An evaluation of the feasibility, cost and value of information of a multicentre randomised controlled trial of intravenous immunoglobulin for sepsis (severe sepsis and septic shock): incorporating a systematic review, meta-analysis and value of information analysis

CRD summary
The authors concluded that there was borderline significant evidence that intravenous immunoglobulin reduced all-cause mortality for patients with severe sepsis or septic shock. There was variation in the treatment effect across trials and the results should be interpreted with caution. This was a well-conducted review and the cautious conclusions reflect the evidence and are likely to be reliable.

Authors’ objectives
To assess the clinical and cost-effectiveness of intravenous immunoglobulin for adult patients in the UK with severe sepsis or septic shock. The feasibility, cost and value of information for a multicentre randomised controlled trial were discussed, but not covered by this abstract.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL), and Cochrane Infectious Diseases Group Trials Register were searched for articles from 2002 to October 2009, to update a previous review (see Other Publications of Related Interest). The search strategy was reported; there were no language restrictions. Existing systematic reviews were manually screened.

Study selection
Eligible for inclusion were randomised controlled trials (RCTs) comparing standard polyclonal intravenous immunoglobulin or polyclonal intravenous immunoglobulin enriched with immunoglobulin M versus no intervention, placebo, or another standard or immunoglobulin-M-enriched polyclonal intravenous immunoglobulin. Trials had to be conducted in a critical care setting, in which most patients were 18 years or older and had clinically accepted severe sepsis or septic shock. The primary outcome of interest was all-cause mortality. Other outcomes included adverse events.

The included trials were published between 1981 and 2007. The mean age of patient groups ranged from 31 to 65.9 years. The definition and severity of sepsis varied across trials. About half the trials used the immunoglobulin-M-enriched polyclonal intravenous immunoglobulin, Pentaglobin, and where reported, the average daily dose ranged from 0.15 to 0.35g per kg per day. The other intravenous immunoglobulins were various doses of Sandoglobulin, Polyglobin N, Intraglobin F, Endobulin SD, Gamma-Venin, and Gaminune N. The controls received no treatment or 0.1% to 20% human albumin solution. All treatments were given with standard care, which varied across trials. Treatment lasted between two and seven days. Other outcomes were reported, including the duration of mechanical ventilation and the duration of critical-care unit stay or acute hospital stay.

One clinician screened studies for inclusion and this was verified by a second clinician.

Assessment of study quality
Two reviewers independently assessed trial quality according to the Jadad scale, covering randomisation, allocation concealment, blinding, and intention-to-treat analysis. Trials were rated out of a maximum score of five.

Data extraction
Data on all-cause mortality were extracted to calculate odds ratios and 95% confidence intervals. Adverse event data were also extracted.

One clinician extracted the clinical data, and this was confirmed through discussion with other experts. The remaining data were extracted independently by two reviewers, with duplicate extraction performed for about half the studies.
Methods of synthesis
Random-effects and fixed-effect models were used to combine the odds ratios and 95% confidence intervals. Adverse event data were presented in tables. Statistical heterogeneity was assessed using Cochran Q and $I^2$. Subgroup analyses were performed for patients with septic shock, those with other severe sepsis, and by sepsis score cut-off values. Data were grouped by other characteristics, such as type of intervention, type of control, treatment dose, treatment duration, quality criteria, and patient risk of death at baseline (full details were reported).

A network analysis was conducted using a Bayesian Markov chain Monte Carlo model. Odds ratios and 95% credible intervals were calculated for various comparisons. Different models were explored to identify the key covariates responsible for heterogeneity.

Publication bias was assessed through inspection of funnel plots and Peter’s test for asymmetry.

Results of the review
Seventeen RCTs (2,300 patients; range 21 to 682) were included in the review. Eleven RCTs scored three or more on the Jadad scale, but the scoring was inconsistent across trials. Patients were assessed upon discharge from the critical care unit, or at up to 70 days.

Compared with control, polyclonal intravenous immunoglobulin statistically significantly reduced mortality, using both fixed-effect (OR 0.68, 95% CI 0.54 to 0.84; $I^2=46.9%$; 17 RCTs) and random-effects models (OR 0.47, 95% CI 0.32 to 0.69; $I^2=46.9%$; 17 RCTs).

Subgroup analyses indicated that the effects were stronger with immunoglobulin-M-enriched polyclonal intravenous immunoglobulin and when controls received no treatment. Trials of higher quality showed weaker treatment effects compared with those of lower quality. The treatment effects were stronger with increasing duration of treatment, but weaker with increasing daily dose and volume. Other subgroup results were reported.

There was evidence of publication bias according to the funnel plot and Peter’s test.

Bayesian network analyses indicated that the best fitting treatment comparison model was immunoglobulin-M-enriched or standard polyclonal intravenous immunoglobulin versus albumin versus no treatment, with duration of treatment a covariate. The effect was stronger for longer durations of treatment; in most trials treatment lasted for three days. Standard or enriched polyclonal intravenous immunoglobulin produced a statistically significant reduction in all-cause mortality compared with albumin after three days of treatment (OR 0.75, 95% CrI 0.58 to 0.96). Full results were reported.

Cost information
For all-cause mortality, using the best-fit model with duration of treatment as a covariate, the incremental cost-effectiveness ratio of intravenous immunoglobulin over standard care was £20,850 per quality-adjusted life-year gained.

In the other models, the incremental cost-effectiveness ratio ranged from £16,177 per quality-adjusted life-year gained to intravenous immunoglobulin being dominated by standard care alone, as immunoglobulin was less effective and more costly.

Authors’ conclusions
There was borderline significant evidence that intravenous immunoglobulin reduced all-cause mortality for patients with severe sepsis or septic shock. There was a large amount of variation in the treatment effect across trials and the results should be interpreted with caution.

CRD commentary
The review question and inclusion criteria were clear. The literature search was adequate and no language restrictions were applied, reducing potential for language bias. Publication bias was assessed and evidence of bias was found. Appropriate methods were used to assess trial quality, but there was some inconsistency in the scores reported for individual trials. Attempts were made to reduce reviewer error and bias at different stages of the review process. Comprehensive methods were used to combine the data and explore statistical heterogeneity. The authors
acknowledged the potential for bias in the trial methods and that relevant trials might have been missed.

This was a well-conducted review and the authors' conclusions reflect the evidence and are suitably cautious. Their recommendations are likely to be reliable.

Implications of the review for practice and research

Practice: The authors stated that intravenous immunoglobulin for severe sepsis should remain colour-coded black, as a treatment that is not recommended.

Research: The authors stated that further research was needed to investigate the mechanisms of action of intravenous immunoglobulin, and then design multicentre RCTs to assess long-term survival, quality of life, and costs, for patients with severe sepsis.

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Record Status
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