HHS Public Access

Author manuscript

*J Allergy Clin Immunol Pract*. Author manuscript; available in PMC 2022 August 01.

Published in final edited form as:

*J Allergy Clin Immunol Pract*. 2021 August ; 9(8): 2968–2982. doi:10.1016/j.jaip.2021.03.002.

# Hidden Dangers: Recognizing Excipients as Potential Causes of Drug and Vaccine Hypersensitivity Reactions

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## Abstract

Excipients are necessary as a support to the active ingredients in drugs, vaccines and other products and they contribute to their stability, preservation, pharmacokinetics, bioavailability, appearance and acceptability. For both drugs and vaccines these are rare reactions however for vaccines they are the primary cause of immediate hypersensitivity. Suspicion for these “hidden dangers” should be high in particular when anaphylaxis has occurred in association with multiple chemically distinct drugs. Common excipients implicated include gelatin, carboxymethylcellulose (CMC), polyethylene glycols (PEG) and products related to PEG in immediate hypersensitivity reactions (IHRs); and propylene glycol (PG), in delayed hypersensitivity reactions (DHRs). Complete evaluation of a suspected excipient reaction requires detailed information from the product monograph and package insert to identify all ingredients that are present and to understand the function and structure for these chemicals. This knowledge helps develop a management plan that may include allergy testing to identify the implicated component and to give patients detailed information for future avoidance of relevant foods, drugs and vaccines. Excipient reactions should be particularly considered for specific classes of drugs where they have been commonly found to be the culprit (e.g. corticosteroids, injectable hormones, immunotherapies, monoclonal antibodies, and vaccines). We provide a review of the evidence-based literature outlining epidemiology and

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Conflicts of Interest: The authors declare that they have no conflicts of interest to disclose.

mechanisms of excipient reactions and provide strategies for heightened recognition and allergy testing.

**Keywords**

excipient; allergy; inactive ingredient; anaphylaxis; vaccine; drug; biologic; corticosteroid; polyethylene glycol (PEG); polysorbate; carboxymethylcellulose (CMC); gelatin; alpha-gal

## Case:

A 57 year old male patient with an occupational history of working as an electrician and a mechanic exposed to oil absorbers and transformer fluids presented to our clinic for evaluation of a suspected medication allergy causing anaphylaxis. Two years prior to presentation, he had a severe anaphylactic reaction to an injection of methylprednisolone acetate, in which the active ingredient was attributed as the cause without formal testing. Upon further review of his history, however, he described multiple subsequent episodes of anaphylaxis to different brands of bowel preparations containing polyethylene glycol (PEG) 3350. Skin prick testing was positive to PEG 3350 (Miralax) at 170 mg/ml, 17 mg/ml & 1.7 mg/ml and to methylprednisolone acetate (PEG 3350 containing) at 4 mg/ml. Intradermal testing was positive to triamcinolone acetonide (polysorbate 80 containing) at 1 mg/ml and 0.1mg/ml, and to conjugated pneumococcal vaccine (polysorbate 80 containing) (Figure 1). Using ELISA and an electrochemiluminescent assay, the patient's serum was found to be positive for specific IgE and IgG directed against polyethylene glycols. These antibodies demonstrated increasing binding avidity as molecular weight increased beyond PEG 1000. The patient then demonstrated negative skin testing to polyethylene glycol 300 followed by oral tolerance of polyethylene glycol 300. A diagnosis of IgE mediated hypersensitivity to high molecular weight polyethylene glycols and polysorbate 80 was made.[1] The patient was instructed to avoid PEGs with molecular weight of 400 and above, and to avoid polysorbates. After a literature review and databases searches, he was given a list of potential drugs to avoid, along with training on how to look up the active and inactive ingredients of medications using a US federal database of medication package inserts.[2] During several almost four years of follow-up he has avoided any further reactions, and consults his allergy team for shared decision making when deciding whether a medication, vaccine or other product is likely to cause him any issues.

## Introduction and Classification of Allergic Reactions to Excipients:

The U.S. Food and Drug Administration (FDA) defines excipients or inactive ingredients of pharmaceutical formulations as "any component of a drug product other than the active ingredient."[3] Excipients are necessary as a support to the active ingredients in a drug or vaccine; contributing to stability, preservation, pharmacokinetics, bioavailability, appearance and acceptability by the patients, among other functions. Thus, excipients are part of the formulation of almost all drug and vaccine preparations and could be hidden allergens when they are not correctly declared in the information of the drug composition. For this reason, excipients have come under greater scrutiny in the context of increasing reports of individual

hypersensitivity reactions (HSRs) in the scientific literature, because excipient allergies, though rare, can have implications on patient safety during daily clinical practice. It is notable that for drugs it is assumed that the parent compound is the culprit which is typically the case; however excipient allergy is an important consideration as it is often missed due to this assumption. For vaccines, where true anaphylaxis occurs in around 1 per million doses given,[4] it is actually the excipient which is the more likely culprit and investigation should proceed accordingly.

In the present review article, we will focus on the most excipients that are shared between multiple products and are most likely to be missed despite being the true culprit in reactions to commonly used drugs, classes of drugs and vaccines. These include carboxymethylcellulose (CMC), gelatin, PEG and PEG derivatives such as the PEG sorbitans (polysorbates), PEG castor oils (e.g. cremophor) and PEG-propylene glycol copolymers (poloxamers) that are most commonly implicated in immediate hypersensitivity reactions (IHRs); and propylene glycol (PG), in delayed hypersensitivity reactions (DHRs). We have not included a detailed review on some other preservatives such as sulfites since anaphylaxis would be extremely rare, even though asthma exacerbation is more common. We will also review those excipients which appear to be the dominant allergens for a certain drug class, rather than the active ingredient itself, as is the case of injectable corticosteroids (CS) with CMC and PEG. For vaccines there are other considerations including gelatin, galactose-alpha-1,3-galactose (alpha-gal) and polysorbate 80 (PS80). More recently with the Pfizer-BioNTech and Moderna SARS-CoV-2 mRNA vaccines issued emergency use authorization (EUA) there have been concerns regarding cases of anaphylaxis and the possibility that the shared PEG-2000 lipid construct in the lipid nanoparticle that acts as a carrier system for the SARS-CoV-2 spike protein mRNA could be an allergen, though this has not yet been proven in any cases. Because the structure and chemistry of excipients are not as frequently conceptualized compared to the active drug product, we will first introduce the key excipients identified in our review, sorted alphabetically, based on the reported reaction phenotypes.

## Immediate hypersensitivity

IHRs to excipients have been increasingly reported, by suspected IgE, non-IgE and complement-system (C-system) mediated mechanisms (also known as C activation-related pseudoallergy (CARPA)), with varying levels of supportive mechanistic evidence. The most relevant excipients involved in IHRs are summarized in Table I.

