

## REVIEW

# Hypersensitivity to polyethylene glycol in adults and children: An emerging challenge

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**Abstract.** Hypersensitivity reactions to polyethylene glycol (PEG) is an emerging challenge and the interest about this disease is growing since PEG is considered one of the possible causes of coronavirus disease 2019 (COVID 19) vaccine-associated anaphylaxis. PEG is used in a wide variety of pharmaceutical, medical, industrial, cosmetic, and food products and can be an active ingredient or used as an excipient. PEG is present in several medications, and it may or may not be present in different formulations and dosages of the same drug. Lack of standardization nomenclature, inadequate labelling of products and lack of knowledge about PEG involvement in hypersensitivity reactions expose patients at risk of presenting multiple reactions before a diagnosis could be made. In this review we describe the main cases published in literature and propose an allergy work-up and management. ([www.actabiomedica.it](http://www.actabiomedica.it))

**Key words:** Polyethylene glycol hypersensitivity, PEG allergy, vaccine allergy, drug allergy

## Introduction

Interest on hypersensitivity reactions (HRs) to polyethylene glycol (PEG) has increased in the recent months, since this polymer was suspected as one of the possible causes of coronavirus disease 2019 (COVID 19) vaccine-associated anaphylaxis even. However, its pathogenetic role is still debated (1, 2). In Pfizer-

BioNTech and Moderna mRNA vaccines, mRNA is packaged in lipid nanoparticles added with PEG 2000 molecules to protect the mRNA after injection and increase their water-solubility and bioavailability (3).

A Centers for Disease Control and Prevention (CDC) analysis of the Vaccine Adverse Reporting System (VAERS) showed that the incidence of anaphylaxis for mRNA COVID-19 vaccines can be about

2 to 8.5 times (3) the incidence reported in the 2016 Vaccine Safety Datalink Project for all vaccines (1.31 per million of doses).

Vaccines against COVID-19 are an essential intervention to control the current pandemic especially for allergic individuals (4) and so the safety profile is important. For these reasons a particular interest around the hypersensitivity reaction to PEG is arising.

PEG is a water-soluble macromolecule used in a wide variety of pharmaceutical, medical, industrial, cosmetic, and food products. PEG belongs to a family of hydrophilic polymers of ethylene oxide, often denominated with a numerical value referring to the ethylene oxide units in each molecule (cosmetic industry) or to the molecular weight (pharmaceutical industry) (5).

As an active ingredient, PEG 3350 and 4000, also known as macrogols, are present in colonoscopy preparations or in laxative solutions. More frequently, PEG is used as excipients (inactive ingredient) in a multitude of medications both injectable and oral, suppositories, ointment bases, lubricants, ultrasound gels, wound dressings, bone cement and sealants (5). For example, PEG 3350 is present in methylprednisolone acetate and medroxyprogesterone acetate, PEG 6000 in different types of medications such as European formulations of penicillin antibiotics and effervescent medications, PEG 20000 in calcium-containing supplements for gastroesophageal reflux disease and dyspepsia (6). Lower molecular weight (MW) PEG is often present in toothpaste, cosmetics, moisturizers, mouthwashes, hand sanitizers, shower gels, and soaps.

In addition, an increasing number of PEG-modified (PEGylated) drugs are being developed and approved for marketing (7,8). PEGylation is a process whereby PEG of various molecular weights are attached to drugs for the purpose of enhancing water solubility, shielding the drug from rapid clearance, and prolonging its half-life. PEGylated medications are used in cancer, gout, hepatitis, and immunotherapies (9).

PEG is generally considered to have low toxicity and to be biologically inert. Although allergy to PEG is rare, immediate type HRs, often severe, has been described with increasing frequency in the past two decades. A reported death following PEG-induced

anaphylaxis after glucocorticoid injection containing PEG was reported in a 24-year-old man, previously developing urticaria after glucocorticoid injection (10).

The lack of standardization in the nomenclature of PEG, the inadequate labelling of products and the lack of knowledge about their involvement in HRs may lead to wrong diagnosis and occurrence of adverse reactions to many unrelated products (5).

The aim of this review is to summarize the main data reported in literature on HRs to PEG, focusing on the allergy work-up and management.

