Allergy

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POSITION PAPER OPEN ACCESS

Hypersensitivity to Excipients in Drugs: An EAACI Position Paper

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Received: 17 February 2026 | **Accepted:** 9 March 2026

Keywords: drug hypersensitivity | excipients | gelatine | methylcellulose | polyethylene glycol

ABSTRACT

Drugs contain active pharmaceutical ingredients and excipients, compounds which enhance the pharmacokinetics, stability and palatability of the pharmaceutical formulation. While most drug hypersensitivity reactions (DHR) are caused by active ingredients, excipients may also be involved. Excipient-related DHR are easily overlooked and may lead to repeated anaphylaxis in patients exposed to pharmaceutical formulations containing different active ingredients. We performed an extensive review of the literature to provide practical recommendations on when to suspect and how to diagnose and manage excipient hypersensitivity. Where literature was limited, the collective experience of the authors was taken into consideration. Excipient hypersensitivity should be suspected in patients with a history of anaphylaxis to multiple drugs with chemically unrelated active ingredients and specific drug classes such as oral laxatives and injectable depot steroids or progestogens. Polyethylene glycol, methylcelluloses, gelatine, povidone and mannitol were identified as the most common culprits of DHR. DHR evaluation should include review of the product monograph to ascertain the presence of possible culprit excipients. Specific diagnostic tests for excipients should be performed when appropriate, including skin, in vitro and provocation testing with pure excipients and drugs with and without the excipient as controls. We provide consensus-based excipient-specific recommendations on diagnostic testing based on best available evidence.

Abbreviations: BAT, basophil activation test; CGMP, current good manufacturing practice; CMC, carboxymethylcellulose; DHR, drug hypersensitivity reaction; DPT, drug provocation test; EAACI, European Academy of Allergy and Clinical Immunology; EDTA, ethylenediaminetetraacetic acid; EHR, electronic health record; EMA, European Medicines Agency; ENDA, European Network for Drug Allergy; FDA, Food and Drug Administration; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IDT, intradermal test; IM, intramuscular; IV, intravenous; MW, molecular weight; PEG, polyethylene glycol; PS, polysorbate; PVP, polyvinylpyrrolidone; RUO, research use only; SC, subcutaneous; sIgE, specific immunoglobulin E; SMB, sodium metabisulphite; SPT, skin prick test; ST, skin test.

Rik Schrijvers and Toon Ieven contributed equally to this work.

1 | Introduction

Drug hypersensitivity reactions (DHR) are frequent and associated with significant morbidity and mortality [1–3]. They are mostly directed against active ingredients such as β-lactam antibiotics. However, in some cases, they may be caused by inactive ingredients called excipients [4, 5].

Excipients are added to almost all drug and vaccine formulations in order to enhance their physicochemical properties (e.g., powder homogenisation, non-adherence, water or lipid solubility, tablet compression and/or coating, stabilisation, preservation), to enhance palatability (e.g., colouring or flavouring), to influence drug delivery (pharmacokinetics) or to enhance drug effects (pharmacodynamics) [6].

In contrast to active ingredients, the ability of excipients to trigger DHR is often overlooked. Recently, suspected allergic reactions to COVID-19 vaccines [7] have dramatically increased interest in excipients as a potential cause of drug and vaccine hypersensitivity. Nevertheless, literature on excipient hypersensitivity is mainly limited to individual case reports and small case series and the causality and pathophysiological mechanism is not always clear, generally resulting in a low level of evidence and lack of standardised practices regarding diagnosis and management.

As classical 'hidden allergens', excipients can result in clinically challenging situations such as multiple reactions to structurally unrelated drugs, reactions to only some formulations of a specific drug or reactions to drugs not usually associated with allergy such as laxatives and injectable depot steroids or progestogens. From the patient's perspective, excipient hypersensitivity can be life-threatening and frightening, especially when the culprit remains unidentified [8].

This position paper aims to review the existing evidence on those excipients most commonly reported to produce DHR, to highlight major red flags for timely recognition and identify and propose best practices in the diagnosis and management of excipient hypersensitivity.

2 | Methods

2.1 | Definition of Excipients

The European Medicines Agency (EMA) [4], Current Good Manufacturing Practices [9] and U.S. Food and Drug Administration (FDA) [10] define excipients (syn. inactive ingredients) as the constituents of the pharmaceutical form other than the active ingredient [6].

2.2 | Inclusion Criteria

Based on group experience, polyethylene glycols (PEGs) and related substances (i.e., polysorbates [PS] and poloxamers), gelatine, (carboxy-)methylcellulose (CMC), povidone and mannitol were the excipients most commonly reported as elicitors of DHR. In addition, literature screening identified benzyl alcohol, ethylenediaminetetraacetic acid (EDTA), metacresol, metabisulphite and (methyl-)paraben as rare culprits of excipient DHR (Table 1 and Appendix S2). Excipients only anecdotally implicated in DHR (e.g., trometamol, benzalkonium chloride) were excluded due to paucity of evidence. Excipients exclusively implicated in localised reactions after topical contact (e.g., contact dermatitis) were excluded unless they were also reported to elicit systemic reactions. Similarly, food additives not implicated in DHR were excluded.

2.3 | Data Sources

In June 2024, articles in English with data on drug excipient hypersensitivity were identified by searching the MEDLINE database (National Library of Medicine) through PubMed for all available publication years. Search terms included the names and known synonyms of the respective excipients or excipient class combined with '(allergy OR anaphylaxis OR drug allergy OR drug hypersensitivity)'. Only cases with a plausible history of immediate or delayed systemic excipient-related DHR were included [11]. These required (1) clinical history compatible with DHR and (2) sensitisation to the excipient adequately demonstrated through reproducible diagnostic testing, which was assessed by the task force members. Additional articles were included through screening of reference lists and upon suggestion by task force members. The personal clinical experience with excipient allergy of task force members was considered when other reliable sources of evidence were lacking.

2.4 | Data Extraction and Analysis

Task force members were assigned specific excipients and topics (2 to 5 authors per topic and 2–3 topics per author). The relevance of identified articles was evaluated by the assigned authors on the basis of title and abstract according to the above-mentioned criteria (Table 2). Articles meeting inclusion criteria and of sufficient quality were analysed in detail and recorded in a standardised format using a predefined master table (available as Appendix S1, including references for individual articles). This table was also used for descriptive statistical analyses. Data collected and summarised by individual assigned author(s) were presented to and discussed by the entire group during regular meetings.

2.5 | Recommendations on Diagnosis and Management

There is a need to standardise testing and management of excipient allergy. Based on the literature search and group experience, consensus-based recommendations on diagnosis and management (Table 3) as well as recommended ST procedures (Table 4, Appendix S3) were formulated. Given the exclusively retrospective dataset and small number of reported cases for most excipients, quality of evidence and strength of recommendations were considered to be universally low and thus not scored using the GRADE system [22]. Alternatively, authors were asked to vote on final recommendations using a standardised form with agreement noted in Table 3.

TABLE 1 | Overview of drug excipients implicated in immediate DHR including their molecular formula, synonym(s) and pharmaceutical function(s).

Excipient	Polyethylene glycol (PEG)[b]	Poloxamer[d]	Polysorbate (PS)[e]	Gelatine	Carboxy-methylcellulose (CMC)[f]	Povidone	Mannitol	Benzyl alcohol	Ethylenediamine-tetraacetic acid (EDTA)	Metacresol	Metabisulphite	Methyl paraben
Molecular formula[a]	H-(O-CH_2-CH_2)$_n$-OH	OH-(C_2H_4O)$_a$-(C_3H_6O)$_b$-(C_2H_4O)$_a$-H	$C_{64}H_{124}O_{26}$[e]	Mixture of hydrolysed animal collagen fragments	$C_8H_{16}O_8$	$(C_6H_9NO)_n$	$C_6H_{14}O_6$	C_7H_8O	$C_{10}H_{16}N_2O_8$	C_7H_8O	$Na_2S_2O_5$	$C_8H_8O_3$
E-number	—	—	E433[e]	E441	E466	E1201	E421	E1519	E385	—	E223	E218
CAS number	25322-68-3	9003-11-6	9005-64-6	9000-70-8	9004-32-4	9003-39-8	9003-39-8	100-51-6	60-00-4	108-39-4	7681-57-4	99-76-3
Synonyms	Poly(oxyethylene) glycol, Macrogol, polyethylene oxide (PEO)[c]	Poly(oxyethylene)-polyoxy-propylene block copolymer	PEG sorbitan monooleate	—	Carmellose, cellulose gum	Polyvinyl-pyrrolidone (PVP), polyvidone	D-mannitol, mannite, mannosan, manna sugar, cordycepic acid	Benzene-methanol, phenylcarbinol, phenylmethanol, benzoyl alcohol, α-hydroxy-toluene, α-cresol	Edetic acid	3-methyl-phenol, m-cresol, 3-hydroxy-toluene	Disodium pyrosulphite	Methyl parahydroxy-benzoate
Trade names	Carbowax	Pluronic, lutrol, kolliphor, synperonic	Tween	Pharmagel, gelfoam, puragel	Blanose, aquacel, tylose, almelose	Kollidon, plasdone	Pearlitol	—	Versene	—	—	Nipagin M
Function (excipient)	Solvent, plasticiser, ointment and suppository base, lubricant (tablets), thickener, stabiliser, PEGylation	Solubiliser, emulsifier, wetting agent, (thermo) gelling agent	Solubiliser, emulsifier, wetting agent, stabiliser	Gelling agent, binder (capsules), encapsulating agent, stabiliser (for proteins)	Thickener, binder, suspending agent, disintegrant, stabiliser	Solubiliser, binder (tablets), film-former, suspending agent, stabiliser	Diluent (tablets), bulking agent, sweetener, cryoprotectant	Preservative, solvent, viscosity-reducing agent	Chelating agent, antioxidant, stabiliser	Preservative	Preservative, antioxidant	Preservative
Function (as API)	Osmotic laxative	—	—	Plasma expander, haemostatic agent	Eye lubricant	—	Osmotic diuretic, tonicity agent	Antiparasitic (delousing agent), topical antiseptic, (mild) local anaesthetic	Metal chelator	Topical antiseptic	—	—

Abbreviations: API, active pharmaceutical ingredient; CAS, chemical abstract service; DHR, drug hypersensitivity reaction; MW, molecular weight.

