The efficacy of amino acid-based formulas in relieving the symptoms of cow's milk allergy: a systematic review


CRD summary
The authors concluded that amino acid-based formula improved symptoms and growth in infants and children with cow's milk allergy who were intolerant of extensively hydrolysed formula, but further research is required. Given the limited evidence from diverse generally small studies reporting multiple outcomes, a more cautious conclusion may have been more appropriate.

Authors' objectives
To evaluate the efficacy of amino acid-based formulae in patients with cow’s milk allergy and compare amino acid-based formulae with other specified formulae.

Searching
The following electronic resources were searched in July or August 2004: the Cochrane Library; Turning Research Into Practice database (TRIP); National Electronic Library for Health (NELH); the Children’s National Service Framework (NSF); and PubMed. Search terms were reported. Reference lists were also screened. Experts were contacted for additional studies. No restrictions were placed on the date of publication or language, but studies had to have an English translation.

Study selection
Randomised controlled trials (RCTs), non-randomised controlled clinical trials, before-and-after clinical trials and observational studies that evaluated oral or enteral amino acid-based formulae (100% amino acids) in patients of any age, with confirmed or suspected cow’s milk allergy, were eligible for inclusion. Studies had to compare amino acid-based formula with soy-based formula and/or extensively hydrolysed formula and/or cow’s milk (formula). Patients could be well-nourished or malnourished. Studies had to assess gastrointestinal, dermatological, respiratory or behavioural symptoms or growth.

All included studies exclusively examined children aged two days to 12 years. In half of the studies, children had confirmed cow’s milk allergy; the other studies were in children with suspected cow’s milk allergy.

Potentially relevant studies were identified from titles and abstracts by an unknown number of reviewers. One reviewer then screened full-papers and selected studies. Inclusions and exclusions were then verified by a second reviewer.

Assessment of study quality
One reviewer classified studies by design according to the Quality of Evidence Quality Assessment Scale from 1 (highest grade) to 6 (lowest grade). In addition, RCTs were assessed using the Jadad scale (randomisation, blinding and withdrawals) in which the maximum possible score was 5 points. The assessment was verified by a second reviewer and by 'independent assessment'.

Data extraction
Results were reported as differences between treatment groups or changes from baseline.

The authors did not state how data were extracted for the review, or how many reviewers performed the data extraction.

Methods of synthesis
The studies were grouped by comparator and study design, and combined in a narrative synthesis. Differences between studies precluded planned meta-analysis.
Results of the review
Six randomised controlled trial (RCTs, including three head-to-head studies with 147 children and three open or double-blinded food challenge RCTs with 66 children), seven before-and-after clinical trials (n=195 children) and seven cohorts or case reports (n=8 children) were included. Three RCTs scored 5 points out of 5 on the Jadad scale; others scored 4, 3 or 2 points. Three RCTs were judged to be poorly described or planned.

Amino acid-based formula versus extensively hydrolysed formula (six RCTs, five before-and-after clinical trials, five cohorts or case reports): Three head-to-head comparison RCTs found no significant differences between amino acid-based formula and extensively hydrolysed formula in improvements in gastrointestinal or dermatological symptoms. Two RCTs reported significant differences in one or two measures of growth favouring amino acid-based formula. One RCT reported no difference in two of three growth measures. Three cross-over challenge RCTs found that there were no significant differences in the number of children developing gastrointestinal, respiratory or behavioural problems between amino acid-based formula and extensively hydrolysed formula.

Amino acid-based formula versus soy-based formula (two cross-over RCT challenge trials, two before-and-after clinical trials, two cohorts or case reports): One cross-over challenge RCT reported adverse effects following challenge with soy in children asymptomatic on amino acid-based formula. The other cross-over challenge RCT reported no adverse effects of amino acid-based formula in children tolerant to soy.

Amino acid-based formula versus cow’s milk or milk-based formula (two cross-over RCT challenge trials, two before-and-after clinical trials, two cohorts or case reports): The two cross-over challenge RCTs reported tolerance of amino acid-based formula.

Other results, plus results for before-and-after clinical trials and cohorts or case reports, were also reported.

Authors’ conclusions
Amino acid-based formula improved symptoms and growth in infants and children with cow’s milk allergy who were intolerant of extensively hydrolysed formula, but further research is required.

CRD commentary
The review question was clearly stated and inclusion criteria defined for interventions and participants. Inclusion criteria for study design and outcomes were broad and multiple. The absence of specified primary outcomes raised the potential for selective reporting of positive results and for results being statistically significant merely by chance. Also, inclusion criteria required that studies compared two formulae but some of the included studies had no control treatment. Several relevant sources were searched, but no attempts were made to minimise publication or language bias. Appropriate methods were used to minimise reviewer error and bias during the validity assessment and parts, but not all, of the study selection process; it was not clear whether similar steps were taken in study extraction. The validity of RCTs was assessed using specified criteria, but the quality of other studies was not assessed other than by grading the study design. In view of the diversity among studies, a narrative synthesis, with studies grouped by design, was appropriate. It appeared that different numbers of children were challenged with different formulae in challenge tests which could have influenced results. No studies of alternative formulae for children intolerant to amino acid-based formula were included. Interpreting the review findings was difficult given the reporting of multiple outcome measures, reliance upon a small number of diverse studies with small sample size, and inconsistent reporting of differences between treatments (rather than changes from baseline in controlled trials). In view of the limitations of the evidence, a more cautious conclusion about the effects of amino acid-based formula may have been more appropriate.

Recommendation regarding further research appeared justified.

Two of the authors have previously received support for research from SHS/Nutricia, presented lectures at meetings sponsored by these organisations or contributed to technical advisory panels.

Implications of the review for practice and research
Practice: The authors stated that, in infants with rectal bleeding who are being considered for amino acid-based formula treatment, a cow’s milk challenge should be undertaken to ensure the bleeding is due to intolerance.
Research: The authors stated that further research is required to evaluate the medical and economic costs of initially treating infants at high risk of extensively hydrolysed formula intolerance with amino acid-based formula. Evaluations of the long-term use of amino acid-based formula are also required. Studies evaluating amino acid-based formula should report the time to symptom resolution.

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