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Anaphylaxis to Excipients in Current Clinical Practice: Evaluation and Management

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Introduction:

Excipients, are inactive ingredients of drugs that are not under the same regulation as the parent drug and are used to stabilize, preserve, or enhance the pharmacokinetics, bioavailability of the active ingredients and palatability of the preparation. In the event of a reaction to a particular drug, it is typically assumed that the reaction is due to the active ingredient, and for many drugs and drug classes that assumption is correct. However, many excipients are also potential allergens, and should not be overlooked in patients with a compatible medical history (Table 1).

Excipient allergy is overall rare and hence often missed or misdiagnosed due to lack of awareness of the need to carefully review the drug ingredients. In addition, some excipients also have an unearned reputation for being “inert” that may cause them to be dismissed from a suspect line-up. For these reasons, excipient allergy can often be overlooked by everyone involved, despite a history of life-threatening reactions.

For the patient, excipient allergy can be frightening and potentially disruptive to healthcare delivery. It may present as multiple reactions to structurally unrelated drugs, as reactions to only some formulations or doses of a specific drug, or as reactions to drugs not usually associated with allergy such as laxatives and injectable corticosteroids. Due to variations

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in drug formulation that have arisen across different national healthcare systems and pharmacopoeias, the same allergy may also present with reactions to different drugs, in different geographical settings.

While the underlying mechanism of anaphylaxis is not apparent in all cases of immediate excipient hypersensitivity, IgE mediated anaphylaxis does appear to be the most likely and has been reported for the allergens selected in this review, which are: Polyethylene glycols, polysorbates, carboxymethylcellulose, mannitol, povidone, protamine, gelatin, and galactose-alpha, 1,3, galactose (alpha-gal) (Figure 1). We have also included poloxamers, due to multicenter observations from the authors that these compounds may have cross reactivity with PEGs. While we have focused on excipients to which anaphylaxis has been demonstrated repeatedly or to their potentially cross-reactive substances, this review does not exclude the possibility that other excipients with rare allergic potential (such as tromethamine¹ or hypromellose²) could emerge over time. As our knowledge grows, evidence for the allergenicity of an excipient should ideally pass through a sequence of initial reports, validation, and confirmation of the mechanism.

Polyethylene containing excipients

These excipients share the common structural feature of repeating ethylene oxide units, and include polyethylene glycols, polysorbates, and poloxamers. (Figure 2)

Polyethylene glycols (PEGs) (Macrogols)

Polyethylene glycols (PEGs) also called macrogols, are polymers of repeating ethylene oxide units, in which the number of ethylene repeats, each weighing 44 g/mol, determines the molecular weight of the compound. The term macrogol was initially chosen to refer to the PEG used as an excipient in drugs and devices to differentiate from PEG used as an excipient in cosmetic products. The nomenclature of PEGs is based on either the number of repeating units (e.g. PEG 76, as typically used in topical products), or the molecular weight $76 \times 44 \text{ g/mol} = \text{PEG 3350}$ typically used in pharmaceutical products.³ Understanding this structural concept is crucial, because a wide variety of excipients in current use also contain chains of repeating ethylene of various lengths, such as PEG sorbitans (polysorbates), poloxamers, PEG castor oils (cremophor), and others. Cross-reactivity amongst polyethylene compounds is currently the most important unknown for PEG allergy, affecting our ability to advise patients on what truly needs to be avoided.

PEGs have many properties and are found in a wide variety of products. They are used as surface coating and pill binders in tablets, as the active ingredient in laxatives and can be conjugated directly to an active ingredient to prolong or potentiate the active ingredient's mechanism of action (PEGylation). On a publicly available database of FDA regulated products⁴ a focused search for PEG 3350 content (on August 17th, 2021) finds 1,434 products available in the United States of which laxatives, bowel preparations, film coated tablets, topical gels, and parenteral steroids are typical representatives. Although not strictly speaking an excipient, PEG-lipid compounds are utilized in mRNA technologies to construct the lipid nanoparticle carrier system. The intent is to stabilize the construct and protect those

lipid microspheres from complement activation. The mRNA vaccines against COVID-19 are the first widely used vaccines utilizing this technology.

Poloxamers

Poloxamers, like other PEG derivatives, are commonly used in pharmaceutical and cosmetic products as surfactants, stabilizers, and solubilizers.²³ Poloxamers are copolymers arranged in a triblock structure formed by a hydrophobic central chain of polypropylene glycol surrounded by two hydrophilic chains of PEG²³ (Figure 2). While there are more than 50 poloxamers with a similar chemical structure, they differ in their molecular weight (MW) due to the variable number of polypropylene glycol and PEG units. Therefore, each type of poloxamer has a different hydrophilic-lipophilic balance. Poloxamer 188 and poloxamer 407 are the most prevalent due to their great solubility in water.²⁴ MW vary from 1,100 to 14,000 g/mol. The generic term “poloxamer” is commonly followed by a numerical value of three digits: the first two digits, multiplied $\times 100$, indicates the MW of the hydrophobic core of propylene glycol, and the last digit, multiplied $\times 10$ gives the percentage of the hydrophilic PEG content. Poloxamer 188 contains roughly 80% ethylene oxide repeats by weight, with two 75-repeat polyethylene chains (~ 6600 g/mol out of an average 8400g/mol) and poloxamer 407 contains around 70% ethylene oxide repeats by weight, with two 98-repeat polyethylene chains ($\sim 8,624$ g/mol out of an average 12,600 g/mol)²⁵

Polysorbates

Polysorbates are surfactants commonly used as emulsifiers, solubilizers and stabilizers in cosmetic and pharmaceutical products as well as food agents.²⁸ Polysorbate 80 has been used in vaccines and biologic pharmaceutical drugs for years, though only one case of anaphylaxis linked with polysorbate 80 in a vaccine had ever been reported prior to this becoming a concern during the COVID pandemic,^{29,30} suggesting it is a rare allergen. Polysorbates are derived from pegylated sorbitan esterified with a lipophilic group of fatty acids; e.g. lauric acid in the case of polysorbate 20 or in the case of polysorbate 80 - oleic acid.²⁸ (Figure 2) The generic term “polysorbate” is followed by a number, e.g. 20, 40, 60 or 80. This number represents not the number of repeating ethylene oxide units but qualitatively the lipophilic group associated with the pegylated sorbitan portion. Polysorbates such as polysorbate 80 have 20 to 24 PEG units linked to the lipophilic group of fatty acids with a PEG MW between 880 g/mol and 1056 g/mol.

