term prophylaxis against new exacerbations has been demonstrated in adults, in whom after 6 h of successful symptomatic treatment, intravenous methylprednisolone followed by oral methylprednisolone proved effective against relapses within 7–10 days, as compared with placebo [32]. Some of the patients were, however, re-evaluated by telephone only. A later study by the same group used a similar design [33], and found an intramuscular injection of a repository GCS as effective as a tapering schedule of oral methylprednisolone for the protection against relapses within a week. A single infusion of a high dose of methylprednisolone in out-patients presenting in a deteriorating asthmatic condition has proved effective in reducing the number of readmissions within a one-week period [16].

Two placebo-controlled studies in children [18, 20] demonstrated protection against relapses within a two weeks follow-up period, even though the treatment was discontinued after a few days. Another study demonstrated a protective effect of intravenous methylprednisolone administered during the acute attack against re-exacerbations during the following 4 weeks [22].

Design of studies of acute steroid effects

A proper evaluation of the value of GCS therapy on parameters of pulmonary function necessitates an observation period sufficiently long to ensure the appearance of an effect. The fact that LITENBERG and GLUCK [12] and McFADDEN et al. [14] did not find GCS therapy superior to placebo is probably due to the short observation periods. The study by FANTA et al. [11] clearly fulfilled most of the “optimal criteria”. This study demonstrated a clear effect on FEV₁, and FVC 12–24 h after intravenous hydrocortisone 14 mg·kg⁻¹·24 h⁻¹. In children, 4 of 6 studies succeeded in demonstrating the superiority of adding GCS to the symptomatic treatment. One of the studies failing to demonstrate any effect on FEV₁ found an effect when evaluating arterial blood gas values. In all, 11 of 13 studies succeeded in demonstrating an effect either on pulmonary function, arterial blood gas values, or a reduced hospital admission rate, when GCS therapy was added. The two studies finding no significant difference were either not randomized [13] or used an observation period of only 6 h [14].

Steroid resistance, i.e. lack of response to administration of GCS, is a well-known phenomenon in chronic asthma [34, 35], and is also likely to occur in acute asthma. To our knowledge, no investigations have succeeded in depicting which patients per se might or might not benefit from early GCS therapy added to the symptomatic treatment applied in acute severe asthma.

Difficulties in differentiating between acute asthma and chronic obstructive airways disease are relevant in adults only. Some papers have not established a convincing diagnosis of bronchial asthma in all patients (e.g. ATS criteria [9]), thus clearly eliminating patients with other pulmonary diseases such as deteriorating chronic bronchitis [10, 12–14, 16, 23, 25]. One study in patients with chronic obstructive pulmonary disease presenting with acute respiratory insufficiency demonstrated a significant increase in FEV₁, 18 h after administration of methylprednisolone 0.5 mg·kg⁻¹ intravenously every 6 h compared with placebo [36].

An effect of GCS therapy on pulmonary function was demonstrable 4–12 h after administration for relief of acute asthma [11, 18, 21], and similar results have been obtained in chronic asthma [37–41]. In studies where only a single dose of GCS was administered, the effect ceased within approximately 12 h in both acute asthma [21] and chronic asthma [37, 39–41]. Accordingly,
maintenance treatment of inhaled topical steroids in a once-daily dosing regimen has proved less efficient than twice-daily [42]. Frequent dosing during the initial treatment of acute severe asthma is therefore recommended, a 3-4 times daily regimen being superior to once-daily only.

**Oral versus intravenous treatment**

Thirteen studies have applied intravenous GCS therapy only, 5 have applied oral treatment only, and 5 have applied both. There seems to be no consistent difference in efficacy with regard to route of administration. The addition of intravenous methylprednisolone to a course of oral prednisolone proved no better than oral prednisolone alone [26]. Oral and repository intramucular corticosteroid therapy also seemed equally effective [33]. This is supported by the finding that oral administration of non-enteric coated prednisolone tablets results in maximum plasma concentration levels within 15-30 min [43].

