

weeks). These patients developed acute urticaria with a large local reaction at the injection site. Severe dermographism occurred a few days to 2 weeks after the initiation of intramuscular progesterone injections and persisted for weeks to months. The dermographism was generalized over the affected cutaneous area. Intramuscular injections were discontinued, and these patients were subsequently treated with a different vehicle of progesterone administration (Crinone 8%, 90 mg vaginally), with no further documented reactions.

The diagnosis of dermographism was confirmed by graded pressure induced by stroking the skin on the back with a tongue blade. Dermographic reactions occurred with minimal pressure provocation.

Skin testing with progesterone powder in cottonseed oil (50 mg/mL) mixed with 10% benzyl alcohol was performed in 9 patients. Histamine (1 mg/mL) and saline were used as the positive and negative controls. Positive skin prick test results to progesterone in cottonseed oil were documented in 4 patients (defined as wheal diameter greater than 4 mm above the negative control), whereas the results of skin prick testing to cottonseed oil alone were negative in all patients. Intradermal skin test results were positive to progesterone in cottonseed oil in all 9 patients, demonstrating greater than 6-mm wheal responses for each patient. Intradermal test results in 4 controls were negative. Specific IgE determinations (Pharmacia CAP System; Pharmacia, Uppsala, Sweden) were completed for cottonseed and were negative (<0.35 kU/L) in 8 patients. An open oral challenge test to progesterone (Prometrium) was performed in a single patient with no adverse reaction, and all others received intravaginal progesterone cream with no adverse events. The acute urticarial reaction generally resolved within weeks, although milder residual symptoms persisted for months. Patients were advised to avoid progesterone in cottonseed oil and use an alternative form of progesterone if necessary. Dermographic urticaria was treated with histamine₁-antihistamines for symptomatic relief.

Symptomatic dermographism is the most common physical urticaria and may be associated with the systemic use of drugs.⁵ Dermographism has been reported in up to 5% of the general population.⁶ Passive transfer studies have suggested an IgE-mediated reaction induced by stroking of the skin. Therefore, many patients appear to have an abnormal circulating IgE that confers a particular form of pressure sensitivity to dermal mast cells.⁷ In this series of patients, we identify a close temporal relationship between the

appearance of symptomatic dermographism with the intramuscular injection of progesterone in cottonseed oil.

We propose that this unusual allergic reaction is related to this combination of progesterone in cottonseed oil, although the exact mechanism remains unclear. This is the first reported series of patients with symptomatic dermographism associated with progesterone in oil, although there has been an isolated case report documenting hypersensitivity to progesterone in oil for patients undergoing fertility treatment.⁴ We recommend alternative forms of progesterone in the treatment of allergic individuals.

In conclusion, progesterone in cottonseed oil may lead to the development of an acute dermographic response. Patients may be treated with topical progesterone without allergic reactions. Specialists who provide care to patients using progesterone in oil products should be aware of these adverse reactions and their management.

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ANALYSIS OF ANAPHYLAXIS CASES AFTER VACCINATION: 10-YEAR REVIEW FROM THE NATIONAL VACCINE INJURY COMPENSATION PROGRAM

The National Vaccine Injury Compensation Program (VICP) was established in 1986 in response to vaccine safety concerns. A unique feature is a table of compensable injuries, the Vaccine

Injury Table (VIT). Anaphylaxis is a listed adverse event with an interval of 0 to 4 hours for vaccines containing tetanus toxoid (tetanus, diphtheria, and pertussis vaccine and tetanus-diphtheria [Td] vaccine), pertussis (diphtheria, pertussis, and tetanus [DPT] and diphtheria and tetanus toxoids with acellular pertussis [DTaP] vaccines), measles, mumps, and rubella (MMR), inactivated polio virus (IPV), and hepatitis B virus (HBV).¹ In 2009, the VICP charged the Institute of Medicine with the task of completing a comprehensive review of the medical literature regarding adverse events related to vaccines so that the VIT could be updated.² Concurrent with the Institute of Medicine's review, we undertook a systematic analysis of the VICP's anaphylaxis case experiences.

The VICP administrative database was queried for all cases submitted to the VICP alleging "anaphylaxis or anaphylactic shock" for the 10-year period from January 1, 2000, through

Disclosures: Dr Johann-Liang is an employee of the US Department of Health and Human Services.

Disclaimer: The positions expressed and recommendations made in this article do not necessarily represent those of the US government.