Non-polyethylene derived excipients:

Carboxymethylcellulose (E466 – Europe, Carmellose/Croscarmellose – Australia and Asia)

Carboxymethylcellulose (CMC) is an organic polysaccharide compound derived from cellulose via an alkali-catalyzed reaction with chloroacetic acid.³⁴ CMC is found as an ingredient in film coated tablets, ophthalmic drops, oral suspensions, foods, and as a stabilizer for some injectable, parenteral drugs. It is confusing for patients and physicians alike that different regions have different names for carboxymethylcellulose.

Mannitol

Mannitol is a sugar occurring naturally in many plants, fruits, vegetables and fungi. Medical uses include inducing osmotic diuresis, reducing raised intracranial or intraocular pressure and as an inhalational irritant used in bronchial inhalational challenge to assess airway hyperreactivity. It is used as a food additive labelled E421 according to the European Directive on food additives,³⁹ and as a low calorie sweetener due to poor intestinal absorption.⁴⁰ Mannitol is also used as an inactive ingredient in a wide variety of tablets where it functions as a sweetener, diluent, tonicity agent and a bulking agent. In addition, it is used in anticoagulant blood bags as part of the red cell preservative.⁴

Povidone

Povidone is also known as polyvinylpyrrolidone, PVP, or when used in food, E1201 according to the European Directive on food additives. It is a hydrophilic polymer originally developed as a plasma expander. Povidone is currently used in medications as a synthetic vehicle for suspension and dispersal of drugs, in other tablets as a binder and disintegrator, as povidone-iodine in skin disinfectants used before surgery and wound antiseptic solutions, as a lubricant in ophthalmic solutions (including eye drops and contact lenses), in cosmetic products, and as a food additive.⁴ A common myth of patients and health care providers is cross-reactivity between povidone and radiocontrast dyes. There is no relationship.

Protamine

Protamine is a highly cationic peptide historically derived from salmon spermatozoa, but now produced primarily through recombinant technologies. Protamine is administered as an active agent for heparin reversal after cardiac bypass surgery. It is also used in various preparations of intermediate duration insulins (such as neutral protamine Hagedorn "NPH" insulin) as an excipient that slows insulin absorption, but not in newer fast or long-acting insulins.^{4,49} Protamine is not used as an excipient outside of insulin preparations.⁴

Gelatin

Gelatin is an animal-derived product made by denaturing collagen from mammal/fish skins and bones using heat and dilute acids or bases. As an excipient, its intended role is to stabilize the active ingredients, or to comprise the bulk of an oral drug containing tablet, capsule, or chewable candy/wine gum formulations. As an active ingredient, gelatin has use in topically and intraoperatively applied hemostatic drugs.⁵⁸ Gelatin is found in topical gelatin-based hemostatic products containing porcine^{59–62} or bovine^{61–64} gelatin. It is also found in gelatin-containing vaccines.²⁹

Alpha-gal

Galactose-alpha-1,3 galactose (alpha-gal) is a disaccharide added by alpha 1,3 galactosyl transferase to the surface of non-primate mammalian cell membranes and cellular synthesized peptides. Because many drugs contain mammalian derived active or inactive ingredients, alpha-gal can be considered an unintended excipient allergen.

Alpha-gal allergy is found in many countries all over the world and is related to the bite of endemic ticks that produce sensitization due to the presence of alpha-gal in their salivary glands and gut.^{69,70} Patients may (but will not always) recall an inflamed tick bite in the weeks or months preceding the onset of their alpha-gal symptoms and can also occasionally experience recall urticaria at the site of the bite during a subsequent reaction to alpha-gal.⁷¹ In terms of drugs, alpha-gal allergen is found in products with mammal derived ingredients or manufacturing processes using mammalian cell lines, such as cetuximab,⁷² infliximab,⁷³ porcine derived pancrelipase,⁷⁴ heparin,⁷⁵ MMR vaccine,⁶⁶ varicella vaccine,¹⁷ bovine collagen,^{76,77} gelatin capsules,⁷⁸ and gelatin-based colloid plasma expanders.⁶⁵ Varicella zoster vaccine was previously found to contain alpha-gal,⁶⁷ in a version that is no longer commercially available in the United States. Due to use of mammalian ingredients and mammalian cell lines in pharmaceutical manufacturing processes, and a large number of affected patients in endemic areas, there is currently an unmet need to evaluate drugs more widely for this allergen in both the pre-approval and post-marketing phases.

Overall Management of Excipient Allergy:

In general, patients with a proven excipient allergy need to be adequately educated on the name of their allergen, its potential cross-reactivities, how to read medication and food labels including the presence of different nomenclature used in different countries (e.g. CMC), how to risk-assess and identify their target allergen within a product, and how to engage their families and healthcare providers in keeping them safe. Epinephrine autoinjectors are recommended for excipients that are difficult to avoid, and when the index reaction is severe. Wallet cards or medical alert bracelets can protect patients from unintentional medical exposures in the event of altered mental status. Key times at which a patient is at highest risk of exposure include healthcare encounters with new providers or interactions in which new medications will be given (the operating theater, provider from a new specialty becoming involved in the patient's care, during hospital admissions). Consultation with the allergist in these situations can reduce patient and non-allergy provider anxiety, while improving safety.

Limitations and Barriers to Optimal Excipient Allergy Management:

When considering the need to test for an excipient allergy, there are some key elements and limitations that currently need to be accounted for.

Firstly, the differences across healthcare systems are myriad. The primary challenge in even evaluating *the possibility* of an excipient allergy is knowing how to access the necessary information in a drug's product information and to identify ingredients most likely to be allergenic. Once the ingredient list has been located, it is then important to remember that requirements to declare the drug's inactive ingredients, amounts and molecular weights (especially with PEGs) may vary across national boundaries. Another barrier at this stage is that there can be many synonyms and cross-reactive compounds (for example: PEG is often called macrogol and the poloxamers and polysorbates also contain PEGs of varying lengths). Therefore, it is important to determine the different aliases by which an excipient can be labelled. Because generic drugs containing the same active ingredient are frequently

manufactured by multiple competing companies, it is also crucial to recognize that inactive ingredients may vary at the level of the manufacturer or even different doses of the same drug preparation. All these barriers are most easily overcome by the use of comprehensive databases on approved drug formulation, that can be accessible to the practitioner. In future directions, access to such databases should be standardized within national healthcare systems, with the possibility of transnational databases of drug formulations over time.