### **Clinical presentation of hypersensitivity reactions to PEG**

#### *Adults*

Wenande et al (5) reviewed 37 cases of PEG immediate HRs published between January 1977 and April 2016. The mean age was 47 years (range 24–86); no reactions were reported in children. More than half (54%) of HRs caused by PEG-containing products were associated with laxative solutions or bowel preparations. Offending products included corticosteroid formulations, throat tablets, vitamin/mineral preparations, disinfectants, ultrasound gels, antiemetics, antiepileptics, anticoagulants, analgesics, antidepressants, anti-inflammatory drugs, antibiotics, and reflux medication as well as toothpaste, dental floss, cosmetic and pharmaceutical creams, shampoos, and paints. The symptoms were immediate and often severe, fulfilling criteria for anaphylaxis in 76% of cases, including anaphylactic shock. Common manifestations were pruritus, tingling, flushing, urticaria and angioedema, hypotension, and bronchospasm. Anaphylaxis always occurred when PEG-containing products were administered parenterally or in perioperative period, while only 36% of oral exposures triggered an anaphylactic reaction. Skin and mucosal exposure resulted in contact urticaria. No cases of HRs to PEGs in foods were reported. Diagnosis relied only on clinical history in 13 (35%) cases, skin prick tests (SPT) with PEG resulted positive in 19 (86%) of 22 cases. Two of the three remaining patients with negative SPT results developed positive reactions to intradermal tests

(IDT) with PEG 4000 at 0.1% and 0.0001%. The third patient with multiple HSRs to PEG 4000-containing products was negative to SPTs, IDTs (0.1%) and patch testing for the polymer. Oral challenge was conducted in three cases using PEG 4000, all of which were positive with systemic reactions in two cases. Systemic reactions (mostly cutaneous symptoms and, in one case cough) were reported in two cases following SPT with 1% PEG 8000 and with multiple molecular weights of PEG simultaneously tested. Three of five (40%) IDTs resulted in systemic reactions with 10% PEG 3350 and 0.1% PEG 4000, including anaphylaxis in two instances.

Circulant PEG-specific IgE was negative in two cases. Basophil activation test (BAT) was performed in four cases using PEG 400, 3350, 4000 and 6000. Two cases had positive results: the first for PEG 3350 and 6000 the second using PEG 4000 and 6000. Both patients had positive SPT results to PEG. Two other studies found negative results in BAT for PEG 400, 3350, 4000 and 6000, despite positive SPT and IDTs for the same MWs. The Authors also described the occurrence of delayed onset of contact dermatitis to PEG applied at irritated skin, often in combination with known sensitizers such as nitrofurazone (5).

Berndt et al (11) reported a case of a 42-year-old woman experiencing two anaphylactic reactions, after Vicks Nyquil® Cold & Flu Nighttime Relief Liquid and GeloRevoice® lozenges, respectively. In addition, she had a history of contact urticaria after application of the shaving gel Hawaii Feeling® as well as an ointment used for common cold (Eucabal balsam S®). Prick-to-prick testing using the implicated products and macrogol 6000 were inconclusive due urticarial dermatographism to saline solution. BATs using macrogol 6000 at dilutions of 2.5%, 0.25%, 0.025%, and 0.0025% were negative. The oral challenge with macrogol 6000 induced generalized urticaria. Giangrande et al (12) reported an adult with a history of an immediate hypersensitivity systemic reaction to macrogol 4000 contained in an evacuant solution together with positive SPT and positive BAT to PEG 4000.

Cerdà et al (13) described a 29-year-old woman who developed several local and systemic type I HRs including a severe anaphylactic reaction to different pharmacologic and cosmetic products contain-

