diarrhea. The symptoms improved with scheduled diphenhydramine. A thorough review of the patient's recent new food or medication exposure revealed that she took a dose of over-the-counter PEG-3350 (Miralax, Bayer) 4 hours before the onset of the first reaction, and again took it 2 hours before the onset of the second reaction. She was started on high-dose fexofenadine and instructed to discontinue this PEG-containing product. Serum asparaginase levels obtained revealed undetectable levels, consistent with the drug's typical half-life. After discontinuing PEG-3350, she did not have any recurrence of allergy-related symptoms. Skin prick testing was deferred because of the high potential for a false-negative test result given the recent mast cell degranulation during the acute reaction, and because she was actively undergoing chemotherapy.

The molecular weight of PEG can range from 200 to 35,000 g/mol.[1] The one used in Moderna and Pfizer-BioNTech vaccines has an average molecular weight of 2000 g/mol, whereas over-the-counter and generic PEG used for constipation measures 3350 g/mol and pegaspargase measures an average of 5000 g/mol. In recent years, there has been growing recognition of IgE-mediated, immediate hypersensitivity reactions to PEG.[1] Literature review by Wenande and Garvey[2] identified 37 case reports of an immediate hypersensitivity reaction to PEG-containing products, 28 (76%) of these reports were consistent with IgE-mediated anaphylaxis. Stone et al[1] reviewed the US Food and Drug Administration Adverse Event Reporting System database from 1989 through 2017 and noted 133 reported events of anaphylactic reaction or shock with PEG, and suggested an average of 4 cases per year of PEG-associated anaphylaxis with laxative use or colonoscopy preparation, highlighting that the incidence of these reactions is more common than recognized. When given intravenously, pegaspargase has an approximate half-life of 5.3 days and is recognized for a high incidence of drug-induced reactions.[3] A large trial reported that systemic hypersensitivity reactions occurred in 5.4% of intramuscular and 3.2% of intravenous infusion groups, with most reactions occurring during the second or third dose.[4]

Non–IgE-mediated mechanisms can also lead to anaphylaxis. One such important pathway described in animal models and clinical studies is the complement activation–related pseudoallergy to liposomal pegylated nanoparticle–based pharmaceutical preparations, in which anti-PEG IgM and IgG can trigger complement activation and production of C3a and C5a (anaphylatoxins), which then mediate a powerful immunologic response resulting in anaphylaxis.[5,6] Increasing seropositivity to PEG in healthy individuals and those with allergy has been reported in the literature, despite a lack of evidence that these antibodies lead to an immunogenic or anaphylactic response in all cases. To date, most commercially available anti-PEG assays have lacked specificity with minimal to no diagnostic use in clinical settings.[7] A recent case series proposed that individuals can develop a reaction to PEG from 1 molecular weight category but may be able to tolerate another. Moreover, progressive exposure to a similar molecular weight category may increase the risk of severe allergic reactions. Two of the 5 patients who underwent intradermal testing developed anaphylaxis, and 1 patient had a systemic reaction after skin prick testing, exhibiting the need for considerable caution when proceeding with skin prick and intradermal testing.[8]

This clinical case of an 11-year-old girl with anaphylaxis to 2 different PEG-containing medications, first given intravenously and second by the oral route, illustrates the potential for adverse reaction with different administration routes and molecular weights of PEG. As such, it highlights the importance of identifying previous potential hypersensitivity reactions to PEG-containing products when obtaining a history. This is of particular significance now, as PEG continues to be more frequently included in medication and vaccine development, coinciding with increasing reports of allergic or anaphylactic reactions. Furthermore, subsequent PEG exposures, such as repeated vaccinations, may increase sensitization, resulting in a higher risk for IgE-mediated hypersensitivity reaction.[1]

If a patient's clinical history is consistent with IgE- or non–IgE-mediated anaphylaxis to a PEG-containing product, we suggest the avoidance of pegylated drugs if a suitable alternative is available. If the patient's reported reaction is ambiguous, the medication or vaccine of concern should be given in a clinically monitored setting under the supervision of an experienced medical team, with full access to all appropriate anaphylaxis-related medications. This also underscores the need for a reliable and safe diagnostic tool to accurately identify PEG hypersensitivity.

