

reported.^{5–7} Absorption of bacitracin through open wounds and exposed vessels may lead to high serum drug levels. It is important for allergists to review all records and communicate with anesthesiologists and surgeons. Reliance on the anesthesia medication record alone may be insufficient because use of topical antibiotic irrigation solutions may not be listed there. When asked, patients may even recall allergic reactions to bacitracin ointment in the past.

A comprehensive drug allergy evaluation for intraoperative anaphylaxis should include evaluation of all antibiotic exposures, including irrigation solutions, as a potential cause of anaphylaxis. Bacitracin skin testing is not standardized, and its predictive value is unknown. Approaches used in previous case reports of anaphylaxis and elevated serum tryptase levels include skin prick testing to bacitracin at the same strength of commercial bacitracin in ointment (500 U/g) and/or solution (150 U/mL).⁵ Because of variability with skin testing with ointments, skin testing with solutions may be preferred when available, particularly when intradermal testing for drugs is planned.

As this case exemplifies, it is important for physicians to be aware of bacitracin's sensitizing capacity. Although it is a rare cause of intraoperative anaphylaxis, potential allergy to bacitracin irrigation solution should be investigated in appropriate situations (such as when it is applied to damaged skin or mucosal surfaces). Awareness of bacitracin allergy is important for patients (so they can accurately report drug allergies) and for the anesthesiologists, surgeons, and allergy specialists caring for these patients. Increased knowledge of this may prevent subsequent exposures.

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Is avocado an emerging culprit in food protein–induced enterocolitis syndrome?



Food protein–induced enterocolitis syndrome (FPIES) is a poorly understood, immunologically mediated, gastrointestinal, food-associated hypersensitivity that often presents in infants and toddlers.¹ Incidence data are limited; estimates vary from 1.5 to 30 per 10,000 infants.^{2,3} Despite being more prevalent than previously thought, diagnostic delay is common⁴ and practitioner awareness of FPIES appears to be low.⁵ Reactions are typified by profuse vomiting, often accompanied by diarrhea, lethargy, and pallor, and may progress to severe dehydration, acidosis, and shock.^{1,4,6} FPIES has an acute form, with symptom onset 1 to 4 hours after an isolated ingestion of the trigger food, and a chronic form, with insidious onset with repeated, chronic ingestions. Diagnosis is clinical, based on typical presentation with resolution in hours (in acute) to days (in chronic), and is confirmed with oral food challenge in unclear cases.¹ Although reactions may be severe, overall disease prognosis is generally good, with most cases resolving in the first few years of life.^{1,4} Rigorous understanding of pathophysiology is lacking but does not appear to rely on IgE-mediated mechanisms. Altered cytokine profile elaborated by intestinal mucosa (with increased tumor necrosis factor α and decreased transforming growth factor β) is believed to contribute to increased intestinal permeability and fluid shifts. Peripheral activation of the immune response may explain systemic symptoms (lethargy, hypotension).¹ It is not known why certain foods are more commonly implicated in FPIES than others.

Cow milk, soy, grains, and egg are the most commonly reported culprits in FPIES, but many other foods have been implicated.^{3,4,7–9}

FPIES has been uncommonly reported with avocado,^{3,4,9} and recently published international consensus guidelines list avocado among the low-risk foods.¹ We report a perceived higher prevalence of FPIES to avocado, with 3 of 14 patients with FPIES presenting to a single practitioner in New York City during a 12-month period reporting FPIES reactions with avocado. These cases are summarized below and in Table 1.

Case 1 is a now 2-year-old boy with a history of atopic dermatitis. At 6 months of age, a few hours after eating salmon, he developed profuse vomiting and lethargy, prompting an emergency department visit; symptoms resolved in 1 hour without intervention. Subsequently, at 6 to 7 months of age, he developed profuse emesis, gray coloring, profound lethargy, and decreased responsiveness 4 hours after avocado ingestion. Symptoms again resolved without intervention within approximately 1 hour of onset. A subsequent exposure to avocado at 10 months of age resulted in a similar reaction.

Case 2 is a now 10-month-old girl with a history of atopic dermatitis and poor weight gain. At 7 months of age, starting 3 hours after ingestion of approximately 2 oz of avocado, she developed multiple episodes of forceful vomiting that lasted 90 minutes, followed hours later by diarrhea, which persisted for 2 days. Three weeks later, she developed 2 episodes of emesis that started 2 hours after ingesting 1 oz of avocado. At 8.5 months of age, 2.5 hours after ingesting banana, which she had tolerated several times previously, she developed profuse emesis and lethargy that lasted 4.5 hours.

