Reviewer's report

Title: Double-blind placebo-controlled food challenges in children with alleged cow's milk allergy: prevention of unnecessary elimination diets and determination of eliciting doses

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Reviewer: Heli Salmi

Reviewer's report:

The article addresses a clinical problem very often encountered in paediatrics, namely, if the number of children following unnecessary elimination diets for suspicion of food allergy really could be reduced by more accurate diagnostic procedures. In addition, the authors aim to find out what amount of allergen (here, cow’s milk protein, CMP) is generally tolerated; this would be critical to be able to provide those patients who do have food allergy with evidence-based information about dietary restrictions. The questions posed by the authors are relevant in clinical practice and defined well enough. According to the authors, this is the largest study assessing the amount of tolerated allergen, which makes the results more interesting even if the research question is neither completely new nor original. Finally, the authors even compare their results on the amount of tolerated allergen to previously published ones, which adds to the scientific merits of the article and compensates for the fact that the study population (even if the largest published?) is not very big (N = 25 for the children studied for the tolerated dose).

The study is well designed and the follow-up has succeeded remarkably well.

The authors conclude that excluding cow’s milk allergy by double-blind placebo controlled food challenge does, in effect, stop unnecessary elimination diets in children without allergy. Interestingly, they find that most patients tolerate rather large amounts of CMP and that infants are more tolerant than older children.

A) Major compulsory revisions:

1. The authors describe statistical methods in the Methods part, but the results of the statistical tests are not shown in the figures or tables (they are expressed in the text, though). As figures and tables should be understandable without reading the article text in detail, this information needs to be fitted into Table 2.

2. I am not familiar with the cumulative distribution curves (or the statistical analyses behind these), in which the authors have fitted individual MEDs in this study and previously published ones. This may only illustrate my unsatisfying statistical skills, but I doubt that the average reader might have similar problems. Could some kind of scatter plot with individual MED values (in this study, at least, if those from the literature are not directly comparable) be used in addition of this cumulative distribution curve (which I understand as some kind of a regression
curve fitting the individual MEDs)? Or could the individual MEDs be represented in a separate figure to help the reader understand their distribution?

B) Minor essential revisions

1. The article is well written and the Introduction and Discussion include a thorough review of the literature. This makes the article more trustworthy and interesting, but especially the Introduction could be more concise. Some of the very basics (definition of allergies, prevalence, consequences of unnecessary diets) could be left out, as this kind of an article hardly is interesting to someone without any previous knowledge on (paediatric) allergies.

2. The study population should be defined in more detail to help the reader decide if the results can be generalised to their practice. The authors do not explain in the Methods, what kind of hospital the patients were from. This information is crucial to understand if the study population represents otherwise healthy children from some geographic area, children with some other underlying medical conditions, or even children followed in a tertiary centre. This information is then provided in the Discussion but it would make the article clearer to include it in Methods. In addition, it would be essential to explain more thoroughly if the children were otherwise healthy and referred only for suspicion of allergy, or if e.g. children with gastrointestinal diseases, developmental delay, behaviour problems, etc. were included.

3. I wonder if Table 4 could be made more informative e.g. by regrouping the individual patients differently. It seems to me that clinically, the most relevant thing would be to know how many patients had severe acute reactions from small amounts of allergen, etc. Could the patients possibly be regrouped by the reaction type, severity, or the eliciting dose? The representation that the authors have chosen does not seem to make the most of this valuable data. In contrast, I find Tables 2 and 3 remarkably well designed and clear.

C) Discretionary revisions

1. Many readers, including myself, may not be very familiar with the amount of milk (or similar foods) that the studied amounts of CMP (in mg) represent. This information is provided in the text, but it could make Figure 1 and Table 4 more informative to include some description of the amount of milk that 18 mg, 720 mg or 1080 mg represent (= were the patients able to tolerate a drop, a few millilitres, or even half a cup of milk?).

2. The finding that infants tolerate larger amounts of milk than do older children is very interesting and could deserve even more speculation. The idea that the authors present is that infants with high MEDs gain tolerance (and, thus, that MEDs could possibly be used as prognostic factors) and only those with low MEDs are left with allergy when they grow older. Could it also be so that this represents some kind of a selection bias, with small children being referred more easily for diagnostic evaluation (even if they are not very allergic)? Or that infants, in general, consume more milk and those with relatively high MEDs come to seek medical attention as compared to older children with similar MEDs who would just start drinking less milk and never seek advice (and diagnosis)?
3. The authors explain very clearly why sIgE values were not measured, and this information is crucial as in many other countries, sIgEs are routinely determined. I feel it would have been very interesting to obtain the sIgE levels for milk in those children with acute (probably IgE+) reactions, and to see if sIgE levels correlate with the MED or with the severity of the reaction in this population. This information is hardly available any more, but it would perhaps have added to the value of the study.

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**
I declare that I have no competing interests.