ing PEG. SPTs and BATs were performed to several pharmacological and cosmetic products, but only those containing PEGs and their derivatives were positive. Stone et al (14) described two adults with recurrent immediate HRs, including anaphylaxis, during preparation for colonoscopy and after methylprednisolone acetate injections, all of them containing PEG 3350. Both patients underwent SPTs and IDTs with serial dilutions of PEG 3350 and common corticosteroids. Patient 1 had positive SPT to PEG 3350 at dilutions 1:1, 1:10, 1:100 and methylprednisolone acetate (containing PEG 3350) undiluted. IDTs to triamcinolone acetonide (containing polysorbate 80) at 1 mg/ml and 0.1mg/ml resulted positive. During IDTs the patient developed a sensation of throat and body itching, with urticarial rash expanding from testing sites treated with cetirizine. Afterwards the patient was able to tolerate a low MW PEG oral challenge with PEG 300. Patient 2 had negative SPT to PEG 3350 and negative IDT to methylprednisolone acetate, but positive testing to triamcinolone acetonide. Upon challenge with PEG 3350 he developed anaphylaxis requiring adrenaline and emergency department transfer. Both patients were able to tolerate parenteral steroids that did not contain macrogols. Serum specific IgE against PEG were detected in both patients, but not in two healthy adult controls. Sellaturay et al (15) described five cases of confirmed PEG allergy in adult patients. Four of the five cases developed anaphylaxis to medications containing PEG with different MWs (from 3350 to 20.000) with one near-fatal anaphylaxis resulting in cardiac arrest. Three cases were confirmed with positive SPT to PEG, one with a positive IDT and one with a positive oral challenge (anaphylaxis). Two patients developed anaphylaxis following IDT to PEG and one a systemic allergic reaction (without hypotension or respiratory distress) following PEG SPTs. Cox et al (16) described six cases of PEG allergy in adult patients with a history of allergy to multiple drugs. The first patient experienced anaphylaxis after IM Depo-Provera (containing PEG-3350) but tolerated similar progesterone in the oral contraceptive pill. The second patient experienced acute urticaria and angioedema following esomeprazole (containing macrogol) ingestion and anaphylaxis following minimal ingestion of osmotic laxative (PEG 3350); in addition, the patient

described contact urticaria with specific cosmetics containing PEG 100. Case 3 had anaphylaxis within minutes after intake of effervescent vitamin C and developed urticaria, angioedema, and throat tightness with difficulty swallowing after ingestion of an osmotic laxative. This patient reported a history of urticaria associated with Vimovo® (esomeprazole and naproxen) and similar symptoms during a dental procedure. All identified agents contained high-molecular-weight (HMW)-PEG. Case 4 presented two episodes of anaphylaxis respectively to osmotic laxative (PEG 3350) and PEG-containing effervescent phosphate replacement preparation (PEG 4000). The fifth patient was referred for 2 episodes (angioedema, paresthesia, throat tightness) requiring adrenaline after domperidone suppository (containing PEG 400 and 1000) and oral ibuprofen (containing PEG 6000). The last case similarly had multiple adverse drug reactions, including anaphylaxis, following a betadine dressing (PEG 400, 6000), oral and intramuscular diclofenac (PEG 8000 and HMW PEG), and contact urticaria with various cosmetics (LMW and HMW PEG). The patients experienced an average of 3 allergic episodes before a formal diagnosis. SPTs with PEG 3350 were positive in all patients, except one patient in which diagnosis was confirmed by oral challenge with PEG 3350 (Movicol®). Bruusgaard-Mouritsen et al (17) reported a series of ten PEG allergic adults. Before diagnosis, 80% of the patients had experienced one or more anaphylactic reactions requiring adrenaline treatment with one case of perioperative cardiac arrest. Anaphylaxis was primarily caused by oral medications such as antibiotic/analgesic tablets, antacids and laxatives followed by injections of depot-steroids, all containing PEG, as well as bone cement (containing Poloxamer 407) and unknown products in perioperative setting. Seven patients reported a median of 3 reactions before diagnosis. Median time from first reaction to diagnosis was 20 months (range 2–120). Diagnosis was confirmed by positive SPT to PEG, using different MWs and concentrations. BAT was positive in 3 of 5 patients.

Sellaturay et al (2) demonstrated that anaphylaxis to the Pfizer/BioNTech vaccine was due to PEG allergy in a 52 year old female. She had a history of allergic reactions to multiple products and anaphylaxis to azithromycin, all containing PEG 6000. SPTs

were negative to all PEG (400, 600, 2000, 3350, 4000, 6000, 8000 and 20.000) at 0.1% concentration, to the Pfizer/BioNTech vaccine, to its excipients, polysorbate 80 and to the AstraZeneca COVID-19 vaccine. SPT to PEG 4000 at 1% concentration resulted positive with a systemic reaction after twelve minutes.

### *Pediatric age*

Only two cases are described in the literature. Hamano et al (18) reported a child with recurrent immediate reactions to macrogol. At 3 years of age, he experienced generalized urticaria and coughing a few minutes after oral administration of olopatadine hydrochloride containing PEG 4000, improved in 3 hours without medical treatment. Two months later, after anesthesia with xylocaine pump spray 8% (containing PEG 400) at a dental office, he developed generalized urticaria and repetitive vomiting, which required medical treatment in the emergency department. Moreover, he sometimes developed urticaria with diphenhydramine hydrochloride cream 1%, containing PEG 2200, lidocaine cream (EMLA® cream 5%) containing polyoxyethylene hydrogenated castor oil > 100000, or heparinoid lotions (Hirudoid® lotion 0.3% containing cetomacrogol 1000, or BESOFTEN® lotion 0.3%, containing polyoxyethylene polyoxypropylene glycol 8350). SPTs were performed using different MWs (macrogol 100, 200, 1500, 4000, 6000, and 20 000). The SPT results were positive to macrogol 4000, 6000, 20000 and negative to macrogol 100, 200, 1500. Gorkay et al (19) reported the case of urticaria following irrigation with PEG 3350 for poisoning in a 3-year-old boy.