**Dose-response relationship and side-effects**

Only 2 of 11 studies demonstrated a dose-response relationship with regard to ventilatory capacity. The doses used in the different studies varied from 50 mg of oral prednisolone (corresponding to 40 mg of methylprednisolone) to intravenous hydrocortisone 80 mg·kg⁻¹ (corresponding to 1.12 g of methylprednisolone to a 70 kg person) during the first 24 h after admission. Two non-controlled studies have tried to emphasize the plasma cortisol level necessary for alleviation of the acute asthma [44, 45]. It has been suggested that the minimum plasma level of 11-hydroxycorticosteroid should be 1.5 mg·l⁻¹ [44]. The basis for this is, however, mainly theoretical. No significant relationship exists between the initial cortisol level on admission, and pulse rate, FEV₁, FVC, or PaO₂ [45]. Regardless of plasma cortisol, patients responded equally well to the symptomatic treatment, and thus did not require GCS therapy.

Side-effects from GCS therapy mainly occur after long-term treatment. A number of side-effects might occur even after short-term therapy with GCS, probably of a dose-dependent nature. They include psychological disorders, ulcurs pepticum, diabetogenic effect, water retention [46], acute myopathia [47], bradycardia [48] and even sudden cardiac death [49, 50].

No study has demonstrated any protective effect of systemic GCS therapy during the acute exacerbation or protection from later exacerbations. Addition of, or increased doses of, systemic GCS therapy is therefore indicated only for treatment of the actual exacerbation. Inhaled GCS therapy should be used for maintenance therapy in consideration of the severity of the asthmatic state.

The mode of action of GCS therapy in asthma is still relatively unknown [5-7, 51-53]. In chronic asthma, several studies have demonstrated increased ventilatory capacity as early as 3-6 h after treatment [37, 39-41, 54], although other studies have failed to demonstrate such a relationship [55]. The change in protein synthesis towards increased production of lipocortin is thought to account for most of the action of GCS therapy. The shift in protein synthesis probably takes place within 6-8 h, which coincides with the time when an effect was demonstrated in many of the papers reviewed by the authors. Lipocortin is known to inhibit phospholipase A₂ and thus some of the mediators from immediate hyper-sensitivity. Furthermore, restoration of β-receptors is probably also relevant [10, 38, 56].

In conclusion, many of the 24 studies reviewed in this paper suffer from severe drawbacks with regard to design. In spite of this, most of the studies succeeded in demonstrating an effect of GCS therapy either on parameters of pulmonary function, on arterial oxygen tension, or on reduced hospital admission rate. The use of GCS therapy in acute severe asthma is therefore recommended as a supplement to symptomatic treatment. In adults, a dose of 100-200 mg of methylprednisolone divided into 3 or 4 doses is sufficient, and higher doses increase the risk of side-effects. In children, even smaller doses are sufficient. Furthermore, oral and intravenous administration seems equally safe.

**References**


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Le traitement aux glucocorticostéroïdes est une des pierres angulaires du traitement de l'asthme. Sa valeur dans l'asthme sévère aigu fait toujours l'objet de débats. Beaucoup des articles publiés sur le sujet comportent des problèmes méthodologiques. Dans 8 des 13 études contrôlées par placebo, le traitement aux glucocorticostéroïdes (GCS) s'est avéré supérieur au placebo, que l'évaluation porte sur le résultat en matière de fonction pulmonaire, de tension des gaz du sang, ou de taux d'admission hospitalière. Le point le plus important en ce qui concerne le traitement par GCS dans l'asthme sévère aigu semble de dosage fréquent, qui doit être typiquement de 4 administrations par jour. Les administrations orale et intraveineuse semblent d'efficacité égale. Deux seulement des dix études ont pu démontrer une relation dose-réponse. Ces deux études incluaient de très petites doses de glucocorticostéroïdes. Des doses de 100 à 200 mg de methylprednisolone par 24 h. semblent aussi efficaces que les doses élevées. Un effet protecteur à l'égard des rechutes pendant un certain temps après le traitement aux glucocorticostéroïdes n'a été démontré que pour des périodes ne dépassant pas 4 semaines, et ce seulement chez les enfants. Jusqu'ici, aucune étude n'a pu décrire les catégories de patients qui pourraient ou non bénéficier de l'addition de glucocorticostéroïdes au traitement symptomatique de l'asthme sévère aigu.