Secondly, it is important to consider the characteristics of the patient being tested, along with the limitations of the testing modality being utilized. True excipient allergy patients are rare but patients reporting “allergy” to multiple drugs are common. Standardized skin test protocols and excipient panels are useful in the authors’ experience, and continuously being refined. Further information on non-irritant concentrations will evolve with time and experience. However, it is also difficult to set up an excipient panel in a small clinic/office. Many practices may not deem that such a panel is needed as the number of positive tests will be very low, while the requirement to perform such testing in specialized centers is higher. Toward that end, skin testing protocols/panels that are validated and readily available are needed in the future. In the meantime, it is recommended that future publications to the literature also provide data on skin testing results from healthy controls. We have provided such data, when available, for test protocols suggested in this paper (Table 3).

Thirdly, there are not many excipient allergies for which *ex vivo* testing approaches are commercially available or widely utilized, alpha-gal and gelatin allergy being the key exceptions. While scientific reports have shown promise in this area for further excipients, there is a need for scalable collaborations between excipient allergy researchers and the laboratory testing industry to meet this need for confirmatory tests. In future directions, testing modalities that can screen drugs for key allergens prior to market approval or as a post-marketing safety step will be invaluable. A hope is that in the future, standardized excipient allergy quantification would lead to comprehensive databases that clearly reveal the presence, molecular weight (if applicable) and quantity of key allergens in the drug.

Conclusions:

In conclusion, excipient allergies are uncommon but underrecognized reactions that are potentially fatal. This is due largely to a limited awareness of these ingredients as allergens, the challenges in ascertaining drug ingredients within and across healthcare systems, the ubiquity of many of these ingredients in otherwise innocuous or important drugs and the variable nature of allergic responses within sensitized individuals. To answer these challenges, management should focus on increased awareness and recognition, clearly confirming the diagnosis, educating patients and other healthcare providers about their allergy, teaching patients how to search ingredient lists, and careful avoidance in collaboration with their providers. Knowledge about the sensitization pathways, epidemiology and host risk is paramount and international collaboration to obtain large cohorts to study will be essential. The work of such collaborations should focus on standardized skin testing, validation of confirmatory *ex vivo* tests, and encourage readily available access to national drug formularies with information on both active and inactive ingredients.

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Synopsis:

Excipients are the inactive ingredients in a drug or product, and are there to stabilize, preserve, or enhance the pharmacokinetics and bioavailability of the active ingredients. Excipient allergy is rare and hence often missed or misdiagnosed due to lack of awareness of the need to carefully review all drug ingredients. For the patient, excipient allergy can be frightening and potentially disruptive to healthcare delivery. This narrative review will provide a clinically oriented, international, collaborative perspective on excipient allergy testing, management of future healthcare safety, limitations in our testing modalities, and barriers to optimal care.

Key points:

- Excipient allergy is uncommon and often missed or misdiagnosed due to lack of awareness of the need to carefully review the drug ingredients. This is particularly important when clear reactions have occurred to structurally unrelated drugs.
- The primary challenge in even evaluating *the possibility* of an excipient allergy is knowing how to access the necessary information in a drug's product information and to identify ingredients most likely to be immunogenic. It is important to consider the historical characteristics of the patient being tested as points of information on pre-test probability, along with the limitations of the testing modality being utilized.
- Skin testing protocols/panels that are validated, harmonized across healthcare systems, and readily available are needed. In the meantime, it is recommended that future publications to the literature also provide at least some data on skin testing results from healthy controls.
- Given how uncommon these reactions are there is a clear need for international collaborations between the Allergists and immunologists who see the patients, excipient allergy researchers, and the laboratory testing industry to meet a need for confirmatory tests.

Clinics Care Points:

- Cross-reactivity between PEGs, polysorbate 80 and poloxamers, which share long chains of repeating ethylene oxide units can possibly be determined by skin testing, but how clearly this skin test cross-reactivity translates into clinical cross-reactivity upon drug challenge remains to be determined.
- Individuals with parenteral sensitivity to CMC who have demonstrated tolerance to small amounts of oral CMC and other celluloses such as hypromellose can be advised to read labels and avoid injectable medications and high dose mucosal/enteral drugs containing CMC.
- Because CMC (carboxymethylcellulose) is a common additive to foods and medications, it is recommended that the rare patients who react at lower doses via the oral route should be provided with an epinephrine autoinjector and counseled on strict avoidance.
- In those who are allergic to protamine, avoidance of protamine during cardiac surgery anticoagulation reversal and the use of non-protamine containing insulins are the mainstays of management.
- Patients with mammalian gelatin allergy should undergo testing for alpha-gal allergy.

The Usual Suspects? Allergenic Excipients Implicated in Rare Cases of Anaphylaxis

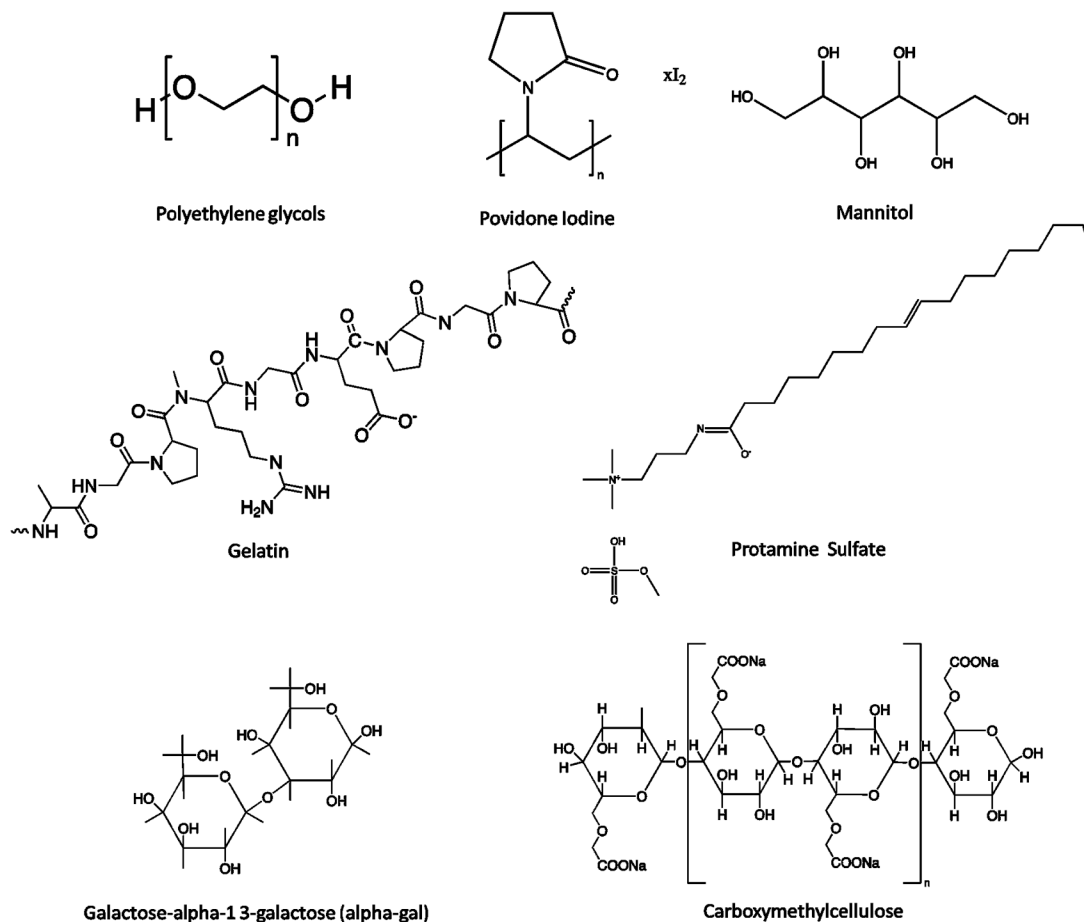
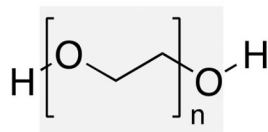
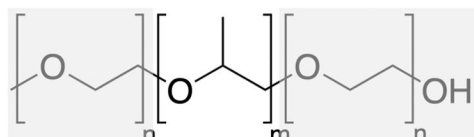