### *Hypersensitivity to PEGylated drugs*

Few cases are described in literature. Chan et al (20) described a case of anaphylaxis with the infusion of pegylated liposomal doxorubicin in an ovarian cancer patient. No investigation was performed to identify the underlying mechanism. Fernandez et al (21) described two children with B precursor acute lymphoblastic leukemia who developed HRs to PEGylated E. coli asparaginase and Erwinia asparaginase. They tolerated native E. coli asparaginase. In the second pa-

tient, anti-PEG IgG antibodies were detected.

McCabe et al (22) reported the case of a 37-year-old woman with psoriatic arthritis who experienced anaphylaxis after certolizumab pegol, the only PEGylated Fc free anti-TNF monoclonal antibody currently available. In addition, she had a history of anaphylactic reaction to Movicol®. SPT revealed a reaction to Movicol® (negative at 15 min but positive at 30 min); adalimumab SPT was negative at 1/100 (0.4 mg), 1/10 (4 mg) and 1:1 (40 mg), thus confirming that the allergen was the PEG component rather than the anti-TNF portion of the drug. Kranz et al (23) reported an anaphylaxis to PEGlyted (PEG 5000) liposomal perflutren, a perfluorocarbon gas used as echocardiography contrast, in an adult patient with two prior immediate hypersensitivity reactions to oral PEG-3350 while undergoing colonoscopy preparation. The presence of anti-PEG specific IgE and positive SPT to HMW PEG in this patient suggested an IgE-mediated hypersensitivity to PEG.

Oh et al (24) reported a case of anaphylaxis developed few minutes after the fourth infusion of PEGylated recombinant factor VIII (Rurioctocog alfa pegol) in a 2-year-old boy with severe haemophilia A. Afterwards the patient received Rurioctocog alfa for over 1 year without any adverse effects. The levels of anti-PEG IgM, IgG and IgE were analyzed in his serum 1 week, 8 weeks and 32 weeks after the hypersensitivity event by enzyme-linked immunosorbent assay (ELISA). Anti-PEG IgM was detectable only 1 week after the event and IgG levels peaked at 1 week after the event and then declined rapidly. Anti-PEG IgE were not detected. SPTs for Rurioctocog alfa pegol as well as Rurioctocog alfa were negative.

### **Immunological mechanisms of immediate-type PEG hypersensitivity**

#### *IgE-Mediated Reaction (Type I)*

There are many cases of PEG-associated reactions with an immediate positive skin test response; this suggests an IgE-mediated HR (6). An IgE-mediated mechanism for anaphylaxis to PEG has been suggested by identification of specific IgE against PEG,

currently used as a research tool (independent laboratory methods), in PEG-allergic patients with skin test positive (14, 23). The positivity of BAT for PEGs, as found in some studies, constitutes further support to the hypothesis of a possible role of IgE (5, 12,17).

#### *IgG/C-system activation mediated hypersensitivity reactions*

PEGylation is a process whereby PEGs of different MWs are attached to drugs with the purpose of shielding the drug from rapid clearance and prolonging its half-life, or to enhance water solubility (9). This is different from drugs that contain PEG as an inactive ingredient.

As mentioned previously PEG can also be attached to liposomes (PEGLip); PEGLip encapsulating drugs and PEGylated drugs can cause IHRs by a C-system activation leading to complement activation-related pseudoallergy (CARPA) (6).

Several reports have shown that up to 70% of patients who have undergone treatment with PEGylated therapeutics will develop anti-PEG IgG antibodies (7). PEG IgM and IgG can cause complement-activation related pseudoallergy, in which IgG-mediated activation of the C-system leads to the generation of C3a, C4a, and C5a, which are potent activators of inflammation and are called anaphylatoxins due to their ability to cause non IgE-mediated mast cell degranulation. This pathogenetic mechanism was reported mainly with chemotherapeutics, such as PEGylated liposomal doxorubicin and PEG-asparaginase and recently, and with recombinant factor VIII (6). Recent evidence highlights the causal role of anti-PEG Abs triggering classical pathway initiation of CARPA, at least for the case of PEGLip (7). 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 can increase their efficacy and safety (27).