[a]See Appendix S2 for structural formulae and more detailed description of the chemical structures.

[b]PEGs are linear chains with variable length consisting of ethylene glycol subunits (MW of 44 Da per subunit). The PEG number indicates the total MW in Dalton.

[c]Polyethylene oxide (PEO) is mostly used for PEGs with a MW exceeding 100 kDa (i.e., > 2200 ethylene glycol subunits).

[d]Poloxamers contain two PEG chains of variable length connected to a central polyoxypropylene (PPO) block. The first two digits in the poloxamer number indicate the MW of the central PPO block and the final digit indicates the weight percentage made up by the PEG chains (e.g., poloxamer 108, 407).

[e]Polysorbates consist of a sorbitane core with four PEG sidechains (five ethylene glycol subunits per sidechain equivalent to PEG 220) and an esterified variable fatty acid tail which determines the polysorbate number. The table refers to polysorbate 80 which is most frequently implicated in DHR.

[f]Carboxymethylcellulose (CMC) is by far the most frequently implicated methylcellulose derivative in immediate DHR. Only one case of a non-CMC methylcellulose-related DHR to hydroxypropylmethylcellulose (HPMC) has been described.

TABLE 2 | Overview of articles on immediate DHR to excipient in drugs retrieved and selected for analysis.

	PEGs (incl. PEG, polysorbate, poloxamer)	Gelatine	Methylcelluloses (incl. CMC, HPMC)	Povidone	Mannitol	Benzyl alcohol	EDTA	Metacresol	Metabisulphite	Methyl paraben
No. of articles retrieved[a]	1864	670	279	502	389	99	383	10	216	117
No. of articles selected	159	48	199	16	3	4	1	1	1	3
No. of cases (selected and analysed)	119	103	45[b]	16	4	4	1	1	1	3
Median age (range)[c]	45 (12–88)	19 (1–85)	53 (14–80)	29.5 (4–59)	40.5 (32–73)	38 (16–55)	57	12	37	44 (10–45)
Female/Male	81/38	51/52	18/26[a]	5/11	2/2	1/2	0/1	1/0	1/0	1/2
ST confirmation, *n*/*n* tested	98/118	48/52	45/45	13/13	4/4	4/4	1/1	0/1	0/1	3/3
Challenge confirmation, *n*/*n* tested	30/32	6/6	1/1	3/3	1/1	0/0	1/1	1/1	1/1	1/1
In vitro confirmation, *n*/*n* tested	46/65	56/61[d]	10/18	5/7	1/4	0/0	1/1	0/0	0/0	0/0
Systemic reactions during ST, *n*/*n* reported (%)	25/115[e] (21.7)	0/52 (0)	0/37 (0)	1/13 (7.7)	0/4 (0)	0/4 (0)	0/1 (0)	0/1 (0)	0/1 (0)	0/3 (0)

Note: No. of articles retrieved via PubMed query (allergy OR anaphylaxis OR drug allergy OR drug hypersensitivity) AND (listed excipient), performed December 2024.
Abbreviations: CMC, carboxymethylcellulose; DHR, drug hypersensitivity reaction; EDTA, ethylenediaminetetraacetic acid; HPMC, hydroxypropylmethylcellulose; PEG, polyethylene glycol; ST, skin test.
[a]For one patient, sex was not specified.
[b]Another 3 cases with delayed type hypersensitivity were identified.
[c]Age distributions are shown in Figure 1.
[d]Only taking sIgE into account (another 6 patients had positive BAT and no sIgE determination).
[e]Outcome was not clearly reported in all cases.

TABLE 3 | Consensus-based recommendations on the diagnosis and management of immediate DHR potentially caused by excipients.

Topic			Recommendation	Agreement	Comments
1. General	1.1. Clinical suspicion	1.1.1.	Workup of any immediate DHR should start with review of the culprit monograph to identify the active ingredient and presence of potentially allergenic excipients	100%	i.e., PEG, gelatine, (carboxy)methylcellulose, povidone, mannitol, benzyl alcohol, EDTA, metabisulphite, paraben
		1.1.2.	Excipient allergy should be suspected in the following situations:		
		1.1.2.a	• reactions to drugs with an excipient as active ingredient	100%	e.g., PEG-based oral laxatives, gelatine-based plasma expanders, IV mannitol, povidone-iodine solution
		1.1.2.b	• reactions to two or more drugs- or rarely, drug(s) and food(s) or cosmetics containing the same excipient	100%	Excluding delayed type hypersensitivity reactions (e.g., contact dermatitis) to cosmetics
		1.1.2.c	• reactions to injectable depot formulations	100%	Especially depot corticosteroids or progestogens that can contain PEG, CMC or povidone
		1.1.2.d	• reactions to any drug if workup for the active ingredient is negative or if the active ingredient is tolerated in another drug/brand	100%	Including perioperative reactions with negative testing for culprit drugs
	1.2. Diagnosis	1.2.1	ST is the primary diagnostic modality for excipient allergy. ST panels should include the following elements and SPT should always be performed first:	100%	See Table 4 for suggested ST reagents and concentrations. As per ENDA/EAACI recommendations, sterile and non-irritant injectable formulations should be used for IDT [12–14]
		1.2.1.a	• drug or product that caused the index reaction (i.e., culprit)	100%	
		1.2.1.b	• pure excipient, preferably in sterile injectable form (i.e., pharmaceutical ground substance)	100%	Alternatively, a drug containing the same excipient but a different active ingredient as the culprit can be used
		1.2.1.c	• other drug/product containing the same active ingredient without the excipient	100%	
		1.2.1.d	• relevant cross-reactive compounds	100%	
		1.2.2.	In vitro tests such as BAT may be considered to complement ST in complex cases	91% (1/11 abstain)	BAT procedures should adhere to EAACI recommendations; Results should be interpreted with caution due to limited evidence in most cases
		1.2.3.	DPT may be considered in cases that remain unexplained despite ST (and in vitro tests)	91% (1/11 disagree)	Careful risk–benefit analysis is essential as evidence on optimal protocols and safety is limited

(Continues)

TABLE 3 | (Continued)

Topic		Recommendation	Agreement	Comments
1.3. Management	1.3.1.	Avoidance of drugs containing the excipient and relevant cross-reactive compounds is recommended	100%	
	1.3.2.	An allergy warning card and notification in the electronic healthy record should be provided and patients should be instructed in how to identify the excipient in drugs and products	100%	Caution is warranted when providing lists of excipient-free drugs as these can vary across brands and may change over time
	1.3.3.	Regular medication and personal care products containing the culprit excipient or potential crossreactive compounds that were consistently tolerated since the index event may be continued	100%	Use of the exact same brand is strongly recommended as excipient content can vary between brands
	1.3.4.	Excipient-free drugs are always preferred when a new drug is initiated	100%	Pharmacist advice is recommended in case of doubt
	1.3.5.	If an excipient-free drug is not available, supervised in-hospital administration of essential/vital excipient-containing drugs (e.g., polysorbate-containing chemotherapeutics or biologicals) may be considered after careful risk–benefit analysis	100%	Administration can be stepwise, graded or even desensitisation-based; Careful risk–benefit analysis is essential as evidence for such procedures is limited
	1.3.6.	An adrenaline autoinjector should be provided in patients with a history of severe and/or recurrent reactions or when strict avoidance is not feasible	100%	e.g., total avoidance of exposure to PEG-related compounds is virtually impossible
1.4. Unmet needs	1.4.1.	Prospective, multi-centre studies for the validation of standardised ST panels and in vitro tests	100%	
	1.4.2.	Broader access to (pure, sterile) excipients suitable for in vivo and in vitro tests	100%	
	1.4.3.	Insight in the natural evolution of excipient allergy and role of (hidden) excipient exposure in sensitisation	100%	
	1.4.4.	Standardised and universal nomenclature and labelling for all excipients in drugs, foods and cosmetics including amount	100%	Ideally, application of these aspects should be enforced through supranational regulations and include harmonisation between cosmetics and drug regulations

(Continues)

TABLE 3 | (Continued)

Topic			Recommendation	Agreement	Comments
2. PEG	2.1. Clinical suspicion	2.1.1.	In addition to the situations mentioned under 1.1. PEG allergy should be suspected in the following cases:		
		2.1.1.a.	• reactions to drugs containing PEG and/or the structurally related polysorbates and poloxamers	91% (1/11 abstain)	See Table S1 for brand names of culprit products; a history of reaction or tolerance to PEG-containing COVID-19 vaccines should not be considered a reliable predictor for PEG allergy or tolerance, respectively
		2.1.1.b.	• any reaction to oral PEG-based laxatives and/or injectable depot steroids or progestogens	91% (1/11 abstain)	
		2.1.1.c.	• any reaction to a PEG-containing drug in combination with a history of local and/or (mild) systemic immediate reactions to cosmetics	91% (1/11 abstain)	Culprit cosmetics can include shaving products, skin creams, toothpastes, soaps, ...
	2.2. Diagnosis	2.2.1.	ST is the primary diagnostic modality for PEG allergy. ST for PEG should adhere to the following principles:	100%	
		2.2.1.a	• preferential use of pure pharmaceutical-grade PEGs spanning a broad MW range	100%	See also Table 4 and Appendix S3 for suggested ST reagents and concentrations that may be used to assemble a ST panel; In PEG resource-limited settings, a basic screening ST can be done using SPT with 50% w/v dilution (500 mg/mL) of a PEG 3350-based oral laxative and with a prick-to-prick SPT with crushed PEG 20,000-containing tablets (e.g., Flagyl, Gaviscon Peppermint)
		2.2.1.b	• in case of limited access to PEG ST reagents and/or limited experience, referral to a centre with experience in PEG allergy diagnosis is strongly recommended	100%	
		2.2.1.c	• due to a high risk of systemic reactions during PEG ST, SPT should always precede IDT and ST should be halted as soon as a positive result is obtained	100%	See also Appendix S3 for detailed outline of the suggested ST procedure; Risk of systemic reactions is likely determined by the MW and (cumulative) PEG dose administered
		2.2.1.d	• IDT with pure PEG solutions should only be performed in experienced centres, using sterile injectable solutions and only if preceding SPT up to PEG 6000 (or PEG 20,000, if available) were negative	100%	PEG IDT are associated with a higher risk of systemic reactions

