

Letters

COMMENT & RESPONSE

Risk of Appendicitis in IgE-Mediated Allergy

To the Editor We read with interest the recent work by Salö et al,¹ reporting a low odds ratio of complicated appendicitis (adjusted odds ratio, 0.33; 95% CI, 0.18-0.59) in a subgroup of patients with documented IgE-mediated allergy. However, the conclusion of lower risk of complicated appendicitis in allergic children is not necessarily valid. The prevalence of allergy in the population at risk of appendicitis in the study was not presented, and therefore, the absolute risk of complicated appendicitis could be the same as in the nonallergic group, provided that the allergic children had an increased risk of uncomplicated appendicitis. If the proportion of allergic to nonallergic children with appendicitis is as reported in the study, the absolute risk of complicated appendicitis would be equal in allergic and nonallergic children, given a prevalence of allergy of 7%. With a prevalence of allergy lower than 7%, the absolute risk of complicated appendicitis in allergic children would be higher than in nonallergic children.

However, reliable and applicable information on the prevalence of IgE-mediated allergy is available from the Swedish BAMSE cohort,² where a composite prevalence of IgE sensitization and allergic symptoms to pollen, fur and mites, or egg and milk, was found in 18% of children at age 8 years and 28% at age 16 years.³ This range provides a reasonable estimate on the prevalence of IgE-mediated allergy, and the proportion found in the appendicitis cohort was lower (16.9%) with median ages of 11 and 10 years in the allergic and nonallergic subgroups. Data on antibiotic allergies were not available, but the postulated effect on the risk of complicated appendicitis was found to be small by Salö et al.¹

IgE sensitization was further found in 35% of children at age 8 years and in 46% at age 16 years in the BAMSE cohort,

and allergy-related symptoms, regardless of IgE sensitization, were found in around 30%.⁴ If the causal mechanism of altered appendicitis pathophysiology is associated with IgE sensitization, rather than the manifestation of allergic symptoms, the authors' hypothesis that allergy influences the severity of appendicitis may also be extended to the absolute risk of any appendicitis.

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1. Salö M, Gudjonsdottir J, Omling E, Hagander L, Stenström P. Association of IgE-mediated allergy with risk of complicated appendicitis in a pediatric population. *JAMA Pediatr*. 2018;172(10):943-948. doi:10.1001/jamapediatrics.2018.1634
2. Wickman M, Kull I, Pershagen G, Nordvall SL. The BAMSE project: presentation of a prospective longitudinal birth cohort study. *Pediatr Allergy Immunol*. 2002;13(s15)(suppl 15):11-13. doi:10.1034/j.1399-3038.13.s15.10.x
3. Wickman M, Asarnej A, Tillander H, et al; MeDALL consortium. Childhood-to-adolescence evolution of IgE antibodies to pollens and plant foods in the BAMSE cohort. *J Allergy Clin Immunol*. 2014;133(2):580-582. doi:10.1016/j.jaci.2013.09.009
4. Ballardini N, Bergström A, Wahlgren C-F, et al. IgE antibodies in relation to prevalence and multimorbidity of eczema, asthma, and rhinitis from birth to adolescence. *Allergy*. 2016;71(3):342-349. doi:10.1111/all.12798

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In Reply We thank Dahlberg and Everhov for their implicit validation of the representativeness of our study cohort and for advertising the fact that IgE-mediated allergy was associated with a reduced odds of complicated appendicitis.¹ In our center, children with IgE-mediated allergy had 3 times lower risk of complicated appendicitis (adjusted odds ratio, 0.33; 95% CI, 0.18-0.59), after adjustment for age, sex, primary health contacts, seasonal antigenic exposure, allergy medications, and duration of symptoms. We appraised unmeasured confounding but not the risk of selection bias, and we therefore welcome the endorsement offered by Dahlberg and Everhov. The rate of our primary exposure was on par with the mean allergy prevalence in their unique BAMSE project,² an ongoing, longitudinal, prospective birth cohort including more than 4000 Swedish children.

Our study was hypothesis driven based on previous literature that suggested distinct immune cell responses for uncomplicated and complicated appendicitis,^{3,4} with IgE being the immunologic trigger or defender similar to other diseases.^{5,6} Still, Dahlberg and Everhov are correct in their comment about odds ratio being only a relative measure and that an alternative and possibly equally intriguing explanation to our findings would be that allergic children in fact have an increased risk of uncomplicated appendicitis. This uncertainty, combined with the considerable clinical relevance associated with such substantial risk modification, clearly commends confirmation in prospective cohorts elsewhere.

The suggested protective allergic association implies that an immunologic disposition potentially modifies the clinical pattern of appendiceal disease. Further pathogenesis research and immunology research in this area could elucidate the guts of appendicitis and hopefully lead to novel opportu-

nities for predicting disease severity in clinical practice. Our study was not powered enough to reliably rule out effect-modification by allergy medications, in which case there may even be direct preventive or therapeutic implications.

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1. Salö M, Gudjonsdottir J, Omling E, Hagander L, Stenström P. Association of IgE-mediated allergy with risk of complicated appendicitis in a pediatric population. *JAMA Pediatr*. 2018;172(10):943-948. doi:10.1001/jamapediatrics.2018.1634
2. The BAMSE project. <https://snd.gu.se/en/catalogue/study/ext0037>. Accessed December 5, 2018.
3. Rubér M, Andersson M, Petersson BF, Olaison G, Andersson RE, Ekerfelt C. Systemic Th17-like cytokine pattern in gangrenous appendicitis but not in phlegmonous appendicitis. *Surgery*. 2010;147(3):366-372. doi:10.1016/j.surg.2009.09.039
4. Andersson RE, Lambe M. Incidence of appendicitis during pregnancy. *Int J Epidemiol*. 2001;30(6):1281-1285. doi:10.1093/ije/30.6.1281
5. Sahami S, Kooij JA, Meijer SL, Van den Brink GR, Buskens CJ, Te Velde AA. The link between the appendix and ulcerative colitis: clinical relevance and potential immunological mechanisms. *Am J Gastroenterol*. 2016;111(2):163-169. doi:10.1038/ajg.2015.301
6. Wu LC, Zarrin AA. The production and regulation of IgE by the immune system. *Nat Rev Immunol*. 2014;14(4):247-259. doi:10.1038/nri3632