## IgE mediated immediate hypersensitivity:

### Carboxymethylcellulose

CMC is a semisynthetic hydrosoluble polymer derived from cellulose, used as a stabilizing and viscosity-increasing agent in foods and pharmaceuticals.[5] It has been reported in association with immediate hypersensitivity, mainly reported as an allergen in anaphylaxis to barium sulfate suspensions used as contrast media[6, 7] and CS (Table II). An IgE mediated mechanism has been demonstrated in many cases with skin testing and in some cases by specific IgE testing, but specific IgE directed against CMC was also found in 36 (9%) of

384 patients tested in a Japanese series during routine health examinations, suggesting a gap between sensitization and symptoms.[7, 8] CMC has been reported as a cause of immediate onset hypersensitivity to lidocaine gels and considered as a potential cause in anaphylaxis to these topicals.[9, 10] Of note, CMC was previously implicated in anaphylactic reactions to benzathine penicillin observed in veterinary settings and is also an ingredient in some human formulations of the same drug.[11] In the domain of food allergy, CMC has also been reported as a cause of anaphylaxis to ice creams[12] and popsicles/ice lollies[13] and can be present in a variety of processed foods.[7] The pathway to parenteral sensitization seems different than oral sensitization in the setting of foods, and it is well established that individuals with parenteral sensitivity such as to CS can likely tolerate oral CMC and other celluloses such as hypromellose whereas those sensitized to CMC in foods are particularly sensitized to and have anaphylaxis to much lower doses of oral antigen.[12]

## Gelatin

Gelatin is a product derived from partially hydrolyzed mammalian or fish collagen, and is found in a variety of foodstuffs as well as pharmaceuticals and vaccines, where it has long been used as a stabilizer, for the preparation of tablets and capsules, and for hemostasis.[14] Gelatin is present as an inactive ingredient in a wide variety of medications, but can also be the active ingredient in some medications such as hemostatic gels and gelatin-based solutions for fluid resuscitation (Gelofusine®).[15, 16] IgE mediated anaphylaxis to gelatin is thought to be the predominant mechanism of immediate hypersensitivity.[17] Intraoperative anaphylaxis is reported with topical gelatin-based hemostatic products (Floseal®) or sponges (Gelfoam®) due to porcine[18–21] or bovine[20–23] gelatin allergy. For this excipient it is important consider a previous history of meat allergy, as shown in two of these cases with reactions to canned pork meat with gelatin also known as aspic, a gelatin dish made with a meat stock or consommé in a mold to contain other ingredients, in which the authors recommended inquiring about gelatin allergy not only in drugs but also in food and gelatin containing vaccines,[17] as part of preoperative assessment.[18, 22]

## Gelatin/ Alpha-gal

Galactose-alpha 1,3-galactose is an unintended excipient allergen in several medications, and its presence as a relevant excipient allergen is typically determined by content of gelatin, and possibly by other mammalian ingredients.[24, 25] IgE-mediated anaphylaxis is the only known mechanism at the present time.[24] It must also be considered in premature degeneration of porcine heart valves[26] and reactions to drugs that utilize manufacturing techniques that rely on mammalian cell lines or antibodies.[24] Cases of anaphylaxis with bovine gelatin hemostatics and gelatin containing vaccines in alpha-gal allergic individuals have corresponded with alpha-gal specific binding assays to provide evidence that patients sensitized to alpha-gal moieties from mammalian meat may react to gelatin-containing drugs, though they may also be co-sensitized/co-allergic to gelatin.[27–29]

## Polyethylene glycols (PEGs)

The larger family of PEGs are polyether compounds derived from ethylene oxide (Figure 2) with wide ranging use as excipients and conjugated pharmaceuticals.[1] As an active ingredient, PEG 3350 and 4000, also known as macrogols, are laxatives and

bowel preparations that have been implicated in anaphylactic reactions.[1, 30–32] PEG 3350 is particular has also been identified as key excipient allergens in reactions to methylprednisolone acetate and medroxyprogesterone acetate.[1, 33, 34] PEG 6000 has been involved in IHRs with different type of medications such as European formulations of penicillin antibiotics and effervescing medications.[35–37] (Table 1) PEG 20000 has been implicated in anaphylaxis after use of calcium containing supplements for GERD and dyspepsia such as a chewable Gaviscon tablet available in the United Kingdom and Europe but not the United States where it does not contain PEG.[33] Other IHRs were reported with both PEG 4000 and 6000[38], PEG-8000[39], and both PEGs and Laureth-9.[40] Frequently, patients also reported previous IHRs with various PEG-containing drugs.[30, 33, 37, 38, 40] An IgE mediated mechanism for anaphylaxis to PEGs has been demonstrated by independent laboratory methods showing specific IgE in skin test positive patients.[1, 41, 42] Plasma samples have also showed anti-PEG specific IgG antibodies (Abs) from the same patients had binding that increased in direct proportion to the molecular weight (MW) of PEG tested.[1] There may also be a lower limit of molecular weight beyond which patients do not react to PEG, as binding did not begin until a PEG of molecular weight 1000, and several patients have demonstrated oral tolerance of low molecular weight PEG in the presence of high molecular weight PEG.[1, 42]

## PEGylated liposome (PEGLip)

PEGylated nanoparticles (1–100 nm), where PEG is conjugated to a micelle (closed lipid monolayers within a fatty acid core) or liposome (lipid bilayer) are used as a pharmaceutical delivery vehicle for different kinds of drugs and more recently, mRNA vaccines.[43] A case of anaphylaxis with a PEG 5000 liposomal perflutren microbubble echocardiogram contrast was reported in a patient who previously had anaphylaxis to oral PEG-3350 while undergoing colonoscopy preparation.[42] This patient was shown to have PEG allergy with positive skin testing to multiple products including PEG3350, PEG8000, polysorbate 20, 80, poloxamers (subsequent to the original report) along with PEG sIgE.[42] Mechanistically, this case demonstrates the PEG content of PEGylated liposomes can be a relevant allergen for this class of drugs and contraindicate their use in PEG allergic patients.[42] The same PEGylated liposomal contrast agent had previously received a black box warning in 2008 for anaphylaxis.[42] A much higher number of cases of anaphylaxis have been reported to the FDA for PEGylated perflutren when compared to an alternative perflutren microbubble using a human albumin construct.[42] Immediate hypersensitivity reactions to PEGylated liposomes through a CARPA mechanism have also been reported, primarily to PEGylated liposomal doxorubicin.[44, 45]

## Polysorbates (PSs)

PSs are structurally similar to PEGs, with repeating side chains that are derived from ethylene oxide, (Figure 2), and are used in medicines for their similar pharmaceutical properties.[1] PS20 and PS80 are involved in IHRs with different types of medications.[46–51] Curiously, reactions with PS20-containig omalizumab have been observed both after a year of uneventful treatment[46] and with the first injection.[47]

### PEG and Cross Reactivity with PEG Sorbitans (polysorbates (PS) and poloxamers)

IHRs due to both PEG and PS have been reported in the same patients.[1, 52–55] Several patients who became allergic to polysorbates appear to have be sensitized via PEGs, with an IgE mediated mechanism.[1, 54, 55] Cross-reactivity between PEG-3350 and PS80, a PEG sorbitan (Figure 2) that carries 20 moles of ethylene oxide per mole of oleic acid and sorbitol[56] has been seen in patients who reacted to both[55], and also demonstrated in patients with positive skin testing to both and a history of IHRs to PEG.[1] The results of these studies showed an IgE-mediated mechanism for PEG allergy and highlighted the possibility that IHRs to PEG with cross-reactive PS hypersensitivity may be underrecognized in clinical practice.[1] Authors on these papers have recommended avoidance of both PEGs and polysorbates in these cases.[1, 52–55] These findings are suggestive that at least in some cases sIgE are directed against the chemical structure of repeating ethylene oxides shared by PEGs and polysorbates. Cross-reactivity between PEGs and poloxamers has also been reported for the same reason.[57] (Figure 2) Cross-reactivity with other structurally analogous molecules such as hydroxyethyl starch and cremophor has also been posited.[54, 55, 58, 59]