Figure 1:
Key allergenic excipients covered in this review

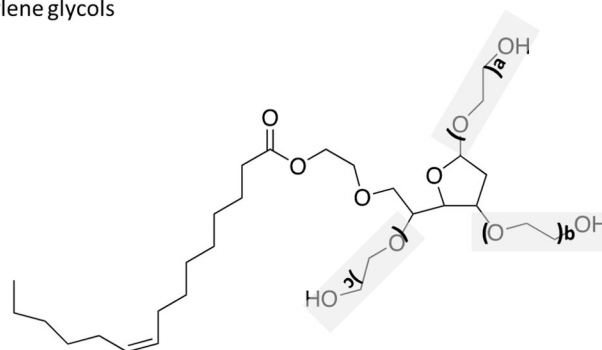
Polyethylene Containing Excipients



Polyethylene glycols



Poloxamers



Polysorbate 80

Sum of polyethylene repeats in a + b + c is 20

Key: shaded portions denote polyethylene chains

Figure 2:

Key polyethylene containing excipients: the polyethylene glycols, poloxamers, and polysorbates.



Figure 3.

Skin prick test results in patient diagnosed two weeks after anaphylaxis to a depot steroid injection containing PEG 3350. Note that SPT is negative to PEG 6000 and lower MW, but positive to polysorbate 80, poloxamer 407 and PEG 20.000 at 0.01% and 0.1% solution. Patient consent obtained.



Figure 4:
Positive intradermal skin testing to carboxymethylcellulose (Carb), in a patient with anaphylaxis to triamcinolone injection containing carboxymethylcellulose (T), with otherwise negative corticosteroid testing. Patient consent obtained.

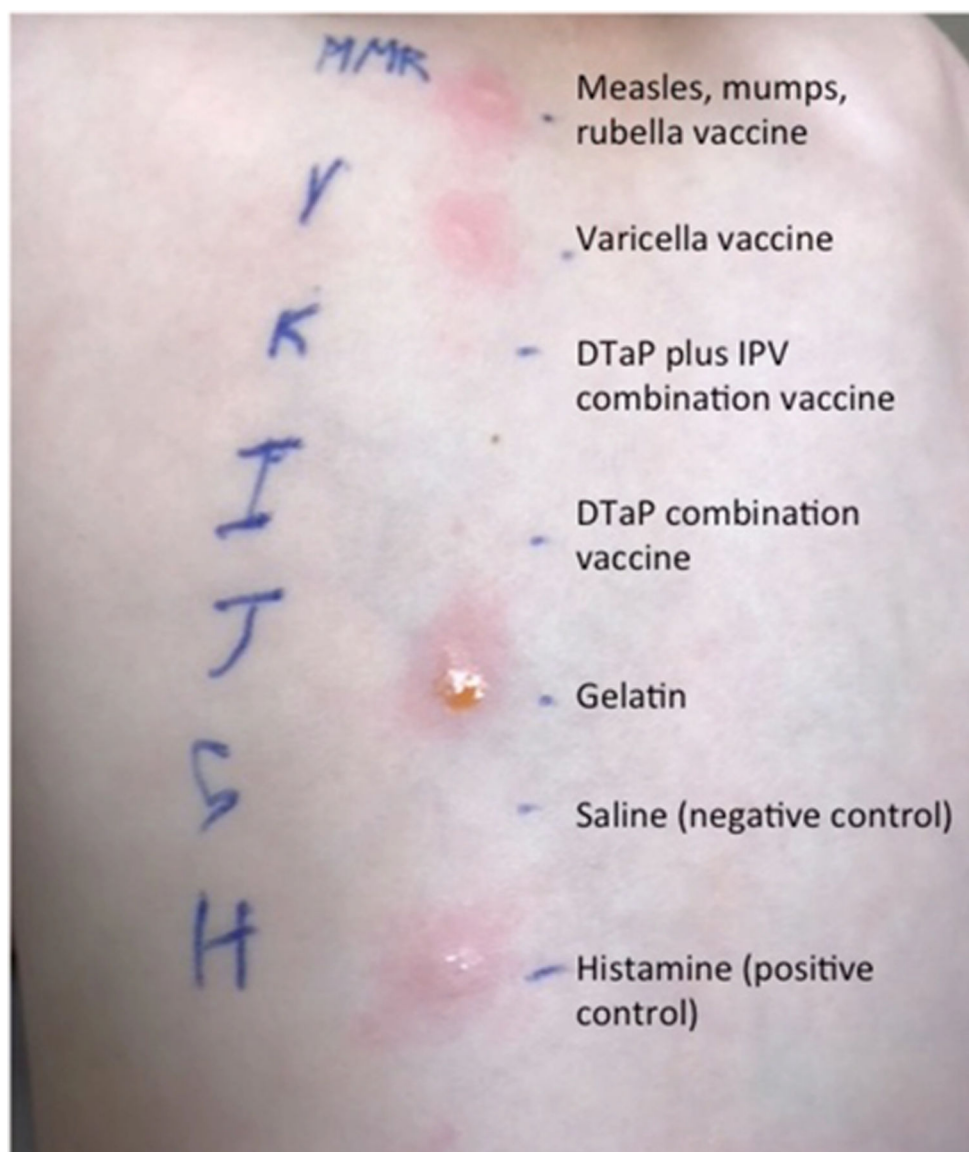


Figure 5: Positive vaccine and gelatin skin prick testing in a patient with alpha-gal allergy and a reaction to gelatin containing vaccines. From Stone et al., J Allergy Clin Immunol Pract⁶⁶