(Continues)

TABLE 3 | (Continued)

Topic		Recommendation	Agreement	Comments
	2.2.1.e	• timely testing after the index reaction is recommended (4 weeks to 4 months); SPT with high MW PEGs (up to PEG 20,000 if available) are recommended when exceeding this interval	91% (1/11 abstain)	It has been demonstrated that PEG 20,000 SPT show persistent positivity in patients retested over time even when SPT with lower MW PEGs become negative [15]
	2.2.1.f	• ST with polysorbate and poloxamer should be performed in all cases to assess cross-sensitisation	100%	See also Table 4 and Appendix S3: ST should include at least PS80 and poloxamer 407; ST positivity to polysorbates and poloxamers might indicate a more severe (and persistent) PEG allergy phenotype [16]; Note that rare cases of isolated polysorbate allergy, distinct from PEG allergy, have also been described [16–18]
	2.2.2.	If available, BAT may be performed in patients with a plausible clinical history to confirm the diagnosis	91% (1/11 disagree)	Basophil stimulation with PEGylated lipid nanoparticles (e.g., mRNA vaccines, PEGylated liposomal doxorubicin) has been demonstrated in three separate cohorts to enhance BAT sensitivity while maintaining specificity [16, 19, 20]; A risk of false positivity after recent COVID-19 infection reported by one group [21] could not be confirmed in other studies [16, 19, 20]
2.3. Management	2.3.1.	Strict avoidance of PEGs of all MW and administration routes is recommended in all PEG allergic patients except for drugs/products fulfilling recommendation 1.3.3. and taking recommendation 1.3.5. into account	91% (1/11 abstain)	The MW threshold for ST positivity does not adequately predict clinical reactivity as the latter may vary depending on augmenting factors, cumulative dose, administration route and interval since index reaction
	2.3.2.	Avoidance of polysorbates and/or poloxamers is only recommended in PEG allergic patients with ST-proven cross-sensitisation and/or clinical cross-reactivity (i.e., reactions) to these excipients	91% (1/11 abstain)	Allergic reactions to polysorbates and poloxamers occur in a minority of PEG allergic patients
	2.3.3.	Patients with isolated polysorbate allergy should only avoid polysorbates	82% (2/11 abstain)	Limited evidence suggests tolerance of PEGs and poloxamer in these patients [16]

(Continues)

TABLE 3 | (Continued)

Topic			Recommendation	Agreement	Comments
	3.4. Unmet needs	2.4.1.	Insight in factors determining individual thresholds for dose and MW needed to elicit clinical reactions	100%	
		2.4.2.	Insight in the prevalence and clinical relevance of poloxamer and polysorbate sensitisation	100%	
		2.4.3.	Insight in the mechanism and phenotype of isolated polysorbate allergy	100%	
3. Gelatine	3.1. Clinical suspicion	3.1.1.	In addition to the situations mentioned under 1.1. gelatine allergy should be suspected in the following cases:		See also Table S1
		3.1.1.a	• anaphylaxis occurring in perioperative or intensive care settings	91% (1/11 abstain)	
		3.1.1.b	• vaccine-related anaphylaxis, in particular to MMR and/or varicella vaccines	91% (1/11 abstain)	
		3.1.1.c	• food-related reactions, in particular to mammalian meat (i.e., alpha-gal) and/or gelatin-based food products (gummy sweats, marshmellows)	91% (1/11 abstain)	
	3.2. Diagnosis	3.2.1.	All patients should undergo ST using SPT and IDT with sterile gelatine-containing IV formulations (e.g., plasma-expanders)	100%	See also Table 4 for suggested ST reagents and concentrations
		3.2.2.	All patients should undergo sIgE measurement for gelatine and alpha-gal using standard commercial assays	100%	
		3.2.3.	If available, BAT may be performed to aid diagnosis in complex cases	91% (1/11 abstain)	

(Continues)

TABLE 3 | (Continued)

Topic			Recommendation	Agreement	Comments
	3.3. Management	3.3.1.	Strict avoidance of all parenteral gelatine-containing pharmaceuticals is recommended in patients with gelatine and/or alpha-gal allergy	100%	
		3.3.2.	Avoidance of gelatine-containing foods and oral drugs is only recommended for patients with a history of reactions after oral gelatine exposure	100%	Most patients tolerate oral gelatine exposure; In case of doubt, an oral food challenge can be considered, although the potential role of augmenting factors should be taken into account
		3.3.3.	In patients with asymptomatic alpha-gal sensitisation, caution regarding exposure to parenteral gelatine-containing pharmaceuticals or vaccines may be advised	100%	The risk of gelatine-related DHR in alpha-gal sensitised patients remains unclear
	3.4. Unmet needs	3.4.1.	Insight in the degree of overlap (i.e., cross- or co-sensitisation) between gelatine and alpha-gal allergy	100%	While co-existing sensitization to gelatine and alpha-gal is frequent, isolated gelatine sensitisation is reported by some authors
		3.4.2.	Insight in the risk of hypersensitivity to parenteral gelatine-containing pharmaceuticals (e.g., vaccines) in patients with asymptomatic alpha-gal sensitisation	100%	
4. Methyl-cellulose	4.1. Clinical suspicion	4.1.1.	In addition to the situations mentioned under 1.1. methylcellulose allergy should be suspected in the following cases:		See also Table S1
		4.1.1.a	• reactions to methylcellulose-containing injectable depot steroids, topical agents (e.g., anaesthetic gels, eyedrops and enteral barium contrast solutions)	100%	Most common culprits are depot steroids
		4.1.1.b	• rarely, reactions to CMC-containing foods (ice cream, ...) can offer additional clues	100%	

(Continues)

TABLE 3 | (Continued)

Topic			Recommendation	Agreement	Comments
	4.2. Diagnosis	4.2.1.	ST is the recommended primary diagnostic modality for methylcellulose allergy and should include:	100%	See also Table 4 for suggested ST reagents and concentrations
		4.2.1.a	• SPT (and IDT if possible) with a (sterile and preservative-free) CMC-containing eyedrop	100%	
		4.2.1.b	• if available, ST may be performed with other celluloses (e.g., HPMC, HEC, HPC)	100%	Evidence on ST with other (non-CMC) methylcelluloses is limited (four case reports)
		4.2.2.	If available, BAT may be performed to aid diagnosis in complex cases	91% (1/11 abstain)	
	4.3. Management	4.3.1.	Strict avoidance of all parenteral methylcellulose-containing pharmaceuticals is recommended taking recommendation 1.3.3. into account	100%	
		4.3.2.	Avoidance of methylcellulose-containing foods is only recommended for patients with a history of food-related reactions	100%	Most patients tolerate oral methylcellulose exposure; in patients without history of reactions to oral exposure, a wait-and-see approach or alternatively, oral food challenge can be considered to offer more certainty, although the potential role of augmenting factors should be taken into account
	4.4. Unmet needs	4.4.1.	Insight in cross-reactivity between (methyl) celluloses	100%	Especially for hydroxypropylcellulose (HPC) which is a widely used excipient
		4.4.2.	Validation of ST with non-CMC methylcelluloses	100%	
5. Povidone	5.1. Clinical suspicion	5.1.1.	In addition to the situations mentioned under 1.1. povidone allergy should be suspected in the following cases:		See also Table S1
		5.1.1.a	• immediate reactions to topical povidone-iodine-containing antiseptic solutions	91% (1/11 abstain)	
		5.1.1.b	• reactions to any oral, topical or parenteral (cros) povidone-containing pharmaceuticals	91% (1/11 abstain)	

(Continues)

TABLE 3 | (Continued)

Topic			Recommendation	Agreement	Comments
	5.2. Diagnosis	5.2.1.	ST is the recommended primary diagnostic modality for povidone allergy and should include:	91% (1/11 abstain)	See also Table 4 for suggested ST reagents and concentrations
		5.2.1.a	• SPT with pure povidone or undiluted povidone-containing eyedrops	91% (1/11 abstain)	Evidence on IDT with povidone is limited (two case reports) but may be considered; task force member experience suggests that concentrations up to at least 1 mg/mL for IDT are non-irritant although validation of specificity in controls is lacking
		5.2.1.b	• if available, ST may be performed with crospovidone to assess cross-reactivity	91% (1/11 abstain)	Evidence on ST with crospovidone is limited (two case reports)
		5.2.2.	If available, BAT may be performed to aid diagnosis in complex cases	82% (2/11 abstain)	
	5.3. Management	5.3.1.	Strict avoidance of all povidone-containing drugs is recommended	91% (1/11 abstain)	Crospovidone avoidance seems prudent in patients with demonstrable cross-reactivity, although evidence is limited
	5.4. Unmet needs	5.4.1.	Insight in the prevalence and clinical relevance of cross-reactivity between povidone and crospovidone	91% (1/11 abstain)	
		5.4.2.	Insight in the relevance of povidone food additives (E1201) as potential food allergens	91% (1/11 abstain)	
		5.4.3.	Validation of IDT with povidone and ST (SPT, IDT) with crospovidone	91% (1/11 abstain)	
6. Mannitol	6.1. Clinical suspicion	6.1.1.	In addition to the situations mentioned under 1.1. mannitol allergy should be suspected in the following cases:		See also Table S1
		6.1.1.a	• reactions to oral or IV mannitol-containing drugs, in particular IV paracetamol formulations	10 0%	
		6.1.1.b	• reactions to mannitol-containing foods (e.g., mushrooms, cauliflower, algae, pomegranate) can offer an additional clue	100%	
	6.2. Diagnosis	6.2.1.	ST is the recommended primary diagnostic modality for mannitol allergy and should include SPT and IDT with pure mannitol in the form of sterile IV mannitol solution	100%	See also Table 4 for suggested ST reagents and concentrations