Although complement has been shown to play a role in HRs to PEG-conjugate agents (8), poor evidence indicates complement activation as the cause of HRs to conventional PEG-containing products. In a patient with immediate-type PEG hypersensitivity Hesselbach et al (28) found values of C3 and C4 within the normal

range. Furthermore, as complement is not preserved in the process of histamine release testing, a complement-mediated mechanism is unlikely in patients with positive histamine release test to PEGs (5).

### Polysorbates and PEG cross-reactivity

Polysorbates are structurally similar to PEG and are used in medicines for their similar pharmaceutical properties (6). Polysorbate (PS) 20 and PS 80 are involved in immediate HRs with different types of medications and immediate HRs due to both PEG and polysorbate have been reported in the same patients (6). Several patients who became allergic to polysorbates appear sensitized through the PEG, with an IgE-mediated mechanism (14,27).

Polysorbate and its degradation products can be intrinsically anaphylactogenic, and this can be a plausible explanation for reports of anaphylaxis in patients receiving polysorbate-containing steroids, vaccines, chemotherapeutics, and biologics. Although there is limited *in vivo* and *in vitro* evidence, an isolated sensitization for polysorbates appears rare and less common than HMW-PEG (7).

Many studies highlighted the possibility that immediate HRs to PEG with cross-reactive PS hypersensitivity may be not recognized in clinical practice (14) and it is recommended avoidance of both PEGs and polysorbates in case of hypersensitivity to any of these (5,14).

### Allergy work-up

An allergic reaction to PEG should be suspected in patients with (5,17,28) systemic HRs to laxatives or bowel preparations; to only certain brand names or doses of the same drug; following invasive procedures or during operations; to PEG containing products or PEGylated drugs where hypersensitivity to the active drug is excluded; to a PEG derivative; to drug/compound containing polysorbate 80/poloxamer 407; to unrelated drugs and products; to mRNA COVID 19 vaccine (2). In these patients it is necessary to obtain a detailed history of medications causing each reaction,

time-course of onset and resolution of symptoms and emergency treatment administered (15,30). Although low-MW PEGs are easily absorbed through the gastrointestinal tract and skin, most immediate reactions are induced by high-MW and in general, the PEG's potential to cause anaphylaxis increases with higher MW(>1000 g/mol) PEG (5,15). It is hypothesized that initial PEG-sensitization could be via cutaneous exposure from cosmetics and hygiene products or absorption of low-molecular-weight (LMW)-PEG in pharmaceuticals; also, gastrointestinal sensitization has been theorized in PEG allergic patients with an impaired epithelial barrier (5).

There may also be a lower limit of MW beyond which patients do not react to PEG, and several patients have demonstrated oral tolerance of low-MW PEG in the presence of high-MW PEG allergy (14,23). Therefore, it is important to determine, if possible, each patient's individual MW threshold thorough drug history, confirming usual medications (including brands) used and tolerated (15).

### Skin tests

When PEG allergy is suspected, SPT with a series of PEG with different MW (PEG 400, PEG 3350, PEG 4000, PEG 8000, PEG 20.000) should be performed. SPTs should begin with diluted concentrations of PEGs using a stepwise approach of increasing concentrations (1:1000, 1:100, 1:10, 1:1), waiting at least 30 mins before progressing to the next concentration to reduce the risk of a reaction (15,28,29) (Table 1). We suggest starting testing with the MW PEG suspected and then evaluate the necessity of further tests with different MWs based on clinical history and drug availability. IDTs should be performed only in SPT negative patients and with considerable

**Table 1.** Non irritating skin prick testing concentrations for PEGs (modified from reference 4)

PEG MW	Step 1	Step 2	Step 3
PEG 400	5:1000		
PEG 3350	1:1000	1:100	1:10
PEG 4000	1:1000	1:100	1:10
PEG 8000	1:1000	1:100	1:10
PEG 20000	1:1000	1:100	1:10

caution, starting with low MWs at low concentration (1:10.000) due to the high risk of systemic reactions (2,5,14,15). Patients should formally give informed consent, as the risk is like a challenge test, and preferably cannulated prior IDTs. IDTs should be avoided or selectively undertaken with special precautions in patients with cardiovascular risks, multiple comorbidities, older patients, as well as those who have had severe HRs (15). In Table 2, a different step-by-step approach in which macrogol 3350 (taken as a model for MW PEG) and polysorbate are tested. In clinical practice, if a panel of different PEGs is not available, it is possible to use drugs containing PEG 3350 (7, 28) (Table 2). Skin testing with PEG derivatives (polysorbate 20, polysorbate 80) are suggested in patients with positive skin testing for PEG to evaluate cross-reactivity (28) (Table 2).

