Meta-analysis: intravenous immunoglobulin in critically ill adult patients with sepsis

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CRD summary
This review concluded that intravenous immunoglobulin therapy improves survival compared with placebo or no treatment. Overall the authors' conclusions appear reliable. However, the included studies had some methodological limitations and the effect was primarily found in patients with severe sepsis or septic shock.

Authors' objectives
To evaluate the effect of polyclonal intravenous immunoglobulin (IVIG) therapy on mortality in critically ill patients with sepsis.

Searching
MEDLINE and the Cochrane CENTRAL Register were searched to May 2006 without any language restrictions; the search terms were reported. The bibliographies of identified meta-analyses and trials were also checked.

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 were required to compare IVIG with placebo or no intervention. In the included studies, the total dose of IVIG ranged from 0.2 to 2 g/kg and the duration of therapy from 2 to 5 days (some studies added extra days if required).

Participants included in the review
The participants were critically ill adults with sepsis defined by criteria of the American College of Chest Physicians-Society of Critical Care Medicine. Studies were eligible if the majority of the participants were aged 18 years or older. The participants in about half of the included studies had severe sepsis or septic shock.

Outcomes assessed in the review
The primary outcome was death. The secondary outcomes were length of intensive care unit (ICU) stay and days of mechanical ventilation.

How were decisions on the relevance of primary studies made?
Two authors independently assessed studies for relevance. Any disagreements were resolved by consensus or by referral to a third reviewer.

Assessment of study quality
Validity was assessed using the Jadad scale, which gives a score between 0 and 5 based on randomisation, blinding and handling of attrition. The authors did not state how the validity assessment was performed.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Data on the numbers of deaths in each treatment group were used to derive relative risks (RRs) and 95% confidence intervals (CIs). Data on continuous outcomes were extracted as differences between treatment groups and were used to derive a weighted mean difference and 95% CI. Authors were contacted for additional data or clarification where necessary.
Methods of synthesis
How were the studies combined?
The studies were combined by meta-analysis using a random-effects model (DerSimonian and Laird). Publication bias was assessed using a funnel plot of effect size versus standard error.

How were differences between studies investigated?
Statistical heterogeneity was assessed (p<0.10 was considered significant) and the I-squared statistic was computed. Sensitivity analyses were performed to investigate the effect on the pooled RR of death; the variables examined were dosage regimen, duration of therapy, methodological quality, date of publication, disease status and diagnosis, and start date of therapy.

Results of the review
Twenty RCTs (n=2,671) were included.

Five trials scored 1 on the Jadad scale, three scored 2, eight scored 3 and four scored 5.

Patients treated with IVIG had a significantly lower risk of death compared with control patients (pooled RR 0.74, 95% CI: 0.62, 0.89, p=0.001). There was no significant difference between the groups in length of ICU stay (5 trials) or days of mechanical ventilation (2 small trials).

The funnel plot provided no clear evidence of publication bias. The sensitivity analysis indicated that severe sepsis or septic shock, a dosage of 1 g/kg or more, and a duration of therapy longer than 2 days were associated with increased survival benefit and explained most of the heterogeneity between studies.

Authors' conclusions
IVIG therapy confers a survival benefit compared with placebo or no therapy.

CRD commentary
This review addressed a clear question and the inclusion criteria were clear. The authors searched only two databases so it is possible some relevant studies could have been missed. Unpublished studies were not sought but publication bias was assessed and no clear evidence for it was found. No language restrictions were imposed, thereby reducing the possibility of language bias in the review. Appropriate methods were used to reduce bias and errors in the study selection process; methods used in the quality assessment and data extraction were not reported. Quality was assessed using a standard (albeit limited) method and the results were used in the data synthesis.

Adequate details of the primary studies were presented. The studies were combined by meta-analysis and sources of heterogeneity in the analysis were explored. Nine of the included studies were funded by industry; the funding sources in the remaining 11 studies were not reported. The authors’ conclusions reflect the evidence presented and appear reliable; the small sample size and methodological limitations of many of the included studies also support their recommendation for further research.

Implications of the review for practice and research
Practice: The authors did not state any implications for practice.

Research: The authors stated that polyclonal IVIG should be evaluated in a large RCT in a well-defined population at high risk of death who are receiving the current standard of care for sepsis.

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