A systematic review of antithrombin concentrate use in patients with disseminated intravascular coagulation of severe sepsis

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CRD summary
This review concluded that antithrombin may increase survival in patients with disseminated intravascular coagulation due to severe sepsis, but there was insufficient evidence to make recommendations for clinical practice. The authors' tentative conclusions appear appropriate in view of the limited evidence, but poor reporting of the review methods makes it difficult to assess the review's reliability.

Authors' objectives
To evaluate the effects on mortality of antithrombin therapy for the treatment of disseminated intravascular coagulation (DIC) associated with severe sepsis.

Searching
MEDLINE (1985 to 2005), the Cochrane Controlled Trials Register (1988 to 2005), ClinicalTrials.gov and the U.S. Food and Drug Administration website were searched between 1985 and 2005; search terms were reported for the MEDLINE search. In addition, reference lists were screened. Studies were only included if they were reported in English.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were eligible for inclusion in the review.

Specific interventions included in the review
Studies that compared antithrombin concentrate with placebo were eligible for inclusion. The included studies used different regimens of antithrombin concentrate over 4 or 5 days (details were reported). Two studies did not administer concomitant prophylactic heparin treatment (in these studies a supranormal antithrombin level was achieved in the treatment group); in the third study concomitant heparin was given and a normal antithrombin level was achieved.

Participants included in the review
Studies of patients with severe sepsis and DIC or plasma antithrombin levels less than 70% were eligible for inclusion. The review also included studies with subgroups of participants that met these inclusion criteria. The review included patients with DIC who presented with severe shock, patients with severe sepsis or postsurgical complications with antithrombin levels less than 70%, and a subgroup of patients with severe sepsis in whom the diagnosis of DIC was made post hoc.

Outcomes assessed in the review
Studies reporting mortality were eligible for inclusion. The review primarily assessed death from any cause, but death from specific complications such as major bleeding were also reported. Deaths were assessed at 28 or 30 days post-intervention.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
Studies were assessed using a modified version of the criteria described by Cronin et al. These criteria included: patient selection; baseline similarity of the treatment groups; method of randomisation; blinding; description of the
intervention; reporting of contamination and cointervention; reporting of complications; reporting of intention-to-treat data; adherence to protocol; explicit definition of septic shock; and the use of allocation concealment. The maximum possible score was 14.5 points. 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. Percentage values for all-cause mortality were extracted and odds ratios (ORs) with 95% confidence intervals (CIs) calculated.

Methods of synthesis
How were the studies combined?
Pooled ORs with 95% CIs were calculated using a random-effects model.

How were differences between studies investigated?
Statistical heterogeneity was assessed using the chi-squared statistic. Clinical heterogeneity amongst studies was also discussed.

Results of the review
Three RCTs (n=364) were included.

The study quality scores were 11 (2 studies) or 13 (1 study).

There was a lower risk of death that just reached statistical significance in patients who received antithrombin compared with the control: 35% versus 45.1% (OR 0.649, 95% CI: 0.422, 0.998, p=0.049). No statistically significant heterogeneity was detected (p=0.387).

There was no significant difference in the risk of major bleeding between patients who received antithrombin compared with the control. Bleeding was reported in 8 patients who received antithrombin and 7 patients who did not.

Authors' conclusions
Findings suggest that antithrombin may reduce short-term death rates in patients with severe sepsis and DIC, but there was insufficient evidence to make recommendations for clinical practice.

CRD commentary
The review addressed a clear question that was defined in terms of the participants, intervention, outcomes and study design. Several relevant sources were searched and some attempts were made to minimise publication bias, although some relevant data might have been missed through the inclusion of English language studies only. The methods used to select the studies, assess validity and extract the data were not described, so it is not known whether any efforts were made to reduce reviewer error and bias. Validity was assessed and the results reported.

Two of the three included reports were based on subgroup analyses of RCTs, one of which was produced by one of the review authors; however, the limitations of these data were discussed. Pooling data statistically appeared appropriate, statistical heterogeneity was assessed, and clinical differences between the studies were discussed. Few major bleeding events were reported and so the evidence for this outcome was limited. Overall, the authors' tentative conclusions appear appropriate in view of the limited evidence, but poor reporting of the review methods makes it difficult to assess the reliability of the review.

Implications of the review for practice and research
Practice: The authors stated that no recommendations for practice can be made until further research is carried out.
They suggested that, in view of the potential for increased bleeding, therapeutic and possible prophylactic heparin should not be given during antithrombin treatment.

Research: The authors stated that the review's findings need to be confirmed in further RCTs.

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