(Continues)

TABLE 3 | (Continued)

Topic		Recommendation	Agreement	Comments
6.3. Management	6.3.1.	Strict avoidance of all mannitol-containing drugs is recommended	100%	
	6.3.2.	Avoidance of specific mannitol-containing foods is only recommended for patients with a history of reactions to these foods	100%	Limited evidence suggest a risk of reactions to mannitol-containing foods with variable patterns; In patients without history of reactions to oral exposure, a wait-and-see approach or alternatively, oral food challenge can be considered to offer more certainty, although the role of potential augmenting factors should be taken into account
6.4. Unmet needs	6.3.3.	Insight in the risk of hypersensitivity to mannitol-containing foods	100%	

Abbreviations: BAT, basophil activation test; CMC, carboxymethylcellulose; DHR, drug hypersensitivity reaction; DPT, drug provocation test; EDTA, ethylenediaminetetraacetic acid; HEC, hydroxyethylcellulose; HPC, hydroxypropylcellulose; HPMC, hydroxypropylmethylcellulose; IDT, intradermal test; IV, intravenous; MMR, measles-mumps-rubella vaccine; MW, molecular weight; PEG, polyethylene glycol; sIgE, specific IgE; SPT, skin prick test; ST, skin test.

3 | Results

3.1 | General Aspects

Literature search identified the largest number of DHR cases for PEG ($N = 119$) and gelatine ($N = 103$) with much fewer cases for the remaining excipients (< 50 cases per excipient) (Table 2 and Appendix S1).

Age and gender distributions suggest different patterns for different excipient allergies (Figure 1, Table 2) with a female predominance for PEG, male predominance for povidone and methylcellulose and equal ratio for gelatine. Age distributions also varied broadly: for gelatine from infancy to elderly; for povidone from children to young adults; and for PEG and mannitol mostly from adolescence to elderly.

Clinical manifestations were variable, with anaphylaxis occurring in the majority of reported cases and fatalities rarely reported (Figure 1). Reported delays between exposure and symptom onset varied from 1 min up to 1 h. While prospective evidence on quality-of-life is lacking, limited retrospective studies [8] as well as clinical experience suggest a major impact of excipient allergies on patients' daily lives. The unexpected, severe and/or recurrent nature of allergic episodes can result in significant anxiety, leading to avoidance of essential medications and reliance on self-management strategies.

Reported reactions were triggered by a multitude of drugs (Table S1) administered through a variety of routes including parenteral (intravenous [IV], intramuscular [IM], intradermal, subcutaneous [SC]) as well as oral, skin and mucosal exposures, perioperative (i.e., surgical site) application and/or food ingestion. Virtually all excipients were capable of triggering reactions through multiple exposure routes. In addition, individual patients often experienced multiple reactions to various drugs with different active ingredients before excipient allergy was diagnosed. Cross-reactivity between structurally similar excipients was mainly described between PEGs, PS and poloxamer; gelatine and alpha-gal; povidone and crospovidone; and rarely between methylcelluloses.

In most cases, diagnosis was based on skin testing (ST) including skin prick (SPT) and intradermal tests (IDT). A lack of standardised concentrations and testing reagents was observed for all excipients. Systemic reactions during ST were frequently reported with PEG on both SPT and IDT, but only rarely for others. In vitro assays such as the basophil activation test [23] (BAT) and serum specific IgE (sIgE) measurement supported the diagnosis in some cases. Drug provocation tests [24] (DPT) were used in a considerable number of patients without standardised protocols.

3.2 | Specific Topics

3.2.1 | Polyethylene Glycol

PEGs are linear polymers of ethylene glycol formed through polymerisation of ethylene oxide. Poloxamers and PS contain PEG chains and share physicochemical properties with linear PEGs

TABLE 4 | Consensus-based recommendations for excipient skin testing reagents and concentrations (see Appendix S3 for details of PEG ST).

				SPT recommendations		IDT recommendations[d]	
Excipient	**Product type (excipient content)**	**Sources (examples)[a]**	**Sterile**	**Dilutions**	**Concentrations**	**Dilutions**	**Concentrations**
PEG 300	Ground substance (liquid)	Sigma-Aldrich	No	Undiluted	Unknown	—	—
PEG 400	Ground substance (liquid)	Fagron	Yes	Undiluted	Unknown	—	—
PEG 3000	Ground substance (powder)	Sigma-Aldrich, Merck	No	50% w/v	500 mg/mL	—	—
PEG 3350	Oral laxative (liquid or powder)	MiraLAX, Forlax, Movicol, Laxido	No	50% w/v	500 mg/mL	—	—
	Injectable depot steroids (29 mg/L)	Depo-Medrol, Depo-Provera	Yes[b]	Undiluted	29 mg/mL	0.1-10% v/v	0.29–2.9 mg/mL
PEG 4000	Ground substance (powder)	Fagron	Yes	10% (w/v)	100 mg/mL	0.01%–0.1% w/v[f]	0.1–1 mg/mL[f]
PEG 6000	Ground substance (powder)	Sigma-Aldrich, Merck, Carl Roth	No	50% w/v	500 mg/mL	—	—
PEG 20,000	Ground substance (powder)	Sigma-Aldrich	No	0.01-20% w/v[d]	0.1–200 mg/mL	—	—
	Crushed tablets (0.2%; 3%)	Flagyl; Gaviscon Peppermint	No	~90% w/v[e]	14; 300 mg/mL	—	—
Polysorbate 80	Ground substance (liquid)	Fagron	Yes[c]	Undiluted	1 mg/mL	0.1%–10% v/v	0.001–0.1 mg/mL
Poloxamer 407	Ground substance (powder)	Sigma-Aldrich	No	10% w/v	100 mg/mL	—	—
Gelatine	IV plasma expander (40 g/L = 40 mg/mL)	Gelofusine, Haemacell	Yes	10% v/v–undiluted	4–40 mg/L	1% v/v – undiluted[g]	0.4–40 mg/mL
Carboxymethyl-cellulose	Preservative-free eyedrop (10 mg/mL)	Celluvisc, Viscofresh	Yes	Undiluted	10 mg/mL	1%–10% v/v[h]	0.1–1 mg/mL[h]
Povidone	Preservative-free eyedrop (50 mg/mL)	Oculac	Yes	Undiluted	50 mg/mL	[i]	[i]
Mannitol	IV mannitol (100 g/L)	Mannitol Baxter, Mannitol Braun	Yes	Undiluted	100 mg/mL	0.1%–10% v/v	0.1–10 mg/mL

Abbreviations: IDT, intradermal test; IV, intravenous; PEG, polyethylene glycol; SPT, skin prick test; v/v, volume-to-volume ratio; w/v, weight-to-volume ratio.
[a]Not applicable for all regions/countries: always check for locally available equivalents and their exact composition (see Summary of Product Characteristics or SmPC).
[b]Sterile form for IDT available in the form of PEG 3350-containing injectable drugs (i.e., Depo-Medrol, Depo-Provera).
[c]Sterile form for IDT available as pure pharmaceutical-grade ground substance (from Fagron, Belgium).
[d]Due to risk of systemic reactions SPT with PEG 20,000, and all IDT should be done stepwise starting at lowest concentration with 20 min intervals between steps; testing should be halted when a positive reaction is obtained.
[e]Crushed tablet diluted in 2–3 drops of saline (0.1–0.15 mL).
[f]IDT with pure PEG have been published but data on sensitivity, specificity and safety are limited and a high rate of systemic reactions has been observed.
[g]IDT with undiluted (i.e., 100%; 40 mg/mL) gelatine-containing plasma expander was found to be non-irritative in > 50 nonallergic controls (KB, unpublished observation).
[h]Some authors report that IDT with carboxymethylcellulose appears to be non-irritant up to at least 1 mg/mL, although validation in a larger group of nonallergic controls (> 10) is lacking.
[i]IDT with povidone have been reported but data are too limited to formulate recommendations.

