syndrome). The risk for anaphylaxis is significant, as is the chance of spontaneous resolution. Negative results of cold stimulation testing do not exclude anaphylaxis risk. Patients and families should be counseled regarding the risks of swimming, and epinephrine prescription is appropriate.

REVIEWER COMMENTS: This article follows a previous report from the same group, which described similar findings in 2004, with practical findings for patient management. ACU is uncommon, with an estimated incidence of 0.05%. The authors of this report deliver several important take-home messages: (1) ACU carries real risk for anaphylaxis; (2) counseling should address risks of swimming and other cold exposures; (3) prescribing epinephrine autoinjectors is appropriate for patients with ACU; (4) the ice cube test cannot be used to exclude anaphylaxis risk; (5) disease resolution is less likely in patients with anaphylaxis; (6) patients with ACU have greater risks of asthma, rhinitis, eczema, and food allergy; and (7) nearly 10% of children and adolescents may outgrow this diagnosis in time.

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INSECT STING ALLERGY

A Longitudinal Study of Hymenoptera Stings in Preschool Children

Clifford D, Ni Chaoimh C, Stanley E, O'B Hourihane J. *Pediatr Allergy Immunol*. 2019;30(1):93–98

PURPOSE OF THE STUDY: To prospectively determine the incidence of Hymenoptera stings in children <5 years.

STUDY POPULATION: This is a prospective longitudinal observational study of Irish newborns from the BASELINE Cohort Study. This study included 2137 newborn infants who were recruited from 2008 to 2011 and managed until 5 years of age.

METHODS: Trained researchers administered questionnaires at 6 months, 12 months, 2 years, and 5 years of age. The questionnaires were used to inquire about the occurrence of sting events. At ages 2 and 5 years, all children were seen for visits and underwent skin prick testing (SPT) to bee, Vespula, and 9 other common allergens. A positive test result was a wheal 3 mm or greater, with histamine as a positive control. If the SPT result was positive or the children reported a history of a sting event, allergy-specific immunoglobulin E (spIgE) was collected.

RESULTS: Of the 2137 newborns identified, 1226 were managed for the complete 5 years. At 6 months, 6 of 1809 (0.33%) children reported sting events. At 1 year, 16 of 1691 (0.9%) children reported sting events. At 2 years, 77 of 1209 (6.8%) children reported sting events. SPT was performed at age 2, with 11 positive results out of 1232 tests (0.89%). At 5 years, 268 of 1226 (21.9%) had reported sting events with 0 systemic reactions. SPT was performed at age 5, with 4 of 937 (0.4%) children having positive test results. None of the children that had positive SPT results at age 2 had positive results at age 5. Thirty-nine children underwent spIgE testing, with only 2 having positive results (5.1%). Of the 2 patients who tested spIgE positive, 1 had a history of a sting event without reaction and negative SPT result, and the other had a positive SPT result at age 2 years that was negative by age 5 without a sting event. Children who had a positive SPT result (62.5%) to bee or wasp were found to have a higher rate of allergic sensitization to aeroallergen and food in comparison with children with negative SPT results (23.8%). Of the total 367 sting events, 10 stings (2.7%) were systemic reactions reported by the parents that did not require evaluation or treatment by a physician.

CONCLUSIONS: Hymenoptera sting incidence increases with age. A positive SPT result does not correlate with sting history and does not predict venom allergy in patients who have not been stung. Venom SPT should not be performed in the general preschool-aged population.

REVIEWER COMMENTS: This study highlights the low incidence of Hymenoptera sting events and reactions in the general preschool population. The findings confirm that "screening" tests for venom allergy should not be performed in the preschool population because results do not correlate with clinically significant reactions. Testing should be reserved for those with a clinical history suggestive of venom hypersensitivity, consistent with existing recommendations.

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Food Allergy

IGE–MEDIATED FOOD ALLERGY

Early–Life Gut Microbiome and Egg Allergy

Fazlollahi M, Chun Y, Grishin A, et al. *Allergy*. 2018;73(7):1515–1524

PURPOSE OF THE STUDY: To examine the association between early-life gut microbiota and the development of egg allergy.

STUDY POPULATION: Data from 141 children, 66 with egg allergy and 75 controls, from the multicenter Consortium of Food Allergy Research study from 5 centers were analyzed. Subjects were enrolled from age 3 to 16 months. Baseline characteristics were as follows: 73% white, 67% boys, 39% breastfeeding, and 90% taking solid foods.

METHODS: At enrollment, fecal samples were collected and egg-specific serum immunoglobulin E and egg skin prick tests were performed. To characterize the gut microbiome, 16S ribosomal RNA sequencing was used. Analysis for the primary outcome measure of egg allergy at enrollment and the secondary outcomes of egg sensitization at enrollment and resolution of egg allergy by age 8 years were performed with respect to characteristics of the gut microbiome.

