Corticosteroid therapy for acute lung injury, acute respiratory distress syndrome, and severe pneumonia: a meta-analysis of randomized controlled trials

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CRD summary
The review concluded that low-dose corticosteroids administered within 14 days of disease onset may reduce all-cause mortality in patients with acute lung injury, acute respiratory distress syndrome, and severe pneumonia, but that the evidence was inconclusive. These cautious conclusions fairly reflect the evidence, and appear likely to be reliable.

Authors' objectives
To evaluate the effects of systemic corticosteroid therapy compared with placebo or standard care on hospital mortality in patients with acute lung injury, acute respiratory distress syndrome, or severe pneumonia.

Searching
MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL) were searched from inception to May 2008, with no language or publication status restrictions; search terms were reported. Conference proceedings of five relevant medical societies were searched (2003 to 2008), as were bibliographies of included studies and relevant reviews.

Study selection
Randomised controlled trials (RCTs) that compared corticosteroid therapy with placebo or standard care, for which mortality and dose/duration data was obtainable, were eligible for inclusion. In eligible trials, 70% of the population had to have acute lung injury, acute respiratory distress syndrome, or severe pneumonia, and 90% had to be aged 16 or over.

Hospital mortality was the primary outcome. Secondary outcomes were mortality at 28 days, duration of mechanical ventilation, days alive and off mechanical ventilation at day 28, length of intensive care unit stay, and length of hospital stay, as well as incident infections, gastrointestinal bleeding, pancreatitis, hyperglycaemia, and neuromyopathy.

In included trials, the corticosteroids studied were hydrocortisone, methylprednisolone, or prednisolone; most trials using low doses (up to 2mg/kg/day of methylprednisolone or equivalent). It appeared that all trials were placebo-controlled. The mean age of participants ranged from 34 to 72 years (where reported); the percentage of men ranged from 38 to 81%. Nearly half the trials recruited only patients with severe pneumonia (who had lower illness severity scores than patients in trials of acute lung injury, or acute respiratory distress syndrome). Included trials used APACHE II, APACHE III, or SAPS II to assess illness severity (where reported). Trials were published from 1956 to 2007.

One reviewer screened titles and abstracts, with a second reviewer screening the exclusions of the first reviewer. Full texts were selected for inclusion independently by both reviewers. Disagreements were resolved by consensus.

Assessment of study quality
Trial quality was evaluated by assessing the following criteria: method of randomisation, allocation concealment, blinding, analysis of intention-to-treat data, and whether trials avoided the risk associated with stopping for perceived benefit

It appeared that two reviewers performed the quality assessment.

Data extraction
Data were extracted in order to calculate risk ratios (RR) or mean differences (MD) with 95% confidence intervals (CI). Authors were contacted to obtain key missing data.

Data was extracted independently by two reviewers with disagreements resolved by consensus.
**Methods of synthesis**
Meta-analyses were performed to calculate pooled risk ratios or mean differences, using a random-effects model. Heterogeneity was evaluated using I^2.

Pre-specified sensitivity analyses investigated the effect of dosage, and of trials stopping early. Post hoc analyses explored the effect of treatment duration, and timing of drug initiation.

Funnel plots were used to assess publication bias.

**Results of the review**
Twelve RCTs were included in the review (n=1,014 patients from table 1). Nine trials used adequate methods of randomisation. Eight trials adequate methods of allocation concealment. Nine trials had adequate blinding. Nine trials used intention-to-treat data for analyses. Four trials had adequate avoidance of the potential bias related to stopping because of apparent benefit (and three trials were stopped early). One (old) trial was reported as not using randomisation methods.

**Mortality outcomes**: Corticosteroids did not significantly reduce hospital mortality (RR 0.84, 95% CI 0.66 to 1.06; 12 RCTs; I^2=29%); similar results were seen for 28-day mortality (seven RCTs). In subgroup analyses, low dose corticosteroids resulted in lower hospital mortality (RR 0.68, 95% CI 0.49 to 0.96, nine RCTs, I^2=30%), but higher doses did not (three RCTs).

**Secondary outcomes**: Corticosteroid treatment increased the number of days alive and off mechanical ventilation (MD 4.8 days, 95% CI 1.6 to 8.0 days, I^2=68%). There was no significant difference between groups for risk of infection (seven RCTs), although a subgroup analysis suggested that risk of infection increased in patients receiving high doses (two RCTs). Reported adverse events included neuromyopathy, gastrointestinal bleeding, hyperglycaemia, and pancreatitis.

**Authors’ conclusions**
Low-dose corticosteroids administered within 14 days of disease onset may reduce all-cause mortality in patients with acute lung injury, acute respiratory distress syndrome, and severe pneumonia. However, the overall quality of the evidence precluded definitive conclusions.

**CRD commentary**
The review addressed a clear question and was supported by appropriate eligibility criteria. However, these criteria were not strictly adhered to, since one non-randomised study was included (although this study contributed very few events to the meta-analyses). Attempts to identify all relevant studies in any language were undertaken by searching relevant databases, conference proceedings and checking references. Suitable methods were employed to reduce the risk of reviewer error and bias during the review processes.

Trial quality was assessed and was used in interpreting the results of the review. Primary trial details were tabulated. Appropriate methods were used to pool data and assess heterogeneity.

The authors’ conclusions were suitably cautious and reflected the evidence available; they appear likely to be reliable.

**Implications of the review for practice and research**
The authors did not state any implications for practice

**Research**: The authors stated that further rigorous, adequately powered RCTs were needed.

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