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Polyethylene glycol and polysorbate skin testing in the evaluation of coronavirus disease 2019 vaccine reactions

Early report

In December 2020, the US Food and Drug Administration (FDA) issued emergency use authorizations for coronavirus disease 2019 (COVID-19) vaccines from Pfizer-BioNTech and Moderna, and widespread vaccination is ongoing. Contraindications to

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Table 1
Characteristics and Skin Test Results of Patients With Reaction to First COVID-19 Vaccine Dose and Previous PEG/Polysorbate Allergy[a]

Patient	Age/ sex	Previous allergic disease	Culprit agents	Symptoms	Anaphy-laxis[b]	Time to onset	Treatment	ED	Time to resolution	Skin test performed	Time from reaction to the skin test	Skin test result	Time between vaccine doses	Vaccine outcome[c]
1	24F	None	Pfizer-BioNTech vaccine	Urticaria	No	3 h	Antihistamines	No	4 d	PEG	12 d	Negative	23 d	No reaction
2	54F	Drug allergy	Pfizer-BioNTech vaccine	Tachycardia, rhinorrhea	No	10 min	None	No	10 min	PEG, MP acetate	7 d	Negative	18 d	No reaction
3	36F	None	Pfizer-BioNTech vaccine	Facial flushing	No	5 min	Antihistamines	No	1 h	PEG, MP acetate, TC acetonide	20 d	Negative	21 d	No reaction
4	52M	Venom anaphylaxis	Pfizer-BioNTech vaccine	Oral pruritus, throat fullness	No	Immediate	None	No	5 min	PEG	10 d	Negative	21 d	No reaction
5	45F	Food allergy	Pfizer-BioNTech vaccine	Urticaria, throat tightness	No	8 h	None	No	Unknown	PEG	20 d	Negative	29 d	No reaction
6	33F	Asthma, venom anaphylaxis	Pfizer-BioNTech vaccine	Urticaria, tachycardia	No	15 min	Antihistamines	No	12-24 h	PEG	20 d	Negative	23 d	No reaction
7	20M	Vaccine allergy (flu)	Moderna vaccine	Angioedema	No	3 h	Steroids, antihistamines	Yes	24 h	Expanded[d]	20 d	Negative	N/A	Not given
8	22F	Allergic rhinitis	Moderna vaccine	Angioedema, wheezing, throat pruritus	Level 1	20 min	Antihistamines, steroids	Yes	6 h	Expanded[d]	21 d	Negative	51 d	Minor lip/ tongue tingling
9	69M	Drug allergy	Moviprep (PEG)	Rash, flushing	No	During prep	Antihistamines	No	1 h	PEG	2 y	Negative	N/A	No reaction (Pfizer)
10	73F	Asthma, drug allergy	Moviprep (PEG)	Headache, nausea	No	Unknown	Unknown	No	Unknown	PEG	5 y	Negative	N/A	No reaction (Moderna)
11	46F	Vaccine allergy (flu)	Methylpre-dnisolone acetate (PEG)	Urticaria, dizzy, flushing	No	15 min	Epinephrine, steroids, antihistamines	No	12 h	Expanded[d]	3 mo	Positive (PEG and MP acetate)[e]	N/A	Not given
12	74M	Drug allergy	Triamcinolone acetonide (polysorbate 80)	Urticaria, wheezing	Level 1	1 h	Steroids, antihistamines	Yes	Unknown	PEG, MP acetate, TC acetonide	3 y	Negative	N/A	No reaction (Pfizer)
13	55F	Anaphylaxis	Influenza vaccines[f] (polysorbate 20/ 80)	Flushing, wheezing, cough, throat tightness	Level 1	20 min	Epinephrine, steroids, antihistamines	Yes	Unknown	PEG, Polysorbate 20	7 y	Negative	N/A	No reaction (Pfizer)
14	67F	Food allergy, anaphylaxis	MiraLAX (PEG)	Oral urticaria	No	2 h	Unknown	No	Unknown	Expanded[d]	Unknown	Negative	N/A	No reaction (Moderna)
15	60M	Vaccine allergy (Shingrix)	Shingrix (polysorbate 80)	Flushing, urticaria	No	2 h	Antihistamines, steroids	Yes	2 d	Expanded[d]	3 mo	Negative	N/A	No reaction (Moderna)