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doi:10.1016/j.anai.2011.01.014

Table 1. Vaccine Injury Compensation Program Cases of Anaphylaxis and Allergic Reactions, 2000–2009

Case no.	Patient age group/sex ^a	Medical and allergy history	Vaccine	Signs, symptoms, and adverse events	Interval	Treatment and tests	Outcome	Brighton
Cases of Anaphylaxis								
1	Adult/M	Obesity, asthma, dermatitis, CAD; allergic rhinitis, dapsone allergy	HBV	Diaphoresis, SOB, LOC, respiratory arrest and cardiovascular collapse	15 min	Epinephrine, atropine	Death	Level 1
2	Geriatric/M	Type 2 diabetes mellitus, HTN, CAD after coronary artery bypass graft, dementia, dysrhythmia	Td	Choking, SOB, face/neck/whole-body swelling, intubation by EMS unsuccessful, hypotension, respiratory arrest	30 min	Epinephrine ×3, atropine ×3, unsuccessful intubation	Death	Level 1
3	Geriatric/F	HTN; penicillin allergy	Influenza	Apnea, tongue swelling, hypotension and respiratory arrest	2 min	Defibrillation; epinephrine ×3	Death	Level 2
4	Adult/F	Kidney stones, endometriosis, asthma, gastritis, migraines, UTIs; cephazolin, sulfa drugs, allopurinol allergies	Td	Dizziness and nausea, erythematous rash over arms/chest, diaphoresis, wheezing, diffuse erythema, respiratory distress	Within seconds	Ammonia, methylprednisolone, diphenhydramine	Chronic anxiety, arthritis, and dizziness	Level 2
5	Adult/F	Asthma	HPV	Abdominal pain, felt hot and flushed, throat tight, diffuse itching, SOB, wheezing, sinus tachycardia	1 hr by history from patient	Epinephrine, diphenhydramine, methylprednisolone	Recovery to PIS	Level 2
6	Pediatric/F	None	DTaP, IPV, MMR	Abdominal pain, hives, decreased consciousness, hypotension	Minutes to hour	Diphenhydramine, epinephrine	Recovery to PIS	Level 2
7	Pediatric/M	30 weeks premature, cataracts, lens replacement; latex allergy, IgE positive to gelatin	DTaP, IPV, MMR, HAV	Cough, sore throat, welts, SOB, wheezing, urticaria	2 hours	Diphenhydramine, oral steroids	Recovery to PIS	Level 1
8	Infant/M	Seizures	DTaP	After nap, shallow breathing, then found apneic and cyanotic, respiratory arrest	20–30 min	Pathology report: interstitial edema	Death	Level 2
9	Infant/M	None	IPV, HBV	Unresponsive in car, nosebleed, respiratory arrest	2–3 hours	Tryptase level, 79 ng/mL	Death	Level 2
Cases of Possibly Allergic Reactions–Not Anaphylaxis								
10	Adult/F	Urticaria, smoking, depression; amoxicillin allergy	MMR	Felt funny, heart racing, chest tightness, throat swelling, rales	10–12 min	Epinephrine, steroids, oxygen, diphenhydramine	Recovery to PIS	None
11	Adult/F	Smoking, sinus tachycardia	HBV	Numbness of hands/feet, tingling, pruritus, SOB	15 min	Epinephrine, diphenhydramine	Recovery to PIS	None

Table 1. (Continued) Vaccine Injury Compensation Program Cases of Anaphylaxis and Allergic Reactions, 2000–2009

Case No.	Patient age group/sex ^a	Medical and allergy history	Vaccine	Signs, symptoms, and adverse events	Interval	Treatment and tests	Outcome	Brighton
12	Adult/F	None	HBV	Headaches, hot and achy, nausea	30 min	Diphenhydramine, hydroxyzine, ketorolac, promethazine, lorazepam	Recovery to PIS	None
13	Pediatric/M	Hives and fever after previous Hib	DPT/Hib	Screaming at 2 hours later, rash at site of injection	2 hrs	Trimethoprim-sulfamethoxazole for positive urine culture	Recovery to PIS	None

Abbreviations: CAD, coronary artery disease; DTP, diphtheria, pertussis, and tetanus; DTaP, diphtheria and tetanus toxoids with acellular pertussis; ED, emergency department; EMS, emergency medical services; HAV, hepatitis A virus; HBV, hepatitis B virus; Hib, *Haemophilus influenzae* type b; HPV, human papillomavirus; HTN, hypertension; IPV, inactivated polio virus; LOC, loss of consciousness; MMR, measles, mumps, rubella; PIS, preimmunization status; SOB, shortness of breath; Td, tetanus-diphtheria; UTI, urinary tract infection.