## Non-IgE mediated immediate hypersensitivity

### Cremophor and PS80

Cremophor is a “PEG Castor Oil”) that is a synthetic surfactant made by reacting castor oil with ethylene oxide (Figure 2). The specific mechanism underlying cremophor-induced HSRs is not fully understood, and there appears to be more than one type of immediate reaction.[59] Cremophor is predominantly involved in anaphylaxis to chemotherapeutics and immunosuppressives[60]such as paclitaxel, cyclosporine, and tacrolimus[59, 61–63] (Table I). SPT results and immediate symptoms suggest an IgE-mediated mechanism in some cases.[62, 64] However, studies showed that cremophor stimulates the C-system[65] and oleic acid, a component of cremophor, causes histamine release.[66] In addition, reactions to drugs such as paclitaxel, which is one of the more common drugs in use that has cremophor as an excipient, have symptoms such as fever and pain in addition to IgE mediated symptoms which is more in keeping with complement activation.[67–69] These patients may tolerate rechallenge with the drug.[69] Involvement of IgG Abs was also suggested in some studies.[62] Authors who reported these cases suggested a potential cross-reactivity of cremophor and PS80 at the oleic acid moiety, since some patients subsequently had symptoms with other PS80-containing products. Cremophor and PS80 have the ability to interact with proteins activating the C-system[70, 71], which can lead to downstream effects including acute reactions mimicking anaphylaxis. This mechanism explains why each agent causes reactions and oleic acid present in both excipients could explain cross-reactivity.[61] Other polysorbates such as 20, 40, 60 do not have an oleic acid moiety, though they do contain PEG.[72]

## IgG/ C-system activation mediated hypersensitivity reactions

### PEGylation on pharmaceuticals

PEGylation is a process whereby PEGs of various molecular weights are attached to drugs for the purpose of shielding the drug from rapid clearance and prolonging its half-life, or to enhance water solubility.[73] This is different from drugs that contain PEG as an

inactive ingredient. PEGylated drugs in which IgG mediated activation of the C-system leads to IHRs were reported mainly with chemotherapeutics, such as PEGylated liposomal doxorubicin and PEG-asparaginase[74–77] and recently, with recombinant factor VIII.[78]

As mentioned previously, PEG can also be attached to liposomes (PEGLip). PEGLip encapsulating drugs cause IHRs by a C-system activation leading to complement activation-related pseudoallergy (CARPA).[79–81] Recent evidence highlights the causal role of anti-PEG Abs triggering classical pathway initiation of CARPA, at least for the case of PEGLip.[81] A correct measurement of anti-PEG Abs and individual proneness for C-system activation might predict the rise of adverse immune reactions to PEGylated drugs and thereby increase their efficacy and safety.[81] It is important to recognize that IgG mediated reactions to PEG may also correspond with failure to tolerate desensitization and accelerated clearance of PEGylated drugs.[82, 83]

### Delayed hypersensitivity

The most relevant excipients involved in DHRs are summarized in Table III.

## Allergic Contact Dermatitis

Allergic contact dermatitis (ACD) has been demonstrated with a wide variety of excipients, and patch testing with these agents should be considered especially in scenarios of reactions to medications where the active ingredients are dissimilar.

### CMC

CMC has less commonly been reported in DHRs with various different type of medications such as oral antiepileptic medications, NSAIDs, levothyroxine, and injectable corticosteroids.[84]

### PEG

The lower MW PEGs (200–400) are mainly implicated in ACD with topical medications, such as nitrofurazone preparations.[85–88] Cross-reactivity occurred between these low MW liquid PEGs, but not with the higher MW solid PEGs 1000–6000.[85]

### Propylene Glycol (PG)

PG, a small molecule which is structurally distinct and unrelated to PEG despite a similar sounding name, is an emollient and emulsifier found in cosmetics, medications, and foods. It is also the most commonly reported excipient in DHRs and was therefore granted the dubious honor of being named the American Contact Dermatitis Society's Allergen of the Year for 2018.[89] PG is involved in DHRs with different types of medications.[90–98] It can be difficult to interpret on patch testing due to its effects as a weak sensitizer and an irritant.

## Other delayed systemic hypersensitivity reactions:

Systemic DHRs have also been reported in association with excipients. In particular, three cases of systemic delayed onset rash have been reported to drugs that contained CMC, two

of whom were positive on delayed intradermal testing, and one of whom had the onset of eczematous rash at 24 hours after a CMC challenge.[84] A patient was also reported to have had systemic ACD after a diazepam injection containing PG after a previous contact reaction to a PG-containing lubricant.[92]

## The special case of excipients in reactions to corticosteroids, vaccines, and biologics:

We want to specifically highlight the importance of excipients for patients with hypersensitivity to systemic CS, vaccines, and biologics. Reactions to corticosteroids and vaccines are overall quite rare, but excipients are the most frequently attributable cause.[4, 99] In regards to CS, the awareness of excipient allergy is in rapid evolution. While one literature review as recently as 2015 on IHRs to CS showed excipients were reported responsible for 28.3% of corticosteroid reactions, almost all anaphylaxis due to lactose, CMC and PEG,[99]more recent publications have demonstrated that the majority of corticosteroid anaphylaxis cases in their testing series were actually due to excipients.[100, 101] In one of these, where CMC and PEG were the most frequently implicated, the authors highlight the importance of an accurate diagnosis, for which they proposed a diagnostic algorithm with standard excipient testing.[101] Regarding vaccines, anaphylaxis occurs rarely, in approximately 1 per million vaccine doses administered.[4] The major risk of IHRs during vaccination is the presence of pre-existing allergy to vaccine excipients[4] such as gelatin,[102–104] alpha-gal,[28, 29] and a single case of a reaction to PS80.[4, 105] Altogether over 20 licensed vaccines in the US contain a PS as an excipient, the quantities of PS vary widely and are overall low. Furthermore despite repeat dosing with PS such as for influenza vaccines, anaphylaxis is rare. The pathway of primary sensitization through PS exposure therefore seems to occur uncommonly. Table II summarizes IgE-mediated anaphylaxis due to the excipients present in both CS and vaccines. In addition, the presence of PEGs and PSs in a wide variety of biologic agents makes excipients a key consideration in repeated reactions to separate agents within this class as well.[46, 47, 50, 51] Finally, since we are not isolated from the current events of the SARS-CoV-2 pandemic, it will be crucial to consider the presence of PEG2000 in lipid nanoparticle carrier vehicle and PS80 in excipient formulations of other vaccines still under study respectively of most leading vaccine candidates as potential allergens during safety screening and when evaluating any rare IHRs.[43, 106–108] If these allergens are ultimately implicated as a mechanism for vaccine reactions, true IgE mediated allergy leading to anaphylaxis is likely to be exceedingly rare compared to other less specific mechanisms that will cause mild to moderate symptoms (urticaria, flushing, rash). The implications for giving such vaccines containing PEG2000, PS80, PS20 to patients with preexisting and documented PEG anaphylaxis is currently unknown and at the time of writing this review the current recommendation would be to avoid PEG containing vaccines with consideration for PS containing vaccines being based on the skin testing profile of the individual PEG allergic patient.