Abbreviations: COVID-19, coronavirus disease 2019; ED, emergency department; F, female; M, male; MP, methylprednisolone; PEG, polyethylene glycol; TC, triamcinolone.
[a]Patients 1 to 8: reaction to first COVID vaccine dose; patients 9 to 15: no previous vaccine dose, reported previous PEG or polysorbate allergy.
[b]Determined by using the Brighton criteria.[9]
[c]Refers to second vaccine dose in patients 1 to 8 or first vaccine dose in patients 9 to 15. All doses were given with a 30-minute observation period.
[d]Expanded skin testing included PEG, methylprednisolone acetate, methylprednisolone sodium, triamcinolone acetonide, and polysorbate 20.
[e]PEG 1:1 skin prick: 5 × 5 wheal, 10 × 10 flare; methylprednisolone acetate 0.1 mg/mL intradermal: 6 × 6 wheal, 8 × 8 flare (all measurements in mm).
[f]H1N1 vaccines FluBlok and Fluxrix.

vaccination include a history of immediate allergic reaction to a component or previous dose of an messenger RNA (mRNA) COVID-19 vaccine.[1] As of January 18, 2021, anaphylaxis to the Pfizer-BioNTech (Pfizer Inc, New York, New York, BioNTech SE, Mainz, Germany) and Moderna (Moderna, Inc, Cambridge, Massachusetts) vaccines have occurred at rates of 4.7 and 2.5 cases per million doses, respectively.[2] The mechanism of allergic reaction is unknown, although inactive vaccine components such as polyethylene glycol (PEG) have been proposed as possible culprit antigens.

PEG is a primary ingredient in osmotic laxatives and a widely used excipient in many medications. It has not been previously used in vaccines, and the molecular weight and structure of the PEG 2000 used in the mRNA COVID-19 vaccines are distinct compared with laxative preparations.[3] Allergy to PEG has been described, particularly with higher molecular weight concentrations.[4-6] A review of FDA adverse event reports from 2005 to 2017 revealed an average of 4 cases of anaphylaxis to PEG per year.[5] Skin testing has been successfully used to confirm suspected allergy to PEG-containing laxatives and medications, and guidelines for skin testing with nonirritating concentrations of PEG 3350 and polysorbate are available.[5,7] Recent expert opinion has also provided an algorithm that includes skin testing as part of COVID-19 vaccine reaction evaluation, but the predictive values of PEG and polysorbate skin testing in relation to the risk of hypersensitivity reaction to COVID-19 vaccines are still unknown.[8] We report the first 15 cases of PEG and polysorbate skin testing completed in patients who had allergic symptoms after their first dose of the mRNA COVID-19 vaccines or reported a PEG or polysorbate allergy before their first vaccine dose.

Skin testing was performed in patients referred to the allergy divisions of the Mayo Clinics based in Rochester, Minnesota, and Scottsdale, Arizona. The clinical need for skin testing and test selection was provider-determined at the time of evaluation. PEG 3350 (MiraLAX) testing was performed using sequential skin pricks at 1.7 mg/mL, 17 mg/mL, and 170 mg/mL. Methylprednisolone acetate (PEG-containing), methylprednisolone sodium (control), and triamcinolone acetonide (polysorbate 80–containing) testing were performed starting with a skin prick at 40 mg/mL, with subsequent 1:100 and 1:10 intradermal with an additional 1:1 intradermal administration for triamcinolone. Polysorbate 20 testing was performed and given as a 1:1 skin prick followed by 1:100 and 1:10 intradermally with a 0.5 mg/mL concentration with a sterile water diluent. This study was an institutional review board–approved retrospective chart review.

