Cost-effectiveness of immunoglobulin M-enriched immunoglobulin (Pentaglobin) in the treatment of severe sepsis and septic shock

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of a specific polyclonal intravenous immune globulin preparation (Pentaglobin) for adult patients treated for severe sepsis and septic shock.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of patients with severe sepsis and septic shock.

Setting
The setting was a hospital ICU. The economic study was carried out in Germany.

Dates to which data relate
The effectiveness data and some resource use data were derived from studies published between 1986 and 2002. The majority of the resource use and cost data came from a study published in 2002. The price year was not explicitly stated, but it appears to have been 2002.

Source of effectiveness data
The effectiveness evidence was derived from a synthesis of published studies.

Modelling
A simple decision tree was used to assess the costs and benefits of Pentaglobin and conventional care. Only two possible outcomes, survival or death, were considered after either treatment. The time horizon of the model was unclear, but it might have been that of the ICU stay. Thus, the model followed the patients until discharge from the ICU or until death.

Outcomes assessed in the review
The outcomes estimated from the literature were baseline mortality in the control population, mortality reduction with Pentaglobin, and length of stay (LOS) in the ICU for patients treated with standard therapy and Pentaglobin.

Study designs and other criteria for inclusion in the review
A review of the literature was undertaken to identify relevant primary studies on treatment effectiveness, using the criteria described in a review published by the Cochrane Collaboration. The review focused only on studies in adults (excluding studies in children) and was limited to randomised controlled trials comparing Pentaglobin with a control group that received placebo. Information on sample size, blinding and length of follow-up was provided for each study.

**Sources searched to identify primary studies**
Not reported.

**Criteria used to ensure the validity of primary studies**
The selection of randomised clinical trials as the source of evidence should ensure a high internal validity.

**Methods used to judge relevance and validity, and for extracting data**
Not reported.

**Number of primary studies included**
Nine primary studies provided the clinical data used in the model.

**Methods of combining primary studies**
A meta-analysis approach was used to combine the primary estimates. The data were analysed using either a fixed-effect or random-effects model, depending on evidence of heterogeneity.

**Investigation of differences between primary studies**
Differences among the primary studies were identified. The test of homogeneity revealed that the studies were comparable.

**Results of the review**
The pooled results of the clinical trials (435 patients; control group, n=212; Pentaglobin, n=223) showed that the baseline risk of mortality was 0.4434 in the control population.

Administration of Pentaglobin significantly decreased the risk of mortality in patients with severe sepsis and septic shock, both using a random-effects model (risk ratio, RR=0.5652, 95% confidence interval, CI: 0.306 to 0.7420; p<0.0001) and a fixed-effect model (RR 0.5173, 95% CI: 0.3923 to 0.6829; p<0.001).

There was no significant heterogeneity among trials of Pentaglobin.

The absolute risk reduction with Pentaglobin was 0.1928, thus the number-needed-to-treat to save an additional life with Pentaglobin compared with standard therapy was 5.19 (95% CI: 4 to 9).

In synthesis, the all-cause mortality was 22.9% with Pentaglobin and 44.3% with standard care. Thus, there was a mortality reduction of 19.3% (95% CI: 14.3 to 22.4).

The effect of Pentaglobin on ICU LOS did not differ from conventional care. The two treatments were therefore considered to have the same impact on ICU LOS.

**Measure of benefits used in the economic analysis**
The summary benefit measure used was the number of lives saved with Pentaglobin in comparison with conventional care. This figure was derived directly from the effectiveness analysis. Discounting was not performed, which was
appropriate given the short time horizon of the analysis.

**Direct costs**
The perspective of the hospital was chosen for the analysis. The direct medical costs included in the analysis were for ICU stay, “block” therapies (sepsis therapy, blood therapy, ventilation and renal therapy) and Pentaglobin. The analysis differentiated between survivors and non-survivors. The unit costs and the quantities of resources used were presented separately for some items only (i.e. ICU days and Pentaglobin infusions). The estimation of resource use and costs reflected typical German treatment patterns. Most data were obtained from a German study published in 2002. Thus, although not explicitly reported, the price year seems to have been 2002. Discounting was not performed since the costs were incurred during a short timeframe.