In regards to biologics, reports to the FDA of anaphylaxis to drugs in this class were recently shown to be steadily increasing from 1999–2019, and now reported at a higher annual rate than antibiotics.[109] The mechanisms of these reactions are not currently clear.[109] However,

the prototypical example where a mechanism is clearly defined is alpha-gal allergy and cetuximab,[110] and a large number of these drugs contain PEGs or polysorbates.[1, 54, 109]

## Intolerances:

In addition to allergy, it is important to be aware that excipients which are commonly derived from foods, dyes and sugar sources can also be a source of intolerances to medications as well.[111] Gastrointestinal malabsorption via direct osmotic effects or fermentation are the main potential side effects, with ingredients ranging from those that are well known, such as lactose[112, 113] or wheat starch (gluten)[114] to those that are much less common. These intolerances are mostly beyond the scope of this review, but we would recommend the excellent articles by Reker et al. as a source of information on this topic.[111, 115]

## Helpful Online Resources:

To aid clinicians who are evaluating the possibility of an excipient allergy, recent database resources make it easier to identify all ingredients that are present, to understand the function and structure for these chemicals, to plan for testing and to counsel patients about future drug safety.

NIH Daily Med is a website maintained by the National Library of Medicine, and allows clinicians to look up all **active** and **inactive** ingredients for prescription drugs, over the counter drugs (OTCs), and vaccines in the United States. The “advanced search” feature is helpful for searching a specific excipient and this works best when searching terms suggested from the pop-up list. (https://dailymed.nlm.nih.gov/dailymed/).[2]

PubChem is another useful resource, also from the National Library of Medicine, where users can obtain detailed description of each excipient, their nomenclature, gain information about the drug composition; the chemical structure, and understand their underlying use. (https://pubchem.ncbi.nlm.nih.gov/)[116] There are also resources where chemical structures can be searched based on similarity.

## When to Look for Excipient Allergies in a Patient:

Looking for excipient allergy has been part of standard practice for reactions caused by foods such as gelatin, egg, or milk, when they are present as an excipient in medications or self-care products.[117–123] Further, galactose-alpha-1, 3-galactose, colloquially known as alpha-gal, was discovered as an allergen primarily because of its presence as an unintended molecule in the drug cetuximab before its role in red meat allergy became clear.[110] The most pressing clinical issues in excipient allergy, therefore, are those excipients that are not routinely encountered outside of medications, the scope to which their allergies are a problem in the population, and how to approach such allergies in clinical practice and research.

There are some key principles from current drug allergy practice that can be applied to decide when to test someone, and to prevent unnecessary avoidance of common excipients.

1. It is more common to report an allergy than to actually be allergic.[124–126]
2. Patients may report intolerance symptoms to excipients that are inconsistent with an immunologically mediated adverse event.

   Validated screening approaches do not currently exist for risk-stratifying the pre-test probability of a true excipient reaction as with penicillin allergies[127–130] but use of index reaction history is always helpful in deciding which patients need skin testing, versus a direct challenge, versus reassurance. Higher risk histories should be offered relevant testing if at all possible.[1, 4, 42] Patients presenting with multiple episodes of anaphylaxis potentially associated with structural disparate inciting drugs, vaccines and other products are particularly at high risk for an underlying unrecognized excipient reaction and should be investigated carefully.
3. A diagnosis of allergy to an excipient, just like any other allergy, is best made in the presence of the appropriate symptoms, after confirmatory testing.[131]
4. For vaccines the excipient should be considered a potential culprit until proven otherwise.[4]

It is our belief that higher severity index reactions and reactions to drugs that limit optimal care delivery are more concerning and deserve the highest priority for clarification via testing if possible.

## Practical Advice on Testing and Workup:

When performing immediate or delayed skin testing for excipient allergies, the authors suggest that clinicians keep the following principles in mind, Figure 3.

1. Skin prick testing can be done for almost any drug, but intradermal testing should only be done with sterile drugs.
2. Validated, non-irritating concentrations of many drugs and excipients for skin testing do not exist. For excipients and excipient containing drugs where a testing strategy has not been reported previously to be non-irritating, it is important to skin test for irritant responses in a healthy control, if possible.
3. Design your skin testing strategy to have multiple drugs that contain the same excipient, to serve as controls for other ingredients.
   a. Pure excipients can sometimes be obtained if they are the active ingredient of another medication (polyethylene glycol 3350), or as laboratory grade reagents, but should not be used for intradermal testing unless they are verified to be sterile.
4. Perform skin tests with the same drug (brand name, manufacturer) implicated in the original reaction described by the patient when excipient drug allergy is suspected (the patient who reports allergic reactions with specific drug brands but not with others containing the same active drug but different excipients).
5. Laboratory based testing for certain excipient allergies is an area of active research (Figure 4), and may become available over time.

## Unanswered Questions and Future Directions:

While undeniable evidence support the importance of excipient reactions as “hidden dangers”, our current knowledge is still limited by the lack of clarity in the prevalence and underlying mechanisms of these reactions. For example, among patients with immediate reactions to excipients, it is not clear the extent to which these are IgE-mediated versus IgG/ C-system mediated, or non-IgE mediated and dose-dependent. Validated commercially-scalable testing platforms are sorely needed, though some progress is being made in this area.[41]

Given the overall numbers reported internationally, evidence based approaches for the work-up of excipient reactions are still lacking and many questions remain. What is the positive and negative predictive value of immediate prick testing with excipients? What is the positive and negative predictive value for immediate and delayed intradermal testing? In cases where IgE mediated reactions to excipients are suspected does skin test reactivity wane with time and how does this correlate with clinical reactions on ingestion challenge? What is the true immunological cross-reactivity between PEG and PEG derivatives (e.g. cross-reactivity between PEG and polysorbates, poloxamers, PEG castor oils etc). Is PEG2000 truly implicated in some cases of anaphylaxis associated with mRNA SARS-CoV-2 vaccines and if so how do we recognize these cases and what are the implications for future SARS-CoV-2 vaccines? Is it possible to become desensitized to excipients such as PEG? In the case of excipient allergy causing large local DHRs to vaccines, avoidance does not appear to be warranted however the mechanisms and relevance is unknown in most cases,[4] but we do not know where the line of safety is, in most cases. It may also be difficult to distinguish these cases from reactogenicity to the active component of the vaccine or an Arthus reaction. From our review, there appear to be some useful risk features and approaches which have been identified to avoid future severe reactions in the literature, but work needs to be done to address some significant unknowns. (Table IV)

Another key question demanding further evidence is whether there is a hierarchy of danger in excipient reactions that is determined by route of medication delivery and dose. For example, it seems that the risk of severe reactions to alpha-gal is higher with parenteral or large volume enteral consumption compared to small amount enteral consumption. The presence of alpha-gal allergen in pancrelipase capsules or other mammalian derived excipients may not necessarily precipitate reactions in patients via the oral route.[132, 133] Some patients who have anaphylaxis to CMC via parenteral route are reported to tolerate low dose oral exposure.[8, 134–136]

In addition, patterns of cross-reactivity amongst excipient allergens remain largely unknown. While patients with high MW PEG allergy can have cross-reactivity with PS and other PEG derivatives.[55] Many such patients appear to tolerate PEGs of lower MW and density without symptoms. Cross-reactivity amongst compounds containing polyethylene domains is a very important issue for patient safety indeed, given the thousands of drugs and other products that contain any one of these ingredients.

A final key limitation of excipient allergy evaluation is that avoidance may not always be the best option when confronted with a drug that the patient needs. Desensitization would be anticipated to work for IHRs when there is a compelling need,[137–139] but in the case of parenteral and pegylated formulations in particular, the presence of excipient specific IgG may accelerate drug clearance.[82, 83] It is unknown whether there needs to be any variation in desensitization protocols when an excipient is the allergen, versus the active ingredient.