Between January 15, 2021, and February 1, 2021, 15 patients underwent skin testing; 8 had testing because of a reaction to the first dose of COVID-19 vaccine, and 7 had tested before vaccination because of reported PEG or polysorbate allergies (the characteristics and skin testing results of which are presented in Table 1). All 8 patients with first vaccine dose reactions had negative PEG 3350 testing, whereas 4 patients had methylprednisolone acetate testing, 3 had triamcinolone acetonide testing, and 2 had polysorbate 20 testing—all of which were negative. One patient had a positive polysorbate 20 reaction (given at 1:10 dilution intradermally), but a sterile water given intradermally resulted in an identical wheal and flare in the patient and one of the authors; thus, this test was interpreted as false-positive owing to irritation. A total of 7 patients successfully received their second COVID-19 vaccine dose without premedication or split-dosing, with the final patient delaying the second dose until vaccine skin testing or split-dosing capabilities are available. In the 7 patients with previous PEG or polysorbate allergy, 1 patient had positive testing to PEG 3350 and methylprednisolone acetate with negative testing to methylprednisolone sodium, triamcinolone acetonide, and polysorbate 20. The 6 other patients all tested negative for PEG. The 3 patients with expanded skin testing also tested negative for polysorbate 20, methylprednisolone acetate, and triamcinolone acetonide. All 6 patients who tested negative received the first dose of the vaccine without any reaction. The patient who tested positive is not yet eligible to receive the vaccine.

This is one of the earliest reports on the use of skin testing to evaluate both possible COVID-19 vaccine reactions and previous PEG or polysorbate allergies before vaccination. In our cohort, only 1 patient had positive testing. No patients with reactions to their first vaccine dose had positive testing. It may be hypothesized in these cases that PEG is not the culprit antigen or that non–immunoglobulin E-mediated mechanisms such as complement activation–related pseudoallergy are involved. In addition, the short interval between reaction and skin testing may increase the risk of false negatives. A preliminary success has been seen with the safe administration of the second vaccine dose after negative skin testing after a possible first dose reaction. One area of uncertainty is the ability of skin testing to predict COVID-19 vaccine reactions in patients who report previous PEG or polysorbate allergies. Systemic reactions to PEG are dependent on a combination of the molecular weight and absolute amount of PEG in the culprit medication, which can differ substantially between injectable and oral forms of PEG.[4] Furthermore, the threshold needed to induce a systemic reaction likely differs among individuals.[4] These facts make interpretation of skin tests difficult in patients who have yet to receive a COVID-19 vaccine. An additional area of interest has been the recognition of the innumerable medications and vaccines that contain PEG or polysorbate.[8] One of our patients with a COVID-19 vaccine reaction also reported a possible reaction to a polysorbate 80–containing influenza vaccine. The magnitude of risk these previous reactions confer on individuals yet to receive a COVID-19 vaccine and the ability of skin testing to quantify that risk remains unclear.

Although our cohort size precludes any inferences regarding the predictive value of this skin testing, it is clear that allergists will play an essential role in the COVID-19 vaccination effort. As vaccination numbers increase, the absolute number of adverse reactions will also increase, which will provide opportunities to both refine the testing strategy (with no or limited testing potentially being the best strategy) and address vaccination hesitation, with the ultimate goal being accurate risk stratification and safe vaccine administration to the population as a whole.

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Dupilumab increases aspirin tolerance in aspirin-exacerbated respiratory disease

Check for updates

Aspirin-exacerbated respiratory disease (AERD) is a triad of asthma, nasal polyposis, and intolerance to nonsteroidal anti-inflammatory drugs. Although AERD affects 7% of patients with asthma and 10% of patients with nasal polyposis, it may affect up to 25% to 30% of patients with both asthma and nasal polyps.[1] Furthermore, although many patients are diagnosed based on their clinical history, the gold standard of diagnosis remains an aspirin challenge. After the diagnosis of AERD, treatment is often stepwise, aimed at controlling both lower and upper airway inflammation with topical corticosteroids and leukotriene modifiers. For patients failing typical therapies, aspirin desensitization has been found to improve symptoms, decrease reliance on medications, including systemic steroids, and increase the interval between the surgical interventions for nasal polyposis.[2]

With the increasing availability of monoclonal antibodies for asthma,[3] these agents have also been used in AERD. Dupilumab is a fully human monoclonal antibody to the interleukin receptor-α subunit that inhibits both interleukin (IL)-4 and IL-13 signaling pathways[4,5] and is approved for atopic dermatitis, moderate-to-severe persistent asthma, and chronic rhinosinusitis with nasal polyposis (CRSwNP). Although there are emerging data suggesting efficacy of dupilumab in AERD for improving sinopulmonary symptoms,[6,7] it remains unknown whether dupilumab will affect the threshold dose of aspirin eliciting a clinically meaningful reaction in patients with AERD. We report our experience with 5 patients with AERD who underwent aspirin challenge to confirm the diagnosis of AERD and then a second aspirin challenge while on treatment with dupilumab.