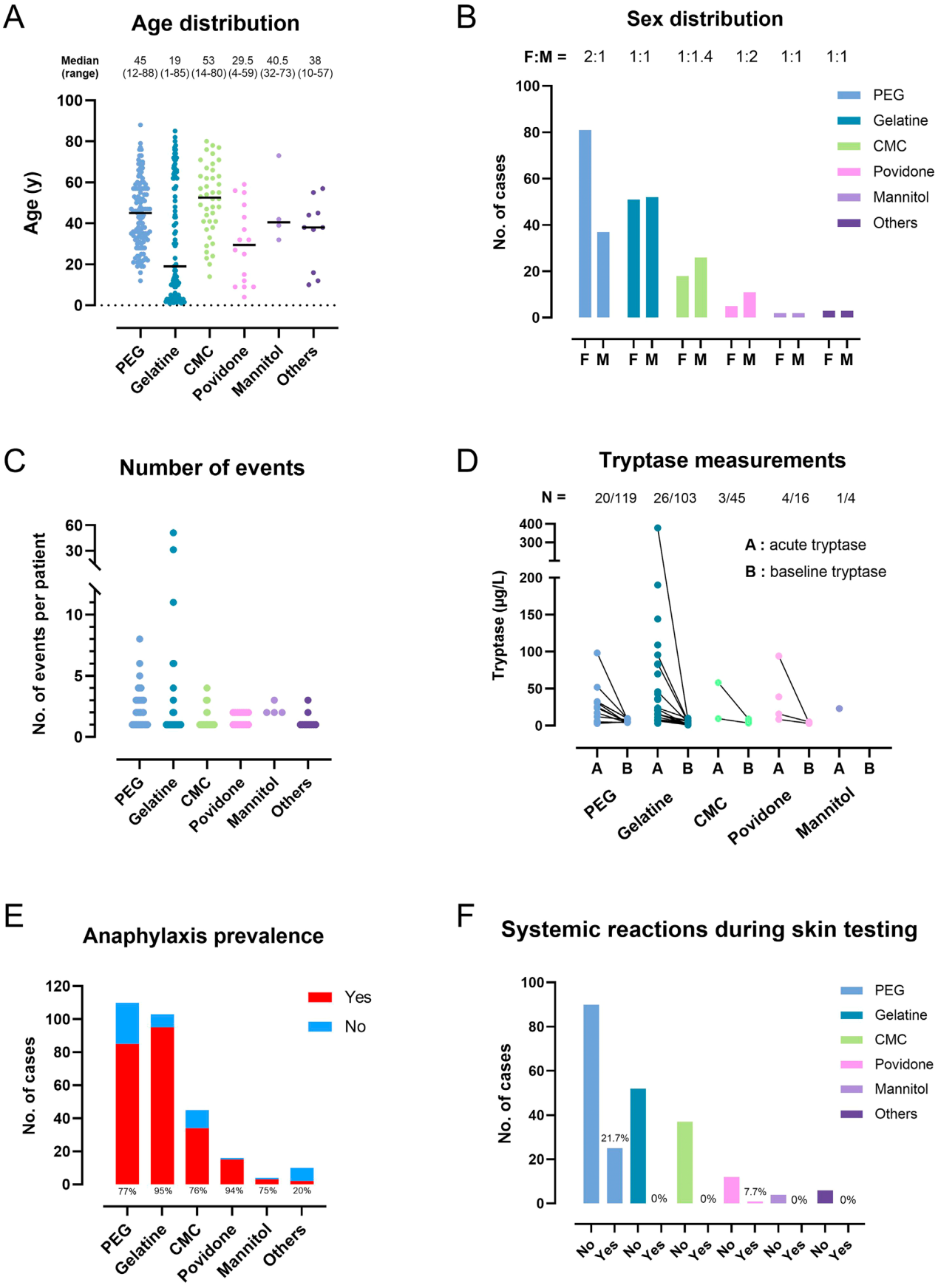

FIGURE 1 | Legend on next page.

FIGURE 1 | Characteristics of immediate drug hypersensitivity reactions (DHR) caused by excipients. (A) Age distribution of various excipient allergies. Horizontal bars indicate medians; (B) Sex distribution of various excipient allergies. Female-to-male ratios are indicated above the bars; (C) Number of events of excipient-related DHR per patient for various excipient allergies. For gelatine, three patients with concomitant alpha-gal allergy reported > 10 reactions to both drugs and foods; (D) Reported acute (A, immediately following excipient-related DHR) versus baseline (B) tryptase values for various excipient allergies. Proportion of informative cases is indicated above the graph; (E) Proportion (see % in or below graphs) and total no. of reported excipient-related DHR fulfilling anaphylaxis criteria for various excipient allergies. (F) Prevalence of systemic reactions occurring during skin testing for various excipient allergies. Proportion of patients reacting during skin testing indicated in % above the graphs. CMC, carboxymethylcellulose; DHR, drug hypersensitivity reaction; F, female; M, male; PEG, polyethylene glycol.

[25]. PEGs are ubiquitously used in pharmaceuticals and cosmetics. They vary in chain length indicated by the PEG number, variably expressed in molecular weight (MW; in g/mol or Dalton) for pharmaceuticals and number of ethylene glycol subunits for cosmetics (Table 1) [26, 27].

While PEG-specific IgM and IgG antibodies are quite prevalent in the general population, PEG-sIgE are rare and risk factors for sensitisation remain unknown [28]. Immediate-type PEG DHR depend on the presence of PEG-sIgE capable of binding ethylene glycol oligomers between 3 and 5 subunits in length [16]. PEG-sIgE crosslinking depends on patient- (i.e., IgE affinity and titre) and PEG antigen-specific characteristics (i.e., dose, MW, exposure route) (Figure S2), resulting in an unpredictable and sometimes even transient allergy phenotype [15, 28]. Certain PEGylated compounds such as PEG castor oil [29] and PEG asparaginase [30] can cause DHR through unknown mechanisms, apparently unrelated to IgE-mediated PEG allergy.

The incidence and prevalence of PEG allergy are largely unknown and likely underestimated. In Denmark, approximately 60 patients have been diagnosed with confirmed PEG allergy (*personal communication LHG and CGM*) resulting in an inferred prevalence of 10 cases per million inhabitants [17, 31]. Pre-COVID pandemic FDA data estimate a U.S. incidence of anaphylaxis to PEG-containing laxatives of five cases per year [32].

We included 119 individual cases of confirmed PEG allergy with an average age of 45 years (range 12–88) and 2:1 female-to-male ratio (Figure 1, Table 2 and Appendix S1). Most cases were reported after the start of the COVID-19 pandemic, highlighting increasing awareness in recent years (Figure S1). PEG-related DHR encompassed a wide spectrum of severity with mucocutaneous signs [33] present in almost all cases (Figure 2). Fatalities potentially resulting from PEG DHR have also been reported, although causality could not be confirmed in all these cases [34, 35]. Most patients experienced reactions after oral (mostly high PEG dose-containing laxatives) and intra-articular or IM (PEG-containing depot steroid) exposure (Figure 2). In addition, reactions after skin and mucosal contact (e.g., cosmetics) and surgical site application (e.g., bone cement) have been reported. Of note, the majority of patients experienced multiple reactions (Figure 2) and many also reported mild symptoms (pruritus, erythema, urticaria, angioedema) when exposed to PEG-containing cosmetics such as soaps, creams, toothpastes and shaving materials [16, 17, 31]. Over half of patients experienced multiple reactions and the diagnostic delay exceeded 1 year in at least one third of cases (Figure 2) [17, 31].

Any PEG can elicit DHR regardless of MW; however, over 50% of reported reactions were caused by PEGs with a MW of 3000–5000 Da (Figures 2 and S2). A MW above 3000 Da was more likely to induce positive ST results (Figure 3). Of note, ST reactivity to higher MW PEGs is often retained whereas lower MW reactivity can be lost when retesting after longer time periods [15]. Since MW thresholds for ST positivity do not always correlate with clinical reactivity thresholds, these should not be used to guide avoidance strategies.

Cross-sensitisation between PEG-containing excipients was assessed through ST in a subset of cases and was present in up to 35.6% ($N = 21/59$) for PS and 46.9% ($N = 15/32$) for poloxamers (Figure 3). Despite this, clinical reactions to polysorbates and poloxamers are rare and cross-sensitisation on ST appears primarily linked to an overall higher level of clinical reactivity to PEG. There have also been reports of patients exhibiting exclusive PS allergy without detectable PEG sensitisation, suggesting that different phenotypes exist, depending on sensitisation to non-cross-reactive PS-specific epitopes [16–18].

PEG allergy should be considered especially in case of anaphylaxis to PEG-containing laxatives, parenteral depot steroid injections and multiple reactions to seemingly unrelated PEG-containing compounds including tablets and/or cosmetics. Diagnosis relies primarily on ST. ST with higher MW PEG can help confirm the diagnosis when lower MW PEGs yield negative results [15]. Caution during ST is warranted, particularly in patients with a history of anaphylaxis, as a high rate of systemic reactions was reported (21.7%) for both SPT and especially IDT (Figures 1 and 3, Table S2). A specific consensus-based ST procedure aimed at mitigating risk while maintaining sensitivity is provided (Tables 3 and 4, Appendix S3). Use of custom PEG-sIgE assays (e.g., ELISA, MSD, dual cytometric bead assays) and a research-use-only (RUO) ImmunoCAP assay have been reported but require use of PEG-free reagents and lack sensitivity [16, 17, 28, 32]. BAT using PEGylated lipid nanoparticles was demonstrated in three independent cohorts [16, 19–20] to have high sensitivity and specificity without increased risk of false positives in PEG-tolerant controls with recent COVID-19 infection and/or vaccination as reported in another study [21]. PEG DPT were used in a small number of cases and might help confirm the diagnosis when other tests are negative or inconclusive, though the risk of severe systemic reactions should be taken into account.

Avoidance remains the key management strategy, requiring comprehensive patient education. While specific brands of PEG-containing medications tolerated since the initial