Case 3 is a now an 11-month-old boy with a history gastroesophageal reflux, poor weight gain, and atopic dermatitis. Between 2 and 7 months of age, he had multiple episodes of profuse vomiting that started 3 hours after intermittent ingestion of cow milk formula followed by diarrhea. The first episode prompted a visit to the

Table 1
Summary of FPIES Cases Induced by Avocado

Feature	Patient 1	Patient 2	Patient 3
Sex	Male	Female	Male
Age at initial FPIES reaction	6 mo	7 mo	7 mo
Age at evaluation	2 y	8 mo	8 mo
Major diagnostic criteria ^a (required)	+	+	+
Vomiting 1–4 hours after ingestion of suspect food and lack of classic IgE-mediated skin and respiratory symptoms			
Minor diagnostic criteria ^a (3 required)			
Repetitive vomiting after the same food	+	+	–
Repetitive vomiting 1–4 hours after different food	+	+	+
Extreme lethargy with any reaction	+	–	– (Mild lethargy)
Marked pallor with any reaction	+	–	–
ED visit with suspected reaction	+	–	+
Need for IV fluids with suspected reaction	–	–	–
Diarrhea within 24 hours	–	+	+
Hypotension ^b	NA	NA	NA
Hypothermia ^b	NA	NA	NA
Dietary history			
Other foods avoided because of FPIES	Salmon	Banana	CM, oats
High-risk FPIES foods tolerated regularly in diet	CM, soy, grains, egg, poultry, legumes, sweet potato, banana	CM, sweet potato	Egg, poultry, banana, sweet potato, green pea
Atopic predisposition			
Personal history of atopy	AD	AD	AD, GER
Family history of atopy	Asthma	Asthma, FA, AR, urticaria	Asthma
SPT wheal, mm ^c			
Avocado	0	3	0
Other foods	0 to cod, salmon, tuna, and strawberry	Egg, 3; soy, 3; wheat, 4; peanut, 4; milk, 0	0 to egg, soy, and oat

Abbreviations: AD, atopic dermatitis; AR, allergic rhinitis; CM, cow milk; ED, emergency department; FA, food allergy; FPIES, food protein–induced enterocolitis syndrome; GER, gastroesophageal reflux; IV, intravenous; NA, not applicable; SPT, skin prick test.

^aAccording to published guidelines, diagnostic criteria for acute FPIES are as follows: all cases should meet the major diagnostic criterion and 3 minor diagnostic criteria.

^bVital signs at time of reactions to avocado not available for review.

^cSPTs were performed with Quintip (HollisterStier, Spokane, Washington) and commercial allergen extracts (Greer Laboratories, Lenoir, North Carolina).

emergency department, where he had an extensive, unrevealing workup. At 7 months of age, 3 hours after first ingestion of oatmeal, he developed repetitive vomiting and lethargy, which resolved in 1.5 hours. One week later, 2 to 3 hours after first ingestion of avocado, he developed projectile emesis followed by diarrhea.

Avocado appears to be a common food trigger among the patients in this center, with 3 of 14 patients with FPIES presenting in a 12-month period reporting avocado as an inciting food. All 3 patients presented at 6 to 8 months of age with repetitive emesis that developed 1 to 4 hours after avocado ingestion. Two patients had repeat exposures to avocado with symptom recurrence. All patients met the diagnostic criteria for acute FPIES to avocado: presentation was consistent with 1 major criterion and 3 of the 9 minor criteria from international consensus guidelines (Table 1).

Although this sample is certainly small, the prevalence of avocado FPIES among patients at the center appears significantly higher than previously reported. Avocado FPIES was reported 5 in 229 Australian cases,³ in 4 of 66 cases from a Philadelphia cohort,⁹ and in no cases from a cohort of 160 patients in New York City.⁴ Among pediatricians referring to the center's practice, avocado is often suggested as one of the first weaning foods; the enrichment of this population with patients who are frequently exposed to avocado at young ages may explain the increased prevalence noted in this center's patients.

For young infants with FPIES, continued expansion of the diet is important for nutrition and development. Guidelines recommend nutritional counseling with provision of a list of specific low-risk foods to be added to the diet at home.¹ For this patient population, nutritional counseling will be informed by awareness of avocado as a potentially common trigger for FPIES.

FPIES is a diagnosis of exclusion that requires a high index of suspicion. The diagnosis can be particularly challenging because of delay in symptom onset after trigger exposure, absence of respiratory and cutaneous findings, broad differential diagnosis, and lack of

confirmatory diagnostic testing other than oral food challenge. Furthermore, some commonly implicated foods in FPIES (such as rice, oat, sweet potato, among others) may be unlikely to cause IgE-mediated allergic responses. A clearer understanding of the underlying pathophysiology of FPIES and appreciation of the broad range of potential food triggers in FPIES will aid practitioners in considering this diagnosis and preventing future, potentially severe reactions.

In summary, avocado may be more commonly implicated as an FPIES trigger than previously thought. Knowledge of avocado as a potentially emerging trigger will aid timely diagnosis and guide complementary food introductions.