There were 3 male and 2 female individuals in our cohort with a median age of 39 years. The average time since diagnosis of AERD was 8.4 years, and the patients had undergone an average of 2 sinus surgeries each. Of the 5 patients, 4 had previously been treated with aspirin desensitization but experienced inadequate improvement of sinopulmonary symptoms and subsequently discontinued aspirin therapy. The fifth patient declined therapy with aspirin desensitization owing to concerns in tolerability. Furthermore, 4 of 5 patients were using nasal corticosteroids, but all 5 patients were on inhaled corticosteroids and long-acting β-agonist for control of asthma. Moreover, 2 patients were on montelukast whereas another was on zileuton.

The first aspirin challenge was conducted before treatment with dupilumab, with the following aspirin doses administered every 75 to 90 minutes: 3 mg, 40.5 mg, 81 mg, 162 mg, and 325 mg. The 3 mg dose was only used if the patient history was suggestive of a possible component of immunoglobulin E-mediated reaction, otherwise the challenges started at 40.5 mg. Patient 1 experienced nasal congestion, dyspnea, and decreased forced expiratory volume (FEV1) of 500 mL (14%) with aspirin 40.5 mg, and this improved with cetirizine and albuterol. Patient 2 experienced tingling in the nose and decreased FEV1 of 514 mL (12%) with aspirin 81 mg, and this improved with diphenhydramine along with albuterol and ipratropium. Patient 3 experienced dyspnea with aspirin 81 mg, and this improved with albuterol. Patient 4 experienced an itchy throat, cough, and decreased FEV1 of 450 mL (16%) with aspirin 81 mg and required therapy with intramuscular epinephrine, diphenhydramine, and albuterol/ipratropium. Patient 5 experienced nasal congestion with aspirin 3 mg, and this improved with diphenhydramine and nasal oxymetazoline.

Owing to poorly controlled sinopulmonary symptoms despite typical medical therapy, all 5 patients were started on dupilumab either for an indication of moderate-to-severe persistent asthma or CRSwNP. After at least 3 months of therapy with dupilumab 300 mg subcutaneously every 2 weeks, all 5 patients tolerated a higher dose of aspirin as compared with their initial aspirin challenge pre-dupilumab (Fig 1). Patient 1 experienced nasal congestion, cough, and decreased FEV1 of 394 mL (11%) with aspirin 162 mg, and this improved with cetirizine and albuterol. Patient 2 experienced decreased FEV1 of 556 mL (13%) with aspirin 325 mg, and this improved with albuterol/ipratropium. The remaining 3 patients tolerated up with aspirin 325 mg without any symptoms. A paired Wilcoxon signed-rank test revealed a significant increase in the aspirin threshold dose before and during treatment with dupilumab ($P = .007$). Finally, 3 of 5 patients in the cohort report ongoing ad lib use of nonselective cyclooxygenase (COX) inhibitors with ibuprofen 200 to 400 mg as needed for analgesia or aspirin 325 mg for cardioprotection.

Therapeutic options for AERD include both aspirin desensitization and treatment with monoclonal antibodies currently approved for the management of moderate-to-severe asthma and CRSwNP. Aspirin desensitization may offer patients the benefit of being able to use nonselective COX inhibitors ad lib in their daily lives. Our case series suggests that treatment with dupilumab increases the threshold dose of aspirin required to elicit a clinically meaningful reaction, and thus may also offer patients with AERD the opportunity to use nonselective COX inhibitors as needed during routine activities. Previous work by our group has revealed that treatment with dupilumab significantly decreases mediators of T2 inflammation in patients with AERD, including total serum immunoglobulin E, serum thymus and activation-regulated cytokine, and urinary leukotriene levels.[7] These changes, found as early as 1 month after initiation of therapy, likely contribute to increased aspirin tolerance in AERD treated with dupilumab. Similar improvement in aspirin threshold in patients with AERD has been found with omalizumab,[8] but not in patients treated with

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