## Conclusions:

Excipient allergies are real, can have profound effects on patient safety and may severely limit drug selection for relevant patient care. IgE mediated allergies are likely to be rare, while non-IgE mediated reactions or intolerance may be far more common. Because we have not routinely looked for them in our practices, most excipient allergies are likely to be undiagnosed at the moment, but testing should focus on those with a convincing reaction history. When confronted with a patient who has a compelling history of a reaction, skin test approaches require a carefully crafted but safe strategy, including use of multiple positive and negative controls. It has been noted by multiple investigators including the authors of this review that anaphylaxis can occur on intradermal testing to PEG containing drugs, therefore sequential prick and intradermal testing should always be performed in multiple steps starting from prick testing at the lowest concentration. It is suggested that testing should focus initially on proving reactivity to the drug containing the excipient, followed by the excipient in a purified form or as an ingredient in other drugs, unless there is a compelling reason to test all at once. Validated skin and laboratory testing strategies are needed for most excipients. Mechanistic and cross-reactivity studies are also needed to answer crucial questions that affect patient care when testing is positive.

Before any drug administration, vaccination or surgery it is necessary to take into account all the excipients that could be present. Comprehensive approaches in the setting of unusual allergy symptoms, including episodes that occurred due to multiple structurally unrelated drugs but also with foods or other products, can unveil the culprit of such reactions which empowers the ability to advise safe future drug and vaccine use.

## Funding Sources:

Dr. Stone receives funding from AHRQ 1K12HS026395-01

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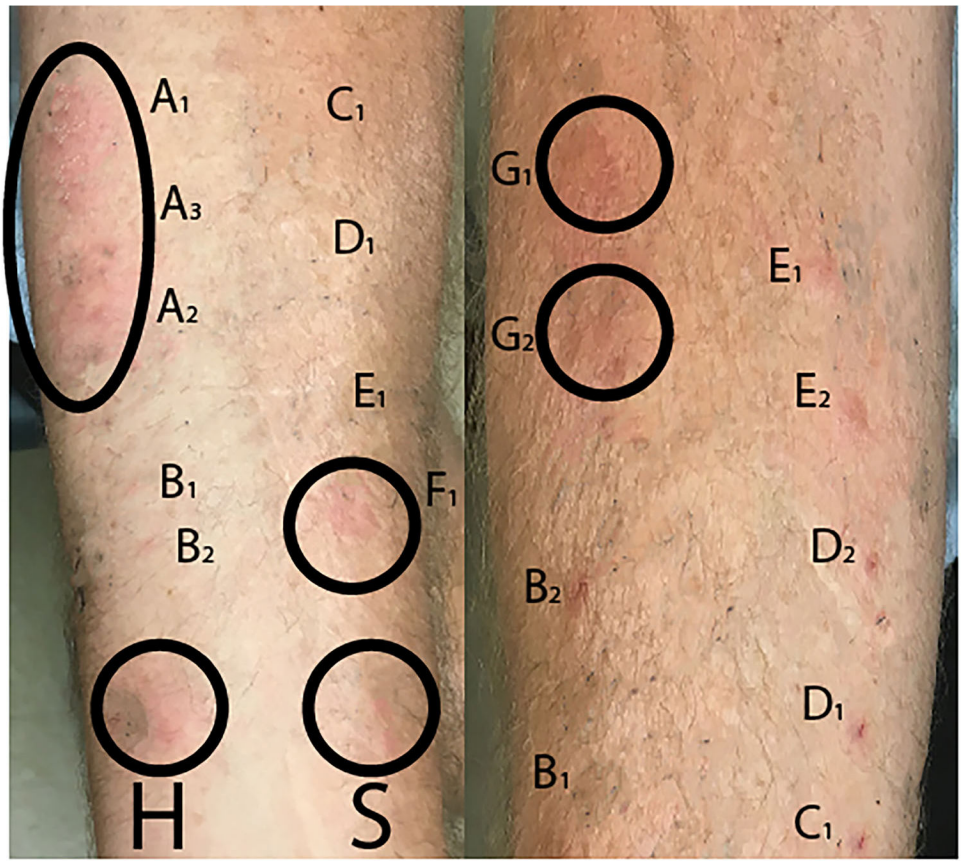
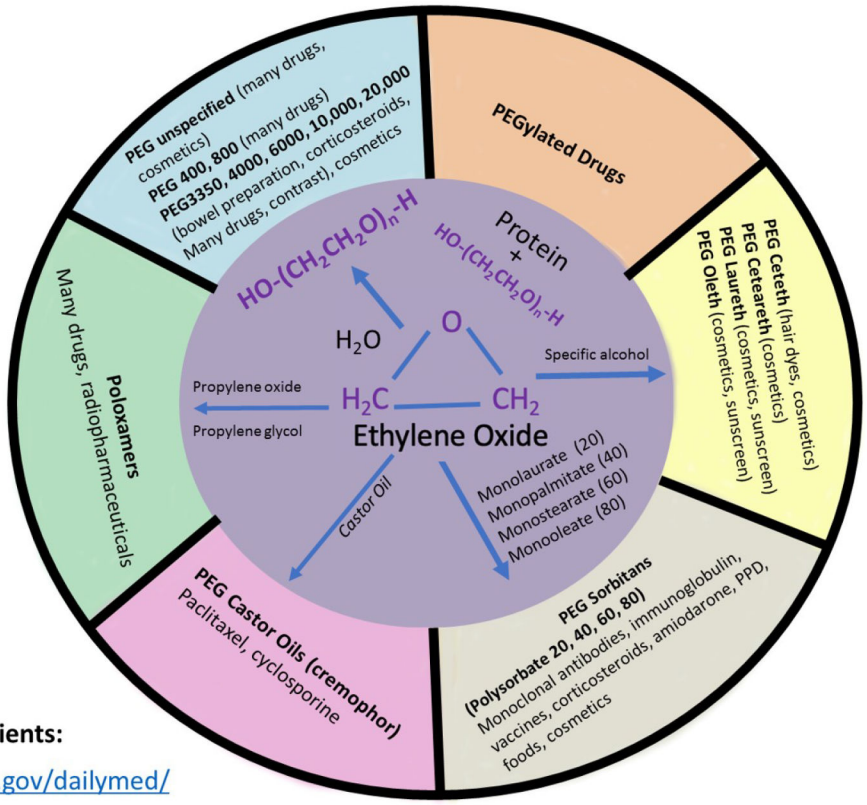



**Figure 1:**

In the left panel is skin prick testing read at 15 minutes demonstrating positive responses to methylprednisolone acetate (MP acetate), and polyethylene glycol 3350 (PEG 3350). S= saline negative control. H = histamine positive control. Other tested corticosteroids were negative. In the right panel is intradermal testing read at 15 minutes, which demonstrates a positive response to triamcinolone acetate at 1mg and 0.1mg. Other tested corticosteroids were interpreted as negative. Key: Drug used is indicated by the letter. A= polyethylene glycol 3350 (Miralax), B=Methylprednisolone sodium succinate 5mg/ml, C=Budesonide 0.6mg/ml, D=Dexamethasone 0.4mg/ml, E= Hydrocortisone 5mg/ml, F=Methylprednisolone acetate 4mg/ml G= Triamcinolone acetate 1mg/ml. A subscript 1= full strength, a subscript 2= 1:10 dilution and a subscript 3= 1:100 dilution. Image/case originally presented in Stone et al. JACI: In Practice, 2019[1]




**Resource to search excipients:**

https://dailymed.nlm.nih.gov/dailymed/

**Figure 2:**

Excipients whose chemical derivation utilizes ethylene oxides, some of which have demonstrated clinical cross reactivity in PEG allergic patients.

