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In response to Frequency of guideline-defined cow's milk allergy symptoms in infants: Secondary analysis of EAT trial data by Vincent et al

To the Editor,

We read with interest the recently published work by Vincent et al,¹ a secondary analysis from the EAT study, which looks at the frequency of non-IgE-mediated cow's milk allergy (non-IgE-CMA) symptoms in children in their cohort. We strongly agree with the primary conclusion that there may be overdiagnosis of non-IgE-CMA. We also share their concerns that overdiagnosis likely contributes to excessive dietary elimination during the key immunologic period in the first year of life. However, we would contest both the assertion that the 'established' incidence of non-IgE-CMA is well known to be 1%, and we also make note of the missed opportunity to evaluate outcomes in the EAT population in relation to the symptom frequency data analysed. Without that analysis, it is more difficult to interpret their findings.

The study of non-IgE-CMA is hampered by differing criteria and guidelines (by specialty and geography) and a lack of a practical gold standard. EuroPrevall² and similar studies were not designed to effectively detect non-IgE-mediated food allergies. They report a ~1% incidence of non-IgE-CMA, but enrollees had to reach out to a study centre with a 'suspected allergy to a food' to even be evaluated before 1 year of age. Most of the time, initial symptoms of non-IgE-CMA are, as the authors' note, quite non-specific and often not obviously related to a specific food consumption. In fact, the most common presentation of non-IgE-CMA in infancy is food protein-induced allergic proctocolitis (FPIAP), which presents in the primary care setting in the first month or two of life. The GMAP study,³ a prospective observational cohort of 1000 healthy infants, which was specifically designed to prospectively determine the incidence of FPIAP as it is diagnosed in the United States, found a staggering incidence of 17% in suburban Massachusetts. We required objective findings of gross or microscopic blood in the stool for diagnosis in addition to clinical symptoms, but the study was observational and thus challenges were almost never done (as the authors' note is also the case in the United Kingdom). Even when analysed by more stringent criteria requiring gross blood in their stools, the cumulative incidence was still 7% in this healthy infant population. Children diagnosed with FPIAP had more family history of food allergies and increased risk of concurrent eczema and subsequent IgE-mediated food allergy (IgE-FA),^{3,4} underscoring the likelihood of a truly shared

pathophysiology. Of course, to the overall point of Vincent et al., the IgE-FA in this FPIAP population could also be compounded (or driven) by the dietary restrictions commonly used to treat these children (which is likely used more, and for longer than necessary, due to lack of guideline-recommended challenges in practice). Therefore, we share the authors' concern that lack of challenges is problematic and that there may be many untoward consequences of overdiagnosis or prolonged dietary restriction in children with suspected non-IgE-CMA.

A major unacknowledged limitation of Vincent et al, however, is that they will have missed almost this entire FPIAP population in their report because the EAT study⁵ was not designed to identify them. EAT did not enroll children until 3 months of age, when most FPIAP has already presented (median age of diagnosis in GMAP was 34 days). EAT also restricted the population to those still exclusively breastfeeding at 3 months of age. If we applied these same criteria to our GMAP cohort, we would have missed 85% of the cases (129 of the 153 cases of FPIAP), because they were no longer exclusively breastfed and/or had already been diagnosed by 3 months, leaving us with a misleading incidence of about 5% (3% with gross blood). Consistent with this selection bias against the predominant presentation of non-IgE-mediated FA, Vincent et al found no association between symptoms analysed and eczema, whereas we found a strong association between eczema and FPIAP in our cohort (OR 1.5, $p = .025$). The fact is that allergists rarely, if ever, see these patients clinically; most are managed by their paediatrician, and some of the more severe or persistent cases are referred to paediatric gastroenterology. We believe this bias has led to FPIAP being significantly understudied and underappreciated in the allergy literature—even as we agree that the diagnosis needs to be more rigorously made.

Perhaps the most central issue with the current status of diagnosis of non-IgE-CMA is that home challenges are rarely done. The iMAP guidelines⁶ clearly require it for confirmation of diagnosis. Therefore, 'overdiagnosis' cannot fairly be blamed on the guidelines themselves, but rather on providers not following them through. While home challenges can be difficult and subject to bias, we believe they are better than no challenge in the absence of an alternative strategy or more accurate test. Furthermore, in our clinical practices, many children fail to react to a challenge 4 weeks after

clear resolution of symptoms with milk elimination. While this could represent an initial 'false-positive' diagnosis, it may also represent a relatively transient process which resolves with a short washout period. Either way, systematic challenges offer value in getting children back on a typical diet early. We suspect the rates of non-IgE-CMA diagnosis/treatment would at least regress to the mean if all children with possible non-IgE-CMA were actually challenged as recommended.

In summary, we agree that (1) the array of symptoms that could be suggestive of a non-IgE-CMA is broad and non-specific and (2) that there is likely to be significant overdiagnosis of non-IgE-CMA given the lack of practical gold standards. However, we would also suggest that (3) the iMAP guidelines have the potential to help for now if they are followed carefully and challenges are actually performed, (4) that the 'true' incidence of non-IgE-CMA may be lower than 17% but surely is higher than 1%, and (5) that multidisciplinary research to address these concerns and identify better diagnostic approaches is essential as most of these children never see an allergist. We may never be able to get at the true incidence of non-IgE-CMA due to the logistical and ethical challenges of diagnostic sigmoidoscopes and DBPCFCs and the lack of a better gold standard. But, we can and must work together across specialties towards better diagnostic and management strategies for these infants. We would welcome a new multidisciplinary international effort (made up of at least allergists, paediatricians and gastroenterologists) to create stricter and more evidence-based guidelines. Without them, we fear the rates of diagnosis of non-IgE-FA, prolonged diet elimination, and perhaps increased IgE-FA as a result will only increase.

CONFLICTS OF INTEREST

There are no conflicts of interest to disclose.

AUTHOR CONTRIBUTIONS

VMM, MM, QY and WGS designed this correspondence, VMM and MM conducted the post hoc data analysis, VMM drafted the correspondence, and all four authors contributed to critical revisions and approved the final manuscript.

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DATA AVAILABILITY STATEMENT

The data that support the findings in this correspondence are available from the corresponding author upon reasonable request.

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