RESULTS: Children with egg allergy, when compared with controls, had increased diversity and distinct taxa in the early-life gut microbiome. Genera from the *Lachnospiraceae*, *Streptococcaceae*, and *Leuconostocaceae* were differentially abundant in children with egg allergy. Compared with controls, purine metabolism was decreased in children with egg allergy (Kruskal-Wallis test, adjusted $P = 0.021$), as assessed by predicted metagenomic function of taxonomic units. Egg sensitization was associated with greater gut microbiome diversity and genera from *Lachnosipaceae* and *Ruminococcaceae*. However, among those with egg allergy, there was no association between early-life gut microbiota and egg allergy resolution by age 8 years.

CONCLUSIONS: This study showed distinguishing characteristics of early-life gut microbiota in children with egg allergy and egg sensitivity.

REVIEWER COMMENTS: This study provides data that could be helpful in targeting preventive or therapeutic interventions for the development of egg allergy. Alterations in the gut microbiome appear to be present in a variety of allergic diatheses, and there may be a potential for impact through restoring the microbiota to a phenotype that more closely resembles nonallergic controls.

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Cesarean Delivery, Preterm Birth, and Risk of Food Allergy: Nationwide Swedish Cohort Study of More Than 1 Million Children

Mitselou N, Hallberg J, Stephansson O, Almqvist C, Melén E, Ludvigsson JF. *J Allergy Clin Immunol*. 2018;142(5):1510–1514.e2

PURPOSE OF THE STUDY: To examine the association between cesarean delivery, preterm birth, low birth weight, small for gestational age (SGA), large for gestational age (LGA), and low 5-minute Apgar score and future food allergy (FA).

STUDY POPULATION: This was a longitudinal cohort study of more than nearly 1.1 million consecutive births (2001–2012) recorded in the Swedish Medical Birth Register for whom there were complete data regarding items of interest for the study.

METHODS: Data collection included sex, mode of delivery, gestational age (GA), birth weight, and 5-minute Apgar score. Hazard ratios (HRs) and confidence intervals (CIs) were calculated to estimate the association between these characteristics and FA up to 2013.

RESULTS: FA was present in 2.5% of children (median age at diagnosis: 1.6 years; range: 0.2–12.8 years), with girls (57.1%) more likely than boys (42.9%) to have FA. FA was positively associated with cesarean delivery (HR: 1.21; 95% CI: 1.18–1.25). Very preterm birth (<32 weeks' GA) was negatively associated with future FA (HR: 0.74; 95% CI: 0.56–0.98), but GAs of 32 to 36 and ≥42 weeks were not associated with risk of FA. The risk for future FA was increased in infants who were LGA (HR: 1.15; 95% CI: 1.10–1.19) and in those with a 5-minute Apgar score <7 (HR: 1.22; 95% CI: 1.10–1.36). In contrast, SGA was not associated with future risk of FA. Adjusting for covariates, the authors calculated that for every 1000 children delivered by cesarean, 5 extra children had FA, as compared with the reference group, and 17% of FAs in children so delivered might be attributable to the mode of delivery. In similar calculations, it was estimated that 13% of FAs in infants who were LGA and 18% of FAs in infants with low 5-minute Apgar scores were attributable to those risk factors.

CONCLUSIONS: Analysis of a large database revealed an increased risk of future FA in children delivered by elective or emergency cesarean as compared with those delivered vaginally. Very preterm infants were at lower risk of future FA. Infants who were LGA and those with a 5-minute Apgar score <7 were also at increased risk of FA.

REVIEWER COMMENTS: We can only speculate reasons for the observed associations in this study. In contrast to the sterility of a cesarean delivery, vaginal delivery exposes newborns to maternal flora. With profound interest in the human microbiome, we can hypothesize that different modes of delivery affect the diversity of gut flora, placing certain groups at risk for FA, other atopic conditions, and perhaps conditions unrelated to allergy and immunology. In future prospective studies, it would be of great interest to examine the intestinal flora of children with and without FA delivered vaginally or by cesarean delivery. We can also speculate that the very preterm infants' neonatal care (including early oral introduction of food) might induce tolerance. An important covariate not examined in all these risk groups was formula versus breastfeeding and duration of nursing. That information could not be gleaned from the database. So how do we use these data in our day-to-day practice? At the least, this study adds to the complexity in identifying risks for FA, providing "food for thought."

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Early–Life Gut Microbiome and Egg Allergy

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Early–Life Gut Microbiome and Egg Allergy

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