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Within-tester repeatability and between-tester reproducibility of skin test endpoint titration

A quality assurance study



Airway response to allergen depends on 2 independent factors: the degree of immunoglobulin E sensitivity to the allergen and the level of lower airway response as quantified by histamine or methacholine challenge.^{1,2} The former can be assessed by skin prick titration (SPT) to determine the skin test endpoint (STE), which for research purposes is the smallest concentration of allergen that produces a skin wheal of approximately 2×2 mm (according to the standard operating procedure for the AllerGen NCE Clinical Investigator Collaborative). Allergen challenges are often performed in research settings when investigating a potential new pharmaceutical therapy for allergic asthma.^{3,4} The allergen concentration causing an immediate response (ie, provocative concentration of allergen causing a 20% decrease in forced expiratory volume in 1 second) can be predicted from the STE and the methacholine response; these data are routinely used to predict a starting allergen inhalation concentration that is safe and relatively time efficient.^{2–5} It is important to note that the STE is relevant only in the research context and has no bearing on clinical practice.

Given the reliance on the STE for the safe performance of allergen challenge testing, it is important to know the within-tester repeatability and between-tester reproducibility of STEs for quality assurance purposes. Only 1 study ($n = 7$) has examined repeatability in SPTs, which found limited insignificant variability in the STE.⁶

Seventeen individuals with allergies were recruited from the local community; 13 (8 men and 5 women; mean age 31 years) completed the study and 4 were excluded for lacking responsiveness to any of the study allergens. Antihistamines were withheld for an appropriate washout before testing.⁷ Informed consent was obtained before study commencement. This study was exempt from ethics approval because the biomedical research ethics board of the University of Saskatchewan defined this as a quality assurance study.

Participants with a history of SPTs in our laboratory or with a strong clinical history with 1 of the study allergens were not required to undergo preliminary skin prick testing. The study required 3 study visits, 1 with each of 3 testers separated by 1 week. Each visit involved the duplicate STE procedure performed according to the AllerGen NCE Clinical Investigator Collaborative standard operating procedure by a different tester in random order. If a participant was new to the laboratory, then the participant underwent skin prick testing during the first laboratory visit

according to European standards with a histamine positive control and a saline (0.9%) negative control.⁷

The standardized allergen extracts used for the SPTs were cat hair ($n = 10$; 10,000 BAU/mL; HollisterStier, Spokane, Washington), house dust mite *Dermatophagoides farinae* ($n = 2$; 30,000 AU/mL; HollisterStier), and mixed northern grass pollen ($n = 1$; 40,000 PNU/mL; Omega Labs, Montreal, Quebec, Canada). These extracts were diluted in 0.9% saline to make doubling dilutions from 1:8 to 1:1,024 (1:2,048 and 1:4,096 were made for 1 subject with high responsiveness to low concentrations). The same set of dilutions was used for each of a participant's visits. For each SPT, a saline control and increasing concentrations from 1:1,024 (from 1:4,096 in 1 subject) to 1:8 were applied in duplicate to a participant's forearm using a single-head metal lancet. After a 10-minute wait, the wheal sizes were measured at perpendicular angles to record the reaction.

For statistical analysis, the STE ratios were inverted (ie, 1:1,024 became 1,024) and logarithmically transformed. The use of dilution ratios normalized the participants' responses across the 3 study allergens, each of which had a different stock concentration. The resulting STEs were analyzed for within-tester repeatability through 2-way mixed intraclass correlation coefficients (ICCs) of each tester's duplicate STEs. One-way analysis of variance was performed using the smaller of the duplicate STEs measured by each tester for each participant to analyze the between-tester reproducibility. Significance was 2-sided and set at .05. The STE was defined as the allergen concentration causing a wheal no larger than 2×2 mm to maximize patient safety; it is safer to predict a lower starting concentration of allergen for inhalation testing than it is to induce a major allergic response with the first concentration inhaled. Sequence analysis was performed to exclude any potential tester order effect, including the possibility of loss of potency of older concentrations ($P = .9769$).

Each tester produced duplicate STEs with high absolute agreement (tester 1 ICC = 0.955; tester 2 ICC = 0.986; tester 3 ICC = 0.977), which reflects strong within-tester repeatability. In total, 28 of 39 SPTs resulted in identical duplicate STEs; only 1 duplicate measurement differed by 2 doubling dilutions and the remaining differed by only 1. Although the between-tester reproducibility of the overall sample was strong ($P = .3567$; Fig 1), the individual data present important considerations. Between-tester STEs were equivalent to or within 1 doubling concentration in 6 of 13 participants and within 3 doubling concentrations in 3 of 13 participants; however, in 4 of 13 participants, the smallest STE of at least 2 of the testers differed by more than 3 doubling concentrations; this difference is significant in research, because it could translate to the induction of an excessive allergic response in clinical trial participants. Typically, a safe starting concentration for an allergen challenge is

Disclosures: Authors have nothing to disclose.

Funding Sources: Dean's Research Project Funding, College of Medicine, University of Saskatchewan.

Clinical Trial Registration: ClinicalTrials.gov, NCT03489694.