

THE AUTHORS REPLY: Berti asks whether a genetic analysis of ANCA-negative granulomatosis with polyangiitis might be a useful way of supporting or refuting our observation that the associations of *HLA-DP*, *SERPINA1*, and *PRTN3* are primarily with anti-proteinase 3 disease rather than with granulomatosis with polyangiitis. We think this is unlikely to be the case for two reasons, one practical and one theoretical.

First, ANCA-negative granulomatosis with polyangiitis is uncommon, making up approximately 33% of the rare localized form of granulomatosis with polyangiitis and less than 10% of cases of systemic granulomatosis with polyangiitis.¹ It is therefore unlikely that a cohort large enough for meaningful genetic analysis could be assembled, and indeed it is for that reason we excluded ANCA-negative vasculitis from our analysis.

Second, even if we had observed an association between ANCA-negative granulomatosis with polyangiitis and these SNPs, it would not have been possible to prove that this association was not the result of an anti-proteinase 3 immune response. It could be that some cases were ANCA-negative because of the insensitivity of the test method used — something that is known to ac-

count for a proportion of the cases labeled as ANCA-negative granulomatosis with polyangiitis.²

Goldschmeding et al. raise the issue that the enzymatic activity of proteinase 3, perhaps influenced by autoantibody binding and by α_1 -antitrypsin, might play a role in ANCA-associated vasculitis pathogenesis. We referred to this briefly in the article but did not expand on it owing to space constraints. Our genetic data underscore Goldschmeding and colleagues' point that the pathogenic roles of proteinase 3 as an autoantigen and an enzyme are of interest and warrant further examination.

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Since publication of their article, the authors report no further potential conflict of interest.

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DOI: 10.1056/NEJMc1209906

Oral Immunotherapy for Egg Allergy in Children

TO THE EDITOR: In the study by Burks et al. (July 19 issue),¹ 22 of 40 patients (55%) passed the oral food challenge of 5 g of egg-white powder after 10 months of oral immunotherapy with egg-white powder.

However, in the study by Burks et al., no oral food challenge was performed at baseline, although children with a history of anaphylaxis after egg ingestion were excluded. No clinical history of allergic symptoms and no in vitro test reliably predicts clinical food allergy.^{2,3}

How can we be sure that the children had egg allergy at baseline and the results of oral food challenge were related to oral immunotherapy?

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No potential conflict of interest relevant to this letter was reported.

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DOI: 10.1056/NEJMc1209949

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TO THE EDITOR: In the study by Burks et al., the egg-white powder used was made from chicken eggs. The components of egg-white proteins of different avian species are quite different with respect to both the content and the types. So, the desensitization of the patients during the immu-

notherapy was limited to egg white from hens; it was not related to all egg consumption. Chicken egg-white powder may not be very suitable for desensitization in Asians.¹ Do the authors have any data on other egg types?

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DOI: 10.1056/NEJMc1209949

TO THE EDITOR: Although the research of Burks et al. has shown that oral immunotherapy can be used in the treatment of children with egg allergy, we have concerns that this procedure might induce eosinophilic esophagitis due to extensive allergen exposure to the esophagus.¹ Several lines of evidence show that eosinophilic esophagitis can be triggered by extensive esophageal allergen exposure. First, studies have shown seasonal variation of eosinophilic esophagitis disease activity with exacerbations during periods of high pollen exposure.² Second, flare-ups of eosinophilic esophagitis can occur rapidly after reintroduction of the causative nutrients.³ Third, we recently observed two new cases of eosinophilic esophagitis, both of which occurred during ongoing oral immunotherapy for pollen allergy. Fourth, the occurrence of eosinophilic esophagitis after oral immunotherapy with milk has been reported.⁴ Burks et al. report gastrointestinal symptoms as adverse events, but they do not mention eosinophils. Do they have any data on eosinophils in the children with gastrointestinal reactions?

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DOI: 10.1056/NEJMc1209949

THE AUTHORS REPLY: Iacono and colleagues ask whether all the children enrolled were in fact allergic to eggs. Even though the children in our study did not have a baseline oral food challenge, they were considered to have egg allergy on the basis of their clinical history and age-dependent levels of serum IgE to egg white. Previous studies^{1,2} indicate that these criteria would identify children who had egg allergy and were not likely to outgrow their egg allergy during the study. The references cited by Iacono and colleagues are interesting, but they do not invalidate these diagnostic criteria. All the children who underwent the oral food challenge after 10 months of placebo oral immunotherapy did not pass the oral food challenge; these findings strongly suggest that the diagnostic criteria for egg allergy were appropriate and that all the children had egg allergy.

Meng and colleagues correctly point out that there are differences in the egg-white proteins of different avian species and that our study tested responses only to egg white from hens. Egg white from hens is appropriate for evaluating children in the United States. We do not have data on the skin-prick test responses of our study participants to egg-white proteins of other avian species or the skin-prick test responses of children living in Asia to hen and other avian egg-white proteins.

Alpan and colleagues raise the possibility of inducing or exacerbating preexisting eosinophilic esophagitis. In the various studies conducted with food oral immunotherapy,³⁻⁵ the most common allergic side effect leading to withdrawal of the participants was gastrointestinal. In our study, three of the four children who withdrew in the first 10 months had persistent gastrointestinal symptoms. Each child's symptoms diminished after discontinuing the egg-white oral immunotherapy; therefore, further gastrointestinal evaluation, including endoscopic biopsies, was not performed. Because biopsies were not performed, there is no information on eosinophil accumula-

tion. Data are lacking on whether food oral immunotherapy will induce or exacerbate symptoms of eosinophilic esophagitis. The frequency of allergic gastrointestinal side effects of food oral immunotherapy is important to consider in evaluating oral immunotherapy as a potential therapy in the future.

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DOI: 10.1056/NEJMc1209949

Breathtaking Journey

TO THE EDITOR: In their description of a patient with the hantavirus pulmonary syndrome, Rhee et al. (Aug. 2 issue)¹ note that hypoxemia developed after the patient received intravenous fluids. A lack of hemodynamic improvement in response to fluids is a hallmark of the hantavirus pulmonary syndrome,² and fluid restriction is a mainstay of therapy.^{3,4} This serves as an important differentiation between the hantavirus pulmonary syndrome, in which patients tend to die from cardiogenic shock,⁴ and other infections causing distributive (vasodilated) shock. One third of patients with this syndrome die while receiving conventional therapy — in most cases, soon after the onset of cardiopulmonary symptoms.⁴ Because results from serologic testing are not immediately available, review of a blood smear is key, because the occurrence of four of the following five hematologic findings is 96% sensitive and 99% specific for hantavirus: presence of myelocytes, more than 10% immunoblasts, absence of toxic granulations in neutrophils, hemoconcentration, and thrombocytopenia.⁵ Frequently, febrile patients receive fluid boluses at referring facilities before diagnosis, leading to refractory pulmonary edema. This is one factor that led our institution to develop a protocol for the prophylactic placement of femoral vascular-access catheters in anticipation of possible rapid cardiopulmonary decompensation and an emergent requirement for extracorporeal membrane oxygenation (ECMO).⁶ Although the severe cardiopulmonary failure is

life-threatening, its short, self-limiting course makes ECMO an ideal therapy for patients who do not have a pressor response to conventional fluid-replacement treatment.

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DOI: 10.1056/NEJMc1210462

THE AUTHORS REPLY: Frizzell and Boivin add some important observations on the presentation and management of the hantavirus pulmonary syndrome, which may escape the notice of providers in centers that rarely see this condition. The early recognition and linkage of the unusual overlap