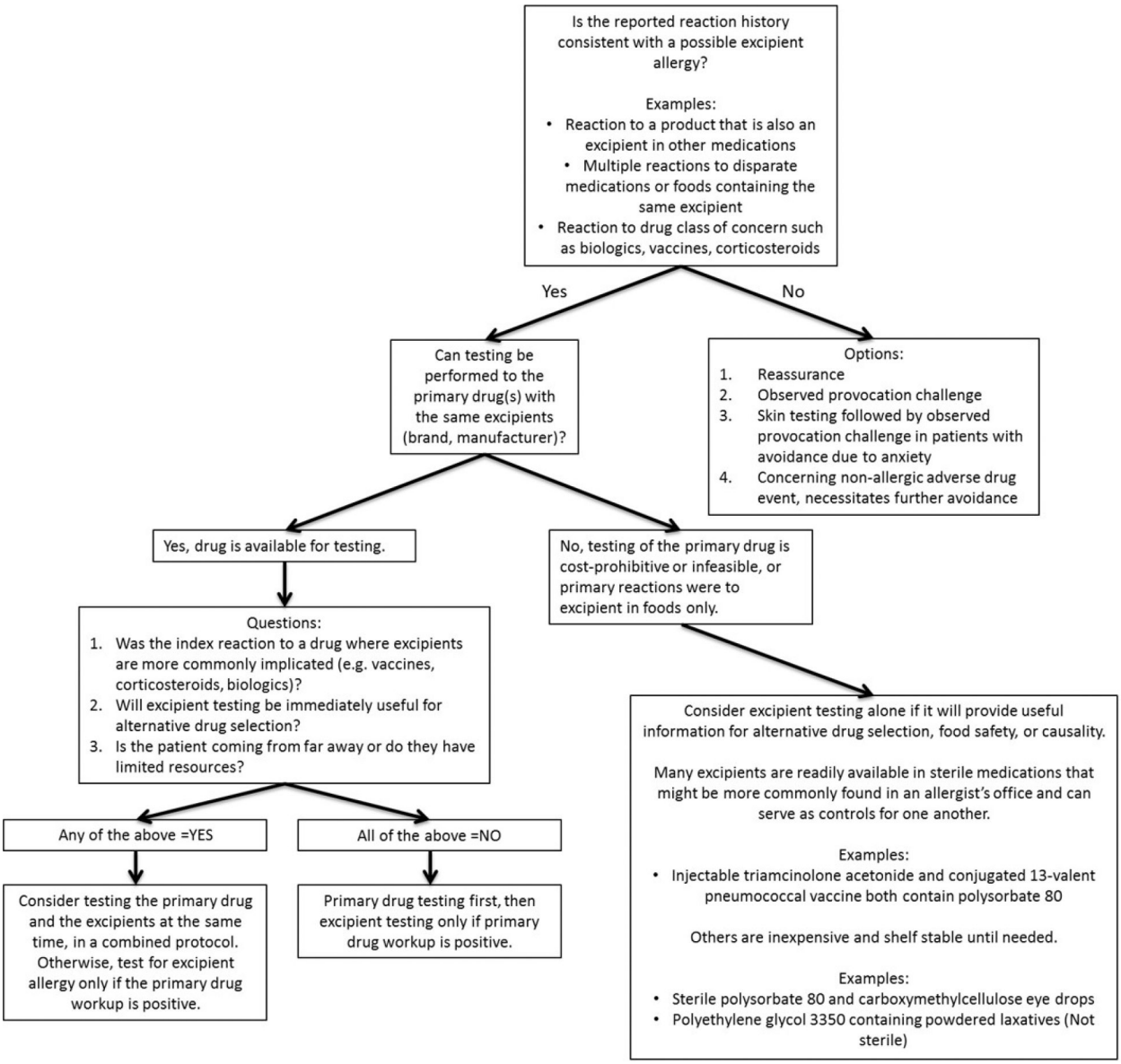



**Figure 3: Flow diagram for an approach to excipient testing.**

Testing of excipients should generally be thought of as the second step after a patient tests positive to an implicated drug. In the setting of certain PEG containing products (e.g. PEG3350, 4000 in laxatives) PEG is the primary drug, however. Consider testing the excipient first if the active or primary drug is expensive or hard to obtain (e.g. biologics that cost thousands of dollars a dose) or infeasible depending on the drug and the setting (e.g. chemotherapy), in which case first step excipient testing may be useful for determining the need for avoiding alternative drugs. If a question is time dependent and crucial regarding future drug or vaccine therapy then testing the primary drug and excipients in a single visit makes the most sense. Testing strategies for certain drugs (e.g. corticosteroids) are available and have controls that are useful (e.g. methylprednisolone acetate has PEG3350 and methylprednisolone sodium succinate does not).

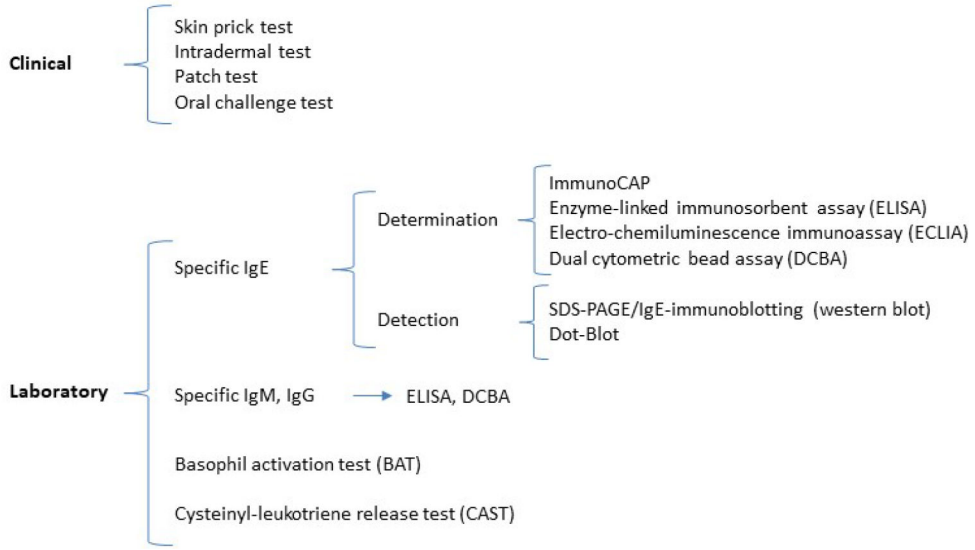



**Figure 4: Clinical and laboratory techniques that have been used in the literature to help confirm an excipient allergy diagnosis.**

In some cases, a personalized diagnosis has been made using, as an example IgE-immunoblotting, to try detecting specific IgE to chemicals where commercial allergen testing is not available. Immunoblotting techniques, both SDS-PAGE/IgE-immunoblotting (western blot) and dot-blot appear to be useful for diagnosis of allergy to several pharmaceutical excipients: CMC[7, 140, 141], casein,[142] macrogols of different MW[37] and povidone or polyvinylpyrrolidone (PVP).[143] The utility of specific IgE detection via ELISA based assays and dual bead cytometric assays have been reported in immediate hypersensitivity to PEGs in several skin test positive patients.[1, 41, 42] Specific IgE to alpha-gal, gelatin, and many other food based excipients appear to have diagnostic utility in excipient reactions and are already commercially available.[28, 29, 132]