#### *In vitro tests*

Serum specific IgE for PEGs are not commercially available, although specific IgE directed against PEG, currently a research tool, has recently been demonstrated in PEG-allergic patients who reacted both to PEGs and, in one case, to a PEGylated liposomal product used as an echocardiogram contrast, by 2 in-

dependent methods (14,23,31). Given the aforementioned studies (5,12,13,17) and variable results of further investigations (32,33,34), further data are needed to evaluate the sensitivity and specificity of BAT to PEG. Measurement of serum tryptase within 30 minutes, 1-2 hours, and 24 hours of the reaction as well as of complement (C3a, C3b C5a) within 1-2 hours of the reaction, may help to elucidate the mechanism of the drug-induced reactions in patients with suspected PEG hypersensitivity (28,31). A tryptase increase is considered significant when the acute tryptase is higher than the basal tryptase level X 1.2 (+2) (35).

#### *Drug provocation test*

Oral challenge with PEG should be considered if skin tests are negative and be carefully titrated from a low dose (5). Due to the high risk of systemic reactions the challenge should be performed in a setting with trained personnel and with available treatment for anaphylaxis. The challenge should be carried out starting from 1:100 or 1:1000 of the single therapeutic dose and then 1/10, 2/10, 7/10 of the single therapeutic dose every 30 min with a minimum of two-hours surveillance after the last dose (36).

**Table 2.** Non irritating skin testing concentrations for PEG3350 and polysorbate (modified by reference 6 and 24).

	PEG 3350		Control <sup>†</sup>	Polisorbate 20	Polisorbate 80 <sup>#</sup>		
	Macrogol for oral solution	Methyl-prednisolone Acetate (Depo-Medrol) <sup>**</sup> (containing PEG 3350)	Methyl-prednisolone Sodium Succinate (Solu-medrol) <sup>&amp;</sup> (without PEG 3350)	Hepatitis A Vaccine or Twinrix	Triamcinolone Acetonide (also contains carboxymethyl-cellulose)	Refresh-steril Eye drops	Prevnar 13
STEP 1 SPT	1:100	40 mg/ml	40 mg/ml	1:1	40 mg/ml	1:1	1.10
STEP 2 SPT	1:10						
STEP 3 SPT	1:1 <sup>§</sup>						
STEP 4 IDT		0,04 mg/ml	0,04 mg/ml	1:100	0.4 mg/dl	1.10	1.100
STEP 5 IDT		0.4 mg/ml	0.4 mg/ml	1:10	4 mg/dl		
STEP 6 IDT		4 mg/ml	4 mg/ml		40 mg/dl		

<sup>†</sup>Methyl-prednisolone sodium succinate does not contain PEG or polysorbate 80 and can be used as an additional control; <sup>\*\*</sup>Some brands of methylprednisolone acetate contain polysorbate and PEG3350 while others only have PEG3350; use methylprednisolone acetate containing PEG3350 only; <sup>#</sup>Refresh Optive Advanced Lubricant eye drops and Pevnar are an alternate source for polysorbate 80 skin testing; <sup>&</sup>Nonirritating skin testing concentrations for methyl-prednisolone sodium succinate and triamcinolone acetonide include a range of 10 to 40 mg/mL for initial skin prick testing with subsequent 10x dilutions; <sup>§</sup> Dissolve 17 gram Miralax packet in 100mL of sterile water for 1:1 solution (170mg/mL). SPT: Slin prick test. IDT: Intradermal test.

## Management

Unfortunately, a complete avoidance of drugs containing PEGs cannot be provided, so the key is to improve the awareness and attention to any new medical preparation. Patients should be educated to carefully evaluate the specifics of product characteristics to detect the presence of PEG. It is also important for the patient to confront pharmacists and all healthcare personnel and let them be aware of his/her allergy. It can be useful to wear alert jewelry or wristband (16). An adrenaline auto-injector is not indicated in drug allergy as the drug is avoidable (37, 38), but it is recommended in patients with PEG allergy because of risk of accidental exposure (15).

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