**Statistical analysis of costs**
The costs were treated deterministically in the base-case.

**Indirect Costs**
The indirect costs were not included in the economic analysis.

**Currency**
Euros (EUR).

**Sensitivity analysis**
A univariate sensitivity analysis was carried out to assess the impact of changes in the effectiveness of Pentaglobin and the baseline mortality risk on the cost-effectiveness estimates. Ranges of values were based on published CIs. A probabilistic sensitivity analysis was also undertaken, using a second-order Monte Carlo simulation, to generate cost-effectiveness acceptability curves.

**Estimated benefits used in the economic analysis**
As already reported, one additional life could be saved for every 5 patients treated with Pentaglobin (95% CI: 4 to 9).

**Cost results**
The total costs per patient were EUR 24,747 with Pentaglobin and EUR 22,711 with conventional care (difference EUR 2,037).

The extra acquisition drug cost of Pentaglobin (EUR 2,761) was only partially offset by a reduction in other resource use.

**Synthesis of costs and benefits**
An incremental cost-effectiveness ratio (ICER; i.e. the incremental cost per life saved) was calculated to combine the costs and benefits of Pentaglobin over usual care.

Under base-case assumptions, the ICER was EUR 10,565.

The univariate sensitivity analysis showed that the ICER ranged from EUR 5,715 to EUR 28,443 on the basis of assumptions made about the baseline mortality risk and relative effects of Pentaglobin with respect to standard therapy.

The multivariate sensitivity analysis suggested that the probability that the ICER of Pentaglobin would be below EUR 12,000 was 56.3%, while the probability that the ICER of Pentaglobin would be below EUR 15,000 was 83.9%.
Authors' conclusions

The addition of Pentaglobin to conventional care for the treatment of adult intensive care unit (ICU) patients with severe sepsis or septic shock was clinically and economically effective in the German context.

CRD COMMENTARY - Selection of comparators

The authors provided a justification for the choice of the comparator, which was selected to reflect standard care. However, the conventional approach for the treatment of adult ICU patients with severe sepsis was not described. You should decide whether this is a valid comparator in your own setting.

Validity of estimate of measure of effectiveness

The effectiveness analysis was based on a review of the literature, the methods and conduct of which were reported in part. The authors stated that the review employed the criteria used in a published review by the Cochrane Collaboration. Extensive information on the design and clinical characteristics of the patients included in the study was provided. Further, the authors explicitly addressed the issue of homogeneity among the primary studies using both random-effects and fixed-effect meta-analyses and a test of heterogeneity. The approach used to combine the primary estimates was reported. The key clinical input was varied in the sensitivity analysis. The authors stated that data from observational (non-experimental) studies would be required to confirm the positive effect of Pentaglobin.

Validity of estimate of measure of benefit

The summary benefit measure (i.e. the number of lives saved) may be comparable with the benefits of other health care interventions, although a much more commonly used measure is the number of life-years saved. The authors noted that the use of lives saved does not incorporate the long-term impact of the intervention. However, the benefit measure based on the number-needed-to-treat is clinically relevant and meaningful.

Validity of estimate of costs

The categories included in the cost analysis were consistent with the perspective of the study. The fact that some unit costs were presented separately from the quantities of these items used will allow the analysis to be replicated in other settings. In addition, the costs were broken down between items for survivors and non-survivors. However, the quantities of resources used and the unit costs for the “block” therapies category were not reported. Much of the economic data were derived from a published study, which should reflect German prices. Statistical and sensitivity analyses of the costs were generally not undertaken. However, a probabilistic sensitivity analysis was performed. The price year was not explicitly reported, which will make reflation exercises in other time periods difficult.

Other issues

The authors did not compare their findings with those from other studies. They also did not explicitly address the issue of the generalisability of the study results to other settings. Limited sensitivity analyses on the costs were carried out, which limits the external validity of the study. However, the authors addressed the issue of the variability and uncertainty in model parameters using a probabilistic sensitivity analysis. The study referred to adult patients treated for severe sepsis and septic shock in the ICU setting, and this was reflected in the authors' conclusions. The authors discussed extensively the limitations of using the number-needed-to-treat to derive a summary benefit measure. Overall, the authors stated that caution is required when interpreting the results of the analysis because of the data available from published studies. Such studies enrolled a small number of patients, had highly selected participants, and differed in methodology and conduct.

Implications of the study

The study results suggest that Pentaglobin might be considered for the treatment of adult ICU patients with severe sepsis and septic shock. Further studies should be carried out to corroborate the current findings in a clinical trial with good methodology and clinically sound results.
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