**Table I.**

Immediate Hypersensitivity Reactions to Excipients (Excluding Cases Related to Vaccines and Corticosteroids).

| Excipient | PMID of Case Reference | Medication type | Clinical manifestations | Evidence for Mechanism |
|---|---|---|---|---|
| **CMC** [6, 7, 9, 12, 13, 141] | 9345076 | Oral barium sulfate contrast media | Anaphylaxis | Skin scratch test |
| | 20128230 | Barium sulfate contrast enema | Anaphylaxis | IDT, BAT, CAST, dot-blot |
| | 22812199 | Ophthalmic CMC drops | Conjunctival erythema and bilateral periocular edema with urticarial lesions | SPT, dot-blot |
| | 10598652 | Lidocaine gel | Hyposthenia, dysesthesia, nasal congestion | SPT negative, positive nasal provocation specific to CMC |
| | 33181345 | Ice Cream | Anaphylaxis | SPT, BAT, OCT |
| | 30765462 | Popsicles/Ice Lollies | Anaphylaxis | SPT, OCT |
| **Cremophor** [59–63] | 26739412 | Paclitaxel, etoposide chemotherapeutic and multivitamin with Cremophor | Anaphylaxis | SPT |
| | 31955702 | Fosaprepitant and paclitaxel chemotherapeutics | Anaphylaxis | np |
| | 9494448 | Intravenous cyclosporine with tolerance of oral cyclosporine | Anaphylaxis | IDT, SPT |
| | 11570623 | First dose anaphylaxis to IV cyclosporine | Anaphylaxis | IDT, SPT, BAT to Cremophor |
| | 31446869 | Vitamin K, cyclosporine, and tacrolimus | Anaphylaxis | np |
| **Gelatin** [18–22] | 22374209 | Intraoperative gelfoam | Anaphylaxis | SPT, sIgE (ImmunoCAP) |
| | 25886695 | Intraoperative gelfoam | Anaphylaxis | sIgE (ImmunoCAP) |
| | 23021035 | Topical gelfoam sponges | Anaphylaxis | SPT, sIgE (ImmunoCAP) |
| | 25577629 | Intraoperative floseal hemostatics | Anaphylaxis | sIgE (ImmunoCAP) |
| | 23752162 | Intraoperative, intraosseous floseal hemostatics | Anaphylaxis | sIgE (ImmunoCAP) |
| **Gelatin/Alpha-gal** [27] | 25439422 | Succinylated gelatin plasma expander | Anaphylaxis | SPT, sIgE (ImmunoCAP) |
| **Mannitol** [144–146] | 15479277 | Chewable cisapride tablet | Anaphylaxis | SPT, sIgE (ELISA) |
| | 25951149 | Paracetamol effervescent sachet | Urticaria and angioedema; anaphylaxis | IDT and OCT |
| | 26603804 | Intravenous paracetamol | Anaphylaxis | IDT |
| **PEG** [30–40, 147, 148] | 23444288 | PEG 3350 Bowel Preparation | Anaphylaxis | SPT |
| | 26203443 | PEG 3350 Bowel Preparation | Anaphylaxis | np |
| | 18479663 | PEG 4000 Bowel Preparation | Urticaria and angioedema | IDT, OCT |
| | 24811032 | PEG 4000 Bowel Preparation | Anaphylaxis | SPT |
| | 16867059 | PEG 6000 in phenoxymethylpenicillin, throat lozenge, fluoride tablets | Urticaria, tachycardia and dizziness | SPT |
| | 17156356 | Bacampicillin antibiotic and citrate de betaine effervescent dyspepsia medication containing PEG 6000 | Anaphylaxis | SPT |

| Excipient | PMID of Case Reference | Medication type | Clinical manifestations | Evidence for Mechanism |
|---|---|---|---|---|
| | 27996956 | Effervescent potassium bicarbonate supplements containing PEG 6000 | Anaphylaxis | SPT, OCT, dot-blot |
| | 22123387 | Nimesulide containing PEG 4000 and paracetamonol syrup containing PEG 6000 | Urticaria and angioedema | SPT, BAT |
| | 26807134 | PEG 8000 transvaginal ultrasound gel | Anaphylaxis | SPT |
| | 29517164 | PEG 4000 containing ultrasound contrast agent (Lumason) | Anaphylaxis | np |
| | 30820197 | Cough syrup containing PEG 6000 | Urticaria, dizziness and dyspnea | SPT, BAT |
| | 33011299 | Medroxyprogesterone acetate containing PEG 3350, laxatives, dyspepsia medications containing PEG 20000, malarone, phenoxymethylpenicillin, clopidogrel containing PEG 6000 | Anaphylaxis | SPT, IDT |
| | 32376486 | Medroxyprogesterone acetate containing PEG 3350, dyspepsia medications containing PEG 20000 | Anaphylaxis | SPT, IDT |
| **PEGylation** [42, 75, 78] | 31954852 | PEGylated liposomal echocardiogram contrast media, also PEG 3350 colonoscopy preparation and methylprednisolone acetate containing PEG 3350 | Anaphylaxis | SPT, ECLIA |
| | 17873110 | PEGylated liposomal doxorubicin | Anaphylaxis | np |
| | 32497373 | PEGylated recombinant Factor VIII | Anaphylaxis | Anti-PEG IgM, IgG (ELISA) |
| **PEG + PS60** [52] | 31389792 | PEG 1500/6000 vaginal suppository, vaginal cream containing polysorbate 60 | Anaphylaxis | SPT, BAT, OCT |
| **PEG + PS80** [53] | 26727768 | Antibiotics and NSAIDs containing PEGs of varying molecular weights and PS80 | Urticaria | SPT |
| **PS20** [46, 47] | 17619560 | Omalizumab | Anaphylaxis | IDT |
| | 29481891 | Omalizumab (with positive testing to a wide variety of other PEG and PS containing biologics) | Anaphylaxis | SPT |
| **PS80** [48–50] | 29306312 | Etoposide chemotherapy | Anaphylaxis | IDT |
| | 15958049 | Recombinant erythropoietin and darbepoietin | Urticaria, pruritus, and orofacial angioedema | SPT, IDT |
| | 21219296 | Adalimumab, ustekinumab containing PS80 | Urticaria | SPT |
| **PS20 + PS80** [51] | 30055223 | Alirocumab (PS20) and evolocumab (PS80) | Injection site reactions | IDT |

Abbreviations: Alpha-gal, galactose-alpha-1,3-galactose; Abs, antibodies; BAT, basophil activation test; CAST, cysteinyl-leukotriene release test; CMC, carboxymethylcellulose; ECLIA, electro-chemiluminescence immunoassay; ELISA, enzyme-linked immunosorbent assay; ESAs, Erythropoiesis-Stimulating Agents; IDT, intradermal test; np, not performed; NSAIDs, nonsteroidal anti-inflammatory drugs; OCT, oral challenge test; PEG, polyethylene glycol; PEGylation, PEG attachment on pharmaceuticals; PS20, polysorbate 20; PS60, polysorbate 60; PS80, polysorbate 80; sIgE, specific IgE; SPT, skin prick test.