Table 1:

Clinical history where excipient allergy should be considered

Excipient	History/Presentation
Any Excipient in General	- Repeated, severe reactions to structurally distinct drugs/products - Severe allergic reactions where allergy to the active ingredient has been excluded - Severe allergic reaction to some formulations or doses of drug, but not others - Severe, unexplained allergic reactions in relation to surgery or invasive procedures
PEG (Macrogol)	- Anaphylaxis to PEG containing bowel preparations, laxatives - Anaphylaxis to injectable corticosteroids (methylprednisolone acetate most common) - Anaphylaxis to other injectable products containing PEG - Anaphylaxis to implantable devices containing PEG - Anaphylaxis to oral tablets or effervescent tablets - Anaphylaxis to PEGylated liposomal echocardiogram contrast or other PEGylated drugs - Anaphylaxis to medroxyprogesterone acetate injections - Anaphylaxis to ultrasound gels - Allergic reactions to polysorbates or poloxamers
Polysorbate 80	- Anaphylaxis to monoclonal antibodies - Anaphylaxis to disinfectant solutions - Anaphylaxis to intraarticular depot-steroids such as methylprednisolone acetate and triamcinolone acetonide - Dexamethasone-lidocaine preparations for intramuscular and intraarticular injection - Subcutaneously injected erythropoietin - Rarely, anaphylaxis to vaccines (only one confirmed case reported) - Allergic reactions to PEGs or poloxamers
Poloxamers	- Anaphylaxis to radiopharmaceuticals, bone cements - Anaphylaxis to injectable drugs containing poloxamers. - Allergic reactions to PEGs or polysorbates
Carboxymethylcellulose (Carmellose, croscarmellose, E466)	- Anaphylaxis to injectable medications (corticosteroids) - Anaphylaxis to CMC containing barium sulfate for imaging - Anaphylaxis to other injectable products (e.g. benzathine penicillin, leuprolide depot) containing CMC - Rarely, anaphylaxis to foods containing CMC - Possibly, anaphylaxis to other drugs containing CMC
Mannitol	- Anaphylaxis to 20% mannitol. - Anaphylaxis to intravenous paracetamol - Less commonly, anaphylaxis to foods containing mannitol
Povidone-Iodine	- Anaphylaxis to intraarticular corticosteroid (paramethasone) - Anaphylaxis to oral tablets - Anaphylaxis to facial creams

Excipient	History/Presentation
	- Anaphylaxis to eyedrops - Anaphylaxis to topical povidone-iodine for wound antisepsis
Gelatin	- Anaphylaxis to gelatin containing foods (marshmallows, wine gums/gummy bears, foods molded within gelatin) - Anaphylaxis to gelatin containing vaccinations - Anaphylaxis to intraoperative colloid plasma expanders, hemostatics (gelfoams, sponges)
Alpha-gal	- Delayed onset anaphylaxis to mammal derived meat, dairy, or gelatin. - Anaphylaxis to cetuximab, infliximab, other partially humanized mAbs - Anaphylaxis to porcine derived pancrelipase - Anaphylaxis to heparin - Anaphylaxis to gelatin containing vaccines (MMR vaccine, varicella vaccine, varicella zoster vaccine) - Anaphylaxis to bovine collagen - Anaphylaxis to gelatin capsules, and gelatin-based colloid plasma expanders

Table 2:

Overview of Allergy to Key Excipients

Excipient	Presentation	Knowns/Unknowns	Management of Proven Allergy
Polyethylene glycol derived compounds			
Polyethylene Glycols (Macrogols)	The most common presentations of PEG allergy are with immediate type reactions including anaphylaxis to PEG containing bowel preparations or laxatives,^{3,5-9} or after injected corticosteroids containing PEG as an excipient.¹⁰⁻¹⁶ Patients may also present with PEG allergy after multiple drug reactions to oral tablets^{9,16} or effervescent oral products containing high molecular weight PEGs, such as PEG 4000–20,000 range.¹⁷ Some rarer presentations include anaphylaxis to intravenous PEGylated liposomal echocardiogram contrast,¹⁸ medroxyprogesterone acetate injections (excipient PEG 3350),^{9,19} and ultrasound gels in contact with mucous membranes (PEG 8000).²⁰ PEGs contained in implantable devices are potentially of concern.	- One key feature of PEG allergy is that reactivity both on skin testing and oral consumption increases with increasing length of the polyethylene chain and thereby higher molecular weight.^{15,21} - A key unknown is whether a lower limit of reactivity exists i.e. if there is a point of PEG molecular weight that is universally safe for all patients with immediate hypersensitivity. - Patient specific IgG antibody binding studies previously demonstrated increasing binding as PEG molecular weight increased beyond 2000g/mol in a couple of patients¹⁵. - A study of skin test reactivity to PEG over time showed that the threshold for skin test reactivity increased over time on lack of exposure, but that it also decreased in a few patients, possibly due to inadvertent re-exposure to PEG.²¹ - The length of the polyethylene chain which a patient is capable of reacting to may also determine clinical cross-reactivity with polysorbate 80 (which typically has 20 ethylene repeats and a polyethylene MW of ~880g/mol.) - The mechanism for PEG anaphylaxis is thought to be IgE mediated^{12,22} and due to the severity of clinical reactions to PEG and risk of systemic reactions (even on SPT) a reliable in vitro test would safely differentiate patients with true PEG allergy from those with multiple drug allergies.	- Management of patients with confirmed polyethylene glycol allergy requires considerable and continued input from the treating allergist. - The patient and their provider will need to learn new skills of label reading and hunting down ingredient lists from reputable sources, such as package inserts or databases. - It is recommended that medical alert bracelets or warning cards be provided as they can be helpful in the event of a patient's altered mental status during a time when acute treatment is needed. - Because PEGs can be encountered frequently in medical settings and with over-the-counter products, resulting in severe and life-threatening allergic reactions, it is recommended that patients be provided with epinephrine autoinjectors and trained in their use.¹⁶
Poloxamers	Anaphylaxis to poloxamer has been described in the literature in two cases with anaphylaxis to poloxamer 238 in radiopharmaceuticals (1 case confirmed with skin testing).^{26,27} Among 17 patients diagnosed with allergy to PEG (skin prick test positive to PEG 3000 and/or PEG 6000 and a clinical history of an allergic reaction to a PEG-containing product) at the Allergy Clinic at Gentofte Hospital, Denmark, 15/17 patients were positive to poloxamer 407 (PEG MW 4444 g/mol) at time of diagnosis. Of these, 3/15 patients have had anaphylaxis to a poloxamer-containing pharmaceutical prior to diagnosis, in one case presenting as a perioperative cardiac arrest after insertion of poloxamer 407 containing bone cement during hand surgery.¹⁶ Similarly, all	- Poloxamers are likely to be skin test positive in PEG-allergic patients. The clinical relevance of this sensitization in patients who have only reacted to PEG is not clear, but poloxamer skin test reactivity seems to be related to PEG MW. - Further, in three patients initially testing negative to low MW PEGs or positive only to high MW PEGs (two patients), poloxamer 407 was positive. Therefore, poloxamer 407 may be a predictor for PEG allergy as the three patients were positive to low MW PEGs at retesting. (Figure 3)(unpublished observation)	Avoidance of poloxamer. Additional testing with analogue structures (PEGs and polysorbates) and management as per PEG allergy if cross reactivity is detected.