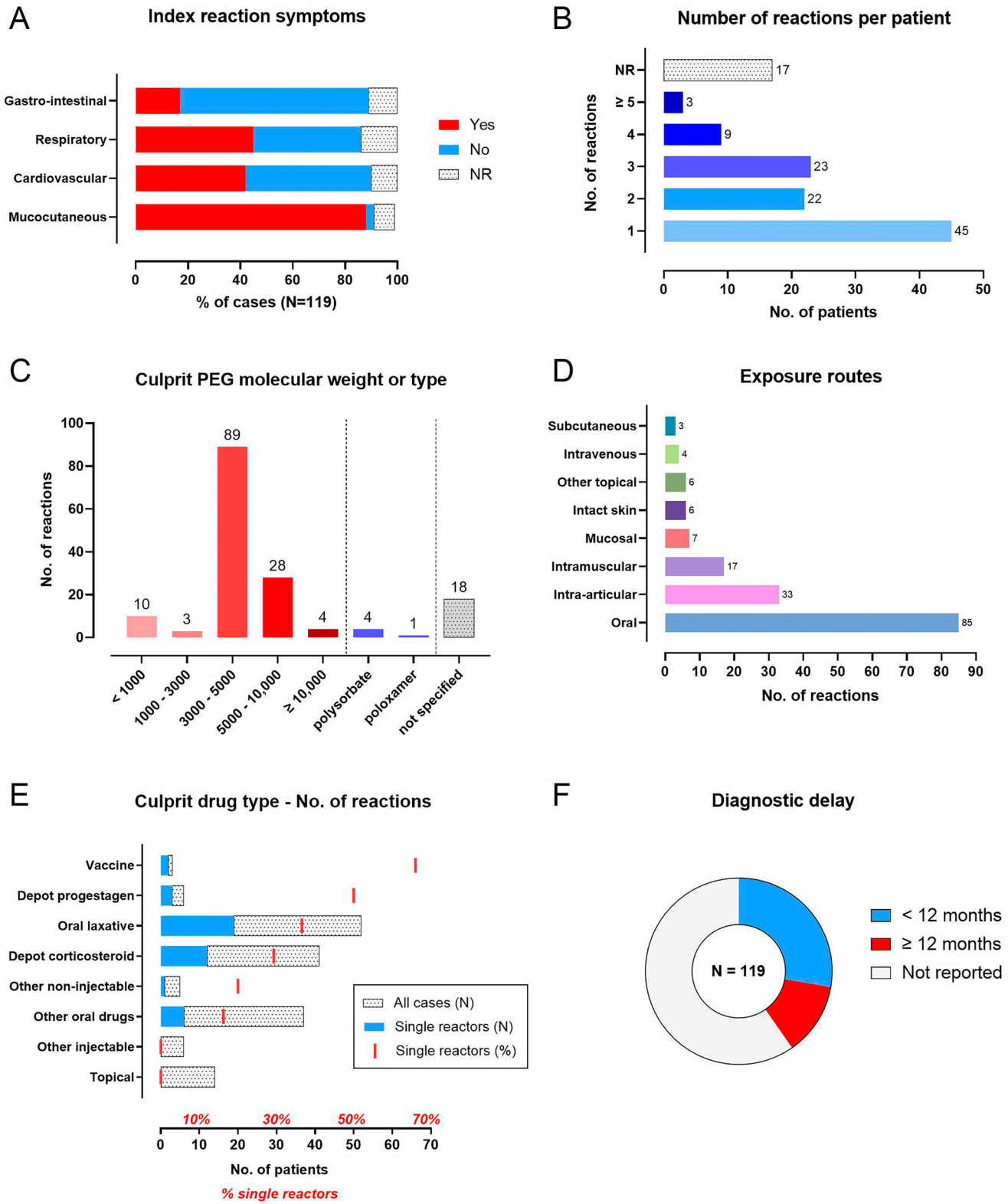

FIGURE 2 | Characteristics of immediate drug hypersensitivity reactions (DHR) to PEG or related compounds. (A) Organ systems involved in index DHR to PEG; (B) Total no. of reported PEG-related DHR per patient; (C) Distribution of culprit PEGs responsible for eliciting DHR according to molecular weight or type; (D) Distribution of exposure routes implicated in PEG-related DHR; (E) Relationship between culprit drug type for index DHR and total no. of reported DHR for that patient. Vertical red bars indicate the proportion of patients for each culprit drug type who experienced only a single reaction; (F) Diagnostic delay between index event and final PEG allergy diagnosis. DHR, drug hypersensitivity reaction; NR, not reported; PEG, polyethylene glycol.

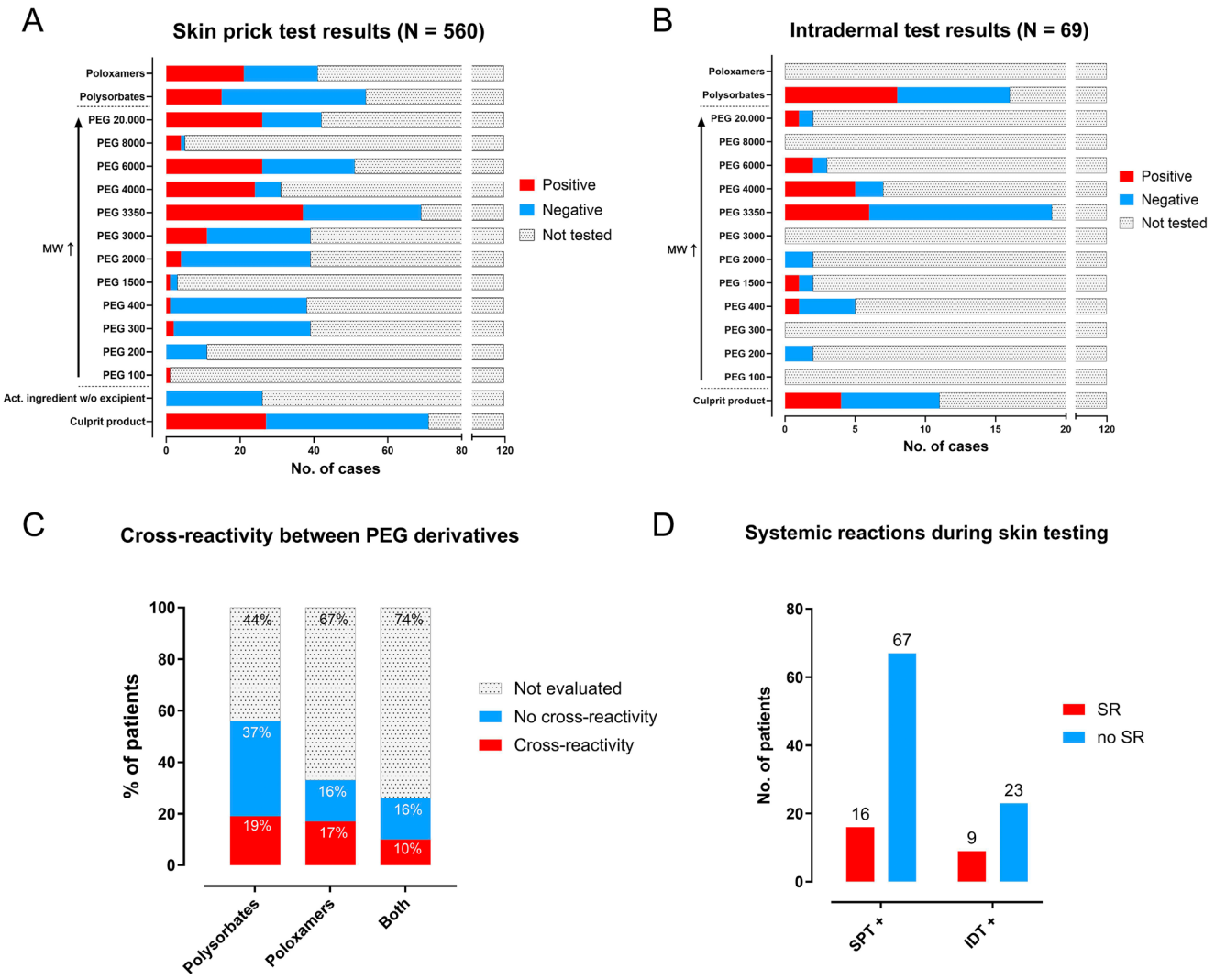

FIGURE 3 | Skin test outcomes in patients with allergy to PEG or related compounds. (A) Reported results of skin prick tests with PEGs of various molecular weights, related compounds, culprit products and drugs containing the same active ingredients as the culprit product without PEG; (B) Reported results of intradermal tests with PEGs of various molecular weights, related compounds and culprit products. (C) Observed cross-reactivity on skin testing between PEGs, polysorbates and poloxamers; (D) Prevalence of systemic reactions during skin testing, stratified according to outcome of the skin test readout. IDT, intradermal test; PEG, polyethylene glycol; SPT, skin prick test; SR, systemic reaction.

index reaction can be continued, newly prescribed and over-the-counter medications should always be checked for PEG content and avoided if possible (Table 3). Pharmacist advice should be obtained in case of doubt. Due to the omnipresent nature of PEGs in everyday life, strict avoidance is challenging and an adrenaline autoinjector should be considered especially in patients with severe and/or multiple reactions. It is unknown whether PEG allergy is amenable to rapid drug desensitisation [36].

3.2.2 | Gelatine

Gelatine is a mixture of polypeptides (average MW 15–300 kDa) resulting from partial hydrolysis of animal collagen, mostly pig- or cattle-derived for drugs or fish-derived in food. Historically, it was first used as a plasma expander and afterwards as a gelling agent in food, beverages and drugs (capsules, suppositories and vaccines) (Table 1).

We identified 103 cases with a median age of 19 years (range 12 months to 85 years) and 1:1 female-to-male ratio (Table 2, Figures 1 and 4 and Appendix S1). Reported culprits include IV plasma expanders ($N = 40$), vaccines ($N = 34$, mainly MMR and varicella vaccines), directly applied surgical glues ($N = 14$) and eye lenses, suppositories, erythropoietin, various drugs in oral gel form, gummy bears and marshmallows ($N < 3$ for each category) (Table S1). Multiple patients with index reactions to parenteral gelatins also experienced reactions upon gelatine exposure in food. Most cases occurred following parenteral exposure (IV, vaccination), followed by topical and rarely oral exposure. Over 90% of reactions were moderate to severe and 2 fatalities were reported [37, 38]. Time to onset was between one and 45 min with 40% reacting within 5 min (Figure 4). SPT and/or IDT were performed in 52 patients with a variety of agents including dissolved gelatine and were positive in 48/52 (sensitivity 92%; Table 2). Gelatine sIgE was positive in 48/55 cases (sensitivity 87%, range 0.78–> 100 kU/L). Alpha-gal sIgE was positive in 8/10 cases (80%). Of note, one case of paediatric anaphylaxis

