

Quintupling or quadrupling inhaled glucocorticoids to prevent asthma exacerbations?

It is rare to be able to write about an important clinical question where there are new paediatric and adult data. The New England Journal of Medicine has recently published two papers looking at whether quadrupling or quintupling inhaled glucocorticoids at the start of an exacerbation can prevent the need to use a burst of prednisolone. The methodologically stronger US study recruited 254 children aged 5-11 years with mild-to-moderate persistent asthma and at least one severe asthma exacerbation in the previous year.¹ Over a year, they were managed with maintenance low-dose inhaled glucocorticoids (fluticasone propionate 88 mcg twice daily) and were randomized to continue low dose or the use of a quintupled dose for a week at the first sign of an exacerbation using a double-blind approach. There was no significant difference in the rate of severe asthma exacerbations between the two groups but the quintupling group had a significantly lower growth rate (0.23 cm per year).

The UK adult study used an open design with participants quadrupling their usual routine inhaled corticosteroid inhaler when their asthma control deteriorated.² It had a pragmatic design where participants were not swapped to the same trial medication. A total of 1922 participants with mild-to-moderate persistent asthma and a history of a severe exacerbation in the last year were randomized and followed for a year. The quadrupling group had significantly less severe exacerbations (hazard ratio 0.81, 95% confidence interval 0.71-0.92).

So two similar trials giving different answers. The conclusions from the adult study look convincing with very large numbers, narrow confident interval and the pragmatic design. Additionally, a subgroup analysis suggested that both mild-to-moderate and severe patients benefited from the intervention. The adult study though was open, and the effect size was not as large as the investigators expected. The paediatric trial enrolled children with less severe asthma, and they also had much fewer exacerbations than expected. But with 254 participants, they still had sufficient power to detect a moderate benefit. So, it is possible that childhood and adult asthma are behaving differently here, and a very large dose of inhaled corticosteroids is only effective in preventing severe exacerbations in adults? This emphasizes the need for timely paediatric studies; treatment recommendations cannot simply be made on the basis of extrapolations from adult data.

In this month's issue of the Journal, Reier-Nilsen et al³ assess whether clinical or immunological factors are associated with the threshold for reactivity at double-blind, placebo-controlled food challenge in children with peanut allergy. They found that basophil activation, peanut skin prick test diameter and the ratio of peanut-specific IgE/total IgE were significantly associated with the threshold of reactivity (Figure 1) and lowest observed adverse events level (LOAEL). Unfortunately, none of the factors were associated with severity—predicting who is a risk of severe reactions is still beyond our ability.

Ruft et al⁴ have developed and validated a disease-specific quality of life questionnaire for cholinergic urticaria. Cholinergic urticaria is a troublesome disease for patients.⁵ The researchers used an established approach, developing a list of potential questions using the published literature, interviews with patients and expert opinion. The prototype questionnaire was then assessed in 88 patients with the data being used to develop the final questionnaire. Their Cholinergic Urticaria Quality-of-Life Questionnaire (CholU-QoL) demonstrated good validity and test-retest reliability. In my experience, these disease-specific questionnaire are very helpful in quantifying the impact of disease on a patient and whether or not a new intervention is helpful for them.

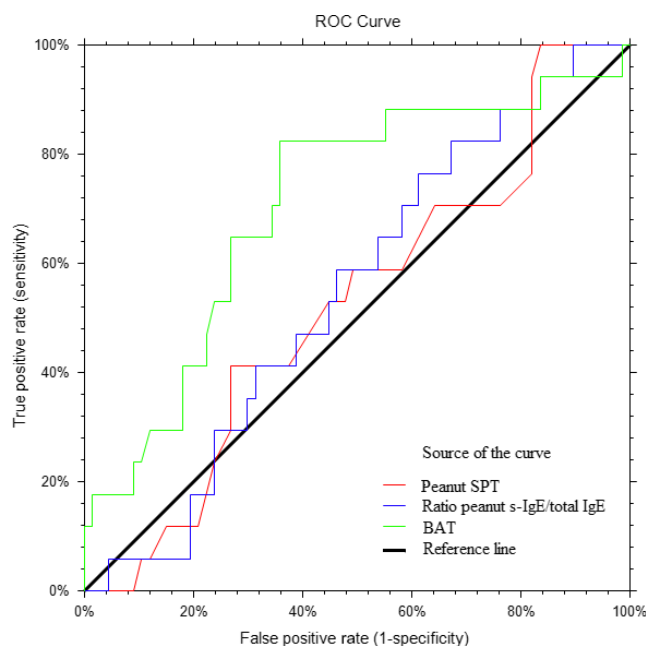


FIGURE 1 Receiver operating characteristic curves predicting very low threshold for allergic reaction to peanut [(see Figure 2 in T. Reier-Nilsen et al. (pp. 415-423)]

Caption to cover illustration: The cover image, by S. Blank et al., is based on the Review Component-resolved diagnostics to direct in venom immunotherapy: Important steps towards precision medicine, DOI: <https://doi.org/10.1111/cea.13090>.

EE This logo highlights the Editor-in-Chief Editorial articles on the cover and the first page of each of the articles.

Lastly, can I be forgiven for mentioning one of my papers? In this issue of the Journal, we publish data on the trajectory of food allergy across the whole of childhood and adolescence.⁶ We have followed up the 1989 Isle of Wight birth cohort at 1, 2, 4, 10 and 18 years (n = 1456). While food allergy is thought to be most prevalent in young children, 4% of 18-year-olds had a good history of an IgE-mediated food allergy. This is half the rate seen in the BAMSE cohort⁷ but we used a more robust definition. The key food allergens in 18-year-olds in the Isle of Wight cohort were peanuts, tree nuts, fruits, wheat, hen's egg and cow's milk. We now need to look at the trajectory into adulthood where information about food allergy at a population level is sparse.⁸

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REFERENCES

1. Jackson DJ, Bacharier LB, Mauger DT, et al. Quintupling Inhaled Glucocorticoids to Prevent Childhood Asthma Exacerbations. *N Engl J Med*. 2018;378:891-901.
2. McKeever T, Mortimer K, Wilson A, et al. Quadrupling inhaled glucocorticoid dose to abort asthma exacerbations. *N Engl J Med*. 2018;378:902-910.
3. Reier-Nilsen T, Michelsen MM, Løedrup KC, et al. Predicting reactivity threshold in children with anaphylaxis to peanut. *Clin Exp Allergy*. 2018;48:415-423.
4. Ruft J, Asady A, Staubach P, et al. Development and validation of the Cholinergic Urticaria Quality-of-Life Questionnaire (CholU-QoL). *Clin Exp Allergy*. 2018;48:433-444.
5. Asady A, Ruft J, Ellrich A, Hawro T, Maurer M, Altrichter S. Cholinergic urticaria patients of different age groups have distinct features. *Clin Exp Allergy*. 2017;47:1609-1614.
6. Venkataraman D, Erlewyn-Lajeunesse M, Kurukulaaratchy RJ, et al. Prevalence and longitudinal trends of food allergy during childhood and adolescence: results of the Isle of Wight Birth Cohort study. *Clin Exp Allergy*. 2018;48:394-402.
7. Vetander M, Protudjer JLP, Lilja G, et al. Anaphylaxis to foods in a population of adolescents: incidence, characteristics and associated risks. *Clin Exp Allergy*. 2016;46:1575-1587.
8. Deschildre A, Lejeune S, Cap M, et al. Food allergy phenotypes: the key to personalized therapy. *Clin Exp Allergy*. 2017;47:1125-1137.