Excipient	Presentation	Knowns/Unknowns	Management of Proven Allergy
	4 PEG allergic patients (PEG 3350, PEG 8000) tested to poloxamer 407 by SPT at Vanderbilt University Medical Center, have tested positive (unpublished observations).		
Polysorbates	Rarely, immediate hypersensitivity to polysorbates has been described in the literature in monoclonal antibodies, disinfectant solutions, intraarticular depot-steroids such as methylprednisolone acetate and triamcinolone acetonide, dexamethasone-lidocaine preparations for intramuscular and intraarticular injection and subcutaneously injected erythropoietin. ^{31–33}	- Polysorbate 80 may be skin prick test positive (Figure 3) or IDT positive when sterile triamcinolone acetonide is used in PEG-allergic patients. However, the clinical relevance of this sensitization is not clear. - Although skin test reactivity may be related to MW to some extent, there seem to be other factors involved as both polysorbate 20 and polysorbate 80 contain similar amounts of PEG (between 20–24 PEG; MW: 880 g/mol-1056 g/mol), but patients and controls test negative to polysorbate 20. - It is possible that the conformation of the molecule or perhaps the binding site between the PEG chain and the lipophilic group may be important for the allergenicity of the molecule, and that the length of the PEG chain may affect reactogenicity in settings outside of the skin.	Avoidance of relevant polysorbates until clinical reactivity can be evaluated further. Additional testing with analogue structures (PEGs and poloxamers).
Non-polyethylene derived compounds			
Carboxymethylcellulose (CMC)	Skin test proven anaphylactic reactions have most commonly been associated with parenteral drugs and oral suspensions containing a large amount of CMC, for example to injectable corticosteroids or to oral barium sulfate contrast suspensions. ^{17,35,36} The majority of reported cases have shown oral tolerance for CMC despite anaphylaxis on parenteral exposure. Rare cases of anaphylaxis to ice creams ³⁷ and popsicles/ice lollies ³⁸ due to CMC has also been reported.	- Validated skin testing protocols are needed, but patients are rare. - Further validation of IgE testing is another area for potential improvement. - It is unknown whether sensitized patients react to low dose CMC-containing foods and CMC film coated tablets or whether reactions only occur on parenteral or high dose mucosal/enteral exposure. Most tolerate all oral exposures. - Cross reactivity to other methylcelluloses is not well described. One patient with anaphylaxis to hypromellose (hydroxypropylmethylcellulose) tested negative to CMC.²	- Because CMC is a common additive to foods and medications, it is recommended that the rare patients who react at lower doses via the oral route should be provided with an epinephrine autoinjector and counseled on strict avoidance. - Individuals with parenteral sensitivity to CMC such as the patient in Figure 4 who have demonstrated tolerance to small amounts of oral CMC and other celluloses such as hypromellose can be advised to read labels and avoid injectable medications and high dose mucosal/enteral drugs containing CMC.
Mannitol	Most case reports of anaphylaxis to mannitol describe reactions to intravenous infusion of 20% mannitol as treatment for raised intracranial pressure and cerebral edema. ⁴¹ However only a few cases have been confirmed on allergy testing so the level of certainty is low. A more recent report describes two patients who presented with anaphylaxis to intravenous paracetamol containing mannitol as an excipient, ⁴² while another report described a	- Mannitol is a hidden excipient in many products and foodstuffs and natural foods. - It is likely that the allergy is simultaneously rare but also underdiagnosed. - The diagnosis should be considered in patients with intermittent episodes of urticaria, unexplained anaphylaxis or confirmed allergic reactions to seemingly unrelated products.	Avoidance of mannitol in both food and medications.

Excipient	Presentation	Knowns/Unknowns	Management of Proven Allergy
	patient with anaphylaxis after oral consumption of effervescent paracetamol tablets containing mannitol and to a mannitol based artificial sweetener. ³⁹ This highlights, that patients may react to mannitol as a “hidden” excipient. The natural occurrence of mannitol in many plants increases the risk of anaphylaxis on ingestion of certain foods in sensitized individuals, cases of anaphylaxis to pomegranate and cultivated mushrooms have been described. ⁴¹	Two of the well investigated cases of mannitol allergy describes reactions to both tablet and natural foods/food supplements^{39,41} and two cases with anaphylaxis to iv administration of mannitol both reported intolerance to mushrooms.⁴²	
Povidone	Povidone anaphylaxis has been described after intraarticular injections of corticosteroids ⁴³ oral tablets ⁴⁴ , facial creams ⁴⁴ , eyedrops ⁴⁵ and topical povidone-iodine swabs for wound antiseptics ⁴⁶ .	- Patients allergic to povidone may be cross-reactive to crosopovidone (called E1202 when used in food according to the European Directive on food additives. Therefore, SPT with crosopovidone should be performed⁴⁴ - Although iodine-containing, povidone is not cross-reactive with radiocontrast materials.	Patients should be instructed in avoidance of povidone by label-checking products, and should receive an allergy warning card with povidone (and crosopovidone) and relevant synonyms listed, and an adrenaline autoinjector.⁴⁴
Protamine	Anaphylaxis to protamine typically presents at reversal of heparin-anticoagulation during open-heart surgery, or with insulin injections. ⁵⁰ In one case series of 3 patients who developed anaphylaxis during cardiac surgery, all three patients were taking long-acting insulins containing protamine as an excipient which was the likely source of allergic sensitisation. ⁵¹ Previous authors had also suggested that sensitization to protamine occurs through to insulin injections. ^{52,53} The incidence of allergic or anaphylactic reactions to protamine in patients on protamine containing insulins is reported to be 0.6% to 2%. ^{54,55}	It was previously thought that protamine allergy might be associated with fish allergy or with vasectomy, but this now appears to be untrue.	- In those who are allergic to protamine, avoidance of protamine during cardiac surgery anticoagulation reversal and the use of non-protamine containing insulins are the mainstays of management. - Desensitization to NPH insulin has been reported, in the event that alternative insulins are not available. - However, it is unclear whether this also results in desensitization to protamine.⁵⁷
Gelatin	A typical gelatin allergy patient will present with reactions that are rapid in onset and overtly related to gelatin such as gelatin containing foods (marshmallows, wine gums/gummy bears, foods molded within gelatin) or medications (vaccinations, capsules, intraoperative hemostatics or gelatin based colloids. ⁶⁵ The pattern of sensitization and time to reaction is thought to be more like a typical food allergy and unrelated to tick bites, unless alpha-gal allergy is an underlying reason/contributing factor for the gelatin allergy.	- It is not currently clear how often gelatin allergy exists independently of alpha-gal allergy, as they are frequently found together.⁶⁸ - It is also unclear whether individual patients might be sensitized to one type of mammalian gelatin, but tolerate others.	- Avoidance of gelatin, test for alpha-gal allergy. - Because gelatin can be found in unexpected places, it is recommended that patients read labels and carry an epinephrine autoinjector. - Fish based gelatins can be used as alternative in those with mammalian gelatin allergy.
Alpha-gal	A typical alpha-gal patient presents with delayed-onset of what is normally associated with immediate IgE type hypersensitivity reactions	Active drugs and excipients that contain alpha-gal due to processes that utilize mammalian ingredients are slowly	Most alpha-gal patients do not react to the small amounts of alpha-gal contained in gelatin-