^a Age range: 11 months to 84 years; adult, 18 to 84 years; geriatric, older than 75 to 84 years; pediatric, 1 to younger than 18 years; infant, younger than 1 year.

December 31, 2009. We reviewed comprehensive medical records and abstracted demographic and clinical data of interest in a deidentified fashion using a prespecified data retrieval form. Cases were categorized as anaphylaxis, possibly allergic–not anaphylaxis, and not anaphylaxis or allergic. The anaphylaxis cases all met the Brighton Collaboration (BC) case definition and were further subdivided into 3 levels of diagnostic certainty using major and minor criteria, with level 1 being the greatest level of certainty.³ Possibly allergic cases were defined as those for which there were signs and/or symptoms compatible with an allergic reaction (eg, respiratory, cardiovascular, or gastrointestinal) occurring within 4 hours of injection but that did not meet any of the BC case definitions for anaphylaxis. Not anaphylaxis or allergic cases had alternative diagnoses. This study was approved by the Colorado Multiple Institutional Review Board.

Fifty-three unique cases alleging “anaphylaxis or anaphylactic shock” were identified, accounting for 3% of the total of 1,819 nonautism claims filed during this time frame.⁴ Of the 53 cases, 9 (17%) were judged to be anaphylaxis and 4 to be possibly allergic–not anaphylaxis. Thirty-six cases (68%) were determined to be not anaphylactic or allergic, which included 15 sudden death cases (sudden infant death syndrome, 4; asphyxia, 3; pneumonitis, 3; cardiac, including myocarditis, 3; homicide, 1; hyperglycemia, 1; with 12 of 15 determined by autopsy), 6 neurologic cases, 4 dermatologic cases, 4 respiratory cases, 3 psychiatric cases, and 2 syncope cases. A petition was filed without medical records in 4 cases. The alleged vaccines for the anaphylactic and possibly allergic–not anaphylactic cases were DPT, DTaP, Td, *Haemophilus influenzae* type b, hepatitis A virus (HAV), HBV, human papillomavirus (HPV), influenza, MMR, meningococcal, IPV, pneumococcal conjugate, and varicella-zoster virus.

Table 1 displays the demographic and clinical characteristics, diagnoses, and outcomes of each of the 9 anaphylaxis and 4 possibly allergic nonanaphylaxis cases. The anaphylaxis cases listed in Table 1 met the BC case definition with sufficient evidence for levels of certainty 1 and 2. For case 9, the elevated serum mast cell tryptase level⁵ met the minor criteria. Case 1 could have been an acute coronary event; case 4 alleged that chronic problems were due to the putative anaphylactic reaction. More than half of the probable cases had a medical history of asthma and/or allergies mainly to antimicrobial drugs (penicillin, sulfa). One child had previous testing demonstrating elevated IgE levels to gelatin, a known risk factor for vaccine-associated anaphylaxis.⁶ These 9 anaphylaxis cases represented 8 different vaccines containing at least 11 different vaccine antigens.

The VIT list for anaphylaxis includes 5 of these vaccines but does not include influenza, HPV, and HAV. The BC definition of anaphylaxis does not include a specific interval from the time of immunization to the onset of anaphylaxis. All of our anaphylaxis cases met the BC diagnostic certainty and, with an interval of 0 to 4 hours, are consistent with the current VIT. Five of 9 cases had an outcome of death. This is unlike other population-based studies, such as the one by the Vaccine Safety Datalink, where none of the episodes resulted in death.⁷ This may be because of the selected nature of our cases and specifically because worse outcomes are more likely to result in a claim. The unique nature of the VICP database has strengths (eg, the comprehensive case materials available for analysis) and limitations (ie, cases may be enriched for certain characteristics). Another limitation is that we only queried the pool of cases alleging anaphylaxis. Hence,

we may be missing cases that were submitted as claims alleging another adverse event but were, in fact, anaphylaxis. Nevertheless, this review represents the first systematic approach in analyzing the VICP experience with anaphylaxis and will be useful when the VIT is updated.