**Table II.**

IgE-mediated anaphylaxis due to excipients present in corticosteroids and vaccines formulations.

| Excipient | PMID of Case Reference | Medication type | Evidence for Mechanism |
|---|---|---|---|
| | | **Corticosteroids** | |
| **CMC** [135, 136, 140, 149–155] | 1285842 | Intraarticular injections of prednisolone acetate and cortivazol | SPT |
| | 7697477 | Intradermal injection of triamcinolone acetonide | SPT, dot-blot |
| | 25613209 | Intradermal injection of triamcinolone acetonide | SPT |
| | 10753030 | Intraarticular injection of triamcinolone acetonide | Skin scratch test, IDT |
| | 12835567 | Intraarticular injection of triamcinolone acetonide | SPT, IDT |
| | 11269902 | Intraarticular injections of triamcinolone acetonide and betamethasone dipropionate | SPT, IDT |
| | 16599249 | Intraarticular injection of triamcinolone acetonide | SPT |
| | 17627664 | Intradermal injection of triamcinolone acetonide | SPT |
| | 18457729 | Intraarticular injection of corticosteroid | SPT, IDT |
| | 19878250 | Intraarticular injection of triamcinolone acetonide | SPT, IDT |
| **Lactose** [156–158] | 15007361 | Dry powder salmeterol and fluticasone inhaler-milk allergic patient | SPT, sIgE (SDS-PAGE/IgE-immunoblotting) |
| | 29197126 | Dry powder budesonide inhaler in milk and possible alpha-gal allergic patient | sIgE alpha-gal (ImmunoCAP) |
| | 21631524 | Intravenous injection of methylprednisolone sodium succinate | SPT |
| **PEG** [1, 159–163] | 18315736 | Intraarticular injection of methylprednisolone acetate (PEG 4000) | SPT, OCT |
| | 23151193 | Intraarticular injection of methylprednisolone acetate (PEG 3350) | SPT, IDT |
| | 23228247 | Intradermal injection of methylprednisolone acetate (PEG 3350) and oral calcium carbonate containing PEG 6000 | SPT, HR |
| | 28078080 | Intraarticular injections of methylprednisolone acetate (PEG 3350) | SPT, OCT |
| | 15813822 | Intraarticular injection of betamethasone dipropionate (PEG 4000) | SPT, IDT |
| | 30557713 | Intraarticular injection of methylprednisolone acetate (PEG 3350) | SPT, IDT, ELISA |
| **PS80** [164] | 27996954 | Intramuscular injection of dexamethasone | SPT, IDT, OCT |
| | | **Vaccines** | |
| **Gelatin** [102–104] | 8473675 | MMR | SPT, sIgE (SDS-PAGE/IgE-immunoblotting) |
| | 9042057 | Varicella | sIgE (ImmunoCAP) |
| | 8977505 | MMR | sIgE (ImmunoCAP) |
| **Gelatin/Alpha-gal** [28, 29] | 27986511 | VZV | sIgE gelatin and alpha-gal (ImmunoCAP) |
| | 29913263 | MMR, varicella | SPT, sIgE gelatin and alpha-gal (ImmunoCAP) |
| **PS80** [105] | 22605841 | HPV | SPT, IDT |

Abbreviations: Alpha-gal, galactose-alpha-1,3-galactose; CMC, carboxymethylcellulose; DTaP-IPV, diphtheria tetanus acellular pertussis-inactivated poliovirus vaccine; HPV, human papillomavirus vaccine; HR, histamine release; IDT, intradermal test; MMR, measles mumps rubella;

OCT, oral challenge test; PEG, polyethylene glycol; PS80, polysorbate 80; SDS-PAGE, sodium dodecyl sulfate polyacrylamide gel electrophoresis; sIgE, specific IgE; SPT, skin prick test; VZV, varicella-zoster virus.

**Table III.**

Delayed Hypersensitivity Reactions to Excipients.

| Excipient | PMID of Case Reference | Medication type | Clinical manifestations | Evidence for Mechanism |
|---|---|---|---|---|
| **CMC** [84] | 21480918 | Antiepileptic drugs (carbamazepine), paracetamol oral tablets | DRESS vs. ACD | OCT/24 h |
| | 21480918 | CS intraarticular injection, piroxicam | Dermatitis | SPT/24 h |
| | 21480918 | Wound dressings and levothyroxine | Contact Dermatitis and Delayed Urticaria | PT, IDT/24 h |
| **PEG** [85–88] | 668343 | Topical medications containing PEG 200, 300, 400 | ACD | PT |
| | 8187530 | Topical medications containing PEG 300, 400, 555 | Eczema | PT |
| | 10594300 | Topical medications containing PEG 300, 400 | ACD | PT |
| | 16487291 | Topical medications containing PEG 400 | ACD | PT |
| **PG** [90–98] | 24603514 | Topical corticosteroid, oral antihistamine | ACD, eczematous dermatitis | PT |
| | 26381657 | Oral cetirizine and hydroxyzine syrups | ACD | PT |
| | 7648882 | Diazepam injection | Systemic ACD | PT |
| | 533293 | KY lubricant jelly | ACD | np |
| | 421460 | Topical steroid cream | ACD | PT |
| | 9739936 | Topical acyclovir cream | ACD | PT |
| | 3308311 | Ultrasound gel | ACD | PT |
| | 28767154 | Ultrasound gel | ACD | PT |
| | 16101873 | Ultrasound gel | ACD | PT |

Abbreviations: ACD, allergic contact dermatitis; AEDs, antiepileptic drugs; CMC, carboxymethylcellulose; CS, corticosteroids; DRESS, drug reaction with eosinophilia and systemic symptoms; h, hours; IDT, intradermal test; np, not performed; OCT, oral challenge test; PEG, polyethylene glycol; PG, propylene glycol; PT, patch test; SPT, skin prick test.

**Table IV:**

Risk Factors for Recurrence of Severe Immediate Hypersensitivity in Future Excipient Exposures

| More likely to cause severe symptoms | Less likely to cause severe symptoms |
|---|---|
| • Parenteral or mucosal exposure<br>– Example: An injection containing CMC or polysorbate 80 versus an oral capsule containing the same allergens<br>• Large dose oral exposure<br>– Grams or milligrams<br>– Examples:<br>♦ Oral Barium contrast is 1.2% carboxymethylcellulose by weight<br>♦ PEG 3350 bowel prep<br>• Type of exposure during original sensitization<br>– Unclear if chronic low dose oral/cutaneous exposure leading to sensitization may lead to a lower reaction threshold when compared to high dose parenteral sensitization.<br>• Patient with previous positive skin test to an excipient or history of multiple reactions<br>• High molecular weight of excipient versus low for some excipients<br>– Example: PEGs and polysorbates<br>♦ Unknown cutoff separating high molecular weight from low, may vary by patient<br>• Receipt of identical excipient or likely cross-reactive excipient | • Low Dose Oral Exposure<br>– Micrograms<br>♦ Example: Carboxymethylcellulose in capsules and foods is in the micrograms range<br>• Safety varies by patient<br>• Some excipients added to foods in a trace amount<br>• Low molecular weight PEG<br>– Unclear cutoff separating high molecular weight from low, some patients tolerate low molecular weight and not high.<br>• Cutaneous exposure only<br>• Agent with structural similarity but unconfirmed cross-reactivity<br>– Example: Cremophor reaction and concern for reactivity to polyethylene oxide compounds<br>– Consider testing if possible prior to use |