Excipient	Presentation	Knowns/Unknowns	Management of Proven Allergy
	(urticaria, angioedema, diarrhea, shortness of breath, anaphylaxis) in relation to oral intake of red meat, dairy, or gelatin.⁷⁰ Parenteral exposure, however, results in rapid onset symptoms.^{66,67,70,72} Most alpha-gal patients do not react to dairy, and even fewer will react to gelatin.⁷⁰ Cofactors for reactions include exercise, alcohol, and nonsteroidal anti-inflammatory medications.⁷⁰ Prior to more recent widespread awareness of alpha-gal allergy in endemic areas,⁸⁰ many patients carried a diagnosis for years as idiopathic anaphylaxis or intermittent urticaria/angioedema.⁸¹ Because of the delayed onset of symptoms, one hallmark for which alpha-gal should be considered is allergic reactions that awaken patients from sleep (due to consumption of meat with the evening meal prior to going to bed.)	becoming clearer from translational studies utilizing patient serum or monoclonal IgE specific for alpha-gal.⁸² - Concern for alpha-gal contamination of other mammalian-derived excipients beyond gelatin needs to be proven, and would be very rare to precipitate reactions at a minimum. - Further, the degree to which any one alpha-gal containing drug can precipitate a reaction in an individual patient is less clear. - Content of alpha-gal does not always guarantee a reaction in a patient, and cofactors such as alcohol may be necessary to elicit reactions in some cases. - Beyond this, patient specific factors for these contextually driven responses remain unknown. - Other red meat allergies, such as those mediated by specific IgE to mammalian albumin, may not have the same drug cross-reactivity patterns observed in alpha-gal.	containing products or dairy products, which means they do not have to avoid these ingredients orally. - The risk increases, however, when drugs are delivered parenterally or have a higher alpha-gal content or with cofactors. - When there is no treatment alternative, skin testing with observed drug challenge prior to drug use has been employed as a strategy,⁷⁴ along with drug desensitization.⁸³

Table 3:
Quantity/Concentrations of Excipients Used in the Literature and by Authors for Allergy Testing

Excipient	Notes on Testing	SPT	Intradermal	Blood testing modalities	Oral Challenge in Skin Test Negative Patients
Polyethylene derived compounds					
Polyethylene glycols of various molecular weights (300–20,000)	- Testing strategies to assess the possibility of PEG allergy (Figure 3) are under active study, with authors recently reporting the utility of using PEGs of the highest molecular weight possible as a key feature for improving clinical sensitivity when SPT to lower MW are negative.²¹ - Cross reactivity to polysorbate 80 and poloxamers, which share long chains of repeating ethylenes can possibly be determined by skin testing. - Translation of skin test cross-reactivity into clinical cross-reactivity upon drug challenge remains to be determined. - Titrated SPT must be performed stepwise and with caution, as systemic reactions can be induced. - When PEG allergy is suspected, the patient should ideally be skin prick tested with the suspected culprit product, low MW PEGs (PEG 300, PEG 2000) and with higher MW(PEG 3000 and PEG	- See Bruusgaard et al. as primary reference.²¹ - Initial test with PEG 300 (1000mg/ml), 2000 (500mg/ml), 3000 (500mg/ml) and 6000 (500mg/ml) increasing to PEG 20,000 in tenfold step increases from 0.1 up to 200mg/ml. Testing is stopped on reaching a positive test - Genofte Allergy Clinic, Denmark (unpublished data) > 600 negative controls on PEG 300, 3000 and 6000, > 200 negative controls on PEG 2000 and > 30 negative controls on PEG 20,000 in above concentrations	- Not routinely performed, sterile grade reagents not available. - Anaphylaxis has been reported.	Under research^{15,18,22}	
Polyethylene glycol 3350 (using commercially available OTC products)		1.7–170mg/ml when starting from 17gm packet mixed	Not routinely performed, unless sterile grade		Challenges using Gaviscon (alginic acid) double action tablets (20,000) ⁹ Open titrated challenges