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RESOLUTION OF BRONCHOMALACIA PRESENTING AS SEVERE ASTHMA BY ENDOSCOPIC INTERVENTION

Difficult to control asthma should make us think of other concomitant airway diseases, mainly if the treatment for the initial presumed diagnosis is failing. A 42-year-old female smoker was referred to our allergy department because of symptoms of urticaria and facial and eyelid edema in the month before her visit. A detailed allergy history also revealed intermittent cough and dyspnea with no apparent trigger or seasonal changes. The patient had no known allergies or atopic diseases. A physical examination revealed diffuse wheezing in both lungs. The results of a test for dermographism were negative. Results of skin prick tests with a panel of food and aeroallergens were negative. Spirometry showed a severe obstruction of airway flow (forced vital capacity [FVC], 3.73 L [91% predicted]; forced expiratory volume in 1

second [FEV₁], 1.77 L [50% predicted]; and FEV₁/FVC ratio, 47%) with a positive bronchodilator test result (FEV₁, +24.5%) and a fraction of exhaled nitric oxide of 33 ppb. A chest radiograph showed air trapping, and the results of a blood test (immunoglobulins, α_1 -antitrypsin, hemogram, and biochemistry) were normal. The patient was diagnosed as having acute idiopathic urticaria and severe persistent nonallergic asthma. We began therapy with salmeterol and fluticasone, 50 to 500 μ g. After 1 month the patient experienced partial clinical improvement, although with persisting dyspnea and expiratory wheezing, leading oral steroid treatment to be ruled out. Spirometry did not show improvement. We performed plethysmography and a diffusion test, the results of both of which were normal. Induced sputum analysis showed Curschmann spirals and leukocytes (99% neutrophils, 1% eosinophils).

A chest computed tomogram with contrast showed mild emphysema in the upper lobes of the lungs. Respiratory infections persisted for the following 2 months, and some exacerbation required care from the emergency department. Spirometries showed no improvement. Because of a lack of improvement, a bronchoscopy was performed.¹

Bronchoscopy revealed a bronchial collapsibility, with significant loss of airway caliber in the left main bronchus, resulting in severe bronchomalacia. Days later, the bronchoscopist placed a Dumon prosthesis in the left main bronchus using an Efer-Dumon rigid bronchoscope (Fig 1).

In subsequent monthly visits, the patient reported good tolerance to the prosthesis and demonstrated clinical improvement. Spirometry also revealed a clear improvement (FVC, 4.07 L; FEV₁, 2.04 L; FEV₁/FVC ratio, 65%), and a bronchodilator test result was negative.

Tracheobronchomalacia is a central airway disease characterized by an increased susceptibility of the tracheal and bronchial lumen to collapse during expiration.² Occurring rarely, broncho-

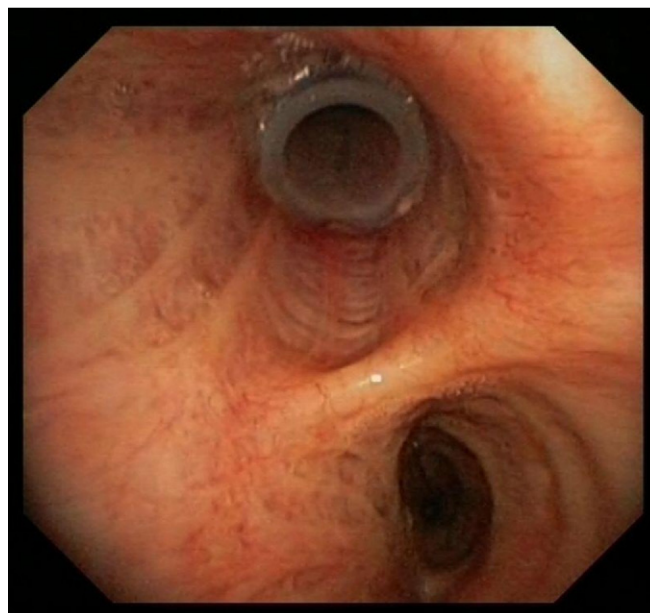


Figure 1. Placement of the prosthesis in the left bronchus.

Disclosures: Dr Sastre reports having served as a consultant to Phadia, Schering-Plough, and GSK, having been paid lecture fees by Novartis, GSK, Stallergenes, and UCB, and having received grant support from Phadia, GSK, and ALK-Abello.

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doi:10.1016/j.anai.2011.01.019