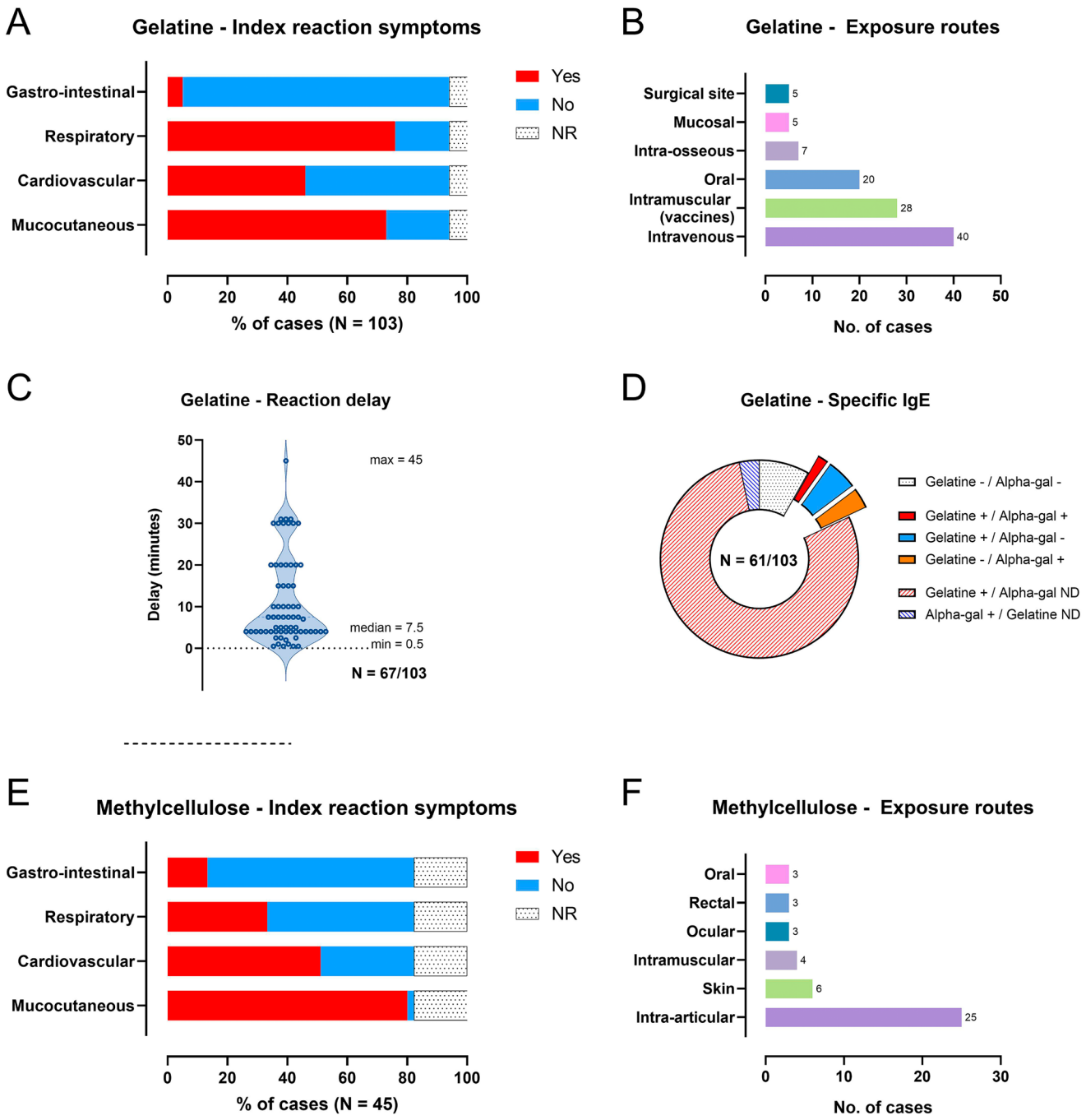

FIGURE 4 | Characteristics of immediate drug hypersensitivity reactions (DHR) to gelatines and methylcelluloses. (A) Organ systems involved in index DHR to gelatines; (B) Distribution of exposure routes implicated in gelatine-related DHR; (C) Distribution of delay between gelatine exposure and reaction onset in minutes; (D) Outcome of gelatine and alpha-gal specific IgE assays in patients with gelatine-related DHR; (E) Organ systems involved in index DHR to methylcelluloses; (F) Distribution of exposure routes implicated in methylcellulose-related DHR. DHR, drug hypersensitivity reaction; NR, not reported.

caused by gummy tablets containing fish collagen was identified, confirmed by positive SPT with the tablets and oral challenge with fish gelatine [39].

Gelatine hypersensitivity should be considered in perioperative, vaccine-related and idiopathic anaphylaxis and specific food-related reactions (mammalian meat, gelatine-based sweets). Testing should include SPT and IDT with a non-irritant IV gelatine preparation and sIgE measurement to gelatine and alpha-gal using commercially available assays (Table 3). Isolated gelatine allergy without alpha-gal sensitisation has been described; however, its frequency is unknown (*unreported case LHG* and [40]).

All gelatine-containing drugs, vaccines, IV fluids and surgical products should be strictly avoided and a warning card should be provided to all patients. If there were reactions to foods in the past, avoidance is advised. If no alpha-gal sensitisation is observed and no food-related reactions were observed, a

wait-and-see approach regarding gelatine-containing foods is possible. Alternatively, an oral food challenge can be provided to offer more certainty. Conversely, parenteral exposure to gelatine (including gelatine-based vaccines) should be avoided in alpha-gal allergic individuals (Table 3) [41, 42].

3.2.3 | Methylcellulose

Methylcelluloses are water-soluble organic derivatives of the polysaccharide cellulose, used as thickening agents, stabilisers, suspending agents or binders, in film coated tablets, ophthalmic drops, oral suspensions, injectable drugs and foods (Table 1).

We identified 44 published cases with immediate DHR to carboxymethylcellulose (CMC) and one to hydroxypropylmethylcellulose (HPMC) [43] (Tables 1 and 2 and Appendix S1). Median age was 53 years (range 14–80 years), and 59% were male (Table 2, Figures 1 and 4). Reactions occurred within minutes, except three cases occurring within 1 h. Skin symptoms, mostly pruritus and urticaria, were most common and 76% of cases fulfilled criteria for anaphylaxis (Figure 4, Appendix S1). A single reaction to injectable depot steroids containing CMC was seen in more than half of the cases, and most remaining cases were triggered by eyedrops, urethral/local anaesthetic gels, cosmetic fillers or barium enemas (Table S1). Seven patients (15.5%) had more than one reaction. The majority of patients showed tolerance of oral CMC intake and only three patients reported reactions to CMC in foods such as ice cream [44], hot chocolate [45] and an ice lolly [46]. All reported cases were immediate reactions and tested positive on ST pointing to an IgE-mediated mechanism (Table 2). Cross-sensitisation to other methylcelluloses was rarely investigated and only one case of cross-reactivity between CMC, HPMC and hydroxyethylcellulose was described [47]. No cases of hypersensitivity to hydroxypropylcellulose have been described and data on crossreactivity between methylcelluloses and hydroxypropylcellulose is lacking.

A positive ST to the culprit drug containing CMC and, if available, pure CMC, with a negative test to an alternative with similar ingredients except for CMC, confirms the suspicion (Tables 3 and 4). Pure CMC may be positive in SPT, but more often on IDT. There is limited experience with in vitro tests and assays for CMC-sIgE that are not commercially available though positive BAT and dot blot have been described. Oral provocation tests with CMC or CMC-containing preparations are usually not required as patients have often tolerated oral CMC exposure in foods or medications prior to allergy investigation, but they can be performed to confirm or disprove oral tolerance. Avoidance of all parenteral (e.g., depot steroids) and topical CMC exposure (e.g., eyedrops, gels) is advised in CMC-allergic patients. Since most patients tolerate oral intake, strict avoidance via the oral route is likely not required in those without a history of reactions after oral/food exposure; however, risk factors for reacting on oral exposure have not been elucidated (Table 3).

3.2.4 | Povidone

Povidone and crospovidone are synthetic polymers derived from N-vinylpyrrolidone used in drug tablets and capsules as film-forming, solubilising or suspending agents, tablet and capsule binders and disintegrants (Table 1). Povidone is frequently used in surgical skin disinfectant, wound antiseptic (povidone-iodine) and in ophthalmic lubricant solutions. Furthermore, (cros)povidone is used in cosmetics and as a food additive (E1201, E1202).

Sixteen case reports on povidone allergy were identified (Table 2 and Appendix S1). Age range was 4–59 years and 11/16 were men. Almost all patients suffered severe reactions with anaphylaxis in 15 cases (93.8%) (Figure 1). Seven (43.8%) experienced multiple anaphylactic episodes and two (12.5%) reported previous local/mild allergic reactions to topical products. The time interval between the first reaction and correct diagnosis varied from months to many years. A wide variety of povidone-containing drugs were reported as culprits through various exposure routes including a wide variety of povidone-containing oral drug formulations, topical agents (e.g., eyedrops, antiseptics for skin or mucosal membranes) and injectable drugs (IV, intra-articular) (Table S1).

Diagnosis is based on exposure history combined with ST with the culprit drug, pure povidone (available as powder dissolved in sterile water or in commercial eyedrop solutions) and if possible, a negative control drug with the same active ingredient without povidone (Tables 3 and 4). A low risk of systemic reactions during ST has been reported ($N = 1/16$; Figure 1, Table S2) [48]. Povidone-positive patients should also be tested for crospovidone sensitisation as cross-reactivity has been described ($N = 1/2$ tested) [49, 50]. In ST negative cases, a titrated oral challenge may be performed. BAT and sIgE assays have been used in some reports although standardised in vitro assays are not commercially available. Patients with proven povidone allergy should avoid all (cros)povidone-containing pharmaceuticals (Table 3). There is insufficient evidence of a risk of food-related reactions in povidone-allergic patients, although data is lacking.

3.2.5 | Mannitol

Mannitol is a polyol or sugar alcohol used as diluent, bulking agent and artificial sweetener. It is also naturally present in algae and mushrooms. Mannitol is absorbed through the gastrointestinal tract and expelled almost unchanged in urine. Due to its osmotic properties, it is also used as a tonicity agent in certain injectable drugs (e.g., some forms of paracetamol) and as treatment for raised intracranial or intraocular pressure (Table 1).