Excipient	Notes on Testing	SPT	Intradermal	Blood testing modalities	Oral Challenge in Skin Test Negative Patients
	6000), and the PEG derivatives poloxamer 407 and polysorbate 80 due to possible cross-sensitization. If SPT is positive, the diagnosis is confirmed. - If SPT with low MW PEGs is negative but clinical suspicion is strong, SPT with high MW PEGs (PEG 20,000 0.1–200mg/ml in stepwise, increasing concentrations) is recommended. If SPT is positive, the diagnosis is confirmed (Figure 3). Once SPT is positive, further testing with higher MW PEGs is not necessary as this may induce systemic reactions due to the increasing allergenicity in increasing MW PEGs. - If SPT is continuously negative, IDT or graded challenges can be considered.²¹ The use of intradermal corticosteroid preparations containing PEG 3350 and polysorbate 80 has been reported in some cases,¹⁵ but may come with a risk of irritant responses when the steroids are used in the range of 1–10mg/ml.	with 100cc sterile water 0.4mg/ml, 4mg/ml 100mg/ml²¹ - Gentofte Allergy Clinic, Denmark > 600 negative controls 100mg/ml - Gentofte Allergy Clinic, Denmark > 10 negative controls 200mg/ml²¹ - Gentofte Allergy Clinic, Denmark > 600 negative controls 0.1mg/ml, 1mg/ml	reagents are available. - Anaphylaxis has been reported. 0.4mg/ml, 4mg/ml of methylprednisolone acetate can be used¹⁵ but not enough evidence on irritant doses. - Not routinely performed, sterile grade reagents not available - Not routinely performed, sterile grade reagents not available - Not routinely performed, sterile grade reagents not available 0.1mg/ml, 1mg/ml of triamcinolone acetonide can be used¹⁵ but not		using PEG 3350¹³ 850 mg oral challenge, using 5ml of 170mg/ml concentration has been used by authors (Krautz, Stone) after 1st dose mRNA vaccine anaphylaxis, prior to 2nd dose vaccine attempt.⁸⁴ Note: common side effect of sticky mouth sensation.
Methylprednisolone acetate (PEG 3350 containing)					
Poloxamer 407					
Poloxamer 188					
Polysorbate 80					
Triamcinolone acetonide (contains polysorbate 80)					

Excipient	Notes on Testing	SPT	Intradermal	Blood testing modalities	Oral Challenge in Skin Test Negative Patients
Non-polyethylene derived compounds					
Carboxymethylcellulose	- Skin testing concentrations have not been validated, but skin prick testing can be performed using CMC powder dissolved in saline. - Certain medications, such as eye drops containing CMC as the only ingredient, along with injectable corticosteroids containing CMC, have been useful in the authors' experience (Figure 4). - Specific IgE testing has been used in a research capacity and appears to have potential utility.³⁶	- Skin prick tests using technique with CMC powder dissolved in saline - Skin prick tests with undiluted CMC single ingredient eye drops - Gentofte Allergy Clinic, Denmark > 600 negative controls with eyedrops 10mg/ml	- No published protocols. - Use sterile products containing CMC. (Figure 5 shows testing using sterile CMC eye drops) 3 healthy controls, not enough information on irritant doses.	Under research³⁶	Oral challenges have been performed using 10mg, 30mg oral doses.³⁷
Triamcinolone acetonide (contains carboxymethylcellulose)		0.1mg/ml, 1mg/ml	0.1mg/ml, 1mg/ml of triamcinolone acetonide can be used¹⁵ but not enough evidence on irritant doses.		
Mannitol	- Skin testing has been positive in a few of the published cases with a clear history suggestive of allergy to mannitol. - Tests performed using a 1:10 (20mg/ml) or 1:100 (2mg/ml) dilution of 200mg/ml mannitol for intradermal testing. - The severity of clinical reactions, skin test positivity	2mg/ml, 20mg/ml⁸⁵ - Gentofte Allergy Clinic, Denmark > 400 negative controls on 150mg/ml	2mg/ml, 20mg/ml^{39,85}	Under research⁴¹	Oral challenges eliciting symptoms have been performed using oral mannitol laxative³⁹

Excipient	Notes on Testing	SPT	Intradermal	Blood testing modalities	Oral Challenge in Skin Test Negative Patients
	and tryptase increase in one case ⁴² suggests an IgE mediated mechanism and this has been confirmed by the demonstration of mannitol specific IgE in one report. ⁴¹				
Povidone	- Testing can be performed by skin prick testing (SPT) which has been employed safely in several reports. - In the authors' experience, a commercially available eyedrop containing 50 mg/ml povidone has tested positive in one case and negative in 475 controls. - Intradermal testing and specific IgE against povidone have been used.^{47,48}	50mg/ml skin prick test has been used⁴⁴ - Gentofte Allergy Clinic, Denmark > 400 negative controls	50mg/ml povidone iodine (aqueous solution) diluted 1:100 with normal saline (0.5 mg/ml) has been used, 1 negative control.⁴⁸	Under research⁴⁷	
Protamine	- Skin prick testing to protamine can be performed at concentrations that are similar to NPH insulin (300–350 µg/ml) diluted from stock protamine 10mg/ml with intradermal testing in a range of 0.3 to 30 µg/ml.⁴⁹ - Protamine appears non-irritant at 10mg/ml for skin prick testing and up to 0.01mg/ml for intradermal testing.⁵¹ - It is important to note that skin sensitization	10mg /ml	0.01 mg/ml. Potentially irritant at higher concentrations.	- Under research⁵⁶ - Commercially available	

Excipient	Notes on Testing	SPT	Intradermal	Blood testing modalities	Oral Challenge in Skin Test Negative Patients
	without signs of overt allergy to insulin injections may occur in diabetics, although it is not known whether this poses a risk of anaphylaxis when high dose IV protamine is administered during cardiac surgery. - Antibody testing to detect serum specific IgG and IgE has also been reported and is commercially available.⁵⁶ - Testing strategies that consider the possibility of reactivity to insulin itself along with other insulin ingredients such as metacresol are recommended.	1 g/ml using food grade gelatin has been used.	Not typically done since sterile grade reagent is preferable.	- Specific IgE testing is commercially available, - Positivity sometimes varies by gelatin (bovine, porcine)	Oral challenge can be performed in those with unlikely allergy.
Gelatin	- Skin prick testing using commercially available food-grade gelatin diluted with saline to a concentration of 1g/ml as per current allergy practice parameters (Figure 5). - Bovine and porcine specific IgE testing can be helpful confirmatory tests. - Patients can sometimes demonstrate specific IgE sensitization to one form of mammalian gelatin but not the other,^{66,67} but in practice they should be considered cross-reactive due to lack of information				

Excipient	Notes on Testing	SPT	Intradermal	Blood testing modalities	Oral Challenge in Skin Test Negative Patients
Galactose-alpha-1,3-galactose	on whether this has clinical significance and labeling that does not report gelatin source. - The diagnosis of alpha-gal allergy primarily relies upon the presence of serum specific IgE directed against alpha-gal in patients with a characteristic reaction history. - When trying to determine whether alpha-gal is the culprit behind an individual patient's reaction to a drug, academic centers in endemic areas have utilized strategies including skin testing, drug-alpha gal sIgE binding assays, basophil activation, and drug and food challenges.	Beef, pork, lamb skin prick tests using standardized reagents at 1:20 wt/vol have been used⁸⁶	Intradermal tests sometimes used in research setting⁸⁶	Mainstay of diagnostic testing is positive serum specific IgE in a patient with likely history.^{87,88}	- Oral challenges using sausage patties have been performed to elicit or rule out symptoms.⁸⁹ - Pork kidneys have very high content, used in some centers.⁹⁰