Anaphylaxis to mannitol is rare [51, 52], albeit potentially underestimated and was initially attributed to hyperosmolarity-induced direct mast cell degranulation [53]. We identified 4 likely cases of IgE-mediated mannitol allergy after oral [54, 55] (in cisapride or paracetamol) or IV (in paracetamol) exposure (Table 2, Figure 1 and Appendix S1) [55, 56]. Mannitol allergy was confirmed through a positive ST with the culprit product and a positive ST with pure mannitol ($N = 3/4$) or a negative ST with an alternative mannitol-free drug containing the same active ingredient as the culprit ($N = 1/4$). Notably, two patients who experienced anaphylaxis to IV paracetamol tolerated oral

paracetamol but had a food allergy to mushrooms [56]. There is no known cross-reactivity with other polyols used as artificial sweeteners in *light* products and as drug excipients (i.e., erythritol, sorbitol, xylitol, maltitol, lactitol) [55].

Avoidance of mannitol-containing oral and parenteral drugs is mandatory. Food avoidance is only advised in patients with a history of food-related reactions, although oral challenge testing might be performed to ascertain clinical reactivity to mannitol-containing foods (Table 3).

3.2.6 | Other Excipients Involved in Immediate Drug Hypersensitivity

In this section, immediate DHR reportedly caused by other excipients including benzyl alcohol, ethylenediaminetetraacetic acid (EDTA), metacresol and (methyl)parabens are summarised (Table S3). Quality of evidence in these cases was deemed insufficient to ascertain unequivocal causal relationships or formulate concrete recommendations.

- Immediate DHR to benzyl alcohol was reported in three cases after exposure to injectable vitamin B12 preparations or corticosteroids [57–59].
- EDTA was identified as the culprit in a case of acute urticaria and angioedema minutes after exposure to radiocontrast media and local anaesthesia [60]. There is insufficient evidence of cross-reactivity between EDTA and ethylenediamine [61].
- Metacresol, found in all available insulin formulations, was reported as the cause of acute urticaria with local injection site erythema in a single paediatric patient [62]. Although rare, metacresol should always be considered in the differential diagnosis of immediate DHR to insulin.
- (Methyl)paraben was reported in three cases as an inducer of immediate skin or respiratory symptoms [63–65].

3.2.7 | Delayed Hypersensitivity to Systemically Administered Excipients

Certain drug excipients are also reported to cause delayed-type DHR following systemic exposure (Table S4). Diagnosis relies on excipient ST through patch tests and/or IDT with delayed reading (contingent upon availability of sterile and nonirritant formulations). Negative ST results for the active ingredient without the excipient can help confirm the diagnosis. In selected cases, provocation tests may be considered. In vitro tests such as lymphocyte transformation tests (LTT) are not validated.

- Sulphites such as sodium metabisulphite (SMB) can cause delayed systemic reactions including maculopapular exanthema and localised or generalised eczematous rashes [66–71]. While SMB sensitisation is frequent and observed in 2.7% of patch-tested individuals [72], systemic symptoms upon SMB exposure are reported in only 4.8% of patch test-positive cases [73]. A history of contact dermatitis to SMB does not predispose towards systemic immediate reactions [74].
- Benzyl alcohol in antiseptics or cosmetics can cause contact dermatitis upon topical exposure with sensitisation observed in 0.3% of patch-tested patients [75]. It is also used as an antimicrobial preservative in injectable drugs and may trigger injection site reactions as well as local and systemic dermatitis upon systemic exposure [76–80]. A single case of delayed urticaria to benzyl alcohol has been reported [81].
- CMC has a low sensitisation rate in patch testing with only 0.8% of at-risk patients with chronic leg ulcers showing positive reactions [82]. Oral medications with CMC have been reported to trigger delayed systemic reactions [83].
- Parabens are a known cause of contact dermatitis with sensitisation estimated at 1.0% of patch-tested patients [84]. Parabens are commonly linked to allergic contact dermatitis to cosmetics and topical medications but may also cause delayed systemic DHR after exposure to paraben-containing local anaesthetics and mucolytics [84, 85].
- Reactions to metacresol are rarely documented, with no exact incidence data [86–88]. Metacresol may cause delayed injection site reactions, especially in insulin formulations [86–88].

3.3 | Special Considerations

3.3.1 | Risk of Reactions to Food-Derived Excipients in Drugs

- Gelatine, carmine red [89], mannitol and CMC [44–46] have been associated with immediate hypersensitivity reactions to both food and drugs containing these substances as excipients.
- The evidence for avoiding retinoids or other drugs that contain peanut or soy oil in patients allergic to these foods is unclear and more studies are needed to clarify this issue [90].
- For various excipients, previous concerns of allergenicity have been invalidated [91, 92]. Examples include lactose in various tablets (although anecdotal contamination of milk protein with lactose in an inhaler was reported [93]), egg in influenza vaccine [94] (with minor exceptions in recommendations [95]) and soybean oil or egg lecithin in propofol [96–98].
- The evidence on corn starch as an excipient causing allergy was considered insufficient by the Group.

3.3.2 | COVID-19 Vaccine Reactions and Excipient Allergy

PEG 2000 and PS80 are used as excipients in all current mRNA- and vector-based SARS-CoV-2 vaccines, respectively [99]. Several anaphylaxis cases were reported early on with excipients assumed to be likely culprits [100]. This resulted in a vaccination ban for (potential) excipient allergic subjects by regulatory agencies [99]. Initial estimates of SARS-CoV-2 vaccine-related anaphylaxis incidence were later adjusted to approximate the rate reported for previous vaccines (from 11 down to 5 per million doses) [101–103]. Reporting and ascertainment bias of passive surveillance data, as well as insufficient recognition of anaphylaxis mimickers such as immunisation stress-related responses [104], inducible

laryngeal obstructions [105], nocebo effects [18, 106] and non-allergic urticarial eruptions [107], were likely explanations for this overestimation. Almost all first-dose reactors could be safely revaccinated [108–111] and evidence for an underlying PEG allergy remains ultra-rare. Moreover, convincing cases of vaccine-related anaphylaxis in patients with preexisting IgE-mediated PEG/PS allergy are scant (Table S5). Conversely, tolerance of many PEG allergic patients to vaccines was rapidly demonstrated through alternative-excipient vaccination [112–116], graded same-excipient vaccination [16, 111, 117–118] and even single-dose same-excipient administration in a substantial number of PEG allergic patients (Table S5). It should be noted that a risk of anaphylaxis to vaccines cannot be completely ruled in PEG allergic individuals due to the variable thresholds of clinical reactivity [119] and potential transient nature of PEG allergy [15, 16]. Nevertheless, current evidence strongly argues against PEG and/or PS80 allergy as relevant causes of SARS-CoV2 vaccination-induced anaphylaxis [120, 121]. Of note, these observations also indicate that tolerance to PEG or PS80-containing vaccines does not rule out PEG and/or PS80 allergy.

4 | Conclusions

Hypersensitivity to drug excipients is an underrecognized yet clinically significant issue that complicates diagnosis and management of drug-related DHR. Traditionally, the focus has been on active ingredients, but increasing evidence shows that excipients—mostly well-tolerated and often assumed to be inert—can trigger severe and often repeated allergic reactions through a variety of exposures. This paper highlights key excipients implicated in immediate and delayed DHR, including polyethylene glycol (PEG), polysorbates, gelatine, methylcellulose, povidone, mannitol and preservatives like benzyl alcohol, metabisulphite and parabens.

Evidence largely stems from case reports, series and observational studies, and despite its generally low level, reveals a substantial clinical impact. Table 3 provides consensus-based recommendations on diagnosis and management of excipient DHR.

Patients with DHR to multiple (chemically unrelated) drugs, administered through different routes or unexplained despite extensive workup should prompt consideration of a hidden allergen such as an excipient. A thorough patient history and review of the product monograph to identify the presence of potentially allergenic excipients are crucial for timely recognition and prevention of repeat DHR. Current diagnostic approaches primarily use ST including SPT and IDT, supplemented by in vitro assays like BAT and sIgE measurement when available. A lack of standardised ST protocols and validated diagnostic algorithms hinders precise diagnosis. Potential cross-reactivity with structurally similar compounds as well as inconsistent naming and labelling conventions add to the complexity of excipient allergy.

Clinicians must remain vigilant [122], utilising all available product information to help avoid inadvertent exposure. Increased awareness, enforcement of standardised naming and labelling conventions, further refinement and validation of diagnostic methods and a better understanding of sensitisation pathways and cross-reactivity patterns will be essential to enhance patient safety in the future (see unmet needs in Table 3).

Funding

This Position Paper was supported by the European Academy of Allergy and Clinical Immunology (EAACI) under the EAACI Taks force on hypersensitivity to excipients in drugs 40713, 2024–2025. RS is supported through a Fonds Wetenschappelijk Onderzoek—Vlaanderen National Fund for Scientific Research (FWO) senior clinical investigator fellowship (Grant 1805523N).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

The data that supports the findings of this study are available in the Supporting Information of this article.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section. **Table S1:** Examples of culprit drugs containing excipients reported to elicit immediate DHR. **Table S2:** Case descriptions for reported immediate systemic reactions during excipient skin testing. **Table S3:** Case descriptions for immediate DHR caused by other drug excipients. **Table S4:** Case descriptions for delayed DHR caused by systemic exposure to drug excipients. **Table S5:** Tolerance of (upper part) and reactions to (lower part) SARS-CoV-2 vaccination in PEG and/or PS allergic patients. **Figure S1:** Evolution of published articles over time retrieved after PubMed search for (drug) allergy (left *y*-axis) or allergy for specific excipients (right *y*-axis). **Figure S2:** Relationship between number of reported PEG-related reactions (represented by size of each circle) and PEG dose (*y*-axis), molecular weight (*x*-axis) and exposure route (see in-figure legend box for colour coding). **Data S1:** all70324-sup-0003-AppS1.xlsx. **Data S2:** all70324-sup-0004-AppS2.docx. **Data S3:** all70324-sup-0005-AppS3.docx.